

# Circulation

## AHA STATISTICAL UPDATE

# 2025 Heart Disease and Stroke Statistics: A Report of US and Global Data From the American Heart Association

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**BACKGROUND:** The American Heart Association (AHA), 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, nutrition, sleep, and obesity) and health factors (cholesterol, blood pressure, glucose control, and metabolic syndrome) that contribute to cardiovascular health. The AHA Heart Disease and Stroke Statistical Update presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, brain health, complications of pregnancy, kidney disease, congenital heart disease, rhythm disorders, sudden cardiac arrest, subclinical atherosclerosis, coronary heart disease, cardiomyopathy, heart failure, valvular disease, venous thromboembolism, and peripheral artery disease) and the associated outcomes (including quality of care, procedures, and economic costs).

**METHODS:** 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 and globally to provide the most current information available in the annual Statistical Update with review of published literature through the year before writing. The 2025 AHA Statistical Update is the product of a full year's worth of effort in 2024 by dedicated volunteer clinicians and scientists, committed government professionals, and AHA staff members. This year's edition includes a continued focus on health equity across several key domains and enhanced global data that reflect improved methods and incorporation of ≈3000 new data sources since last year's Statistical Update.

The 2025 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 2025. 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 Material is available at <https://www.ahajournals.org/journal/doi/suppl/10.1161/CIR.0000000000001303>

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

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

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

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## SUMMARY

Each year, the American Heart Association (AHA), in conjunction with the National Institutes of Health and other government agencies, brings together in a single document the most up-to-date statistics related to HD, stroke, and cardiovascular risk factors in the AHA's Life's Essential 8 (Figure),<sup>1</sup> which include core health behaviors (smoking, PA, diet, and weight) and health factors (cholesterol, BP, and glucose control) that contribute to CVH. In 2024, a complementary construct that expands and includes the CVH framework to incorporate kidney health was developed by the AHA and called CKM health.<sup>23</sup> The CKM syndrome includes stages 0 to 4, which represent the pathophysiological progression from optimal CKM health to prevalent CVD.

The AHA Heart Disease and Stroke 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. CVD produces immense health and economic burdens in the United States and globally. The Statistical Update also presents the latest data on a range of major clinical heart and circulatory disease conditions (including stroke, congenital HD, rhythm disorders, subclinical atherosclerosis, CHD, HF, VHD, venous disease, and PAD) and the associated outcomes (including quality of care, procedures, and economic costs).

Each annual version of the Statistical Update undergoes revisions to include the newest nationally and globally 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. Following are a few



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

AHA indicates American Heart Association.

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highlights from this year's Statistical Update. Please see each chapter for references for these highlights, CIs for statistics reported, and additional information.

## Cardiovascular Health (Chapter 2)

- The AHA Life's Essential 8 scores among NHANES (National Health and Nutrition Examination Survey) 2007 through 2018 participants were significantly associated with the prevalence of CVD. For every increasing 1-SD increment of the AHA Life's Essential 8 score, there was a lower odds of CVD (OR, 0.64).
- CVH score, as measured by the AHA Life's Essential 8, and components were also shown to predict MACEs (first occurrence of IHD, MI, stroke, and HF) within the UK Biobank. Individuals in the lowest quartile (least healthy) compared with the highest quartile (healthiest) had a greater risk for MACEs (HR, 2.07), which was strongest for HF. The authors estimated that a 10-point improvement in the AHA Life's Essential 8 score could have prevented 9.2% of MACEs.
- CVH measured at multiple times across the life course can be used to assess the cumulative exposure to CVH. In the FHS (Framingham Heart Study), participants who maintained a low AHA Life's Essential 8 score (below the median at each examination; AHA Life's Essential 8 scores at examination 2, 69; median at examination 6, 66) scores over an average of 13 years had the highest CVD and

mortality risk (HRs, 2.3 and 1.45) compared with those who had high AHA Life's Essential 8 scores above the examination median at both examinations 2 and 6.

## 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 1.1% and 1.9%, respectively, in 2023.
- 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 2023, the prevalence of past 30-day cigarette use was comparable between NH White youths (1.6%) and NH multiracial youths (1.6%) compared with Hispanic youths (2.1%). In 2021, 11.7% of NH Black adults, 5.4% of NH Asian adults, 7.7% of Hispanic adults, and 11.7% of NH White adults reported cigarette use every day or some days.
- Electronic cigarettes were the most commonly used tobacco product among adolescents in 2023; the prevalence of use in the past 30 days among middle and high school students in the United States was 4.6% and 10.0%, respectively, with 89.4% of adolescent users reporting use of flavored products and 25.2% reporting daily use.

## Physical Activity and Sedentary Behavior (Chapter 4)

- The percentage of high school students who were physically active for ≥60 minutes on all 7 d/wk decreased over the past decade from 28.7% in 2011 to 23.9% in 2021. The percentage of high school students participating in muscle-strengthening activities on ≥3 d/wk decreased over the past decade from 55.6% in 2011 to 44.9% in 2021.
- According to the NHIS (National Health Interview Survey), the percentage of adults meeting the aerobic and muscle-strengthening Physical Activity Guidelines for Americans changed little from 2020 to 2022. The percentage reporting engaging in ≥150 min/wk of moderate-intensity aerobic activity, 75 min/wk of vigorous aerobic activity, or an equivalent combination was 47.9% in 2020 and 48.1% in 2022. The percentage reporting engaging in muscle-strengthening activities of at least moderate intensity and including all major muscle groups ≥2 d/wk was 31.9% in 2020 and 31.5% in 2022. The percentage of adults meeting both aerobic PA and muscle-strengthening guidelines was 25.2% in 2020 and 25.3% in 2022. It is important to note that each of these population prevalence estimates

remains below the goals set by Healthy People 2030.

- In the PROPASS consortium (Prospective Physical Activity, Sitting, and Sleep), among 15 253 adults, a cross-sectional compositional data analysis estimated that replacing less intense activities such as sedentary time, standing, and light-intensity PA, with 4 to 12 min/d of moderate- to vigorous-intensity PA was associated with meaningful cardiometabolic health benefits. For example, the minimum reallocation associated with a statistically significant reduction in body mass index was replacing 7 min/d of sedentary behavior with moderate to vigorous PA. In addition, replacing 4 min/d of light-intensity PA with moderate- to vigorous-intensity PA was associated with a significantly lower hemoglobin A1c.

## Nutrition (Chapter 5)

- The evidence for benefits of healthful diet patterns on a range of cardiometabolic and other disease outcomes is strong. The core elements of a healthy dietary pattern are (1) vegetables of all types; (2) fruits, especially whole fruits; (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.
- Most of the American population does not consume a healthy dietary pattern, as measured by the Healthy Eating Index, which is a measure of diet quality and compliance with the Dietary Guidelines for Americans. Although average diet quality has slightly improved in the past 10 years, the current average score is 59 (on a scale from 0–100). Differences in overall Healthy Eating Index scores are observed across subgroups characterized by age, sex, race and ethnicity, income, pregnancy status, and lactation status.
- Social and environmental factors observed to be associated with diet quality include education, income, race and ethnicity, neighborhood availability of supermarkets, and cost of food. The US Department of Agriculture reported that food-at-home prices will increase by 2.9% (prediction interval, 0.5%–5.3%) in 2024. This is a deceleration relative to the reported increase of 8.6% (prediction interval, 5.6%–11.8%) in 2023. The retail price of eggs increased 1.8% in January 2024, after an increase of 8.9% in December 2023, albeit 28.6%

below prices seen in January 2023. The price for fresh vegetables increased by 2.9% in January 2024 but was almost 1% lower than prices seen in January 2023, at which time the prices remained elevated after a peak in December 2022. Historically, in the first quarter of each year, fresh vegetables experience a seasonal peak in prices. The prices for fresh vegetables are predicted to increase 1.9% in 2024 (prediction interval, –3.0% to 7.0%).

## Overweight and Obesity (Chapter 6)

- According to US data from 2017 to 2020, the prevalence of obesity in adults was 41.8% for males and 41.8% for females; among youths 2 to 19 years of age, the prevalence of obesity was 20.9% for males and 18.5% for females.
- In 2022, all US states had an obesity prevalence >20%, 22 states had an obesity prevalence between 30% and 35%, 19 states had a prevalence of 35% to 40%, and 3 states had a prevalence of ≥40%.
- In 2022, it was estimated that among adults ≥18 years of age globally, 16% (890 million) were obese and 43% adults (2.5 billion) were overweight.

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

- Elevated lipoprotein(a), which is defined as ≥125 nmol/L or ≥50 mg/dL and is present in up to 20% of the population, is associated with increased risk of a range of CVD conditions. Recent recommendations call for measuring lipoprotein(a) at least once in every adult, although screening rates remain low in US adults.
- Among US adults with severe dyslipidemia (low-density lipoprotein cholesterol ≥190 mg/dL), 78.0% reported cholesterol evaluation in the preceding 5 years, with no significant change in screening rates between 2011 to 2012 and 2017 to March 2020.
- The landmark CLEAR outcomes trial (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) testing bempedoic acid versus placebo among statin-intolerant patients showed an overall 13% relative risk reduction in the primary end point; however, recent analyses among the primary prevention patient subgroup showed a 30% relative risk reduction.

## High Blood Pressure (Chapter 8)

- In 2022, the prevalence of high BP in US adults was highest in Mississippi (40.2%) and lowest in Colorado (24.6%). The prevalence of hypertension increases with age and 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  $\geq 65$  years of age.

- A systematic review and meta-analysis of 136 studies with 28 612 children and young adults (between 4 and 25 years of age) showed that the prevalence of masked hypertension was 10.4%.
- A reanalysis from the Spanish Ambulatory Blood Pressure Registry with 10-year follow-up data reported that 24-hour systolic BP was more strongly associated with all-cause mortality (HR, 1.41 per 1-SD increment), which remained robust after adjustment for clinic BP. Elevated all-cause mortality risk was also reported with masked hypertension (HR, 1.24) but not with white-coat hypertension.

## Diabetes (Chapter 9)

- CVDs remain the leading causes of death in individuals with diabetes.
- Composite risk factor control in those with diabetes remains suboptimal, with  $\leq 20\%$  at recommended levels of hemoglobin A1c, BP, and lipids.
- In a meta-analysis of 45 cohort studies, a systolic BP of  $\geq 140$  mmHg (but not  $\geq 130$  mmHg) compared with below this number was associated with a greater risk of cardiovascular outcomes (HR, 1.56). The risk was greater for each 10-mmHg increment in systolic BP (HR, 1.10).

## Metabolic Syndrome (Chapter 10)

- A meta-analysis including 28 193 768 participants showed that the global metabolic syndrome prevalence varied from 12.5% to 31.4% according to the definition considered. The prevalence was significantly higher in the Eastern Mediterranean region and Americas compared with other global regions and was directly related to the country's level of income.
- In the United States, according to data from NHANES 2001 to 2020, the prevalence of metabolic syndrome among youths 12 to 18 years of age was 3.73% for Hispanic youths, 1.58% for NH Black youths, and 2.78% for NH White youths. In 2017 to 2018, Mexican American adults generally had the highest prevalence of metabolic syndrome at 52.2%, followed by NH Black adults (47.6%), Asian/other adults and multirace adults (46.7%), NH White adults (46.6%) and other Hispanic adults (45.9%).
- CKM syndrome was defined as a health disorder attributable to connections among obesity, diabetes, chronic kidney disease, and CVD, including HF, AF, CHD, stroke, and PAD. In the NHANES 2011 to 2018 database, among individuals 20 to 44, 45 to 64, and  $\geq 65$  years of age, stage 0 CKM was

present in 17.35%, 5.45%, and 1.80%, respectively, and risk factors and subclinical CKM (stages 1–3) were present in 80.94%, 85.95%, and 72.03%, respectively.

## Adverse Pregnancy Outcomes (Chapter 11)

- The US national prevalence of gestational diabetes was 8.3% in 2021, an increase of 38% from 2016 according to birth data from the National Vital Statistics System.<sup>4</sup> Rates of gestational diabetes rose steadily with maternal age: In 2021, the rate for mothers  $\geq 40$  years of age was almost 6 times higher compared with that for mothers  $<20$  years of age (15.6% versus 2.7%).
- Among 51 685 525 live births between 2007 and 2019, age-standardized hypertensive disorders of pregnancy rates doubled (38.4 to 77.8 per 1000 live births). An inflection point was observed in 2014, with an acceleration in the rate of increase of hypertensive disorders of pregnancy (from +4.1%/y before 2014 to +9.1%/y after 2014). Rates of preterm delivery and low birth weight increased significantly when co-occurring in the same pregnancy with hypertensive disorders of pregnancy. Absolute rates of adverse pregnancy outcomes were higher in NH Black individuals and in older age groups. However, similar relative increases were seen across all age and racial and ethnic groups.
- A meta-analysis of 20 studies up to 2019 showed the effectiveness of lifestyle intervention and bariatric surgery on reduced risk of hypertensive disorders of pregnancy (OR, 0.45), gestational hypertension (OR, 0.61), and preeclampsia (OR, 0.67).

## Kidney Disease (Chapter 12)

- In 2021, the age-, race-, and sex-adjusted prevalence of ESKD in the United States was 2219 per million people, a decrease of 3.5% from its peak in 2019. The overall prevalence count increased slightly from 807 920 in 2020 to 808 536 in 2021, after having almost doubled from 409 226 in 2001 to 806 939 in 2019.
- The adjusted ESKD incidence decreased in all racial and ethnic groups from 2001 to 2019. After 2019, ESKD incidence increased among Black individuals but not among members of other race and ethnicity groups. In 2021, the incidence of ESKD among Black individuals was 3.8 times the incidence of NH White individuals; the incidence among Native American individuals was 2.3 times as high, and it was twice as high among Hispanic individuals.

- There is a strong and consistent association of reduced estimated glomerular filtration rate and higher urine albuminuria (even within the normal) range with incident and prevalent CVD. The addition of estimated glomerular filtration rate and urine albumin-to-creatinine ratio improves the prediction of CVD beyond traditional risk factors, and they are included in the new American Heart Association Predicting Risk of CVD Events equation. Furthermore, in an analysis of >4 million adults from 35 cohorts, inclusion of estimated glomerular filtration rate and albuminuria significantly improved prediction for CVD mortality beyond the Systematic Coronary Risk Evaluation and atherosclerotic CVD beyond the Pooled Cohort Equations in validation datasets ( $\Delta$  C statistic, 0.027 and 0.010) and categorical net reclassification improvement (0.080 and 0.056, respectively).

## Sleep (Chapter 13)

- Females have  $\approx$ 1.5 to 2.3 higher odds of reporting insomnia symptoms than males.
- Risks of developing obstructive sleep apnea and reporting a sleep disorder are lower in individuals who consume a healthy diet.
- Obstructive sleep apnea severity is associated with higher odds of white matter hyperintensities (mild: OR, 1.70; moderate to severe: OR, 3.9; severe: OR, 4.3).

## Total Cardiovascular Diseases (Chapter 14)

- According to national data, 39.5% of deaths in 2022 attributable to CVD in the United States were caused by CHD.
- In 2022, the age-adjusted mortality rate attributable to CVD in the United States was 224.3 per 100 000. The highest rate was in NH Black males (379.7 per 100 000), and the lowest rate was in NH Asian females (104.9 per 100 000).

## Stroke (Cerebrovascular Diseases) (Chapter 15)

- According to BRFSS (Behavioral Risk Factor Surveillance System) 2022 data, stroke prevalence in adults was 3.4% (median) in the United States, with the lowest prevalence in Puerto Rico (1.8%) and South Dakota (2.1%) and the highest prevalence in Arkansas (4.8%).
- A population-based cohort study from Ontario, Canada, followed up 9.2 million adults for a median of 15 years (2003–2018) and observed 280 197 incident stroke or transient ischemic attack events. Women had an overall lower adjusted hazard of stroke or transient ischemic attack than men

(HR, 0.82), which held true for all stroke types except subarachnoid hemorrhage (HR, 1.29).

- Among 6214 participants without history of stroke in the ELSA (English Longitudinal Study of Ageing) dataset, over 8 years of follow-up, compared with good sleep quality, poor baseline sleep quality was associated with long-term stroke risk (HR, 2.37). Worsened sleep quality was associated with stroke risk among those with good (HR, 2.08) and intermediate (HR, 2.15) sleep quality; improved sleep quality was associated with decreased stroke risk among those with poor sleep quality (HR, 0.31).

## Brain Health (Chapter 16)

- Young-onset dementia, defined as symptoms before 65 years of age, was estimated in a meta-analysis to have a prevalence globally of 1.1 per 100 000 at 30 to 34 years of age, 1.0 per 100 000 at 35 to 39 years of age, 3.8 per 100 000 at 40 to 44 years of age, 6.3 per 100 000 at 45 to 49 years of age, 10.0 per 100 000 at 50 to 54 years of age, 19.2 per 100 000 at 55 to 59 years of age, and 77.4 per 100 000 at 60 to 64 years of age, although data for some age groups were limited in lower- and middle-income countries.
- In a nationally representative cohort study of US veterans (N=1 869 090; individuals  $\geq$ 55 years of age receiving care in the Veterans Healthcare System between 1999 and 2019), there were significant differences in the incidence of dementia by race and ethnicity. The age-adjusted incidence of dementia was higher among underrepresented racial and ethnic groups than White racial and ethnic groups: 14.2 per 1000 person-years in American Indian or Alaska Native participants, 12.4 in Asian participants, 19.4 in Black participants, and 20.7 in Hispanic participants compared with 11.5 in White participants.
- Among 316 669 participants in the UK Biobank with 4238 incident cases of all-cause dementia (mean, 56 years of age) over a median 12.6 years of follow-up, an optimal AHA Life's Essential 8 score (score, 80–100 on a 100-point scale) was associated with a 14% lower risk of incident all-cause dementia (HR, 0.86) and 30% lower risk of vascular dementia (HR, 0.70) compared with a poor AHA Life's Essential 8 score (score of 0–49).

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

- Novel technology such as remote cardiac monitoring during the interstage might help to reduce disparities in outcome. Among families from low, mid, and high socioeconomic groups enrolled in a Cardiac High Acuity Monitoring Program, survival

was no different among the highest- and mid-socioeconomic status groups (mortality OR, 0.997; and OR 1.7, respectively).

- Gaps in care are common among youths with congenital cardiovascular defects. According to results from a single-center study, roughly one-third of youths with congenital cardiovascular defects experience a >3-year gap in clinical care. Factors associated with gaps in clinical care include 14 to 29 years of age (OR, 1.20), Black race (OR, 1.50), a distance of >150 miles from the hospital (OR, 1.81), mother's education of high school or less (OR, 1.17), and low neighborhood-level opportunity (eg, high deprivation; OR, 1.22).
- Risk of multisystem inflammatory syndrome in children is higher in children who have not been vaccinated. The pooled OR for multisystem inflammatory syndrome in children in vaccinated children compared with unvaccinated children is 0.4.

## Disorders of Heart Rhythm (Chapter 18)

- A nationwide, time-stratified case-crossover study using air pollution data from 322 cities in China observed an increased incidence of symptomatic AF and supraventricular tachycardia in the 24 hours after higher pollutant exposure. The change in the odds of onset of symptomatic AF associated with a 10- $\mu\text{g}/\text{m}^3$  (1 mg/m<sup>3</sup> for carbon monoxide) increase in air pollutant concentrations during lag 0 to 24 hours was 0.6% for fine particulate matter <2.5- $\mu\text{m}$  diameter, 1.6% for NO<sub>2</sub>, and 5.7% for carbon monoxide.
- An analysis of the UK Biobank (N=201 856) combined dietary recall of fruit juice and soft drink consumption with the polygenic risk score for AF developed in the cohort. Over a median of 9.9 years of follow-up, consumption of >2 L/wk of sugar-sweetened beverages and artificially sweetened beverages was associated with increased risk of AF in multivariable-adjusted analyses including demographic, social, clinical, and genetic risk factors (HR, 1.10 and 1.20, respectively) compared with nonconsumption of sugar-sweetened beverages or artificially sweetened beverages. Consumption of >2 L/wk of fruit juice was not associated with increased risk of AF (HR, 1.05) compared with nonconsumption. However, consumption of ≤1 L/wk of fruit juice was associated with reduced risk of AF (HR, 0.92) compared with nonconsumption.
- In Canada's single-payer health care environment, screening for AF with a single-lead ECG was determined to improve health outcomes and cost savings. A model indicated that screening 2929 301 individuals identified 127 670 cases of AF and estimated

avoidance of 12 236 strokes with a gain of 59 577 quality-adjusted life-years (0.02 per patient) over the lifetime of screened individuals.

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

- Cardiac arrest secondary to poisoning/overdose continues to rise with a recent study from Sweden highlighting the international concern about polysubstance use as a rising cause of cause of out-of-hospital cardiac arrest. In this recent study, 5.2% of out-of-hospital cardiac arrests were secondary to poisoning primarily secondary to polysubstance use.
- Studies continue to show worse outcomes for individuals with lower socioeconomic status and from people of underrepresented races and ethnicities, highlighting the need for widespread adoption of interventions to improve resuscitative care for at-risk individuals and communities internationally. A recent study showed worse outcomes on all reportable measures for Black individuals with out-of-hospital cardiac arrest, including survival to hospital discharge (OR, 0.81), return of spontaneous circulation (OR, 0.79), and good neurological outcomes (OR, 0.80).
- Data from Get With The Guidelines—Resuscitation have shown a modest improvement in survival in pre-COVID-19 data. Results indicated that both return of spontaneous circulation (unadjusted rate, 55.0%–65.4%; aOR] per year, 1.04) and survival to hospital discharge (unadjusted rate, 16.7%–20.5%; aOR per year, 1.03) improved in an analysis of in-hospital cardiac arrest from 2006 through 2018.

## Subclinical Atherosclerosis (Chapter 20)

- In a harmonized data set analysis of 19 725 Black individuals and White individuals 30 to 45 years of age from CARDIA (Coronary Artery Risk Development in Young Adults), the CAC Consortium (Coronary Artery Calcium), and the Walter Reed Cohort, the prevalence of CAC >0 among White males, Black males, White females, and Black females was 26%, 16%, 10%, and 7%, respectively.
- In an analysis of 4511 participants without known coronary artery disease who were compared with 438 individuals with a prior atherosclerotic CVD event in the CONFIRM international registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry), there was a similar MACE rate of ≈53 per 1000 patient-years for individuals with CAC >300 and those with a history of atherosclerotic CVD. Over a median of 4 years of follow-up, there was a similar

cumulative incidence of MACEs for individuals with CAC >300 or a prior atherosclerotic CVD event ( $P=0.329$ ).

- Compared with traditional risk factors, the C statistic 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;  $P<0.001$ ).

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

- An analysis of data on 17 266 adults with a history of CHD from NHIS 2006 to 2015, the prevalence of premature CHD (<65 years of age for females and <55 years of age for males) was higher among Asian Indian adults (aOR, 1.77) and other Asian adults (aOR, 1.68) than White adults.
- In a study of the 2010 to 2019 National Readmission Database, among 592 015 thirty-day readmissions and 787 008 ninety-day readmissions after index acute MI hospitalization, 30-day and 90-day all-cause readmission rates after acute MI decreased from 12.8% to 11.6% ( $P=0.0001$ ) and 20.6% to 18.8% ( $P=0.0001$ ), respectively.
- In a meta-analysis of 4 retrospective, nonrandomized, observational cohort studies among 184 951 patients  $\geq 18$  years of age diagnosed with non-ST-segment-elevation MI, early treatment (administered within 24 hours) with  $\beta$ -blockers was associated with a significant reduction in in-hospital mortality compared with no  $\beta$ -blocker treatment (OR, 0.43).

## Cardiomyopathy and Heart Failure (Chapter 22)

- According to recent Global Burden of Disease 2021 estimates, the prevalence of cardiomyopathy or myocarditis was 5.26 million and that of HF was 55.50 million.
- In the United States, 6.7 million people (2.3%) lived with HF in 2017 to 2020, and 87 941 people died of HF in 2022.
- Treatments that improve survival are underused in HF, and age- and population-adjusted mortality in the United States has continued to rise over time, reaching 21.0 per 100 000 people in 2022.

## Valvular Diseases (Chapter 23)

- The global prevalence of nonrheumatic VHD in 2021 was 28.4 million.
- Globally, the prevalence of nonrheumatic calcific aortic valve disease was 13.32 million in 2021.
- In 2021, there were 40 000 nonrheumatic degenerative mitral valve deaths globally.

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

- In 2021, there were an estimated  $\approx 523\,994$  cases of pulmonary embolism,  $\approx 756\,514$  cases of deep vein thrombosis, and  $\approx 1\,280\,508$  total venous thromboembolism cases in the United States in inpatient settings. Moreover, an analysis between 2011 and 2018 involving individuals with venous thromboembolism diagnosis observed that 37.6% of all patients were treated as outpatients.
- Data from Pulmonary Embolism Response Team Consortium Registry revealed a mortality rate of 20.6% in high-risk patients and 3.7% in intermediate-risk patients. Among the high-risk individuals, in-hospital mortality rate was 42.1% for those admitted with a catastrophic pulmonary embolism.
- Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research revealed a progressive increase in pulmonary hypertension-related mortality from 2003 to 2020. The age-standardized mortality rate per 1 000 000 patient-years rose from 17.81 in 2003 to 23.89 in 2020, driven by a pronounced increase in deaths in pulmonary hypertension groups 2 through 5.

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

- The prevalence of PAD in the United States is increasing and was estimated at  $>12.4$  million people  $\geq 40$  years of age in 2019.
- Social determinants of health, including low socio-economic status and living in rural communities, are associated with worse outcomes for patients with PAD. For example, lower socioeconomic status (defined as living in a ZIP code with a median household income  $<\$40\,000$ ) was associated with greater risk for amputation (HR, 1.12).
- PAD was the underlying cause of death for 11 596 individuals in 2022.

## Quality of Care (Chapter 26)

- Among 237 549 survivors of acute MI in the US Nationwide Readmissions Database, sex differences in HF hospitalization risk were explored. 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).
- 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  $\geq 66$  years of age living in the 25 largest metropolitan core-based statistical areas. When analyzed by ZIP code, every 1-unit increase in the Distressed Communities Index score was associated with 0.4% fewer TAVR procedures performed per 100 000 Medicare beneficiaries.

- Recent work within a large US registry demonstrated that Black individuals and Hispanic individuals were 27% less likely to receive bystander cardiopulmonary resuscitation at home (38.5%) than White individuals (47.4%; aOR, 0.74) and 37% less likely to receive bystander cardiopulmonary resuscitation in public locations than White individuals (45.6% versus 60.0%; aOR, 0.63). Significant disparities in bystander cardiopulmonary resuscitation exist after controlling for income variables, regardless of the racial and ethnic composition of the location of the arrest.

## Medical Procedures (Chapter 27)

- Percutaneous coronary intervention was the most common cardiovascular procedure in the United States from 2016 to 2021, followed by angioplasty and related vessel procedures (endovascular, excluding carotid) and saphenous vein harvest and other therapeutic vessel removal.
- In 2019, TAVR volumes ( $n=72991$ ) exceeded the volumes for all forms of SAVR ( $n=57\,626$ ). Patients undergoing TAVR in 2019 had a median of 80 years of age (interquartile range, 73–85 years of age) compared with 84 years of age (interquartile range, 78–88 years of age) in the initial years after US Food and Drug Administration approval of TAVR.
- In 2023, 4545 heart transplantations were performed in the United States, the most ever.

## Economic Cost of Cardiovascular Disease (Chapter 28)

- The average annual direct and indirect costs of CVD in the United States were an estimated \$417.9 billion in 2020 to 2021.
- The estimated direct costs of CVD in the United States increased from \$189.7 billion in 2012 to 2013 to \$233.3 billion in 2020 to 2021.
- Direct costs of hypertension by percentage of event type were largest for prescription medicines (30%) and office-based events (30%).

## Conclusions

The AHA, through its Epidemiology and Prevention Statistics Committee, continuously monitors and evaluates sources of data on HD and stroke in the United States

and globally to provide the most current information available in the Statistical Update. The 2025 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.

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The American Heart Association requests that this document be cited as follows: Martin SS, Aday AW, Allen NB, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Bansal N, Beaton AZ, Commodore-Mensah Y, Currie ME, Elkind MSV, Fan W, Generoso G, Gibbs BB, Heard DG, Hiremath S, Johansen MC, Kazi DS, Ko D, Leppert MH, Magnani JW, Michos ED, Mussolini ME, Parikh NI, Perman SM, Rezk-Hanna M, Roth GA, Shah NS, Springer MV, St-Onge M-P, Thacker EL, Urbut SM, Van Spall HGC, Voeks JH, Whelton SP, Wong ND, Wong S, Yaffe K, Palaniappan LP; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Committee. 2025 Heart disease and stroke statistics: a report of US and global data from the American Heart Association. *Circulation*. 2025;151:e41–e660. doi: 10.1161/CIR.0000000000001303

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## Acknowledgments

The writing group thanks its colleagues Michael Wolz at the National Heart, Lung, and Blood Institute; Kimberly Chapoy Casas, Sandeep Gill, Jason Walchok, Anokhi Dahya, Olivia Larkins, Kathie Thomas, Holly Picotte, Tian Jiang, Chandler Beon, Haoyun Hong, Sophia Zhong, and Shen Li from the AHA Data Science team; Nikki DeCleene, Laura Lara-Castorthe, and team at the Institute for Health Metrics and Evaluation at the University of Washington; and Bryan McNally and Rabab Al-Araji at the CARES program (Cardiac Arrest Registry to Enhance Survival) for their valuable contributions and review.

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(Continued)

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(Continued)

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\*Modest.

†Significant.

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[published correction appears in *Circulation*. 2024;149:e1023]. *Circulation*. 2023;148:1606–1635. doi: 10.1161/CIR.0000000000001184

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**ABBREVIATIONS TABLE**

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4D	Die Deutsche Diabetes Dialyze Studie
AAA	abdominal aortic aneurysm
AAMR	age-adjusted mortality rate
AASM	American Academy of Sleep Medicine
ABC-ACS	Age, Biomarkers, Clinical History, Acute Coronary Syndrome Score
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
ACT	Adult Changes in Thought
ACTION	Acute Coronary Treatment and Intervention Outcomes Network
AD	Alzheimer disease
ADRD	Alzheimer disease related dementias
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicro-MR Controlled Evaluation
AF	atrial fibrillation or atriofibrillation
AFFINITY	Assessment of Fluoxetine in Stroke Recovery
AGES	Age, Gene/Environment Susceptibility
AHA	American Heart Association
AHEI	Alternative Healthy 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
ANGEL-ASPECT	Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients With a Large Infarct Core

ANP	atrial natriuretic peptide
aOR	adjusted odds ratio
AP	angina pectoris
APACE	Advantageous Predictors of Acute Coronary Syndromes Evaluation
APO	adverse pregnancy outcome
app	application
ARB	angiotensin receptor blocker
ARGEN-IAM-ST	Pilot Study on ST Elevation Acute Myocardial Infarction
ARIC	Atherosclerosis Risk in Communities
ARIC-NCS	Atherosclerosis Risk in Communities–Neurocognitive Study
ARIC-PET	Atherosclerosis Risk in Communities–Positron Emission Tomography
aRR	adjusted relative risk
ARVC	arrhythmogenic right ventricular cardiomyopathy
ASB	artificially sweetened beverage
ASCOD	atherosclerosis, small vessel disease, cardiac pathology, other causes, dissection
ASCVD	atherosclerotic cardiovascular disease
ASCVD-PCE	Atherosclerotic Cardiovascular Disease Pooled Cohort Equation
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
ATTENTION	Endovascular Treatment for Acute Basilar-Artery Occlusion
AUC	area under the curve
AVAIL	Adherence Evaluation After Ischemic Stroke Longitudinal
AVATAR	Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis
AWHS	Aragon Workers Health Study
AXADIA-AFNET 8	Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease
BAOCHE	Basilar Artery Occlusion Chinese Endovascular
BASIC	Brain Attack Surveillance in Corpus Christi
BASICS	Basilar Artery International Cooperation Study
BEST	Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease

BEST	Acute Basilar Artery Occlusion: Endovascular Interventions vs Standard Medical Treatment
BEST-CLI	Best Surgical Therapy in Patients With Chronic Limb-Threatening Ischemia
BEST-MSU	BEnefits of Stroke Treatment Delivered Using a Mobile Stroke Unit
BiomarCaRE	Biomarker for Cardiovascular Risk Assessment in Europe
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
B_PROUD	Berlin PRehospital Or Usual Delivery of Acute Stroke Care
BRAVO	Building, Relating, Assessing, and Validating Outcomes
BRFSS	Behavioral Risk Factor Surveillance System
BWHS	Black Women's Health Study
CABANA	Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation
CABG	coronary artery bypass graft
CAC	coronary artery calcification
CAD	coronary artery disease
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CARDIA	Coronary Artery Risk Development in Young Adults
CARDIo-GRAM-plusC4D	Coronary Artery Disease Genome Wide Replication and Meta-Analysis Plus Coronary Artery Disease (C4D) Genetics
CARES	Cardiac Arrest Registry to Enhance Survival
CARPREG	Cardiac Disease in Pregnancy
CASCADE	Cascade Screening for Awareness and Detection
CASI	Cognitive Abilities Screening Instrument
CASQ2	calsequestrin 2
CAVIAAR	Conservation Aortique Valvulaire dans les Insuffisances Aortiques et les Anévrismes de la Racine aortique
CCD	congenital cardiovascular defect
CCTA	coronary computed tomography angiography
CDC	Centers for Disease Control and Prevention
CDC-WONDER	Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research
CERAD-TS	Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery, Total Score
CGPS	Copenhagen General Population Study
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
CHAP	Chicago Health and Aging Project
CHARGE-AF	Cohorts for Heart and Aging Research in Genomic Epidemiology—Atrial Fibrillation
CHARLS	China Health and Retirement Longitudinal Study
CHARM	Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity
CHD	coronary heart disease

CHOICE-MI	Choice of Optimal Transcatheter Treatment for Mitral Insufficiency
CHS	Cardiovascular Health Study
CI	confidence interval
CKD	chronic kidney disease
CKID	Chronic Kidney Disease in Children
CKM	cardiovascular-kidney-metabolic
CLARIFY	Community Benefit of No-Charge Calcium Score Screening Program
CLEAR	Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen
CLEAR Outcomes	Clinical Outcomes of Cardiovascular Disease
CLTI	chronic limb-threatening ischemia
CNSR	China National Stroke Registries
COAPT	Cardiovascular Outcomes Assessment of the MiraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
COAST	Comparative Outcomes Services Utilization Trends
COMBINE-AF	A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation
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
CORE-Thailand	Cohort of Patients With High Risk for Cardiovascular Events—Thailand
COSMIC	Cohort Studies of Memory in an International Consortium
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CPR	cardiopulmonary resuscitation
CPVT	catecholaminergic polymorphic ventricular tachycardia
CrCl	Creatine clearance
CRCS-K-NIH	Clinical Research Collaboration for Stroke in Korea-National Institutes of Health
CREOLE	Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans
CRIC	Chronic Renal Insufficiency Cohort
CRP	C-reactive protein
CSA	community-supported agriculture
CSPPT	China Stroke Primary Prevention Trial
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CVD	cardiovascular disease
CVD PRE-DICT	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
DEBATS	Discussion on the Health Effect of Aircraft Noise Study
DHA	docosahexaenoic acid
DIAL2	DIAbetes Lifetime perspective model
DIAMANTE	Diabetes Meta-Analysis of Trans-Ethnic Association Studies
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
e-cigarette	electronic cigarette
ECG	electrocardiogram
ED	emergency department
EDIC	Epidemiology of Diabetes Interventions and Complications
EF	ejection fraction
EFFECTS	Efficacy of Fluoxetine a Randomized Controlled Trial in Stroke
eGFR	estimated glomerular filtration rate
ELSA	English Longitudinal Study of Ageing
EMS	emergency medical services
EPA	eicosapentaenoic acid
EPIC	European Prospective Investigation Into Cancer and Nutrition
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
ERICA	Study of Cardiovascular Risks in Adolescents
ERP	early repolarization pattern
ESC-HFA EORP	European Society of Cardiology Heart Failure Association EURObservational Research Programme
ESKD	end-stage kidney disease
EUCLID	Examining Use of Ticagrelor in PAD
EVEREST	Endovascular Valve Edge-to-Edge Repair
EVITA	Evaluation of Varenicline in Smoking Cessation for Patients Post-Acute Coronary Syndrome
EVT	endovascular thrombectomy
EXAMINE	Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care
FAMILIA	Family-Based Approach in a Minority Community Integrating Systems–Biology for Promotion of Health
FAST-MAG	Field Administration of Stroke Therapy-Magnesium
FDA	US Food and Drug Administration
FDRS	Framingham Dementia Risk Score
FH	familial hypercholesterolemia
FHS	Framingham Heart Study
FIDELIO-DKD	Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FinnDiane	Finnish Diabetic Nephropathy
FINRISK	Finnish Population Survey on Risk Factors for Chronic, Noncommunicable Diseases
FIT	Henry Ford Exercise Testing Project
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
FPG	fasting plasma glucose
FPL	federal poverty level
FRS	Framingham Risk Score
FVL	factor V Leiden
GARFIELD-VTE	Global Anticoagulant Registry in the Field–Venous Thromboembolism
GBD	Global Burden of Diseases, Injuries, and Risk Factors
G-CHF	Global Congestive Heart Failure
GCKNS	Greater Cincinnati/Northern Kentucky Stroke Study
GDMT	guideline-directed medical therapy
GDP	gross domestic product
GLORIA-AF	Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation
GLP1-RA	glucagon-like peptide 1 receptor agonist
GRACE	Global Registry of Acute Coronary Events
GRS	genetic risk score
GWAS	genome-wide association studies
GWTG	Get With The Guidelines
GWTG-AFIB	Get With The Guidelines–Atrial Fibrillation
GWTG-R	Get With the Guidelines-Resuscitation
HANDLS	Health Aging in Neighborhoods of Diversity Across the Life Span
HAPIEE	Health, Alcohol and Psychosocial Factors in Eastern Europe
HAPO	Hyperglycemia and Adverse Pregnancy Outcome
HARMS2-AF	hypertension, age, raised body mass index, male sex, sleep apnea, smoking, alcohol
HbA1c	hemoglobin A1c (glycosylated total cholesterol)
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

HeartScore	Heart Strategies Concentrating on Risk Evaluation
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
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
High-STEACS	High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome
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
HUNT	Trøndelag Health Study
HYVET	Hypertension in the Very Elderly Trial
i3C	International Childhood Cardiovascular Cohort
ICD	implantable cardioverter defibrillator
ICD	<i>International Classification of Diseases</i>
ICD-9	<i>International Classification of Diseases, 9th Revision</i>
ICD-9-CM	<i>International Classification of Diseases, 9th Revision, Clinical Modification</i>
ICD-10	<i>International Classification of Diseases, 10th Revision</i>
ICD-10-CM	<i>International Classification of Diseases, 10th Revision, Clinical Modification</i>
ICH	intracerebral hemorrhage
ICU	intensive care unit
ICU-RESUS	ICU Resuscitation Project
IDF	International Diabetes Federation
IE	infective endocarditis
IE After TAVI	Infective Endocarditis After Transcatheter Aortic Valve Implantation
IHCA	in-hospital cardiac arrest
IHD	ischemic heart disease
IHM	interstage home monitoring program
ILCOR	International Liaison Committee on Resuscitation
IMPROVE	Carotid Intima-Media Thickness (IMT) and IMT Progression as Predictors of Vascular Events in a High-Risk European Population
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
IMT	intima-media thickness
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IPPIC	International Prediction of Pregnancy Complications
IPSS	International Pediatric Stroke Study
IQ	intelligence quotient
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
JHS	Jackson Heart Study
KD	Kawasaki disease
KFRT	kidney failure with replacement therapy
KHANDLE	Kaiser Healthy Aging and Diverse Life Experiences
Kuakini HHP	Kuakini Honolulu Heart Program
LA	left atrial
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
LODESTAR	Low-Density Lipoprotein Cholesterol-Targeting Statin Therapy Versus Intensity-Based Statin Therapy in Patients With Coronary Artery Disease
Look AHEAD	Look: Action for Health in Diabetes
LOOP	Implantable Loop Recorder Detection of Atrial Fibrillation to Prevent Stroke
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
MASALA	Mediators of Atherosclerosis in South Asians Living in America
MASLD	metabolic dysfunction-associated steatotic liver disease
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
MI	myocardial infarction
MIDA	Mitral Regurgitation International Database
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
MoCA	Montreal Cognitive Assessment
MONICA	Monitoring Trends and Determinants of Cardiovascular Disease
MR	mitral regurgitation
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
MSU	mobile stroke unit
MTF	Monitoring the Future
MUSIC	Muerte Súbita en Insuficiencia Cardiaca
MVP	Million Veterans Program
NACC	National Alzheimer's Dementia Coordinating Center
NAFLD	nonalcoholic fatty liver disease
NAMCS	National Ambulatory Medical Care Survey
NCDR	National Cardiovascular Data Registry
NCHS	National Center for Health Statistics
neuro-COVID-19	neurological disorders associated with COVID-19
NFHS-4	National Family Health Survey
NH	non-Hispanic
NHAMCS	National Hospital Ambulatory Medical Care Survey
NHANES	National Health and Nutrition Examination Survey
NHATS	National Health and Aging Trends Study
NHDS	National Hospital Discharge Survey
NHIRD	National Health Insurance Research Database
NHIS	National Health Interview Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
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
NIS	National (Nationwide) Inpatient Sample
NNT	number needed to treat
NOMAS	Northern Manhattan Study
NOTION	Nordic Aortic Valve Intervention
NRI	net reclassification improvement
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
nuMoM2b-HHS	Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be Heart Health Study
NVSS	National Vital Statistics System
NYTS	National Youth Tobacco Survey
OBSERVANT-II	Observational Study of Effectiveness of TAVI With New Generation Devices for Severe Aortic Stenosis Treatment
ODYSSEY Outcomes	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
Offspring	Offspring Study of Racial and Ethnic Disparities in Alzheimer Disease
OHCA	out-of-hospital cardiac arrest
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial and to Telmisartan Randomized Assessment
OPACH	Objective Physical Activity and Cardiovascular Health in Older Women
OR	odds ratio
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
ORION-1	Trial to Evaluate the Effect of ALN-PCSSC Treatment on Low Density Lipoprotein Cholesterol (LDL-C)
ORION-3	An Extension Trial of Inclisiran in Participants With Cardiovascular Disease and High Cholesterol
ORION-9	Trial to Evaluate the Effect of Inclisiran Treatment on Low-Density Lipoprotein Cholesterol (LDL-C) in Subjects With Heterozygous Familial Hypercholesterolemia (HeFH)
ORION-10	Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-Density Lipoprotein Cholesterol
ORION-11	Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-Density Lipoprotein Cholesterol
OSA	obstructive sleep apnea
OVER	Open Versus Endovascular Repair
PA	physical activity
PACE-TAVI	Impact of Right Ventricular Pacing in Patients With TAVR
PAD	peripheral artery disease
PAF	population attributable fraction
PAGE	Placental Abruptio Genetic Epidemiology
PAH	pulmonary arterial hypertension
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
PCE	Pooled Cohort Equations
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PE	pulmonary embolism
PESA	Progression of Early Subclinical Atherosclerosis
PH	pulmonary hypertension
PHIRST	Pulmonary Arterial Hypertension and Response to Tadalafil Study
PINNACLE	Practice Innovation and Clinical Excellence
PLATO	A Comparison of Ticagrelor [AZD6140] and Clopidogrel in Patients With Acute Coronary Syndrome
PM2.5	fine particulate matter <2.5- $\mu\text{m}$ diameter
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke

PORTRAIT	Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories
POUNDS	Preventing Overweight Using Novel Dietary Strategies
POUNDS Lost	Toward Precision Weight-Loss Dietary Interventions: Findings from the POUNDS Lost Trial
PPCM	peripartum cardiomyopathy
PPSW	Prospective Population Study of Women in Gothenburg
PQSI	Pittsburgh Sleep Quality Index
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
PREMIER	Lifestyle Interventions for Blood Pressure Control
PREVEND	Prevention of Renal and Vascular End-Stage Disease
PREVENT	American Heart Association Predicting Risk of CVD Events
ProDiGY	Progress in Diabetes Genetics in Youth
PROFESS	Prevention Regimen for Effectively Avoiding Second Stroke
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PROMINENT	Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes
PROPASS	Prospective Physical Activity, Sitting, and Sleep
PRS	polygenic risk score
PTB	preterm birth
Ptrend	<i>P</i> for trend
PTS	postthrombotic syndrome
PUFA	polyunsaturated fatty acid
PURE	Prospective Urban Rural Epidemiology
PWV	pulse-wave velocity
PY	person-years
QALY	quality-adjusted life-year
QTc	corrected QT interval
RACECAT	Transfer to the Closest Local Stroke Center vs Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory
RCT	randomized controlled trial
REDINSCOR	Red Española de Insuficiencia Cardiaca
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RENAL-AF	Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation
RENIS-T6	Renal Iohexol Clearance Survey in Tromsø 6
REPLACE	Riociguat Replacing PDE5i Therapy Evaluated Against Continued PDE5i Therapy
RESCUE Japan-LIMIT	Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism Japan Large IscheMlc core Trial
REVEAL	Registry to Evaluate Early and Long-Term PAH Disease Management

RE-SPECT ESUS	Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source
RIVANA	Vascular Risk in Navarre
ROSC	return of spontaneous circulation
RR	relative risk (also known as risk ratio)
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 disease 2
SAVR	surgical aortic valve replacement
SBP	systolic blood pressure
SCA	sudden cardiac arrest
SCAPIS	Swedish Cardiopulmonary Bioimage Study
SCD	sudden cardiac death
SCORE	Systematic Coronary Risk Evaluation
SCORE2	Systematic Coronary Risk Evaluation 2
SD	standard deviation
SDB	sleep disordered breathing
SDI	social deprivation index
SE	standard error
SEARCH	Search for Diabetes in Youth
SELECT	Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity
SELECT-2	Trial of endovascular thrombectomy for large ischemic strokes
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
SHEP	Systolic Hypertension in the Elderly Program
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
SMARRT	Systematic Multi-Domain Alzheimer Risk Reduction Trial
SMD	standard mean difference
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen
SND	sinus node dysfunction

SNP	single-nucleotide polymorphism
SpecTRA	Spectrometry for Transient Ischemic Attack Rapid Assessment
SPHERE	Stroke Prevention With Hydroxyurea Enabled Through Research and Education
SPIN	Stroke Prevention in Nigeria
SPRINT	Systolic Blood Pressure Intervention Trial
SPRINT MIND	Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension
SPS3	Secondary Prevention of Small Subcortical Strokes
SSB	sugar-sweetened beverage
STABILITY	Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy
START	South Asian Birth Cohort
STEMI	ST-segment–elevation myocardial infarction
STEP	Semaglutide Treatment Effect in People With Obesity
STEP 1	Research Study Investigating How Well Semaglutide Works in People Suffering From Overweight or Obesity
STEP-HFpEF	Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects With Obesity-Related Heart Failure With Preserved Ejection Fraction
STOP-COVID	Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19
STROKE-AF	Rate of Atrial Fibrillation Through 12 Months in Patients With Recent Ischemic Stroke of Presumed Known Origin
STROKE-STOP	Systematic ECG Screening for Atrial Fibrillation Among 75 Year Old Subjects in the Region of Stockholm and Halland, Sweden
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
Swiss TAVI	Swiss Transcatheter Aortic Valve Implantation
SYNTAX	Synergy Between PCI With Taxus and Cardiac Surgery
SYST-EUR	Systolic Hypertension in Europe trial
TAA	thoracic aortic aneurysm
TAU	transcatheter aortic valve implantation
TAVR	transcatheter aortic valve replacement
TC	total cholesterol
TdP	torsade de pointes
TEER	transcatheter-edge-to-edge repair
TGA	transposition of the great arteries
TGF	transforming growth factor
TIA	transient ischemic attack
TICS	Telephone Interview for Cognitive Status
TIMI	Thrombolysis in Myocardial Infarction
TIPS-3	International Polycap Study-3
TOAST	Trial of ORG 10172 in Acute Stroke Treatment

TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth
TOF	tetralogy of Fallot
T1D Exchange Clinic Registry	Type 1 Diabetes Exchange Clinic Registry
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
TOPMed	Trans-Omics for Precision Medicine
tPA	tissue-type plasminogen activator
TRILUMINATE Pivotal	Trial to Evaluate Cardiovascular Outcomes in Patients Treated With the Tricuspid Valve Repair System Pivotal
TRIUMPH	Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension
TVT	transcatheter valve therapy
TyG	Triglyceride-glucose
UDS	Uniform Data Set
UI	uncertainty interval
UK	United Kingdom
UNICEF	United Nations Children's Fund
USRDS	US Renal Data System
VF	ventricular fibrillation
VHD	valvular heart disease
VIPS	Vascular Effects of Infection in Pediatric Stroke
VISP	Vitamin Intervention for Stroke Prevention
VITAL	Vitamin D and Omega-3 Trial
VITAL-HF	Vitamin D and Omega-3 Trial–Heart Failure
Vmax	aortic valve peak jet velocity
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
WATCH-TAVR	WATCHMAN for Patients With Atrial Fibrillation Undergoing TAVR
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
Young ESUS	Young Embolic Stroke of Undetermined Source
YRBS	Youth Risk Behavior Survey

## 1. ABOUT THESE STATISTICS

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The AHA works with the NHLBI of the NIH 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:

- ARIC—CHD and HF incidence rates
- BRFSS—ongoing telephone health survey system
- CARES—OHCA
- GBD—global disease prevalence, mortality, and healthy life expectancy
- GCNKSS—stroke incidence rates and outcomes within a biracial population
- GWTG—quality information for AF, CAD, HF, resuscitation, 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
- NHANES—disease and risk factor prevalence and nutrition statistics
- NHIS—disease and risk factor prevalence
- NVSS—mortality for the United States
- USRDS—kidney disease prevalence
- WHO—mortality rates by country
- YRBS—health-risk behaviors in youth and young adults

### Disease Prevalence

Prevalence is an estimate of how many people have a condition at a given point or period in time. The CDC/NCHS conducts health examination and health interview surveys that provide estimates of the prevalence of diseases and risk factors. In this Statistical Update, the health interview part of the NHANES is used for the prevalence of CVDs. NHANES is used more than the

The 2025 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 2025. 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.

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 2025 Statistical Update is to present the latest estimates of the number of people in the United States and globally 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 2025 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 the 2025 Statistical Update to present estimates of the percentage of people with high LDL-C, high TC, elevated triglycerides, low HDL-C, hypertension, overweight, obesity, and diabetes. BRFSS 2022 and NHIS 2022 data are used for the prevalence of sleep issues. The NHIS 2021 data, BRFSS 2022, and NYTS 2022 are used for the prevalence of cigarette smoking. The prevalence of PA is obtained from the National Survey of Children's Health 2022, YRBS 2021, and NHIS 2022.

### Incidence and Recurrent Events

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 events 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.

### 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. Therefore, it is useful 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 2022 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 2025 Statistical Update include the number of deaths for which the disease is the underlying cause. Three exceptions are Chapter 8 (High Blood Pressure), Chapter 19 (Sudden Cardiac Arrest), 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, SCA, 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>1,2</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 2022 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 2021 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 2019 of the CDC/NCHS. ED visit estimates are from

the HCUP 2021 National Emergency Department 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 *ICD-9* and *ICD-10*, 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 from the WHO in Chapter 14 (Total Cardiovascular Diseases) 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 2025 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 2022. 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 2021. The numbers of visits to primary health care professionals' offices are for 2019. Except as noted, economic cost estimates are for 2020 to 2021.

## 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 and ethnic 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 collaborates with the Institute for Health Metrics and Evaluation to report statistics for the AHA Statistical Update from the GBD. This is an ongoing global effort to quantify health loss from hundreds of causes and risks from 1990 to the present for all countries. GBD produces 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.

The 2025 AHA Statistical Update uses GBD estimates that were produced for 1990 to 2021 for 204 countries and territories and stratified by age and sex.<sup>7–9</sup> These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. PAH has been added to the GBD study as a cause of disease burden. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in results across GBD cycles for both the most recent and earlier years.

For more information about the GBD and to access GBD resources, data visualizations, and most recent publications, please visit the study website.<sup>10</sup>

The 2025 Statistical Update [Supplementary Material](#) includes additional global and regional CVD statistics.

## Liver Disease Terminology

Beginning in the 2025 Statistical Update, MASLD is used instead of NAFLD. This updated terminology is consistent with the global Delphi consensus statement,<sup>11</sup>

which was co-led by the American Association for the Study of Liver Diseases. It was recognized that the term NAFLD carries multiple limitations, including its use of potentially stigmatizing language, the exclusionary nature of the diagnosis, and the lack of identification of the root cause of the condition. MASLD addresses these limitations and is the preferred nomenclature moving forward.

## Genetics

Genetic studies are reported in many chapters of the Statistical Update and are useful in identifying CVD heritability, risk factors, diagnoses, therapeutic targets, and patterns among high-risk groups. However, the current literature predominantly reflects data from White European populations, which constitute nearly 80% of genetic studies despite making up only 16% of the global population.<sup>12</sup> Moreover, studies done among underrepresented racial and ethnic populations consist largely of individuals of East Asian ancestry, with individuals of African, Latin American, and Indigenous ancestry less represented.<sup>13</sup> Data-sharing limitations attributable to privacy issues and identification risk also affect the availability of diverse genetic datasets.<sup>14</sup> The underrepresentation of diverse racial and ethnic groups within genetic and genomics research<sup>15</sup> underscores a critical gap that warrants consideration when reviewing the Statistical Update.

## Gender Identity/Sex

The Statistical Update recognizes the important differences between sex and gender identity. The authors therefore use the following definitions, based on statements of the AHA and National Academies,<sup>16,17</sup> to distinguish sex and gender. Sex is used to describe the biological characteristics determined by chromosomes, gonads, sex hormones, or genitals and categorized as male or female. Gender is recognized as a multidimensional construct that may have cultural, social, and linguistic dimensions and reflects an inner sense of being such as being a girl/woman, a boy/man, a combination of girl/woman and boy/man, or something else or having no gender at all. Historically, the terms sex, male, and female have been used throughout the Statistical Update for consistency and because most studies have assessed sex as opposed to gender. Recognizing the need to evolve in our approach, beginning in 2025, the Statistical Update reports gender when collected specifically by studies and when self-identified individually by study participants. The writing group acknowledges that the terms sex and gender are commonly used interchangeably in the referenced literature, and the terminology in a primary publication may not accurately reflect the important distinction between sex and gender. In the Statistical

Update, we strive to use language that reflects our interpretation of the underlying study methodology and is attentive to the fundamental differences between these 2 terms. When explicit language to indicate evaluation of gender methodology is not reported, we presume that the authors intended the biological variable of sex and use that term consistently in the Statistical Update.

## 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>.

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

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## 2. CARDIOVASCULAR HEALTH

**See Tables 2-1 through 2-10 and Charts 2-1 through 2-8**

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In 2010, the AHA released its 2020 Impact Goals 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) 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 not have clinically manifest CVD and also have optimal levels of all 7 CVH components, including not smoking, a healthy diet pattern, sufficient PA, normal body weight, and normal levels of TC, BP, and FPG in the absence of medication treatment.

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 to measuring CVH: AHA's Life's Essential 8.<sup>2</sup> The components of AHA's Life's Essential 8 include updates for the original 7 CVH components to provide metrics that more broadly recognize the scope of current health behaviors and practices with a more refined and continuous scale for better contrasting interindividual differences in CVH at a given point in time and improved tracking of intraindividual changes in CVH over time. Furthermore, sleep health was added into the CVH metrics, given 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 youths. Recent methodological work has demonstrated that statistical models using demographics and those factors often available in routinely collected data such as EHR systems (BMI, smoking, hypertension, hypercholesterolemia and diabe-

The 2025 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 2025. 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.

tes) may be able to estimate the AHA's Life's Essential 8 score, offering the potential to use the AHA's Life's Essential 8 framework even when data on some of the behavioral metrics are missing.<sup>3</sup> It is important to note that the AHA presidential advisory recognized psychological health and well-being and social determinants of health not merely as individual CVH metrics equivalent to one of the AHA's Life's Essential 8 metrics but as foundational factors underlying all 8 CVH components.

With this updated approach to assessing CVH, this chapter now provides statistical updates focusing on the newer CVH metrics as the health research and clinical practice fields migrate toward the use of AHA's Life's Essential 8, with attention also given to the 2 foundational influences on CVH. 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

**(See Table 2-2 and Charts 2-1 through 2-8)**

- Multiple independent investigations have confirmed the importance of having ideal levels of CVH components, along with the overall concept of CVH, based on the original Life's Simple 7 metrics and updated to include AHA's Life's Essential 8. Findings include strong inverse, stepwise associations in the United States and in recent meta-analyses 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, the number of carotid artery plaques, and CAC prevalence and progression; with physical functional impairment and frailty; with cognitive decline and depression; and with longevity.<sup>4-8</sup> CVH has also been shown to be associated with various diseases and conditions, including periodontitis,<sup>9</sup> depression<sup>10</sup>, osteoarthritis,<sup>11</sup> MASLD,<sup>12</sup> and cancer.<sup>13</sup> These associations were observed in all populations in the United States, including underrepresented racial and ethnic populations.<sup>14</sup> Similar relationships have also been seen in different populations internationally and in certain patient populations such as cancer survivors.<sup>7,15-25</sup>
- AHA's Life's Essential 8 scores among NHANES 2007 through 2018 participants were significantly associated with the prevalence of CVD. For every increasing 1-SD increment of AHA's Life's Essential 8 score, there was a lower odds of CVD (OR, 0.64 [95% CI, 0.60–0.69]).<sup>26</sup> The strength of the association between AHA's Life's Essential 8 score and CVD was strongest in younger individuals (20–59 years of age) and women. Recent work to elucidate the molecular mechanisms underlying the

association between CVH and CVD events found that metabolomic profiles were associated with CVH and partially mediated the relationship between CVH and HF in the Framingham cohort.<sup>27</sup> Other biomarkers considered have included early kidney dysfunction; urinary ACR in the normal range moderated the impact of CVH on all-cause mortality.<sup>28</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, having a greater number of ideal health factors is associated with a graded decrease in risk of incident CVD, and conversely, across any level of health factors, having a greater number of ideal health behaviors is associated with a graded lowering of incident CVD risk.<sup>29,30</sup> Use of technology has been shown to be differentially associated with health factors compared with behaviors.<sup>31</sup> Data from the JHS found that among these older adults, 88% of participants used internet and mobile technology. This study demonstrated that although no association of internet and mobile technology was seen with overall CVH score, using technology to track health was associated with having ideal BP, BMI, and cholesterol (all  $P<0.05$ ), and having ideal PA was associated with using smart devices ( $P=0.012$ ).
- 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 the original Life's Simple 7 CVH metrics (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 1-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 participants (HR, 0.91 [95% CI, 0.86–0.96]) and Black participants (HR, 0.93 [95% CI, 0.87–0.98]).<sup>32</sup> A similar association between CVH score and incidence of stroke was also observed in a large Chinese cohort.<sup>33</sup> Arterial stiffness mediates almost 10% of the relationship between CVH and stroke risk.<sup>34</sup>
- CVH score, as measured by AHA's Life's Essential 8, and components were also shown to predict MACEs (first occurrence of IHD, MI, stroke, and HF) within the UK Biobank.<sup>35</sup> Individuals in the lowest quartile (least healthy) compared with the highest quartile (healthiest) had a greater risk for MACEs (HR, 2.07 [95% CI, 1.99–2.16]), which was strongest for HF. The authors estimated that a 10-point improvement in AHA's Life's Essential 8 score could have prevented 9.2% of MACEs. Similar findings were seen in the Heart SCORE

study, a biracial community-based population, over a median follow-up of 12 years.<sup>36</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>37</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 CARDIA study observed a very low rate of CVD (aHR, 0.14 [95% CI, 0.09–0.22]) and CVD mortality (aHR, 0.17 [95% CI, 0.03–0.19]) over 32 years of follow-up being associated with a high (12–14 of 14 points) versus low (<8 points) level of CVH in late adolescence or early adulthood, as classified by Life's Simple 7.<sup>38</sup>
- CVH, as measured at multiple times across the life course, can be used to assess the cumulative exposure to CVH. In the FHS, participants who maintained low AHA's Life's Essential 8 scores (below the median at each examination; AHA's Life's Essential 8 scores at examination 2=69 and median at examination 6=66) over an average of 13 years had the highest CVD and mortality risk (HRs, 2.3 [95% CI, 1.75–3.13] and 1.45 [95% CI, 1.13–1.85]) compared with those who had high AHA's Life's Essential 8 scores above the examination median at both examinations 2 and 6.<sup>39</sup>
- 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>40</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 of the original 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 (aHR, 0.67 [95% CI, 0.59–0.75]) and mortality (aHR, 0.80 [95% CI, 0.72–0.89]) subsequently compared with

remaining in poor CVH over time.<sup>41</sup> Reduced CVD risk associated with improvement of CVH over time was also observed in the elderly and very elderly populations without CVD.<sup>42</sup>

- Ideal CVH in parents was associated with greater CVD-free survival in offspring, and maternal CVH (0–4 versus 10–14 CVH scores) was found to be a more robust predictor of an offspring's CVD-free survival (aHR, 2.09 [95% CI, 1.50–2.92]) than paternal CVH (aHR, 1.30 [95% CI, 0.87–1.93]).<sup>43</sup> Furthermore, better maternal CVH at 28 weeks' gestation during pregnancy was significantly associated with better offspring CVH in early adolescence: Having just 1 poor maternal CVH metric (versus all ideal) in pregnancy was associated with a 33% lower chance of offspring attaining ideal CVH (aRR, 0.67 [95% CI, 0.58–0.77]) between 10 and 14 years of age.<sup>44</sup> Long-term data from the FHS show that parental CVH affects offspring DALYs such that offspring of mothers in ideal compared with poor CVH had an additional 3 healthy life-years, although no association was seen with paternal CVH.<sup>45</sup>
- The Cardiovascular Lifetime Risk Pooling Project showed that adults with all optimal risk factor levels (similar to having ideal CVH factor levels of cholesterol, blood sugar, and BP, as well as not smoking) have substantially longer overall and CVD-free survival than those who have poor levels of  $\geq 1$  of these CVH factors. For example, at an index of 45 years of age, males with optimal risk factor profiles lived on average 14 years longer free of all CVD events and 12 years longer overall than people with  $\geq 2$  risk factors.<sup>46</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 of CVD.<sup>47,48</sup> Another report based on a large dataset from the UK Biobank found that having ideal CVH compared with poor CVH attenuated the all-cause and cardio-metabolic disease-related mortality for males and females and was associated with life expectancy gains of 5.50 years (95% CI, 3.94–7.05) for males and 4.20 years (95% CI, 2.77–5.62) for females at an index of 45 years of age among participants with cardiometabolic diseases and correspondingly 4.55 years (95% CI, 3.62–5.48) in males and 4.89 years (95% CI, 3.99–5.79) in females for people without cardiometabolic diseases.<sup>49</sup>
- Better CVH as defined by both the Life's Simple 7 and AHA's Life's Essential 8 scores is associated with less subclinical vascular disease,<sup>8,18</sup> better global cognitive and domain-specific performance and cognitive function,<sup>50</sup> higher incidence of MCI,<sup>51</sup> slower cognitive decline,<sup>53</sup> greater total brain volume, lower WMH volume, greater hippocampal

volume,<sup>54</sup> and lower hazard of subsequent dementia.<sup>55–57</sup> Among participants of the FHS, having favorable CVH was associated with a marginally lower risk of dementia (HR, 0.45 [95% CI, 0.20–1.01]).<sup>55</sup> A recent systematic review suggests that CVH is associated with incident dementia in a linear manner; however, the shape of the relationship differs, depending on when the risk factors are measured, with a linear relationship with midlife risk factors and a more J-shaped relationship with older-age risk factors.<sup>58</sup> At 5 years of age, children with better CVH have greater neurodevelopment as measured by the intelligence quotient.<sup>59</sup> Data from the longitudinal study ELSA-Brazil found that higher baseline AHA's Life's Essential 8 scores were associated with slower decline in global cognition, memory, verbal fluency, and the Trail-Making Test B.<sup>53</sup> Apolipoprotein E carrier status<sup>54</sup> and acculturation<sup>60</sup> have been demonstrated to modify the effects of CVH on cognition.

- Better CVH is also associated with fewer depressive symptoms,<sup>61–63</sup> lower risks of proteinuria<sup>64</sup> and chronic obstructive pulmonary disease,<sup>65</sup> lower risk of AF,<sup>66</sup> and lower odds of having elevated resting heart rate.<sup>67</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 MASLD.<sup>68</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 1-unit increase in CVH among US adults.<sup>69</sup>
- CVH has consistently been associated with frailty and multimorbidity in later life.<sup>70</sup> Better CVH in midlife was associated with a lower prevalence of frailty in a large community-based cohort study, ARIC,<sup>71</sup> such that for every 1-unit greater midlife Life's Simple 7 CVH score, there was a 37% higher relative prevalence of being in robust health as opposed to being frail (relative PR, 1.37 [95% CI, 1.30–1.44]). It is important to note that the UK Biobank has also shown that frailty and poor psychosocial health modify the relationship of CVH with CVD such that individuals who are both frail or in poor psychosocial health (social isolation and loneliness) and in poor CVH have the greatest risk of CVD.<sup>70,72</sup> Having  $\geq 5$  ideal Life's Simple 7 metrics was associated with a lower odds of having multiple disabilities within the 2017 to 2019 BRFSS data.<sup>73</sup> Among adults  $\geq 65$  years of age with  $\geq 5$  ideal CVH components, 78.8% (95% CI, 77.6%–79.9%) had

- no disabilities compared with only 61.2% (95% CI, 60.1%–61.9%) among those with <5 ideal metrics.
- 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>74</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>75</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>76,77</sup> A recent publication from the MESA study found that greater social disadvantage as measured by an aggregated score across 5 social determinants of health domains was associated with greater odds of unfavorable CVH risk factors, including hypertension, diabetes, smoking, and obesity, and higher risk of CVD, consistent with the notion of social determinants of health as a foundational factor for CVH.<sup>78</sup> The MESA study also found that health literacy, which is highly disparate by race and ethnicity and SES, was associated with Life's Simple 7 scores in older age such that limited personal health literacy had a 31% lower odds of optimal Life's Simple 7 score (OR, 0.69 [95% CI, 0.50–0.95]).<sup>79</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>80</sup> Data from BRFSS identifying racial and ethnic and geographic disparities in CVH among females of childbearing age in the United States showed that 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 regions were identified as having significantly lower prevalence of ideal CVH.<sup>81</sup> A systematic review and meta-analysis summarized the finding on demographic differences and socioeconomic 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>82</sup> In addition to these broad markers of SES, NHANES data shows disparities in CVH among those who have lower household food security even among those that participate in Supplemental Nutrition Assistance Program with Life's Simple 7 mean CVH scores for those with high, marginal, low and very low food security of 66.9 (SD, 0.4), 65.4 (SD, 0.6), 63.9 (SD, 0.8), and 62.3 (SD, 0.8), respectively.<sup>83</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>84</sup> A cross-sectional study from REGARDS found that neighborhood characteristics mediated a portion of the racial disparities in ideal CVH such that neighborhood physical environment, neighborhood safety, neighborhood social cohesion, and discrimination explained 5%, 6%, 1%, and 11%, respectively, of the racial disparities in CVH.<sup>85</sup> This and other recent reports on the association between better neighborhood perceptions and higher CVH score in Black communities<sup>86,87</sup> and the relationship between greater perceived social status and higher CVH score in the Hispanic/Latino population in the United States<sup>88</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>89</sup> described knowledge gaps and outlined potential steps toward equity in CVH, which is the objective of the interim<sup>90</sup> and longer-term<sup>91</sup> Impact Goals set forth by the AHA.
- Reproductive factors, including higher BMI in pregnancy, greater gestational weight gain, and a history of infertility, have been associated with worse CVH in middle-aged females.<sup>92,93</sup> Among Project Viva participants, 34% of female individuals had experienced infertility, and those with a history of infertility had an average CVH score that was 2.94 points lower (95% CI, -5.13 to -0.74) compared with those without a history of infertility after adjustment for demographics, SES, and reproductive factors.<sup>93</sup>
- Having more ideal CVH components in middle age has been associated with lower non-CVD and CVD health care costs in later life.<sup>94</sup> An investigation of 4906 participants in the Cooper Center Longitudinal Study reported that participants with ≥5 ideal CVH components in the original metrics 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>94</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>95</sup>

- The 2022 AHA presidential advisory on AHA's 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>2</sup> Since the publication of the AHA presidential advisory on AHA's Life's Essential 8, Lloyd-Jones et al<sup>96</sup> reported CVH prevalence estimates in the United States, analyzing NHANES data from 2013 to 2018 using the updated metrics. Independently, another report using 6 cycles of NHANES data from 2007 to 2018 focused on trajectories of overall and component CVH scores under the updated metrics for US adults between 18 and 44 years of age by sex and race and ethnicity subgroups, over 3 periods in time, each with 2 cycles, 4 years of NHANES data combined.<sup>97</sup> Similar statistics produced by the AHA using NHANES data are presented in the next section (Table 2-2 and Charts 2-1 through 2-8).
- Two additional reports used NHANES data from 2005 to 2018 to quantify CVH using the AHA Life's Essential 8 metrics and linked the NHANES participants to the National Death Index mortality file through 2019 to study the association between CVH and life expectancy, as well as all-cause and CVD-specific mortality. From 23 003 US adults 20 to 79 years of age, the life expectancy at 50 years of age, for example, the average number of years of life remaining after age 50, was estimated to be 27.3 years (95% CI, 26.1–28.4) in the low-CVH group, defined as CVH overall score <50, 32.9 (95% CI, 32.3–33.4) in the moderate-CVH group (CVH overall score between 50 and 79), and 36.2 (95% CI, 34.2–38.2) years in the high-CVH group, defined as overall CVH score of ≥80.<sup>98</sup> With 19 951 US adults between 30 and 79 years of age over a median follow-up of 7.6 years, the second report found a 58% reduction (HR, 0.42 [95% CI, 0.32–0.56]) in all-cause mortality rate and a 64% reduction (HR, 0.36 [95% CI, 0.21–0.59]) in CVD-specific mortality rate when the high-CVH (score, 75–100) was compared with the low-CVH (score <50) group and a 40% reduction (HR, 0.60 [95% CI, 0.51–0.71]) in all-cause mortality rate and 38% reduction (HR, 0.62 [95% CI, 0.46–0.83]) in CVD-specific mortality rate when the moderate-CVH group (score, 50–74) was compared with the low-CVH group.<sup>99</sup> In a third report analyzing 23 110 US adults ≥20 years of age from NHANES between 2005 and 2014, also matching with the National Death Index data through 2019, the authors reported a 40% reduction (HR, 0.60 [95% CI, 0.48–0.75]) in all-cause mortality rate and a 54% reduction (HR, 0.46 [95% CI, 0.31–0.68]) in CVD-specific mortality rate over a median follow-up of 9.4 years when they compared the high-CVH group (defined as overall CVH score of 80–100) with the low-CVH group (score <50).<sup>100</sup>
- Several reports using UK Biobank data were also produced with the updated CVH metrics. With 250 825 participants observed over a median follow-up of 10.4 years, people in the lowest quartile of the overall CVH score had 2.1- (95% CI, 2.0–2.2) fold higher risk of MACEs (including IHD, MI, stroke, and HF) compared with participants in the highest quartile of CVH score. HF was the MACE component outcome that experienced the greatest elevated risk (HR, 2.7 [95% CI, 2.4–2.9]).<sup>35</sup> The mean difference in life expectancy at 45 years of age between these 2 groups of people was estimated as 7.2 years (95% CI, 5.5–8.9) in favor of people with ≥4 ideal components in the CVH metrics. According to data from 135 199 participants, the life expectancy free of 4 major chronic diseases, namely CVD, diabetes, cancer, and dementia, at 50 years of age was estimated to be 6.9 years (95% CI, 6.1–7.7) longer for males with high CVH level (overall score, 80–100) compared with males at the low CVH level (overall score <50) and 9.4 years (95% CI, 8.5–10.2) longer for females in the high-CVH category compared with females in the low-CVH category. The corresponding estimates were 4.0 years (95% CI, 3.4–4.5) longer for males and 6.3 years (95% CI, 5.6–7.0) longer for females with moderate CVH level compared with their counterparts in the low CVH category.<sup>101</sup> In a study focusing on 33 236 participants with type 2 diabetes who were 40 to 72 years of age at baseline using the same database, people with ≥4 ideal components in the CVH metrics enjoyed a 65% reduction (HR, 0.35 [95% CI, 0.26–0.47]) in diabetes complications and a 47% reduction (HR, 0.53 [95% CI, 0.43–0.65]) in all-cause mortality rate compared with people with no more than 1 ideal CVH metric over a median of 11.7 years of follow-up.<sup>102</sup> Similar favorable risk reductions for risk of dying before 75 years of age were found for males and females with or without type 2 diabetes at the moderate to high CVH levels compared with low CVH among 309 789 adults from the same database.<sup>103</sup>
- Similar associations between greater CVH in childhood using the revised metrics and more favorable health or mortality outcomes were also reported by a Finnish<sup>104</sup> study and 2 Chinese cohort<sup>105,106</sup> studies. The Healthy Start Study contrasted the original Life's Simple 7 and the revised AHA's Life's Essential 8 CVH metrics in 305 children between 4 and 7 years of age and observed modest concordance between these 2 CVH metrics. The authors noted the important role that sleep health played in classifying childhood CVH levels.<sup>107</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: Mean CVH Scores (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 ( $\geq 20$  years of age) are displayed in Table 2-2. 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 youths 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 ( $\geq 20$  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 (Table 2-2).
- The corresponding mean overall CVH score was 78.4 (95% CI, 75.7–81.1) for NH Asian children, 74.1 (95% CI, 72.0–76.2) for NH White children, 72.7 (95% CI, 70.6–76.3) for Mexican American children, 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 adults, 66.0 (95% CI, 64.8–67.2) for NH White adults, 63.5 (95% CI, 62.2–64.8) for Mexican American adults, and 59.7 (95% CI, 58.4–60.9) for NH Black adults (Table 2-2).
  - An article appeared online ahead of print on the same day as the presidential advisory on AHA's 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>96</sup>

## CVH in the United States: Trend in Mean CVH Scores Over Time (NHANES 2007–March 2020)

### (See Charts 2-1 through 2-8)

- The overall trend for national estimates of the 8 CVH components for adults 20 to 79 years of age and trends by race and ethnicity subgroups are displayed in Charts 2-1 through 2-8 (unpublished AHA tabulation using NHANES<sup>108</sup>). Adults who self-reported a history of CHD, MI, angina, or stroke; were pregnant; or were breastfeeding at time of examination were not included in these analyses. Dietary estimates were available only through the 2017 to 2018 NHANES data cycle at the time of this report because of the availability of the Food Patterns Equivalents Database from the US Department of Agriculture, whereas mean scores for the rest of the CVH metrics were derived through the 2017 to March 2020 combined NHANES cycle. As a result, the trends over time for the overall CVH score are not presented here. Furthermore, data for the NH Asian population are available only for CVH evaluation starting from the 2011 to 2012 NHANES data cycle.
  - During this time period, CVH diet scores for US adults remained low and relatively unchanged (Chart 2-1). Adult NH Asian individuals observed slightly higher average diet scores since 2011 to 2012 compared with other race and ethnicity subgroups. The age-adjusted mean score for NH Asian adults in 2017 to 2018 was 47.8 (95% CI, 44.3–55.3). NH Black individuals had the lowest diet score on average during the past decade. In 2017 to 2018, the adjusted mean score for NH Black adults was 22.4 (95% CI, 19.1–27.7).

- Although still low overall, a gradual upward trend in mean CVH PA scores was observed for adults in every race and ethnicity subgroup presented, except for NH Asian adults, for whom the trend is less obvious (Chart 2-2). In the period of 2017 to March 2020, the age-adjusted mean PA scores ranged from 47.9 (95% CI, 45.6–50.3) for Hispanic adults to 57.7 (95% CI, 54.0–61.4) for NH White adults.
- Upward trends in mean nicotine exposure CVH scores were observed for adults in all race and ethnicity subgroups presented (Chart 2-3). The mean scores for the updated nicotine exposure CVH score, which now takes into account secondhand smoking exposure as well, were significantly higher in NH Asian and Hispanic individuals compared with NH White and NH Black individuals. The age-adjusted mean scores ranged between 66.8 (95% CI, 62.7–70.8) for NH Black adults and 87.0 (95% CI, 84.4–89.5) for NH Asian adults during 2017 to March 2020.
- Upward trends were also observed across all race and ethnicity subgroups for the newest addition to the updated CVH metrics, the sleep health score, although the age-adjusted mean scores were significantly lower for NH Black individuals, ranging from 71.5 (95% CI, 69.3–73.6) in 2007 to 2008 to 78.5 (95% CI, 76.4–80.6) in 2015 to 2016 and then to 76.6 (95% CI, 74.9–78.3) in 2017 to March 2020 compared with other race and ethnicity subgroups (Chart 2-4).
- Although mean CVH BMI scores were higher in NH White individuals and NH Asian individuals compared with NH Black individuals and Hispanic individuals, all race and ethnicity subgroups presented here observed a steep downward trend in this CVH metric over the past decade (Chart 2-5). In the period of 2017 to March 2020, the age-adjusted mean BMI scores ranged between 57.5 (95% CI, 54.8–60.2) for NH White adults and 50.3 (95% CI, 48.5–52.2) for NH Black adults.
- Trends in age-adjusted mean scores of the non-HDL lipids metric over the past decade improved for all race and ethnicity subgroups, except for the NH Asian population, for which the mean scores were relatively unchanged (Chart 2-6). NH Black individuals had significantly higher mean scores in this metric, ranging from 69.0 (95% CI, 67.0–71.1) in 2007 to 2008 to 74.9 (95% CI, 72.8–77.0) in 2017 to March 2020, compared with the other race and ethnicity subgroups.
- Although they remained relatively stable through 2014, the mean CVH blood glucose scores had a steady worsening for all race and ethnicity subgroups over the past 6 years (Chart 2-7). The mean scores for all US individuals were 79.4 (95% CI, 78.2–80.6) in 2007 to 2008 and 80.5 (95% CI, 79.4–81.5) in 2013 to 2014 but declined to 76.0 (95% CI, 75.2–76.9) in 2017 to March 2020.
- During this time period, age-adjusted mean BP scores for US adults remained relatively unchanged (Chart 2-8). NH Black individuals had the lowest mean BP score and had a seemingly more pronounced downward trend over time in this CVH metric, from 65.8 (95% CI, 62.2–69.3) in 2007 to 2008 to 57.9 (95% CI, 55.8–59.9) in 2017 to March 2020, compared with the rest of US adult populations.

## Trends in Risk Factors and Causes for YLL and YLD in the United States: 1990 to 2021

(See Tables 2-3 through 2-6)

- The leading risk factors for YLLs from 1990 to 2021 in the United States and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-3.
  - High SBP and smoking remained the first and second leading YLL risk factors in both 1990 and 2021. Age-standardized rates of YLL attributable to smoking declined by 53.9%, whereas age-standardized rates attributable to high SBP declined 47.4%.
  - In 2021, CVH components accounted for 12 (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 2021 in the United States and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-4.
  - IHD was the leading YLL cause in 1990 and second leading YLL cause 2021, with COVID-19 ranking first. Age-standardized YLL rates attributable to IHD declined 55.5%, whereas age-standardized YLL rates resulting from tracheal, bronchus, and lung cancer declined 50.0%.
  - Type 2 diabetes also rose from the 13th to 9th leading YLL cause, whereas AD and other dementias also rose from the 10th to 6th leading YLL cause.
- The leading risk factors for YLDs from 1990 to 2021 in the United States and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-5.
  - High BMI, high FPG, and smoking are among the top 4 leading YLD risk factors in both 1990 and 2021, with high FPG rising in ranking and smoking dropping from the second to the fourth leading YLD risk factor during this time period. Age-standardized YLD rates attributable to smoking declined by 22.8%, and age-standardized rates

attributable to high BMI and high FPG increased by 69.3% and 123.7%, respectively, between 1990 and 2021.

- The leading causes of YLDs from 1990 to 2021 in the United States and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-6.
  - From 1990 to 2021, type 2 diabetes rose from the 10th to 3rd leading YLD cause with a 157.9% increase in the age-standardized YLD rates.

## Trends in Global Risk Factors and Causes for YLL and YLD: 1990 to 2021

### (See Tables 2-7 through 2-10)

- The leading global YLL risk factors from 1990 to 2021 and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-7.
  - High SBP and smoking were the first and second leading YLL risk factors globally in 2021. Age-standardized YLL rates attributable to high SBP and smoking declined 32.3% and 42.5%, respectively, between 1990 and 2021.
  - From 1990 to 2021, high FPG rose from the 14th to 5th leading risk factor of global YLLs with a 1.6% decrease in the age-standardized YLL rates over this period.
- The leading global YLL causes from 1990 to 2021 and the corresponding percent change in age-standardized YLL rates attributable to these risk factors are presented in Table 2-8.
  - IHD rose from the third to second leading global YLL cause between 1990 and 2021, whereas age-standardized YLL rates declined by 31.6% during this period.
  - ICH and ischemic stroke rose from the seventh to fifth and from the 12th to 8th leading cause of global YLL, respectively, between 1990 and 2021.
  - Type 2 diabetes also rose from the 26th to 14th leading global YLL cause, showing a 9.8% increase in age-standardized YLL rate.
- The leading global risk factors for YLDs from 1990 to 2021 and the corresponding percent change in age-standardized YLD rates attributable to these risk factors are presented in Table 2-9.
  - High FPG and high BMI were the first and second leading YLD risk factors globally in 2021, replacing iron deficiency and smoking, which were first and second in 1990. Age-standardized YLD rates attributable to high FPG and high BMI increased 74.6% and 69.0%.
- The leading global causes of YLDs from 1990 to 2021 and the corresponding percent change in

age-standardized YLD rates attributable to these risk factors are presented in Table 2-10.

- From 1990 to 2021, type 2 diabetes rose from the 10th to 7th leading global cause of YLD during this time period with a 94.7% increase in the age-standardized global YLD rate.

## Furthering the AHA's Impact Through Continued Efforts to Improve CVH

### (See Tables 2-3 through 2-6)

- Renewed efforts to maintain and improve CVH will be foundational to successful reductions in mortality and disability in the United States and globally. Individuals with more favorable levels of CVH have significantly lower risk for several of the leading causes of death and YLD, including IHD,<sup>29</sup> AD,<sup>109</sup> stroke,<sup>110,111</sup> CKD,<sup>112</sup> diabetes,<sup>113</sup> and breast cancer<sup>114</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.
- There is increasing recognition that optimizing pre-pregnancy and maternal CVH will result in long-term benefits to the health of the birthing individual and the offspring. See Chapter 11 (Adverse Pregnancy Outcomes) for additional information.
- As the benefits of ideal CVH become increasingly evident, attention is turning to developing interventions to promote CVH with a focus on implementation science.<sup>115</sup> An increasing number of studies are using community-based, school-based, or technology-enhanced interventions to directly improve CVH score.<sup>116-120</sup>

## Global Efforts to Improve CVH

- A recent scoping review examining our knowledge of CVH across low- and middle-income countries revealed that limited data exist on CVH in these countries, 85% are cross-sectional, and 71% came from only 10 countries.<sup>121</sup>
- 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 address relevant national health priorities in ways that facilitate contextualization within individual countries and cultures.

**Table 2-1.** AHA's Life's Essential 8: New and Updated Metrics for Measurement and Quantitative Assessment of CVH

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>122,123</sup> (populations); MEPA <sup>124</sup> (individuals)	Quantiles of DASH-style diet adherence or HEI-2015 (population)  Scoring (population): <table> <thead> <tr> <th>Points</th> <th>Quantile</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>≥95th 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> <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	≥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)	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> <thead> <tr> <th>Points</th> <th>Quantile</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>≥95th 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> <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	≥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)	Points	MEPA score (points)	100	9–10	80	7–8	50	5–6	25	3–4	0	0–2
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(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)																																
	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: <table> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>7&lt;9</td> </tr> <tr> <td>90</td> <td>9&lt;10</td> </tr> <tr> <td>70</td> <td>6&lt;7</td> </tr> <tr> <td>40</td> <td>5&lt;6 or ≥10</td> </tr> <tr> <td>20</td> <td>4&lt;5</td> </tr> <tr> <td>0</td> <td>&lt;4</td> </tr> </tbody> </table>	Points	Level	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: <table> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>Age-appropriate optimal range</td> </tr> <tr> <td>90</td> <td>&lt;1 h above optimal range</td> </tr> <tr> <td>70</td> <td>&lt;1 h below optimal range</td> </tr> <tr> <td>40</td> <td>1&lt;2 h below or ≥1 h above optimal</td> </tr> <tr> <td>20</td> <td>2&lt;3 h below optimal range</td> </tr> <tr> <td>0</td> <td>≥3 h below optimal range</td> </tr> </tbody> </table>	Points	Level	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				
Points	Level																																			
100	7<9																																			
90	9<10																																			
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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: <table> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>&lt;25</td> </tr> <tr> <td>70</td> <td>25.0–29.9</td> </tr> <tr> <td>30</td> <td>30.0–34.9</td> </tr> <tr> <td>15</td> <td>35.0–39.9</td> </tr> <tr> <td>0</td> <td>≥40.0</td> </tr> </tbody> </table>	Points	Level	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 <a href="#">Supplemental Material</a> for suggestions for <2 y of age  Scoring: <table> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>5th–&lt;85th percentile</td> </tr> <tr> <td>70</td> <td>85th–&lt;95th percentile</td> </tr> <tr> <td>30</td> <td>95th percentile–&lt;120% of the 95th percentile</td> </tr> <tr> <td>15</td> <td>120% of the 95th percentile–&lt;140% of the 95th percentile</td> </tr> <tr> <td>0</td> <td>≥140% of the 95th percentile</td> </tr> </tbody> </table>	Points	Level	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								
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	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> <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> <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> <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> <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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(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)																								
	BP	Measurement: Appropriately measured SBP and DBP  Example tools for measurement: Appropriately sized BP cuff	Metric: SBP and DBP (mm Hg)  Scoring:  <table> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>&lt;120/&lt;80 (optimal)</td> </tr> <tr> <td>75</td> <td>120–129/&lt;80 (elevated)</td> </tr> <tr> <td>50</td> <td>130–139 or 80–89 (stage 1 hypertension)</td> </tr> <tr> <td>25</td> <td>140–159 or 90–99</td> </tr> <tr> <td>0</td> <td>≥160 or ≥100</td> </tr> </tbody> </table> Subtract 20 points if treated level	Points	Level	100	<120/<80 (optimal)	75	120–129/<80 (elevated)	50	130–139 or 80–89 (stage 1 hypertension)	25	140–159 or 90–99	0	≥160 or ≥100	Metric: SBP and DBP (mm Hg) percentiles for ≤12 y of age. For ≥13 y of age, use adult scoring. Screening should start no later than 3 y of age and earlier per clinician discretion  Scoring:  <table> <thead> <tr> <th>Points</th> <th>Level</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>Optimal (&lt;90th percentile)</td> </tr> <tr> <td>75</td> <td>Elevated (≥90th–&lt;95th percentile or ≥120/80 mm Hg to &lt;95th percentile, whichever is lower)</td> </tr> <tr> <td>50</td> <td>Stage 1 hypertension (≥95th–&lt;95th percentile+ 12 mm Hg or 130/80 to 139/89 mm Hg, whichever is lower)</td> </tr> <tr> <td>25</td> <td>Stage 2 hypertension (≥95th percentile+12 mm Hg or ≥140/90 mm Hg, whichever is lower)</td> </tr> <tr> <td>0</td> <td>SBP ≥160 or ≥95th percentile+30 mm Hg SBP, whichever is lower, and/or DBP ≥100 or ≥95th percentile+20 mm Hg DBP</td> </tr> </tbody> </table> Subtract 20 points if treated level	Points	Level	100	Optimal (<90th percentile)	75	Elevated (≥90th–<95th percentile or ≥120/80 mm Hg to <95th percentile, whichever is lower)	50	Stage 1 hypertension (≥95th–<95th percentile+ 12 mm Hg or 130/80 to 139/89 mm Hg, whichever is lower)	25	Stage 2 hypertension (≥95th percentile+12 mm Hg or ≥140/90 mm Hg, whichever is lower)	0	SBP ≥160 or ≥95th percentile+30 mm Hg SBP, whichever is lower, and/or DBP ≥100 or ≥95th percentile+20 mm Hg DBP
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AHA indicates American Heart Association; BMI, 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; SMO, 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>127</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.

For children, age-appropriate optimal sleep durations are as follows<sup>128</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

(Continued)

**Table 2-1.** Continued

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>129</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 (LDL-C) levels in normative ranges in the population. For children, thresholds for non-HDL-C were chosen on the basis of NHLBI pediatric guidelines, pediatric LDL-C 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>130</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>131</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*.

Source: Reprinted from Lloyd-Jones et al.<sup>2</sup> Copyright © 2022, American Heart Association, Inc.

**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 score (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 <sup>†</sup>				
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)	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>132</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. Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

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

Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>

**Table 2-3.** Leading 20 Risk Factors of YLL and Death in the United States: Rank, Number, and Percent Change, 1990 and 2021

Risk factors	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
High SBP	2	1	7928.37 (6583.97 to 9106.79)	7479.07 (6017.03 to 8807.80)	-5.67 (-12.93 to 1.70)	-47.43 (-51.55 to -43.73)	467.56 (380.19 to 537.90)	462.45 (365.70 to 552.89)	-1.09 (-10.69 to 7.44)	-47.80 (-52.53 to -43.44)
Smoking	1	2	8626.22 (7434.04 to 9816.94)	7334.37 (6040.21 to 8579.75)	-14.98 (-19.69 to -10.57)	-53.91 (-56.42 to -51.62)	369.59 (314.45 to 427.63)	342.53 (279.69 to 408.00)	-7.32 (-13.40 to -1.45)	-50.51 (-53.67 to -47.56)
High FPG	5	3	3454.63 (2926.15 to 4025.07)	6584.20 (5278.16 to 7909.75)	90.59 (77.04 to 105.54)	4.68 (-2.21 to 12.22)	186.36 (156.69 to 216.88)	383.84 (304.15 to 474.46)	105.97 (88.78 to 124.80)	9.28 (0.40 to 18.69)
High BMI	4	4	3589.44 (1572.40 to 5670.98)	6554.70 (3339.00 to 9600.13)	82.61 (65.21 to 115.16)	1.83 (-8.24 to 21.47)	169.38 (70.83 to 275.49)	334.86 (160.45 to 513.08)	97.70 (79.58 to 135.83)	5.19 (-4.81 to 25.69)
Drug use	16	5	973.22 (872.92 to 1111.92)	4583.68 (4158.73 to 5055.83)	370.98 (318.34 to 429.09)	269.24 (227.75 to 316.07)	23.17 (20.53 to 25.80)	110.33 (100.06 to 120.89)	376.21 (331.78 to 430.54)	244.36 (210.23 to 284.67)
Kidney dysfunction	7	6	2409.70 (1955.84 to 2851.13)	4114.23 (3582.54 to 4589.78)	70.74 (55.81 to 91.24)	-4.94 (-13.01 to 6.29)	150.89 (117.65 to 182.71)	258.12 (213.70 to 294.67)	71.06 (55.31 to 92.94)	-10.18 (-18.40 to 1.28)
High alcohol use	8	7	2122.03 (1890.02 to 2425.16)	3320.01 (2961.75 to 3694.25)	56.45 (45.17 to 67.66)	0.63 (-6.11 to 7.43)	61.49 (54.58 to 72.74)	111.66 (96.41 to 129.04)	81.61 (64.57 to 97.51)	7.25 (-1.80 to 15.56)
High LDL-C	3	8	4744.59 (3236.26 to 6301.13)	3156.69 (2051.13 to 4336.17)	-33.47 (-37.30 to -30.26)	-62.09 (-64.16 to -60.37)	239.69 (151.37 to 331.98)	161.84 (95.73 to 233.54)	-32.48 (-37.13 to -28.78)	-63.67 (-65.80 to -61.87)
Diet low in whole grains	9	9	1626.26 (875.23 to 2329.42)	1539.66 (782.75 to 2266.02)	-5.33 (-10.34 to -0.93)	-45.95 (-48.71 to -43.56)	80.51 (42.86 to 116.95)	76.49 (37.84 to 115.76)	-5.00 (-11.56 to 0.58)	-48.51 (-51.69 to -45.82)
Low temperature	12	10	1209.84 (1068.89 to 1373.00)	1458.33 (1280.92 to 1594.73)	20.54 (12.69 to 26.74)	-37.98 (-41.46 to -34.71)	77.00 (67.45 to 85.78)	93.09 (79.48 to 101.60)	20.90 (14.62 to 24.95)	-37.25 (-40.38 to -35.17)
Diet low in fruits	14	11	1086.82 (433.94 to 1676.50)	1411.95 (845.25 to 1908.91)	29.92 (6.78 to 102.24)	-24.50 (-37.73 to 16.37)	50.24 (20.11 to 78.92)	69.59 (42.08 to 94.62)	38.53 (10.43 to 121.06)	-25.14 (-39.72 to 17.54)
Diet high in processed meat	17	12	964.55 (248.98 to 1579.03)	1391.63 (376.25 to 2275.86)	44.28 (28.03 to 63.92)	-16.60 (-26.14 to -4.53)	42.34 (10.31 to 70.59)	62.30 (16.03 to 102.02)	47.15 (29.75 to 69.95)	-18.54 (-27.48 to -7.03)
Diet low in vegetables	24	13	546.30 (303.67 to 819.41)	1014.76 (695.38 to 1373.26)	85.75 (57.83 to 149.11)	6.54 (-9.35 to 45.53)	26.98 (14.82 to 40.74)	53.38 (35.97 to 72.63)	97.83 (65.96 to 170.99)	5.94 (-10.94 to 43.52)
Diet high in sodium	26	14	498.76 (1.01 to 1914.47)	934.24 (28.10 to 2758.38)	87.31 (40.88 to 3168.70)	7.56 (-20.81 to 1960.94)	27.32 (0.05 to 106.80)	47.95 (1.01 to 152.26)	75.55 (37.97 to 2340.83)	-4.35 (-25.64 to 1351.59)
Diet high in red meat	19	15	943.55 (-0.74 to 1637.59)	916.28 (-0.59 to 1536.24)	-2.89 (-22.96 to 30.69)	-45.17 (-55.62 to -23.47)	42.82 (-0.03 to 78.59)	43.65 (-0.02 to 76.73)	1.93 (-18.95 to 46.81)	-44.62 (-55.46 to -19.42)
Ambient particulate matter pollution	6	16	2649.86 (1193.47 to 4362.26)	913.64 (464.96 to 1423.79)	-65.52 (-84.05 to -27.83)	-80.17 (-90.28 to -59.59)	136.16 (58.51 to 229.14)	50.06 (24.66 to 78.69)	-63.23 (-83.43 to -20.66)	-80.30 (-90.97 to -57.87)
Diet low in seafood omega-3 fatty acids	21	17	803.48 (151.63 to 1395.01)	719.35 (141.58 to 1252.67)	-10.47 (-18.61 to -1.24)	-48.66 (-53.19 to -43.42)	41.75 (7.68 to 74.73)	36.89 (6.93 to 66.67)	-11.65 (-20.38 to -2.03)	-52.18 (-56.43 to -46.93)
LBW	10	18	1375.87 (1338.00 to 1413.13)	702.10 (626.80 to 780.13)	-48.97 (-54.33 to -43.25)	-42.42 (-48.47 to -35.96)	15.30 (14.88 to 15.71)	7.81 (6.97 to 8.67)	-48.98 (-54.34 to -43.25)	-42.43 (-48.47 to -35.97)

(Continued)

**Table 2-3. Continued**

Risk factors	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
Short gestation	13	19	1171.44 (1139.96 to 1205.37)	585.43 (521.95 to 650.54)	-50.02 (-55.25 to -44.29)	-43.62 (-49.51 to -37.14)	13.03 (12.68 to 13.41)	6.51 (5.80 to 7.23)	-50.03 (-55.26 to -44.30)	-43.63 (-49.53 to -37.15)
Occupational exposure to asbestos	22	20	637.57 (464.14 to 817.04)	572.54 (424.12 to 721.95)	-10.20 (-17.73 to -3.62)	-52.08 (-56.10 to -48.35)	33.35 (24.42 to 42.28)	35.00 (25.38 to 43.70)	4.95 (-4.55 to 12.84)	-43.07 (-48.12 to -38.63)

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 Diseases, Injuries, and Risk Factors; 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. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>133</sup>

**Table 2-4. Leading 20 Causes of YLL and Death in the United States: Rank, Number, and Percent Change, 1990 and 2021**

Diseases and injuries	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
COVID-19		1		10 727.15 (10 522.33 to 10 970.50)				483.51 (474.40 to 494.81)		
Ischemic heart disease	1	2	10 632.67 (9910.05 to 10 975.60)	8 529.67 (7 804.26 to 8 948.11)	-19.78 (-21.84 to -17.98)	-55.54 (-56.62 to -54.56)	594.73 (534.53 to 623.66)	493.22 (432.45 to 527.14)	-17.07 (-20.15 to -14.93)	-56.11 (-57.23 to -55.18)
Tracheal, bronchus, and lung cancer	2	3	3743.43 (3606.54 to 3843.86)	3590.39 (3354.03 to 3746.86)	-4.09 (-7.83 to -0.72)	-49.98 (-51.92 to -48.23)	158.06 (150.68 to 163.10)	175.48 (161.00 to 184.74)	11.02 (5.79 to 15.26)	-41.92 (-44.61 to -39.72)
Chronic obstructive pulmonary disease	4	4	1662.86 (1566.50 to 1713.10)	3343.16 (3026.32 to 3499.85)	101.05 (92.60 to 106.61)	8.68 (4.37 to 11.55)	89.78 (82.91 to 93.29)	198.04 (172.63 to 210.19)	120.57 (107.89 to 127.68)	18.15 (11.82 to 21.67)
Opioid use disorders	47	5	213.09 (199.48 to 228.20)	2629.46 (2334.46 to 2959.44)	1133.95 (977.87 to 1332.01)	929.19 (802.89 to 1089.54)	4.23 (3.96 to 4.52)	55.45 (48.82 to 62.98)	1211.24 (1039.51 to 1435.13)	942.37 (811.13 to 1113.20)
AD and other dementias	10	6	1227.53 (309.46 to 3159.50)	2340.44 (607.75 to 5840.62)	90.66 (84.53 to 99.18)	-1.96 (-4.39 to 1.20)	99.96 (25.91 to 258.21)	198.05 (53.30 to 494.05)	98.13 (90.77 to 107.74)	-1.58 (-4.27 to 1.64)
Colon and rectum cancer	6	7	1383.03 (1305.54 to 1434.65)	1577.41 (1475.16 to 1647.06)	14.05 (10.01 to 17.97)	-33.72 (-35.97 to -31.52)	67.23 (61.66 to 70.47)	75.09 (68.06 to 79.71)	11.68 (7.39 to 15.76)	-37.82 (-40.13 to -35.67)
Ischemic stroke	5	8	1391.86 (1243.72 to 1470.86)	1466.87 (1246.16 to 1581.04)	5.39 (-0.26 to 9.17)	-44.01 (-46.63 to -42.10)	99.53 (86.39 to 106.29)	115.56 (94.59 to 126.65)	16.10 (9.02 to 20.34)	-40.63 (-43.59 to -38.66)
Type 2 diabetes	13	9	964.25 (912.59 to 998.80)	1432.05 (1340.27 to 1498.94)	48.51 (43.57 to 53.73)	-16.56 (-19.29 to -13.58)	46.69 (42.89 to 48.88)	70.71 (64.16 to 75.05)	51.45 (45.86 to 56.99)	-17.34 (-20.17 to -14.38)
Other COVID-19 pandemic-related outcomes		10		1342.92 (918.05 to 1816.56)				58.06 (39.51 to 79.47)		
Hypertensive HD	21	11	478.20 (449.51 to 493.05)	1292.24 (1150.28 to 1425.76)	170.23 (144.65 to 196.43)	57.01 (42.27 to 72.24)	24.00 (21.72 to 25.22)	68.69 (58.73 to 76.39)	186.19 (158.02 to 211.62)	52.98 (38.61 to 66.49)

(Continued)

**Table 2-4. Continued**

Diseases and injuries	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
Breast cancer	9	12	1271.60 (1218.46 to 1305.10)	1218.25 (1140.97 to 1274.62)	-4.20 (-8.19 to -0.80)	-45.13 (-47.36 to -43.17)	49.19 (45.89 to 51.00)	53.47 (47.93 to 56.79)	8.71 (2.87 to 12.94)	-40.95 (-43.67 to -38.71)
Motor vehicle road injuries	3	13	1915.28 (1889.64 to 1942.45)	1210.73 (1168.18 to 1249.15)	-36.79 (-38.96 to -34.50)	-50.65 (-52.40 to -48.84)	36.36 (35.73 to 36.95)	27.58 (26.52 to 28.45)	-24.15 (-26.73 to -21.59)	-46.34 (-48.16 to -44.46)
Pancreatic cancer	18	14	623.25 (595.67 to 640.39)	1180.47 (1112.45 to 1225.73)	89.41 (84.95 to 94.19)	3.07 (0.74 to 5.52)	29.02 (27.08 to 30.10)	57.10 (52.18 to 59.93)	96.78 (90.94 to 102.23)	6.30 (3.47 to 9.07)
Self-harm by other specified means	16	15	670.45 (658.52 to 681.89)	1162.73 (1125.23 to 1201.12)	73.43 (66.99 to 79.75)	40.27 (34.83 to 45.54)	14.05 (13.78 to 14.29)	25.40 (24.60 to 26.16)	80.76 (74.92 to 86.76)	36.72 (31.87 to 41.44)
ICH	15	16	790.23 (751.02 to 815.00)	1145.77 (1059.58 to 1203.21)	44.99 (38.11 to 50.72)	-18.96 (-22.59 to -15.80)	35.86 (33.19 to 37.34)	58.17 (52.03 to 61.74)	62.22 (53.51 to 68.64)	-12.61 (-16.88 to -9.23)
Self-harm by firearm	14	17	865.53 (851.41 to 879.94)	1011.87 (976.11 to 1048.33)	16.91 (12.49 to 21.56)	-11.01 (-14.44 to -7.40)	19.22 (18.84 to 19.53)	25.32 (24.43 to 26.25)	31.75 (27.20 to 36.81)	-8.87 (-12.12 to -5.39)
CKD due to type 2 diabetes	66	18	146.04 (119.56 to 176.35)	953.13 (850.81 to 1053.11)	552.63 (463.32 to 659.63)	249.60 (203.65 to 305.04)	7.65 (6.09 to 9.49)	55.21 (47.67 to 61.99)	621.85 (516.79 to 744.38)	282.25 (228.49 to 344.47)
Lower respiratory infections	8	19	1295.09 (1203.68 to 1347.18)	952.55 (859.94 to 1016.05)	-26.45 (-29.36 to -23.05)	-56.57 (-58.26 to -54.54)	70.95 (62.93 to 75.33)	53.89 (45.93 to 58.53)	-24.04 (-27.34 to -20.44)	-59.04 (-60.63 to -57.16)
Endocrine, metabolic, blood, and immune disorders	33	20	290.31 (282.05 to 296.25)	948.30 (891.79 to 985.26)	226.65 (213.35 to 237.12)	91.90 (85.22 to 97.85)	8.99 (8.51 to 9.28)	41.57 (37.42 to 43.81)	362.48 (337.31 to 380.21)	148.08 (137.14 to 156.49)

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; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; GBD, Global Burden of Diseases, Injuries, and Risk Factors; 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. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>133</sup>

**Table 2-5. Leading 20 Risk Factors for YLDs in the United States: Rank, Number, and Percent Change, 1990 and 2021**

Risk factors	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
High BMI	1	1	1786.71 (536.85 to 3240.91)	5088.28 (1908.99 to 8473.08)	184.78 (149.11 to 253.28)	69.25 (49.10 to 110.09)
High FPG	3	2	1083.75 (768.83 to 1430.25)	4290.44 (3092.47 to 5662.93)	295.89 (271.91 to 319.70)	123.66 (110.55 to 137.05)
Drug use	5	3	702.98 (489.37 to 917.95)	3179.31 (2246.54 to 4117.62)	352.26 (308.26 to 400.02)	280.37 (241.38 to 320.31)
Smoking	2	4	1700.48 (1112.35 to 2413.37)	2197.73 (1449.79 to 3095.99)	29.24 (20.62 to 38.08)	-22.75 (-27.48 to -17.94)
High alcohol use	4	5	1030.89 (730.38 to 1425.63)	1258.22 (896.33 to 1719.41)	22.05 (10.21 to 35.76)	-14.28 (-20.64 to -7.06)
High SBP	6	6	532.54 (374.99 to 714.36)	833.93 (569.93 to 1124.12)	56.59 (42.29 to 71.57)	-11.53 (-19.55 to -3.54)
Diet high in processed meat	15	7	199.80 (46.57 to 347.44)	832.30 (198.31 to 1463.39)	316.57 (289.16 to 351.87)	136.56 (121.04 to 156.43)

(Continued)

**Table 2-5. Continued**

Risk factors	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
Low bone mineral density	8	8	414.14 (286.87 to 570.78)	826.57 (584.32 to 1135.66)	99.58 (91.44 to 106.67)	6.69 (2.41 to 10.44)
Kidney dysfunction	9	9	386.30 (281.64 to 495.28)	797.32 (581.45 to 1025.77)	106.40 (97.87 to 116.69)	21.01 (16.73 to 25.85)
Occupational ergonomic factors	7	10	530.40 (374.15 to 714.04)	648.08 (468.77 to 863.33)	22.19 (10.98 to 35.60)	-12.69 (-19.85 to -4.00)
Short gestation	10.5	11.5	382.40 (271.10 to 501.81)	443.46 (316.41 to 573.62)	15.97 (7.11 to 26.16)	-4.39 (-11.84 to 4.17)
LBW	10.5	11.5	382.40 (271.10 to 501.81)	443.46 (316.41 to 573.62)	15.97 (7.11 to 26.16)	-4.39 (-11.84 to 4.17)
Bullying victimization	13	13	239.14 (99.25 to 490.21)	426.95 (183.69 to 819.31)	78.53 (65.97 to 98.72)	60.60 (49.19 to 77.94)
Diet high in red meat	20	14	123.01 (-3.77 to 247.87)	402.80 (-40.34 to 889.97)	227.45 (123.06 to 301.54)	85.91 (26.67 to 125.65)
Diet high in sugar-sweetened beverages	29	15	64.99 (29.95 to 107.09)	376.26 (183.30 to 609.61)	478.99 (373.33 to 614.17)	233.60 (178.60 to 314.64)
Low PA	24	16	86.66 (36.89 to 141.55)	316.06 (134.68 to 533.57)	264.72 (187.63 to 374.15)	103.04 (62.35 to 162.41)
Diet low in whole grains	23	17	98.51 (7.17 to 187.94)	301.83 (49.97 to 566.97)	206.40 (167.95 to 390.22)	77.64 (54.71 to 156.19)
High LDL-C	14	18	226.51 (103.43 to 357.08)	292.94 (122.68 to 479.52)	29.33 (16.86 to 38.97)	-23.33 (-30.04 to -18.18)
Ambient particulate matter pollution	12	19	251.59 (99.28 to 433.64)	287.45 (122.23 to 520.82)	14.26 (-48.40 to 136.06)	-35.13 (-70.65 to 33.38)
Occupational noise	17	20	149.18 (102.03 to 209.56)	227.03 (153.88 to 319.54)	52.19 (46.11 to 59.42)	-8.88 (-11.34 to -5.51)

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 Diseases, Injuries, and Risk Factors; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; PA, physical activity; SBP, systolic blood pressure; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>133</sup>

**Table 2-6. Leading 20 Causes for YLDs in the United States: Rank, Number, and Percent Change, 1990 and 2021**

Diseases and injuries	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
Low back pain	1	1	3610.49 (2585.81 to 4807.83)	4940.71 (3587.05 to 6412.52)	36.84 (28.19 to 45.64)	-7.87 (-13.00 to -1.79)
Other musculoskeletal disorders	2	2	1772.89 (1231.92 to 2420.39)	3749.41 (2670.48 to 5023.71)	111.49 (90.14 to 135.37)	47.30 (32.95 to 63.20)
Type 2 diabetes	10	3	732.34 (513.43 to 1011.01)	3362.56 (2367.85 to 4556.43)	359.16 (328.74 to 395.28)	157.89 (140.73 to 177.06)
Major depressive disorder	5	4	1390.70 (965.05 to 1907.30)	3011.99 (2109.17 to 4042.18)	116.58 (106.42 to 128.17)	74.26 (65.66 to 83.39)
Anxiety disorders	4	5	1659.31 (1140.97 to 2234.00)	2814.41 (1928.98 to 3792.63)	69.61 (60.44 to 79.32)	31.56 (24.87 to 39.31)
Opioid use disorders	23	6	364.82 (250.25 to 478.67)	2688.45 (1885.26 to 3490.01)	636.93 (573.49 to 706.39)	531.11 (474.14 to 592.55)
Age-related and other hearing loss	6	7	1374.55 (957.22 to 1915.25)	2231.33 (1567.63 to 3078.81)	62.33 (58.50 to 66.89)	-5.63 (-7.36 to -3.40)
Migraine	3	8	1704.15 (245.77 to 3727.73)	2129.03 (350.58 to 4628.60)	24.93 (18.96 to 40.59)	-3.26 (-7.50 to 1.36)

(Continued)

**Table 2-6. Continued**

Diseases and injuries	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
Falls	7	9	953.54 (654.28 to 1310.10)	1689.31 (1182.88 to 2359.10)	77.16 (64.49 to 88.36)	-1.21 (-7.45 to 4.30)
Chronic obstructive pulmonary disease	11	10	684.91 (573.21 to 799.03)	1302.96 (1121.32 to 1492.74)	90.24 (79.95 to 103.29)	4.61 (-1.01 to 11.28)
Asthma	8	11	943.69 (609.93 to 1393.83)	1282.33 (837.26 to 1884.59)	35.89 (27.36 to 44.38)	3.39 (-2.31 to 10.24)
AD and other dementias	14	12	561.52 (382.38 to 750.17)	978.20 (673.26 to 1296.85)	74.20 (69.60 to 78.24)	-7.19 (-9.29 to -5.43)
Neck pain	12	13	662.95 (438.46 to 955.28)	919.64 (618.46 to 1301.73)	38.72 (31.55 to 46.36)	-1.12 (-2.02 to -0.22)
Osteoarthritis knee	18	14	457.80 (225.50 to 909.62)	853.43 (420.64 to 1694.29)	86.42 (83.78 to 89.64)	3.51 (2.15 to 4.94)
Schizophrenia	13	15	660.74 (489.98 to 841.53)	824.55 (617.70 to 1040.82)	24.79 (20.90 to 29.69)	-5.80 (-7.72 to -3.54)
Edentulism	17	16	469.54 (295.60 to 668.24)	762.03 (487.56 to 1063.26)	62.29 (54.17 to 73.88)	-5.31 (-11.45 to 2.28)
Alcohol use disorders	9	17	764.87 (514.28 to 1082.15)	758.79 (522.53 to 1053.01)	-0.79 (-7.66 to 6.16)	-22.56 (-26.53 to -18.08)
Ischemic stroke	20	18	438.41 (311.56 to 565.66)	711.18 (514.47 to 902.15)	62.22 (53.36 to 71.18)	-5.77 (-10.65 to -0.79)
Autism spectrum disorders	15	19	495.96 (341.95 to 691.92)	639.14 (443.19 to 891.39)	28.87 (25.33 to 32.02)	1.76 (-0.85 to 4.08)
Osteoarthritis hand	29	20	288.48 (131.02 to 598.75)	558.65 (256.98 to 1145.51)	93.65 (89.12 to 97.79)	5.99 (4.18 to 8.01)

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 Diseases, Injuries, and Risk Factors; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>133</sup>

**Table 2-7. Leading 20 Global Risk Factors of YLL and Death: Rank, Number, and Percent Change, 1990 and 2021**

Risk factors	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
High SBP	8	1	135 752.50 (113 118.36 to 156 253.37)	211 136.57 (178 644.53 to 243 280.84)	55.53 (44.97 to 67.27)	-31.21 (-35.68 to -26.13)	6564.59 (5517.40 to 7510.30)	10 852.11 (9222.90 to 12 535.78)	65.31 (54.16 to 77.29)	-32.32 (-36.69 to -27.64)
Smoking	9	2	122 608.46 (105 374.75 to 140 611.66)	142 365.55 (117 995.67 to 166 529.82)	16.11 (5.39 to 28.17)	-45.49 (-50.47 to -39.86)	4784.43 (4087.94 to 5484.66)	61 750.02 (5047.66 to 7226.38)	29.06 (16.78 to 42.63)	-42.47 (-47.81 to -36.47)
LBW	1	3	246 031.65 (231 912.90 to 260 081.76)	138 557.77 (119 526.12 to 160 524.23)	-43.68 (-51.94 to -34.37)	-41.86 (-50.38 to -32.25)	2735.31 (2578.32 to 2891.55)	15 404.47 (1328.80 to 1784.70)	-43.68 (-51.94 to -34.37)	-41.86 (-50.38 to -32.25)
Ambient particulate matter pollution	12	4	74 375.45 (52 484.13 to 99 095.08)	108 661.22 (79 387.01 to 136 914.50)	46.10 (16.52 to 85.31)	-17.57 (-33.63 to 1.38)	2433.56 (1750.35 to 3155.64)	4718.81 (3480.47 to 5795.95)	93.91 (56.89 to 137.15)	-13.94 (-31.09 to 5.23)
High FPG	14	5	46 610.01 (41 140.65 to 52 187.26)	105 283.73 (90 143.32 to 120 223.12)	125.88 (111.78 to 138.71)	1.78 (-4.30 to 7.41)	2163.06 (1895.07 to 2439.11)	5292.83 (4487.83 to 6114.99)	144.69 (130.26 to 158.94)	1.63 (-4.19 to 7.29)

(Continued)

**Table 2-7.** Continued

Risk factors	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
Household air pollution from solid fuels	3	6	205 113.63 (147 057.37 to 257 059.06)	103 752.49 (68 848.77 to 153 264.41)	-49.42 (-61.30 to -33.03)	-64.58 (-72.21 to -54.46)	4815.87 (3773.99 to 5859.60)	3112.93 (1895.17 to 5188.70)	-35.36 (-53.84 to -6.77)	-66.27 (-75.54 to -52.18)
Short gestation	5	7	174 455.22 (162 603.72 to 187 451.60)	99 206.75 (83 573.53 to 114 779.40)	-43.13 (-51.68 to -33.48)	-41.32 (-50.15 to -31.36)	1939.80 (1807.94 to 2084.28)	1103.12 (929.21 to 1276.26)	-43.13 (-51.69 to -33.48)	-41.32 (-50.15 to -31.37)
High BMI	19	8	34 994.49 (17 325.92 to 54 366.88)	83 680.98 (41 487.23 to 127 115.08)	139.13 (124.05 to 154.30)	10.33 (3.10 to 17.33)	1459.53 (723.04 to 2287.05)	3709.06 (1847.84 to 5658.33)	154.13 (138.15 to 170.49)	8.15 (1.37 to 15.14)
High LDL-C	13	9	57 574.38 (36 489.75 to 78 178.76)	82 478.23 (52 769.79 to 113 372.39)	43.26 (34.83 to 51.70)	-34.45 (-38.05 to -30.56)	2452.01 (1431.74 to 3504.93)	3646.00 (2129.33 to 5262.17)	48.69 (40.45 to 56.94)	-38.06 (-41.08 to -34.70)
Kidney dysfunction	17	10	42 856.40 (37 879.05 to 48 230.60)	75 168.00 (66 346.33 to 84 882.29)	75.40 (64.59 to 87.08)	-18.45 (-23.62 to -13.13)	1864.83 (1596.39 to 2144.98)	3622.84 (3124.32 to 4142.44)	94.27 (81.89 to 106.64)	-20.55 (-25.84 to -15.32)
High alcohol use	18	11	42 842.70 (32 279.95 to 58 544.38)	56 110.48 (43 978.10 to 70 058.86)	30.97 (13.96 to 46.83)	-31.13 (-39.56 to -23.34)	1264.20 (951.65 to 1713.50)	1809.44 (1424.95 to 2280.48)	43.13 (24.75 to 60.45)	-30.98 (-39.43 to -23.03)
Child under-weight	2	12	215 883.72 (121 721.56 to 264 598.12)	47 774.88 (18 056.34 to 69 315.85)	-77.87 (-85.35 to -71.24)	-78.82 (-86.25 to -72.37)	2506.06 (1441.43 to 3057.03)	623.82 (290.97 to 871.50)	-75.11 (-80.95 to -68.88)	-77.37 (-83.29 to -71.38)
Diet low in fruits	21	13	30 185.49 (10 925.62 to 46 314.10)	40 094.17 (16 150.51 to 59 308.53)	32.83 (22.87 to 47.33)	-36.69 (-41.47 to -30.45)	1148.88 (459.28 to 1743.21)	1683.59 (769.76 to 2470.25)	46.54 (34.92 to 65.80)	-35.30 (-40.29 to -28.18)
Unsafe sex	25	14	19 844.25 (16 402.47 to 24 710.14)	38 837.86 (36 382.46 to 42 368.25)	95.71 (66.05 to 129.84)	14.64 (-0.36 to 32.36)	452.92 (384.61 to 544.09)	900.65 (851.04 to 958.89)	98.85 (71.67 to 131.42)	8.05 (-4.97 to 23.72)
Diet high in sodium	22	15	28 119.52 (7 753.53 to 61 403.42)	38 609.26 (8 606.28 to 86 403.22)	37.30 (0.04 to 56.51)	-37.32 (-53.24 to -28.86)	1221.01 (310.50 to 2716.78)	1857.70 (367.76 to 4251.58)	52.14 (9.69 to 70.94)	-34.40 (-51.16 to -26.76)
Unsafe water source	7	16	137 720.30 (80 792.46 to 182 972.60)	36 884.86 (19 088.44 to 52 110.23)	-73.22 (-78.81 to -66.81)	-77.80 (-82.47 to -72.50)	2173.55 (1265.81 to 2913.02)	802.49 (371.67 to 1215.50)	-63.08 (-72.25 to -53.88)	-76.22 (-81.34 to -71.26)
Child wasting	4	17	184 508.62 (104 314.64 to 230 948.34)	36 376.87 (20 015.51 to 49 374.80)	-80.28 (-84.06 to -76.54)	-81.08 (-84.77 to -77.41)	2148.48 (1244.60 to 2671.33)	493.99 (308.33 to 639.31)	-77.01 (-80.60 to -71.84)	-79.27 (-82.61 to -75.08)
Diet low in whole grains	23	18	24 497.82 (11 290.84 to 35 848.82)	35 969.36 (16 558.50 to 53 250.12)	46.83 (38.49 to 55.40)	-31.62 (-35.20 to -27.28)	991.50 (451.55 to 1484.97)	1546.24 (707.30 to 2343.82)	55.95 (47.41 to 64.58)	-33.45 (-36.77 to -29.37)
Second-hand smoke	15	19	44 341.85 (20 204.90 to 68 878.40)	30 755.02 (16 185.97 to 45 598.15)	-30.64 (-37.78 to -17.30)	-58.65 (-62.37 to -53.61)	1162.72 (598.58 to 1741.48)	1292.10 (683.12 to 1896.16)	11.13 (1.49 to 24.06)	-46.70 (-50.89 to -41.71)
Lead exposure	26	20	18 783.14 (-21 40.65 to 39 474.82)	29 744.73 (-3602.56 to 62 130.26)	58.36 (44.90 to 74.84)	-27.30 (-33.32 to -19.98)	816.97 (-93.43 to 1711.64)	1541.91 (-184.92 to 3224.76)	88.73 (72.91 to 107.00)	-18.95 (-25.40 to -11.51)

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 Diseases, Injuries, and Risk Factors; 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. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>133</sup>

**Table 2-8.** Leading 20 Global Causes of YLL and Death: Rank, Number, and Percentage Change, 1990 and 2021

Diseases and injuries	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
COVID-19		1		197 756.74 (187 900.90 to 211 514.62)				7887.55 (7507.14 to 8403.57)		
IHD	3	2	117 315.13 (112 735.36 to 121 467.78)	184 306.89 (172 862.02 to 194 426.01)	57.10 (48.40 to 65.60)	-29.24 (-32.99 to -25.55)	5367.14 (5076.40 to 5562.77)	8991.64 (8264.12 to 9531.13)	6753 (58.76 to 75.87)	-31.57 (-34.86 to -28.33)
Lower respiratory infections	1	3	203 755.78 (180 293.49 to 228 567.30)	82 086.66 (72 180.87 to 92 994.86)	-59.71 (-64.49 to -54.04)	-66.43 (-70.56 to -61.57)	3013.35 (2744.31 to 3291.76)	2183.00 (1979.92 to 2360.08)	-27.56 (-34.84 to -19.60)	-53.62 (-57.60 to -49.43)
Other COVID-19 pandemic-related outcomes		4		77 380.46 (59 949.13 to 102 013.40)				2685.54 (2081.72 to 3597.24)		
ICH	7	5	61 407.14 (57 472.81 to 65 189.60)	76 770.05 (70 172.73 to 83 125.24)	25.02 (12.87 to 38.20)	-39.57 (-45.32 to -33.45)	2341.56 (2184.65 to 2505.96)	3308.37 (3021.08 to 3594.72)	41.29 (27.35 to 56.22)	-36.58 (-42.54 to -29.83)
Neonatal PTB	4	6	116 397.39 (107 040.98 to 125 797.58)	66 505.73 (55 994.02 to 78 854.56)	-42.86 (-52.63 to -32.24)	-41.09 (-51.14 to -30.13)	1294.53 (1190.59 to 1399.07)	739.67 (622.75 to 877.04)	-42.86 (-52.63 to -32.24)	-41.09 (-51.14 to -30.13)
COPD	10	7	50 060.63 (44 915.05 to 54 320.48)	64 922.19 (59 331.48 to 71 143.57)	29.69 (16.35 to 49.94)	-42.12 (-47.95 to -33.27)	2495.51 (2238.99 to 2694.76)	3719.94 (3347.91 to 4084.22)	49.06 (33.73 to 71.73)	-37.12 (-43.37 to -27.68)
Ischemic stroke	12	8	40 721.83 (38 019.83 to 43 819.09)	59 039.55 (53 954.03 to 64 045.61)	44.98 (32.65 to 57.90)	-38.81 (-43.75 to -33.58)	2317.11 (2131.46 to 2475.55)	3591.50 (3213.28 to 3888.33)	55.00 (43.20 to 66.76)	-39.60 (-43.79 to -35.32)
Neonatal encephalopathy due to birth asphyxia and trauma	5	9	79 422.85 (72 767.22 to 90 302.31)	54 290.95 (45 979.55 to 65 231.91)	-31.64 (-43.90 to -18.20)	-29.39 (-42.05 to -15.52)	883.08 (809.08 to 1004.10)	603.61 (511.19 to 725.27)	-31.65 (-43.91 to -18.21)	-29.40 (-42.05 to -15.53)
Malaria	9	10	55 777.04 (28 085.58 to 110 783.92)	52 809.22 (19 553.71 to 105 829.15)	-5.32 (-31.11 to 17.30)	-16.76 (-38.67 to 3.16)	721.19 (352.37 to 1469.09)	748.13 (267.70 to 1536.03)	3.74 (-24.37 to 26.61)	-16.24 (-37.20 to 2.32)
Diarrheal diseases	2	11	185 658.74 (147 478.91 to 220 930.28)	51 430.25 (39 944.52 to 65 879.67)	-72.30 (-77.51 to -66.04)	-77.14 (-81.35 to -71.86)	2932.25 (2308.36 to 3730.01)	1165.40 (793.42 to 1618.36)	-60.26 (-69.00 to -50.61)	-74.54 (-79.24 to -69.59)
Tracheal, bronchus, and lung cancer	18	12	28 194.27 (26 730.88 to 29 658.60)	45 987.99 (41 384.71 to 50 583.69)	63.11 (43.96 to 83.28)	-23.03 (-32.02 to -13.64)	1080.13 (1023.33 to 1135.56)	2016.55 (1820.50 to 2218.37)	86.70 (64.43 to 108.18)	-14.77 (-24.64 to -5.21)
Drug-susceptible tuberculosis	6	13	77 307.26 (67 711.56 to 85 701.36)	38 387.69 (32 908.85 to 44 064.50)	-50.34 (-57.80 to -38.39)	-69.26 (-73.88 to -61.76)	1762.81 (1517.04 to 1960.38)	1048.03 (911.27 to 1199.87)	-40.55 (-50.14 to -24.33)	-68.24 (-73.31 to -59.39)
Type 2 diabetes	26	14	14 978.00 (14 198.18 to 15 703.96)	35 540.86 (33 217.12 to 37 650.46)	137.29 (119.64 to 152.92)	9.37 (1.39 to 16.55)	632.32 (596.87 to 662.08)	1608.12 (1493.44 to 1708.29)	154.32 (136.07 to 170.56)	9.75 (2.22 to 16.60)
Self-harm by other specified means	17	15	31 136.99 (26 340.71 to 33 292.10)	30 115.19 (28 001.01 to 32 227.57)	-3.28 (-10.84 to 14.19)	-38.93 (-43.66 to -27.86)	653.36 (554.41 to 696.72)	689.50 (639.53 to 740.71)	5.53 (-2.47 to 24.07)	-39.44 (-43.97 to -29.02)
HIV/AIDS resulting in other diseases	35	16	11 139.59 (8 673.59 to 14 689.27)	25 846.10 (22 569.59 to 30 128.05)	132.02 (93.39 to 186.85)	53.64 (27.90 to 89.53)	194.17 (150.25 to 258.76)	517.18 (455.53 to 594.71)	166.35 (112.66 to 242.36)	66.72 (33.74 to 113.41)

(Continued)

**Table 2-8. Continued**

Diseases and injuries	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)		Percent change (%), 1990–2021 (95% UI)		Corresponding total No. of deaths, in thousands (95% UI)		Corresponding percent change (%), 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLLs	Age-standardized YLL rate	1990	2021	Total No. of deaths	Age-standardized death rate
AD and other dementias	41	17	9162.52 (2183.29 to 24360.06)	24 750.58 (6224.34 to 63 537.38)	170.13 (154.02 to 192.84)	0.52 (−4.09 to 7.35)	663.29 (163.58 to 1764.99)	1952.68 (512.98 to 4984.74)	194.39 (176.93 to 220.09)	0.47 (−3.78 to 6.99)
Hypertensive HD	25	18	15 093.27 (11 952.15 to 16 947.50)	24 444.47 (20 447.32 to 26 939.40)	61.96 (41.16 to 100.17)	−26.94 (−35.80 to −10.97)	713.94 (577.53 to 795.26)	1332.10 (1121.13 to 1468.85)	86.59 (62.76 to 126.51)	−21.99 (−31.92 to −6.74)
Colon and rectum cancer	30	19	13 970.16 (13 138.71 to 14 756.49)	23 318.79 (21 570.06 to 25 061.55)	66.92 (52.87 to 82.61)	−21.85 (−28.31 to −14.89)	570.32 (536.54 to 597.67)	1044.07 (950.19 to 1120.17)	83.07 (67.74 to 98.13)	−20.33 (−26.05 to −14.27)
Stomach cancer	23	20	22 989.38 (20 384.89 to 25 277.84)	22 460.91 (19 337.84 to 25 781.64)	−2.30 (−13.34 to 11.48)	−53.22 (−58.44 to −46.74)	854.18 (772.89 to 939.97)	954.37 (821.75 to 1089.58)	11.73 (−0.71 to 26.84)	−49.11 (−54.70 to −42.53)

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's Disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; GBD, Global Burden of Diseases, Injuries, and Risk Factors; HD, heart disease; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency virus; 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. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>133</sup>

**Table 2-9. Leading 20 Global Risk Factors for YLDs: Rank, Number, and Percentage Change, 1990 and 2021**

Risk factors	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change, 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
High FPG	3	1	13 737.13 (9554.12 to 18 292.12)	50 398.52 (35 296.76 to 67 505.80)	266.88 (256.28 to 276.65)	74.57 (67.58 to 81.96)
High BMI	4	2	13 047.62 (41 45.76 to 23 434.18)	44 839.11 (16 115.14 to 77 011.54)	243.66 (222.37 to 282.38)	68.99 (57.21 to 90.19)
Iron deficiency	1	3	28 568.55 (19 474.85 to 40 328.91)	32 480.16 (21 893.33 to 46 729.55)	13.69 (9.85 to 17.52)	−18.26 (−21.14 to −15.50)
Smoking	2	4	14 926.36 (9932.27 to 20 860.04)	22 715.11 (15 531.41 to 31 324.57)	52.18 (47.94 to 56.82)	−25.46 (−27.24 to −23.42)
High alcohol use	5	5	11 756.01 (8077.93 to 16 251.38)	16 143.76 (11 228.27 to 22 016.84)	37.32 (30.03 to 45.92)	−20.25 (−23.20 to −16.35)
Occupational ergonomic factors	6	6	10 852.09 (7600.73 to 14 543.67)	15 569.22 (11 026.00 to 20 908.97)	43.47 (37.16 to 50.29)	−18.96 (−21.82 to −15.82)
High SBP	11	7	6671.11 (4711.79 to 8935.96)	14 396.40 (10 133.05 to 19 024.52)	115.80 (108.04 to 124.00)	−2.60 (−5.82 to 0.88)
Short gestation	8.5	8.5	7952.30 (5842.55 to 10 225.72)	13 829.44 (9959.54 to 17 875.55)	73.90 (61.98 to 84.96)	29.12 (20.25 to 37.67)
LBW	8.5	8.5	7952.30 (5842.55 to 10 225.72)	13 829.44 (9959.54 to 17 875.55)	73.90 (61.98 to 84.96)	29.12 (20.25 to 37.67)
Ambient particulate matter pollution	21	10	3084.28 (2028.96 to 4257.89)	11 343.45 (7413.96 to 15 719.93)	267.78 (204.08 to 341.15)	71.56 (41.76 to 106.30)
Kidney dysfunction	13	11	5336.42 (3868.49 to 6890.82)	11 060.30 (8087.37 to 14 240.36)	107.26 (100.76 to 114.18)	−0.66 (−3.26 to 1.95)
Drug use	12	12	5909.15 (4112.40 to 7626.56)	9636.01 (6895.45 to 12 237.82)	63.07 (53.95 to 71.72)	9.28 (3.69 to 14.37)
Low bone mineral density	15	13	4353.49 (3112.57 to 521.27)	8426.85 (5950.12 to 11 347.26)	93.57 (89.83 to 96.79)	−14.39 (−15.75 to −13.29)

(Continued)

**Table 2-9. Continued**

Risk factors	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change, 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
Occupational noise	18	14	3838.06 (2630.90 to 5373.29)	7847.44 (5313.65 to 10980.79)	104.46 (98.35 to 110.33)	8.11 (6.57 to 9.62)
Household air pollution from solid fuels	10	15	6747.06 (4385.96 to 9083.24)	7710.47 (3655.16 to 12591.28)	14.28 (−20.36 to 57.07)	−45.62 (−61.46 to −25.70)
Occupational injuries	7	16	8888.39 (6530.37 to 11938.18)	7518.69 (5280.91 to 10297.45)	−15.41 (−22.06 to −7.55)	−49.89 (−53.74 to −45.01)
Bullying victimization	19	17	3773.89 (1569.01 to 7477.29)	6166.23 (2690.93 to 11884.82)	63.39 (54.21 to 75.72)	22.86 (16.66 to 33.25)
High LDL-C	23	18	2625.91 (1199.83 to 4069.06)	5247.88 (2326.08 to 8335.98)	99.85 (92.64 to 105.48)	−5.35 (−7.27 to −3.51)
Unsafe sex	28	19	1716.63 (1245.92 to 2373.66)	5137.42 (3785.35 to 6878.82)	199.27 (175.94 to 225.03)	84.16 (69.61 to 100.02)
Unsafe water source	14	20	4657.42 (2357.80 to 6905.76)	4833.85 (2166.44 to 7393.32)	3.79 (−9.21 to 13.43)	−22.40 (−31.62 to −15.74)

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 Diseases, Injuries, and Risk Factors; 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. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>133</sup>

**Table 2-10. Leading 20 Global Causes for YLDs: Rank, Number, and Percentage Change, 1990 and 2021**

Diseases and injuries	YLD rank (for total number)		Total No. of YLDs, in thousands (95% UI)		Percent change, 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
Low back pain	1	1	43 386.23 (31 083.94 to 58 355.21)	70 156.96 (50 194.20 to 94 104.69)	61.70 (58.59 to 65.45)	−11.22 (−11.82 to −10.66)
Major depressive disorder	4	2	23 843.69 (16 349.84 to 32 756.81)	46 018.84 (31 460.39 to 62 719.19)	93.00 (87.25 to 98.80)	16.07 (13.19 to 18.97)
Age-related and other hearing loss	6	3	21 269.54 (14 621.10 to 29 605.95)	44 449.94 (30 689.65 to 62 029.88)	108.98 (104.02 to 113.15)	5.31 (4.23 to 6.41)
Migraine	3	4	27 412.20 (4076.61 to 60 325.81)	43 378.89 (6732.64 to 95 079.45)	58.25 (53.75 to 66.10)	1.13 (−4.05 to 2.55)
Other musculoskeletal disorders	7	5	18 979.06 (13 024.02 to 26 393.68)	42 988.18 (29 647.81 to 59 205.44)	126.50 (120.36 to 133.29)	25.82 (23.36 to 28.23)
Anxiety disorders	5	6	22 996.73 (15 814.12 to 31 547.28)	42 509.65 (29 396.72 to 57 729.82)	84.85 (79.23 to 91.63)	18.17 (15.57 to 20.95)
Type 2 diabetes	11	7	9952.99 (6985.11 to 13 797.89)	39 800.01 (28 016.29 to 54 632.81)	299.88 (289.04 to 311.63)	94.66 (89.38 to 99.95)
Dietary iron deficiency	2	8	28 406.13 (19 357.61 to 40 145.95)	32 315.75 (21 779.58 to 46 496.97)	13.76 (9.91 to 17.61)	−18.19 (−21.09 to −15.41)
Falls	8	9	14 846.59 (10 450.14 to 20 001.10)	24 172.95 (16 816.84 to 32 805.34)	62.82 (57.38 to 67.54)	−13.69 (−15.40 to −12.00)
Neck pain	9	10	11 442.36 (7608.94 to 16 334.31)	20 415.50 (13 638.71 to 28 856.64)	78.42 (69.94 to 87.21)	0.14 (−1.52 to 1.77)
Other gynecological diseases	12	11	9882.51 (6702.66 to 14 129.63)	15 603.39 (10 581.11 to 22 034.61)	57.89 (54.69 to 61.67)	−8.84 (−10.97 to −6.46)
COPD	17	12	6796.66 (5696.89 to 7826.09)	14 857.50 (12 405.35 to 17 130.01)	118.60 (112.82 to 123.65)	3.29 (0.94 to 5.53)
Schizophrenia	13	13	8762.31 (6477.26 to 11 263.75)	14 816.61 (10 926.46 to 19 095.36)	69.09 (65.16 to 72.86)	0.64 (−0.48 to 1.71)

(Continued)

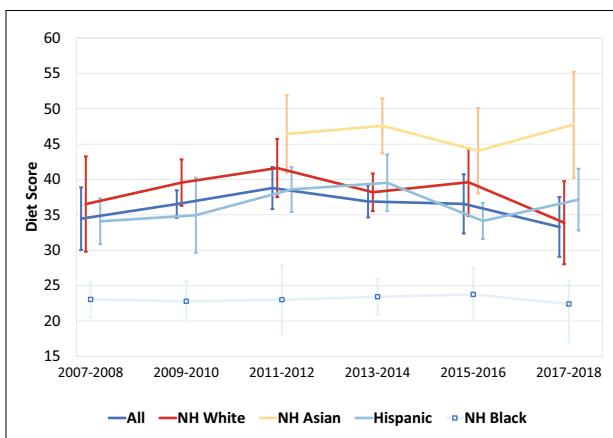
**Table 2-10. Continued**

Diseases and injuries	YLD rank (for total number)		Total No. of YLD, in thousands (95% UI)		Percent change, 1990–2021 (95% UI)	
	1990	2021	1990	2021	Total No. of YLDs	Age-standardized YLD rate
COVID-19		14		14 252.86 (5138.71 to 33 727.83)		
Neonatal PTB	15	15	7952.30 (5842.55 to 10 225.72)	13 829.44 (9959.54 to 17 875.55)	73.90 (61.98 to 84.96)	29.12 (20.25 to 37.67)
Osteoarthritis knee	23	16	5145.34 (2507.48 to 9953.26)	12 019.07 (5858.11 to 23 267.86)	133.59 (131.71 to 135.70)	8.22 (7.55 to 8.95)
Near vision loss	32	17	4316.10 (1937.50 to 8410.60)	11 649.94 (5214.02 to 22 421.66)	169.92 (150.81 to 187.19)	37.92 (28.63 to 46.84)
AD and other dementias	31	18	4409.78 (3029.44 to 5820.65)	11 582.11 (7961.94 to 15 296.79)	162.65 (156.93 to 168.08)	2.63 (1.12 to 3.62)
Autism spectrum disorders	16	19	7868.39 (5351.16 to 11 069.62)	11 544.04 (7842.31 to 16 288.87)	46.71 (44.44 to 48.61)	2.10 (0.56 to 3.41)
Ischemic stroke	21	20	5454.41 (3922.23 to 6953.41)	11 318.37 (8183.93 to 14 471.90)	107.51 (102.50 to 112.50)	-1.67 (-3.59 to 0.08)

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.

AD indicates Alzheimer's Disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; GBD, Global Burden of Diseases, Injuries, and Risk Factors; PTB, preterm birth; UI, uncertainty interval; and YLD, year of life lived with disability or injury.

Source: Data derived from GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>133</sup>

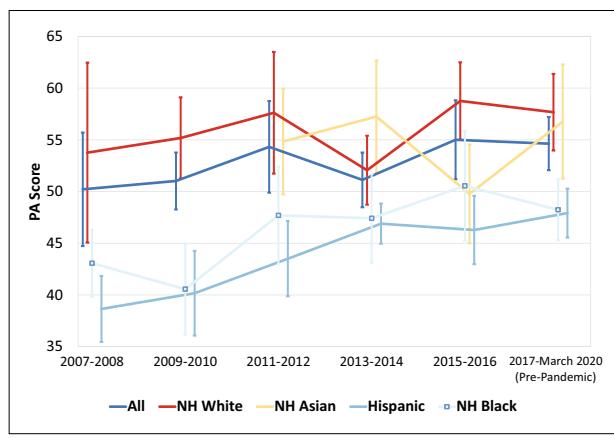


**Chart 2-1. Trends in age-adjusted mean scores (95% CI) for the diet component of CVH among US adults  $\geq 20$  years of age, NHANES 2007 to 2008 through 2017 to 2018.**

Dietary estimates were available only through data up to the 2017 to 2018 NHANES cycle at the time of this report.

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

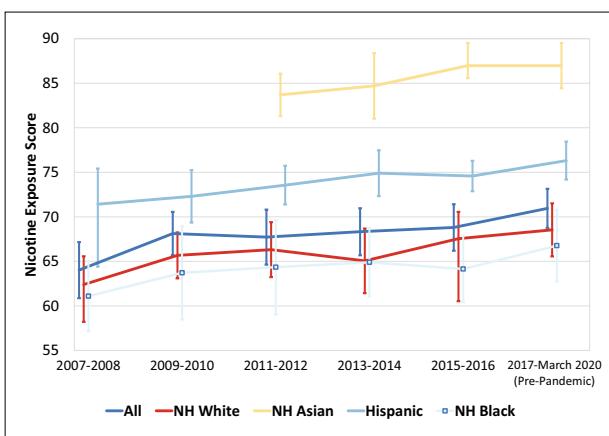
Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>



**Chart 2-2. Trends in age-adjusted mean scores (95% CI) for the PA component of CVH among US adults  $\geq 20$  years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and PA, physical activity.

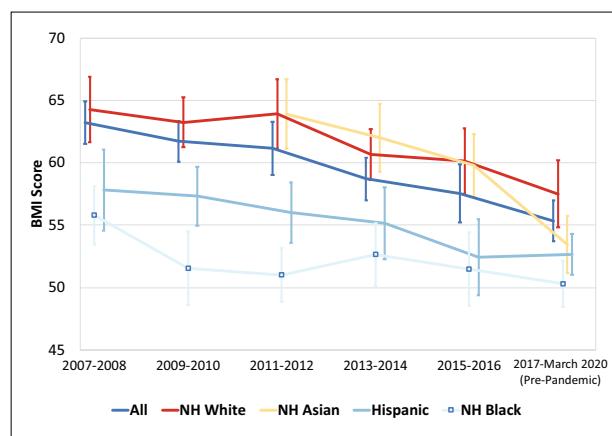
Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>



**Chart 2-3. Trends in age-adjusted mean scores (95% CI) for the nicotine exposure component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

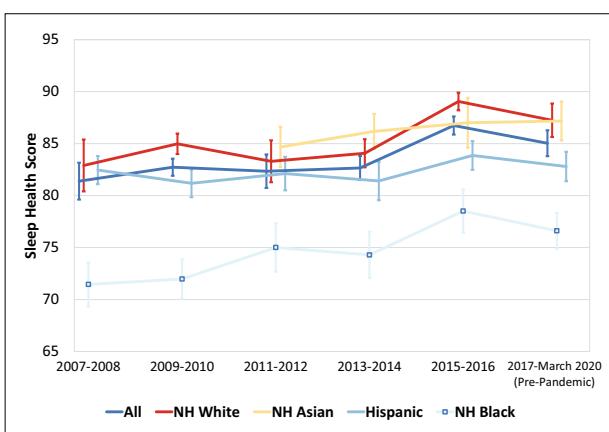
Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>



**Chart 2-5. Trends in age-adjusted mean scores (95% CI) for the BMI component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

BMI indicates body mass index; CI, confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

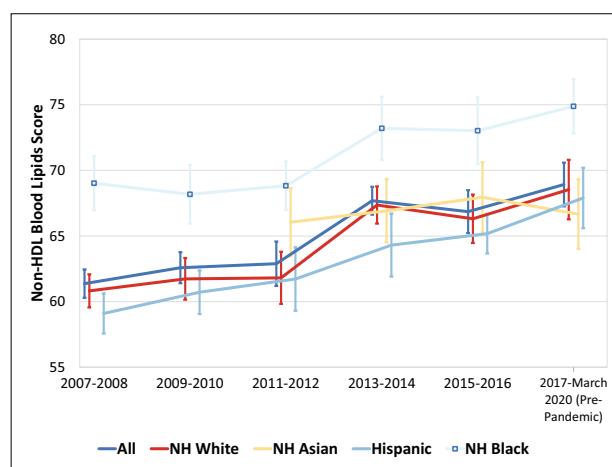
Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>



**Chart 2-4. Trends in age-adjusted mean scores (95% CI) for the sleep health component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

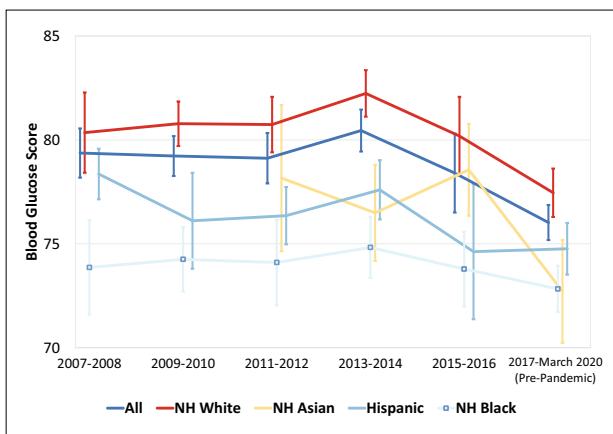
Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>



**Chart 2-6. Trends in age-adjusted mean scores (95% CI) for the non-HDL blood lipids component of CVH among US adults ≥20 years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; HDL, high-density lipoprotein; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

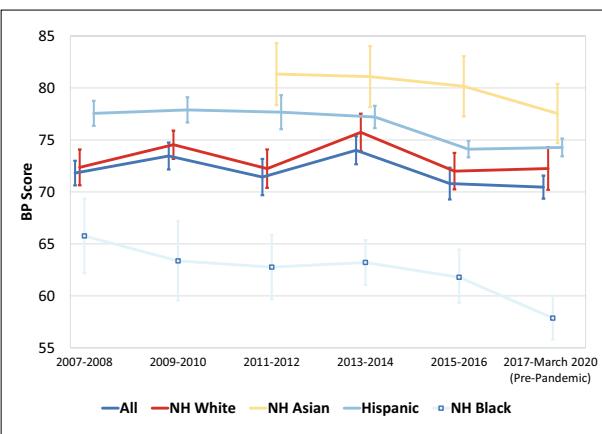
Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>



**Chart 2-7. Trends in age-adjusted mean scores (95% CI) for the blood glucose component of CVH among US adults  $\geq 20$  years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

CI indicates confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>



**Chart 2-8. Trends in age-adjusted mean scores (95% CI) for the BP component of CVH among US adults  $\geq 20$  years of age, NHANES 2007 to 2008 through 2017 to March 2020.**

BP indicates blood pressure; CI, confidence interval; CVH, cardiovascular health; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Source: Unpublished American Heart Association tabulation using NHANES.<sup>108</sup>

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### 3. SMOKING/TOBACCO USE

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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 the AHA's 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 youths who are not enrolled in school; however, in 2016, 97% of youths 10 to 17 years of age were enrolled in school, which indicates that the results of the NYTS are likely broadly applicable to US youths.<sup>5</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>6</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>7</sup> Use of cigars, cigarillos, filtered cigars, smokeless and hookah (ie, water pipe) tobacco, and nicotine pouches 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 2025 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 2025. 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 tobacco use in the past 30 days for middle and high school students by sex and race and ethnicity in 2023 is shown in Chart 3-1.
- In 2023<sup>8</sup>:
  - 27.9% (95% CI, 25.8%–30.2%) of high school students (corresponding to 4.4 million users) and 14.7% (95% CI, 12.5%–17.1%) of middle school students (corresponding to 1.8 million users) reported ever use of any tobacco product.
  - 12.6% (95% CI, 11.1%–14.3%) of high school students (corresponding to 2.0 million users) and 6.6% (95% CI, 5.1%–8.5%) of middle school students (corresponding to 800 000 users) reported current (past 30 days) use of any tobacco product.
  - 1.9% (95% CI, 1.5%–2.4%; corresponding to 290 000 users) of all high school students and 1.1% (95% CI, 0.6%–1.9%; corresponding to 120 000 users) of all middle school students smoked cigarettes in the past 30 days.
  - 1.8% (95% CI, 1.4%–2.4%) of high school students (280 000 users) and 1.1% (95% CI, 0.7%–1.8%) of middle school students (130 000 users) used cigars in the past 30 days.
  - 1.5% (95% CI, 1.1%–2.2%) of high school students (230 000 users) and 0.7% (95% CI, 0.5%–1.2%) of middle school students (80 000) used smokeless tobacco in the past 30 days.
  - 1.2% (95% CI, 1.0%–1.6%) of high school students (180 000 users) and 1.1% (95% CI, 0.8%–1.4%) of middle school students (120 000) used other oral nicotine products in the past 30 days.
  - 1.1% (95% CI, 0.8%–1.6%) of high school students (170 000 users) and 1.0% (95% CI, 0.6%–1.8%) of middle school students (120 000 users) used hookah in the past 30 days.
- Of youths 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>9</sup>
- In 2023, tobacco use within the past month for middle and high school students varied by race and ethnicity<sup>8</sup>:
  - The highest prevalence of tobacco product use was reported among NH multiracial youths (12.6% [95% CI, 8.8%–17.7%]) compared with 11.7% (95% CI, 10.1%–13.4%) in Hispanic youths, 9.5% (95% CI, 7.7%–11.6%) in NH White youths, 9.3% (95% CI, 7.5%–11.3%) in NH Black youths, and 8.0% (95% CI, 4.7%–13.2%) in NH American Indian or Alaska Native youths.

- The prevalence of past 30-day cigarette use was comparable among NH White youths (1.6% [95% CI, 1.1%–2.3%]) and NH multiracial youths (1.6% [95% CI, 1.0%–2.8%]) compared with Hispanic youths (2.1% [95% CI, 1.5%–3.1%]). For cigar use, the prevalence among NH White youths was 1.0% (95% CI, 0.7%–1.4%) compared with 2.2% (95% CI, 1.7%–2.8%) in Hispanic youths, with a higher prevalence among NH Black youths (2.3% [95% CI, 1.4%–3.8%]). For smokeless tobacco use, the prevalence among NH White youths was 1.2% (95% CI, 0.7%–1.8%) compared with 1.6% (95% CI, 1.1%–2.4%) in Hispanic youths. For nicotine pouches use, the prevalence among NH White youths was 1.4% (95% CI, 0.9%–2.2%) compared with 1.9% (95% CI, 1.1%–3.3%) in Hispanic youths. For other oral nicotine products use, the prevalence among NH White youths was 1.2% (95% CI, 0.9%–1.5%) compared with 1.5% (95% CI, 1.1%–2.0%) in Hispanic youths. For hookah use, the prevalence was comparable among Hispanic youths (1.3% [95% CI, 1.0%–1.7%]) and NH multiracial youths (1.3% [95% CI, 0.7%–2.4%]) compared with NH White youths (0.7% [95% CI, 0.4%–1.1%]).
- The percentage of high school (10.0% or 1 560 000 users) and middle school (4.6% or 550 000 users) students who used e-cigarettes in the past 30 days exceeded the proportion using cigarettes in the past 30 days in 2023 (Chart 3-1).

### **Adults**

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

- According to the NHIS 2021 data, among adults ≥18 years of age<sup>4</sup>:
  - 11.5% (95% CI, 11.1%–12.0%) of adults reported cigarette use every day or some days.
  - 13.1% (95% CI, 12.4%–13.9%) of males and 10.1% (95% CI, 9.5%–10.7%) of females reported cigarette use every day or some days.
  - 5.3% of those 18 to 24 years of age, 12.6% of those 25 to 44 years of age, 14.9% of those 45 to 64 years of age, and 8.3% of those ≥65 years of age reported cigarette use every day or some days.
  - 11.7% of NH Black adults, 5.4% of NH Asian adults, 7.7% of Hispanic adults, and 11.7% of NH White adults reported cigarette use every day or some days. Prevalence rates were statistically unreliable for NH American Indian and Alaska Native adults.
  - By income-to-poverty ratio (income level), reported cigarette use every day or some days was 18.3% of people with low (0–1.99) income compared with 12.3% of those with middle (2.00–3.99) income and 6.7% of those with high (≥4.00) income.
  - In adults ≥25 years of age, the percentage reporting current cigarette use was 20.1% for those

with <12 years of education, 30.7% among those with a General Educational Development high school equivalency, 17.1% among those with a high school diploma, 16.1% among those with some college, 13.7% among those with an associate's degree, and 5.3% among those with an undergraduate degree compared with 3.2% among those with a graduate degree.

- 16.8% of those divorced, separated, or widowed; 10.9% of those who were single, never married, or not living with partner; and 10.4% of those married or living with a partner reported cigarette use every day or some days.
- 15.3% of lesbian/gay/bisexual individuals reported current cigarette use compared with 11.4% of heterosexual/straight individuals.
- By region, the prevalence of individuals reporting current cigarette smoking was highest in the Midwest (14.0%) and South (12.4%) and lowest in the Northeast (10.4%) and West (8.9%).
- According to data from BRFSS 2022, the state with the highest age-adjusted percentage of individuals who reported current cigarette smoking was West Virginia (21.9%). The state with the lowest age-adjusted percentage of individuals who reported current cigarette smoking was Utah (6.7%; Chart 3-2).<sup>10</sup>
- In 2021, smoking prevalence was higher among adults ≥18 years of age who reported having a disability or activity limitation (18.5%) than among those reporting no disability or limitation (10.9%).<sup>4</sup>
- According to 2011 to 2022 data from NHIS, smoking prevalence decreased among adults 18 to 24 years of age (19.2% [95% CI, 17.5%–20.9%] in 2011 to 4.9% [95% CI, 3.7%–6.0%] in 2022; average annual percentage change, –11.3% [95% CI, –13.2% to –9.4%]), whereas it remained stable among adults ≥65 years of age (8.7% [95% CI, 7.9%–9.5%] in 2011 to 9.4% [95% CI, 8.7%–10.2%] in 2022; average annual percentage change, –0.1% [95% CI, –0.8% to 0.7%]).<sup>11</sup> Among adults ≥65 years of age, smoking prevalence increased from 13.0% in 2011 to 15.8% in 2022 for those with income <200% FPL but remained stable with no significant change for those of higher income.
- Among individuals who reported cigarette use every day or some days, 28.1% reported having serious psychological stress compared with 10.9% who reported no serious psychological distress; 19.4% were ever told by a health care professional that they had depression compared with 9.9% who had never been told that they had depression.<sup>4</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 2022 is shown in Chart 3-3. Comparing current e-cigarette use (some days) prevalence across the United States, District of Columbia, and territories shows that the lowest age-adjusted prevalence was observed in Puerto Rico (2.4%) and Maryland (2.7%) and the highest prevalence was observed in Alabama (6.4%).<sup>10</sup>

## Incidence

- According to the 2022 NSDUH,<sup>13</sup>
  - ≈1.35 million people ≥12 years of age had smoked cigarettes for the first time within the past 12 months (2022 NSDUH, Table 4.2B). Of those, 437000 were 12 to 17 years of age, 475000 were 18 to 20 years of age, 317000 were 21 to 25 years of age, and 122000 were ≥26 years of age when they first smoked cigarettes.
  - Overall, for underage individuals (12–20 years of age), use of tobacco products in the past month was 5.0% (1.9 million) compared with 20.1% (49.0 million) of individuals of legal age for tobacco (≥21 years of age; 2022 NSDUH, Table 2.1A and 2.1B).
  - Among underage individuals (12–20 years of age), 1.2 million smoked cigarettes in the past month, of whom 200000 reported daily smoking, compared with 39.9 million individuals of legal age for tobacco (≥21 years of age), of whom 23.9 million reported daily smoking (2022 NSDUH, Table 2.1A).
- According to nationally representative data from the PATH study between 2013 and 2016, in youths 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 youths who tried another non-e-cigarette tobacco product, a similar strength of association for cigarette use at 2 years was observed.<sup>14</sup> Similar findings have been reported from a 2017 to 2019 prospective cohort of youths and young adults 15 to 27 years of age.<sup>15</sup> In 2018 and compared with those who reported never using an e-cigarette, those who reported ever e-cigarette use had significantly higher odds of ever use of combustible cigarettes (aOR, 7.29 [95% CI, 4.10–12.97]) and current use of combustible cigarettes (aOR, 8.26 [95% CI, 3.17–21.53]) 1 year later in 2019.

## Lifetime Risk

### Youth

- Per NSDUH data for individuals 12 to 17 years of age, overall, the lifetime use of tobacco products was 8.7%, with lifetime cigarette use of 6.6% (2022 NSDUH, Tables 2.1B).<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 (8.9%) than females (8.4%; 2022 NSDUH, Table 2.13B).
    - Race and ethnicity: Lifetime use was highest among NH American Indian or Alaska Native adolescents (17.7%), White adolescents (10.0%), Hispanic or Latino adolescents (8.0%), NH Black adolescents (7.5%), and NH Asian adolescents (2.2%; 2022 NSDUH, Table 2.13B).

### Adults

- According to 2022 NSDUH data, the lifetime use of tobacco products in individuals ≥18 years of age was 62.0%. Lifetime cigarette use during the same year was 56.4%, of whom 31.8% reported daily smoking (2022 NSDUH, Table 2.1B). Similar to the patterns in youths, lifetime risk of tobacco products varied by demographic factors (2022 NSDUH, Table 2.13B).<sup>13</sup>
  - Sex: Lifetime use was higher in males (69.9%) than females (54.5%).
  - Race and ethnicity: Lifetime use was highest in American Indian or Alaska Native adults (70.5%) and NH White adults (69.5%), followed by Hispanic or Latino adults (51.8%), NH Black adults (50.8%), and NH Asian adults (34.9%).
- In 2022, the lifetime use of smokeless tobacco for adults ≥18 years of age was 15.0% (2022 NSDUH, Table 2.19B).<sup>13</sup>

## Secular Trends

### Youth

- According to data from MTF (8th, 10th, and 12th grades combined), the percentage of adolescents who reported smoking cigarettes in the past month was 2.1% in 2022 and similarly 2.1% in 2023.<sup>16</sup> Data from NSDUH (12–17 years of age) show that the percentage of adolescents who reported smoking cigarettes in the past month was 1.7% in 2021 and 1.2% in 2022 (NSDUH, Table 2.1B).<sup>13</sup>

### Adults

- Since the US Surgeon General's first report on the health dangers of smoking, the age-adjusted prevalence rate of smoking among adults has 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>17</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>18</sup>

- On the basis of NHIS data between 2020 and 2021, the prevalence of cigarette smoking decreased (from 12.5% to 11.5%), whereas the prevalence of e-cigarette use increased (from 3.7% to 4.5%). In 2021, 18.7% (46 million) of US adults reported currently using any commercial tobacco product, including cigarettes (11.5%), e-cigarettes (4.5%), cigars (3.5%), smokeless tobacco (2.1%), and pipes (including hookah; 0.9%).<sup>4</sup>
- According to 2017 to 2020 data from BRFSS, the prevalence of current e-cigarette use increased from 4.4% (95% CI, 4.3%–4.5%) in 2017 to 5.5% (95% CI, 5.4%–5.7%) in 2018 but decreased slightly to 5.1% (95% CI, 4.9%–5.3%) in 2020 primarily among individuals 18 to 20 years of age.<sup>19</sup> Daily e-cigarette use increased slightly throughout 2017 to 2020 (1.5% [95% CI, 1.4%–1.6%] in 2017; 2.1% [95% CI, 2.0%–2.2%] in 2018; and 2.3% [95% CI, 2.2%–2.4%] in 2020), primarily among individuals 21 to 24 years of age.

## CVH Impact

- A 2010 report by 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 (even among individuals who smoke <5 cigarettes/d), 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. It 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>
- In a 2022 cohort study of 551 338 adults, self-reported smoking was associated with a higher risk of all-cause mortality (HR, 2.80 [95% CI, 2.73–2.88]).<sup>22</sup> Associations were similar for both males and females but differed by race (Hispanic race, 2.01 [95% CI, 1.84–2.18]; NH Black race, 2.19 [95% CI, 2.06–2.33]; NH White race, 3.00 [95% CI, 2.91–3.10]; and other NH race and ethnicity, 2.16 [95% CI, 1.88–2.47]).

- 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 ≥20 cigarettes/d and higher pack-years had higher odds of subclinical PAD compared with those who self-reported smoking 1 to 19 cigarettes per day. Individuals who reported current smoking had an increased adjusted odds of ABI <1 (OR, 2.2 [95% CI, 1.5–3.3]) compared with those who never smoked.<sup>23</sup>
- A meta-analysis of 75 cohort studies (≈2.4 million individuals) demonstrated a 25% greater risk for CHD in smoking females than in smoking males (RR, 1.25 [95% CI, 1.12–1.39]).<sup>24</sup>
- Cigarette smoking is a risk factor for both ischemic stroke and SAH in adjusted analyses (RR, 1.9 [95% CI, 1.7–2.2] and 2.9 [95% CI, 2.5–3.5] for individuals who smoke versus those who do not smoke, respectively) and has a synergistic effect on other stroke risk factors such as oral contraceptive use.<sup>25</sup>
- A meta-analysis comparing pooled data of ≈3.8 million smoking and nonsmoking individuals found a similar risk of stroke associated with current smoking in females and males (RR, 1.06 [95% CI, 0.99–1.13]).<sup>26</sup>
- Those who report current smoking have a 2 to 4 times increased risk of stroke compared with those who do not smoke or those who have quit for >10 years.<sup>25,27</sup> Among JHS participants without a history of stroke (N=4410), the risk of stroke was higher among individuals who reported current smoking compared with individuals who never smoked (HR, 2.48 [95% CI, 1.60–3.83]).<sup>28</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>29</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>30</sup>
- A study of 32 428 pregnant females 15 to 49 years of age with data obtained from the NFHS-4 from India examined the relationship between tobacco use and hypertension.<sup>31</sup> The prevalence of hypertension among pregnant tobacco users was significantly higher than that of nonusers (7.5% versus 6.1% respectively;  $P=0.01$ ). The unadjusted odds of having hypertension was 1.17 (95% CI, 1.02–1.3) times higher among tobacco users than nonusers and increased with age ( $P<0.001$ ) and in rural areas ( $P=0.02$ ) after adjustment for other covariates. The association varied inversely with wealth quintile ( $P=0.01$ ), although the association with education status was not significant.

- An analysis from the JHS evaluated the associations of BP with volatile organic compound exposure in nonsmokers and smokers and included 778 never-smokers and 416 age- and sex-matched current smokers.<sup>32</sup> The urinary metabolites of 17 volatile organic compounds were measured by mass spectrometry. Among nonsmokers, metabolites of acrolein and crotonaldehyde were associated with a 1.6-mmHg (95% CI, 0.4–2.7;  $P=0.007$ ) and 0.8-mmHg (95% CI, 0.01–1.6;  $P=0.049$ ) higher SBP, and the styrene metabolite was associated with a 0.4-mmHg (95% CI, 0.09–0.8;  $P=0.02$ ) higher DBP. Current smokers, who were at higher risk of hypertension (RR, 1.2 [95% CI, 1.1–1.4]), had 2.8-mmHg (95% CI, 0.5–5.1) higher systolic BP and had higher urinary levels of several volatile organic compound metabolites. The associations were stronger among those who were <60 years of age and male.
- Short-term exposure to hookah<sup>33,34</sup> 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>35</sup> The high levels of carbon monoxide mask the short-term vascular impairment associated with hookah smoking—a vasodilator molecule—released from the charcoal briquettes used to heat the flavored tobacco product.<sup>36</sup> In a recent meta-analysis of 42 studies, compared with nonsmoking individuals, those who smoke hookah had significantly lower HDL-C ( $-3.39$  mg/dL [95% CI,  $-5.13$  to  $-1.65$ ];  $P<0.001$ ) and higher LDL-C ( $+8.77$  mg/dL [95% CI, 0.55–17.0];  $P=0.04$ ), triglycerides ( $+30.6$  mg/dL [95% CI, 14.4–46.7];  $P<0.001$ ), and fasting glucose ( $+4.66$  mg/dL [95% CI, 0.53–8.80];  $P=0.03$ ).<sup>37</sup> The long-term effects of hookah smoking remain unclear.
- The long-term CVD risks associated with e-cigarette use are not known because of a lack of longitudinal data.<sup>38,39</sup> However, e-cigarette vaping<sup>40</sup> 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>41</sup> In addition, daily e-cigarette use is independently associated with MI (OR, 1.79 [95% CI, 1.20–2.66]), and dual use of e-cigarettes and combustible cigarettes was associated with CVD, as a composite of self-reported CHD, MI, or stroke, compared with current combustible cigarettes users who never used e-cigarette (OR, 1.36 [95% CI, 1.18–1.56]).<sup>42,43</sup> Similar to e-cigarette vaping and despite the absence of tobacco combustion, flavored electronic hookah vaping has been shown to impair endothelial function, likely mediated by oxidative stress acutely.<sup>44</sup>
- Using the longitudinal PATH study cohort (2013–2019), which included 17 539 adults  $\geq 18$  years of age without prior heart condition, hypertension, or high cholesterol at baseline, a study examined the association between smoking status and self-reported hypertension.<sup>45</sup> Time-varying tobacco exposure, lagged by 1 wave, was defined as no use, exclusive established use (every day or some days) of electronic nicotine delivery systems or cigarettes, and dual use. The self-reported incidence of hypertension was 3.7% between waves 2 and 5. In adjusted analysis, exclusive cigarette use was associated with an increased risk of self-reported incident hypertension compared with nonuse (aHR, 1.21 [95% CI, 1.06–1.38]). However, exclusive electronic nicotine delivery systems use (aHR, 1.00 [95% CI, 0.68–1.47]) and dual use (aHR, 1.15 [95% CI, 0.87–1.52]) were not associated with self-reported hypertension.
- 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>43</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), those who smoke 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>46</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>47</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];  $P=3.6\times 10^{-6}$ ), CAD (OR, 1.48 [95% CI, 1.25–1.75];  $P=4.4\times 10^{-6}$ ), and stroke (OR, 1.40 [95% CI, 1.02–1.92];  $P=0.04$ ).<sup>48</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>49</sup> and  $\approx 50\%$  for other smoking measures.<sup>50,51</sup> A much smaller fraction (8.0%) of variation in smoking initiation and other smoking phenotypes is explained by common SNPs<sup>52</sup>;

- these estimates are consistent across ancestral populations.
- Smoking phenotypes have a shared genetic basis, with estimates of genetic correlation showing moderate genetic overlap ( $|r_g|$ —0.30 to 0.63).<sup>52</sup>
  - GWASs have identified loci associated with smoking initiation, heaviness of smoking, smoking regularity, smoking cessation, and age of smoking initiation. In analyses of up to 3.4 million ancestrally diverse participants, common and rare variants at 1346 loci for smoking initiation, 33 loci for age at smoking initiation, 140 loci for cigarettes per day, and 128 loci for smoking cessation were identified.<sup>52</sup> The majority of variants had consistent effect sizes across ancestral populations (African, American, East Asian, and European ancestries), although transportability of PRS across ancestral populations was poor. Novel loci include genes with roles in nervous system function (*NRXN1*) and neurocircuitry in addition (*GRIN2A*).
  - The genetic architecture of smoking shares similarities with alcohol dependence,<sup>52,53</sup> CAD,<sup>52,54</sup> and schizophrenia.<sup>55</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>56</sup>

- Such legislation may reduce the rates of smoking during adolescence—a time during which the majority of those who smoke 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>57</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>58</sup>

- A 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 youths 18 to 20 years of age.<sup>59</sup> Between 2009 and 2019, data from BRFSS showed that statewide adoption of Tobacco 21 legislation was associated with a 2.5-percentage-point decline in current cigarette use among those 18 to 20 years of age.<sup>60</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>61</sup>

## Awareness, Treatment, and Control

### Smoking Cessation

- According to NHIS 2021 data, 66.5% of adults who reported ever-smoking had stopped smoking; the quit rate has increased 11 percentage points since 2012 (55.1%).<sup>4</sup>
  - According to BRFSS surveys, quit attempts varied by state between 2011 and 2017. They increased in 4 states (Kansas, Louisiana, Virginia, and West Virginia), declined in 2 states (New York and Tennessee), and did not change 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>62</sup>
  - According to NHIS 2021 data,<sup>4</sup> among all smoking individuals, approximately two-thirds (66.5%) of adults who report ever-smoking reported having quit smoking, with rates being lower among NH Black individuals (53.7%) than NH White individuals (67.9%); individuals who are single, never married, or not living with a partner (51.6%) than married individuals or those living with a partner (71.1%); those with low income level (income-to-poverty ratio, 0–1.99; 46.1%) than those with high income level (income-to-poverty ratio  $\geq 4.00$ ; 72.5%); lesbian, gay, or bisexual individuals (61.3%) than heterosexual or straight individuals (66.9%); and those with severe psychological stress (45.3%) than those without serious psychological stress (67.7%).
- According to cross-sectional data from the Population Survey Tobacco Use Supplement,

past-year quit smoking attempts slightly declined from 2014 to 2015 (52.9%) to 2018 to 2019 (51.3%), with only 7.5% reporting sustained cessation.<sup>63</sup>

- 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 individuals who smoke who visited a cardiology practice received smoking cessation assistance.<sup>64</sup>
- According to cross-sectional MEPS data from 2006 to 2015, receiving advice to quit increased from 60.2% in 2006 to 2007 to 64.9% from 2014 to 2015. In addition, from 2014 to 2015, the use of prescription smoking cessation medicine was significantly lower among NH Black individuals (OR, 0.51 [95% CI, 0.38–0.69]), NH Asian individuals (OR, 0.31 [95% CI, 0.10–0.93]), and Hispanic individuals (OR, 0.53 [95% CI, 0.36–0.78]) 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>65</sup> From 2014 to 2015, receipt of doctor's advice to quit among US adults who smoke was significantly lower in NH Black individuals (59.7% [95% CI, 56.1%–63.1%]) and Hispanic individuals (57.9% [95% CI, 53.5%–62.2%]) compared with NH White individuals (66.6% [95% CI, 64.1%–69.1%]).
- Smoking cessation reduces the risk of cardiovascular morbidity and mortality for individuals who smoke with and without CHD.
  - In several studies, a dose-response relationship has been seen among those who report current smoking between the number of cigarettes smoked per day and CVD incidence.<sup>66,67</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. Compared with those who continued to smoke, those who quit had lower risks of recurrent major atherosclerotic cardiovascular events, a composite of stroke, MI, and cardiovascular mortality (aHR, 0.66 [95% CI, 0.49–0.88]).<sup>68</sup>
  - Individuals who smoke and 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>66</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 individuals who reported current smoking (HR, 0.61 [95% CI, 0.49–0.76]). However, CVD risks remained significantly higher among those who reported former smoking than among those who reported never-smoking beyond 5 years, and possibly for 25 years, after smoking cessation.<sup>69</sup>

- Among 726 individuals who smoke 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>70</sup>
- Cessation medications (including sustained-release bupropion, varenicline, nicotine gum, lozenge, nasal spray, and patch) are effective for helping those who smoke achieve cessation.<sup>71,72</sup>
- EVITA was an RCT that examined the efficacy of varenicline compared with placebo for smoking cessation among smoking individuals 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 ( $P=0.012$ ; NNT, 6.8). Continuous abstinence rates and reduction rates ( $\geq 50\%$  of daily cigarette consumption) were also higher in the varenicline group.<sup>73</sup>
- The EAGLES trial<sup>74</sup> demonstrated the efficacy and safety of 12 weeks of varenicline, bupropion, or a 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.
- Extended use of a nicotine patch (24 weeks 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>75</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 incentives groups versus 6.0% for usual care;  $P<0.05$  for all comparisons) through at least 12 months of follow-up.<sup>76</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>77,78</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 ≈179 099 QALYs, and prevented ≈17 000 premature deaths in the United States.<sup>79</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>80</sup>
- A randomized trial of e-cigarettes and behavioral support compared with 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>81</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>82</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>83</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 compared with those receiving varenicline monotherapy or among those treated for 24 weeks compared with 12 weeks.
- An RCT comparing combined treatment with varenicline and nicotine patch with placebo and nicotine patch for smoking cessation among smoking individuals who drink heavily showed that combination treatment led to higher smoking cessation rates (44% versus 27.9%;  $P=0.04$ ) and a lower likelihood of relapse (HR, 0.62 [95% CI, 0.40–0.96];  $P=0.03$ ).<sup>84</sup>
- In a multisite RCT of patients who were not ready to quit smoking, investigators showed that patients could be engaged in a brief abstinence game called Take a Break.<sup>85</sup> In this group, there was a 2-fold higher rate of cessation compared with the nicotine replacement therapy group (OR, 1.92 [95% CI, 1.01–3.68]).

## 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>86</sup> Overall mortality among US individuals who smoke is 3 times higher than that for individuals who never smoke.<sup>66</sup>
- On average, according to 2016 data, smoking males die 12 years earlier than never-smoking males, and smoking females die 11 years earlier than never-smoking females.<sup>18,87</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 individuals with current daily (HR, 2.32 [95% CI, 2.25–2.38]) and lifelong nondaily (HR, 1.82 [95% CI, 1.65–2.01]) cigarette smoking had higher all-cause mortality risks compared with never-smoking individuals.<sup>88</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>89</sup>
- Increased CVD mortality risks exist among those who report daily (HR, 1.47 [95% CI, 1.40–1.54]) and nondaily (HR, 1.24 [95% CI, 1.11–1.39]) cigarette smoking compared with those who report never tobacco use<sup>90</sup> and persist for older ( $\geq 60$  years of age) individuals who smoke 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 those who report never tobacco use and 1.37 (95% CI, 1.25–1.49) compared with those who report former smoking.<sup>91</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 rate was 18.4% for males and 10.9% for females.<sup>92</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>93</sup>

- If current smoking trends continue, 5.6 million US children will die of smoking prematurely during adulthood.<sup>20</sup>
- A mendelian randomization study using UK Biobank data reported that individuals who report current smoking had a higher risk of hospitalization (OR, 1.80 [95% CI, 1.26–2.29]) and mortality (smoking 1–9 cigarettes/d: OR, 2.14 [95% CI, 0.87–5.24]; 10–19 cigarettes/d: OR, 5.91 [95% CI, 3.66–9.54]; ≥20 cigarettes/d: OR, 6.11 [95% CI, 3.59–10.42]).<sup>94</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>95–97</sup> Juul came on the market in 2015 and has rapidly become one of the most popular vaping products sold in the United States.<sup>98</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>99</sup> Besides e-cigarettes and Juul, electronic hookahs (ie, electronic water pipes) are a newer category of vaping devices patented by Philip Morris in 2019.<sup>100,101</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>102</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>103,104</sup>
- E-cigarette use has become prevalent among those who reported never smoking a cigarette. 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>105</sup>
- Current e-cigarette user prevalence (every day versus some days) for 2022 in the United States is shown in Chart 3-3.
- According to the NYTS, in 2023,<sup>8</sup> e-cigarettes were the most commonly used tobacco products in youths: Ever use of e-cigarettes was reported by 9.7% of middle school (1.2 million) and 22.6%

of high school (3.6 million) students. In the past 30 days, 4.6% of middle school (550 000) and 10.0% of high school (1.6 million) students reported current e-cigarette use (Chart 3-1).

- Among high school students, rates of current use were higher among females (12.2%) than males (8.0%) and most pronounced among NH multiracial students (14.2%). In middle school students, current use rates among females were 5.6% compared with 3.5% among males, with higher rates among Hispanic students (6.6%) and NH Black students (5.7%) compared with NH White students (3.1%).
- Among middle and high school students who currently use e-cigarettes, 25.2% (95% CI, 19.2%–32.3%) reported daily use.
- Among middle and high school students who currently use e-cigarettes, 34.7% (95% CI, 28.4%–41.7%; corresponding to 740 000 users) reported using e-cigarettes on 20 to 30 days of the past 30 days.
- Among current e-cigarette users, 89.4% (90.3% high school users and 87.1% of middle school users) used flavored e-cigarettes, with fruit (63.4%) being the most common flavor type used compared with candy, desserts, or other sweets (35.0%); mint (27.8%); and menthol (20.1%).<sup>8</sup>
- Among both middle and high school current e-cigarette users, the most commonly used e-cigarette device type was disposables (60.7%), followed by prefilled or refillable pods or cartridges (16.1%) and tanks or mod systems (5.9%).<sup>8</sup>
- According to multiple annual data sets from NYTS data, the proportion among adolescent current tobacco users who reported that the first tobacco product used was e-cigarettes increased from 27.2% in 2014 to 78.3% in 2019 and remained at 77.0% in 2021.<sup>106</sup>
- According to the NYTS data between 2011 and 2020, current exclusive use of e-cigarettes increased significantly at an annual percentage change of 226.8% from 2011 to 2014 and 14.6% from 2014 to 2020, whereas exclusive use of any tobacco product—including cigarettes, cigars, hookahs, and smokeless tobacco—decreased significantly.<sup>107</sup> Among high school students, current exclusive e-cigarette use increased at an annual percentage change of 336.6% during 2011 to 2014 and 15.7% during 2014 to 2020; among middle school students, use increased at an annual percentage change of 10.4% during 2014 to 2020.
- 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>5,9</sup>
- In 2021, 70.3% of US middle and high school students were exposed to e-cigarette marketing (advertisements or promotions).<sup>108</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>109</sup>
  - In 2021, the prevalence of current e-cigarette use in adults, defined as use every day or on some days, was 4.5% according to data from the NHIS. The prevalence of current e-cigarette use was highest among males (5.1%); individuals 18 to 24 years of age (11.0%); lesbian, gay, or bisexual individuals (13.2%); and those reporting serious psychological distress (10.4%).<sup>4</sup>
  - According to 2021 data from BRFSS, current and daily e-cigarette use in adults  $\geq 18$  years of age was higher in sex- and gender-underrepresented individuals.<sup>110</sup> Data show that the prevalence of current e-cigarette use among lesbian or gay adults was 10.7% (95% CI, 9.1%–12.6%), among bisexual adults was 12.2% (95% CI, 11.0%–13.7%), and among heterosexual individuals was 6.8% (95% CI, 6.6%–7.1%). The prevalence of daily e-cigarette use was 5.7% (95% CI, 4.4%–7.5%) among lesbian or gay adults, 6.5% (95% CI, 5.4%–7.8%) among bisexual adults, and 3.2% (95% CI, 3.0%–3.3%) among heterosexual individuals.<sup>110</sup>
  - According to data from BRFSS, most states showed significant increases in the prevalence of current e-cigarette use from 2017 and 2018.<sup>19</sup> Between 2018 and 2020, although several states showed significant decreases (eg, Massachusetts, from 5.6% [95% CI, 4.8%–6.5%] to 4.1% [95% CI, 3.1%–5.3%]; and New York, from 5.4% [95% CI, 4.9%–5.9%] to 4.1% [95% CI, 3.5%–4.7%]), others showed significant increases (eg, Guam, from 5.9% [95% CI, 4.5%–7.9%] to 11.4% [95% CI, 8.7%–14.8%]; and Utah, from 6.1% [95% CI, 5.5%–6.7%] to 7.2% [95% CI, 6.5%–8.0%]).
  - 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 youths 12 to 17 years of age reported ever electronic hookah use.<sup>111</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>112</sup> including volatile organic compounds.<sup>113,114</sup> According to nationally

representative data from the PATH study (2013–2014), there was a significant reduction in urine concentrations of tobacco-specific nitrosamines [including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol], polycyclic aromatic hydrocarbons, and volatile organic compounds when study participants transitioned from exclusive cigarette to exclusive e-cigarette use, with a 92% decrease in 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (from 168.4 pg/mg [95% CI, 102.3–277.1] to 12.9 pg/mg [95% CI, 6.4–25.7] creatinine;  $P < 0.001$ ).<sup>115</sup> However, nicotine levels have been found to be consistent across long-term cigarette and long-term e-cigarette users.<sup>41,116</sup>

- E-cigarette use has a significant cross-sectional association with a less favorable perception of physical and mental health and with depression.<sup>117</sup> In a nationally representative sample of adults from the BRFSS database, whereas former e-cigarette users had 1.60-fold (95% CI, 1.54–1.67) higher odds of reporting a history of clinical diagnosis of depression than never users of e-cigarettes, current e-cigarette users had 2.10 (95% CI, 1.98–2.23) times higher odds. According to 2017 BRFSS data, current e-cigarette adult users reported a significantly higher prevalence of depression (32.4%) compared with former e-cigarette users (27.3%) and nonusers (16.0%).<sup>118</sup> Furthermore, compared with those who do not use e-cigarettes, the odds of self-reported depression was higher among unemployed current (OR, 2.85 [95% CI, 1.63–4.97]) and unemployed former (OR, 1.89 [95% CI, 1.26–2.84]) e-cigarette users.
- 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>119,120</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 occurred in the United States.<sup>121</sup>

- Effective August 8, 2016, the FDA's Deeming Rule prohibited sale of e-cigarettes to individuals <18 years of age.<sup>122</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>123</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>124</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>125</sup>

## Secondhand Smoke

- Data from the US Surgeon General on the consequences of secondhand smoke indicate the following:
  - Nonsmoking individuals who are exposed to secondhand smoke at home or at work have a 25% to 30% increased risk of developing CHD.<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>126</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>127</sup>
- A study of adults 45 to 84 years of age who did not report active smoking—in MESA showed that, during a median follow-up of 17.7 years, individuals exposed to secondhand smoke evidenced by

detectable urinary cotinine >7.07 ng/mL had a significantly higher risk of incident HF compared with those with undetectable urinary cotinine ≤7.07 ng/mL (HR, 1.45 [95% CI, 1.03–2.06]).<sup>128</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>129</sup>
- As of December 31, 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>130</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>131</sup>
- The percentage of the US nonsmoking population with serum cotinine ≥0.05 ng/mL (which indicates exposure to secondhand smoke) declined from 52.5% in 1999 to 2000 to 24.7% in 2017 to 2018, with declines occurring for both children and adults. During 2017 to 2018, the percentage of nonsmoking individuals 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 ≥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>132,133</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>18</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>134</sup>
- According to the CDC and Federal Trade Commission, in 2019, the tobacco industry spent \$8.2 billion on cigarette and smokeless tobacco advertising and promotional expenses.<sup>135</sup> According to data from the Federal Trade Commission, manufacturers spent \$1.0 billion on total e-cigarette advertising and promotion in 2019, which declined to \$719.9 million in 2020.<sup>136</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>137</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>138</sup>
- From 2012 through 2016, e-cigarette sales significantly increased while national e-cigarette prices significantly decreased,<sup>138</sup> with total e-cigarette unit sales exponentially increasing nearly 300% from 2016 through 2019.<sup>139</sup> Together, these trends highlight the rapidly changing landscape of the US e-cigarette marketplace.<sup>138</sup>
- Despite the morbidity and mortality resulting from tobacco use, Dieleman et al<sup>140</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 3-4)

- Of 204 countries and territories in 2021, East Asia and Oceania had the highest mortality rates attributable to tobacco. Mortality rates were lowest for Andean Latin America. (Chart 3-4). In 2021, tobacco caused 7.25 (95% UI, 5.74–8.70) million total deaths in 2021, with 5.68 (95% UI, 4.59–6.73) million among males and 1.57 (95% UI, 1.09–2.06) million among females (Table 3-1).<sup>141</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>142</sup>
- Worldwide, ≈80% of tobacco users live in low- and middle-income countries.<sup>143</sup> According to data from the GBD 2019 study, although the burden of IHD attributable to smoking has declined in >80% of countries from 1990 to 2019, it has remained a critical issue in low- and middle-income countries, especially among men and elderly individuals.<sup>144</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>145</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 GDP. 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>146,147</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>148</sup>
- The CDC examined data from 28 countries in 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–38.2% in Greece). Among those who report current smoking, quit attempts over the prior 12 months also varied, with a median of 42.5% (range, 14.4% in China–59.6% in Senegal). Knowledge that smoking causes heart attacks (median, 83.6%; range, 38.7% in China–95.5% in Turkey) and stroke (median 73.6%; range, 27.2% in China–89.2% in Romania) varied widely across countries.<sup>149</sup>

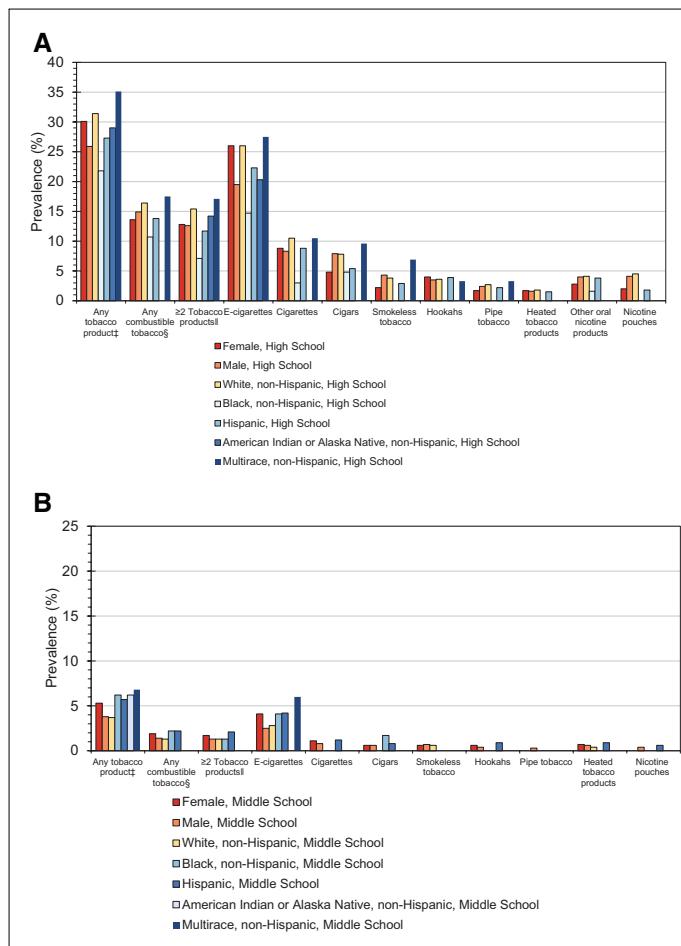
**Table 3-1. Deaths Caused by Tobacco Worldwide, by Sex, 2021**

	Deaths			
	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)	
Total number (millions), 2021	7.25 (5.74 to 8.70)	5.68 (4.59 to 6.73)	1.57 (1.09 to 2.06)	
Percent change (%) in total number, 1990–2021	26.17 (15.68 to 38.15)	31.07 (17.23 to 45.88)	11.12 (−0.26 to 23.38)	
Percent change (%) in total number, 2010–2021	9.28 (0.84 to 18.13)	10.60 (0.48 to 22.09)	4.75 (−3.63 to 13.58)	
Rate per 100,000, age-standardized, 2021	85.66 (67.58 to 102.93)	149.02 (119.51 to 177.25)	33.94 (23.62 to 44.76)	
Percent change (%) in rate, age-standardized, 1990–2021	−42.97 (−47.68 to −37.54)	−41.85 (−47.97 to −35.40)	−49.92 (−54.75 to −44.67)	
Percent change (%) in rate, age-standardized, 2010–2021	−19.75 (−25.87 to −13.31)	−19.10 (−26.41 to −10.78)	−23.53 (−29.66 to −17.24)	
PAF (%), all ages, 2021	10.68 (8.51 to 12.69)	15.07 (12.40 to 17.59)	5.19 (3.70 to 6.79)	
Percent change (%) in PAF, all ages, 1990–2021	−14.32 (−20.01 to −8.77)	−13.73 (−19.50 to −7.60)	−21.66 (−27.09 to −15.45)	
Percent change (%) in PAF, all ages, 2010–2021	−14.57 (−19.05 to −9.77)	−14.79 (−19.32 to −9.97)	−16.64 (−21.33 to −11.37)	

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>141</sup>

**Chart 3-1. Prevalence (percent) of tobacco use in the United States in the past 30 days by product,\* school level, sex, and race and ethnicity† (NYTS, 2023).**

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

E-cigarette indicates electronic cigarette; and NYTS, National Youth Tobacco Survey.

\*Smokeless tobacco was defined as chewing tobacco, snuff, dip, or snus tobacco products. Other oral nicotine products were defined as lozenges, discs, tablets, gums, dissolvable tobacco products, and other products. In 2023, dissolvable tobacco products were reclassified from smokeless tobacco to other oral nicotine products. Because of missing data on the past 30-day use questions, denominators for each tobacco product might be different. (*Continued*)

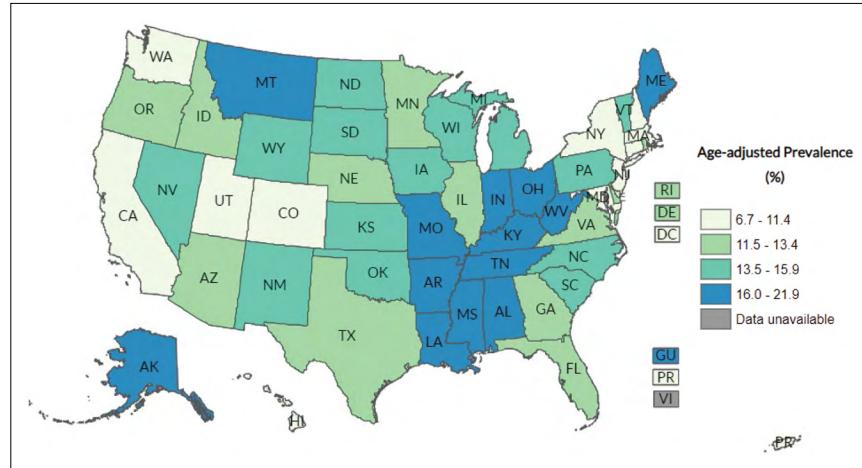
**Chart 3-1. Continued.** †Black people, White people, and people of other race are non-Hispanic; Hispanic people could be of any race. Non-Hispanic people who selected >1 race were classified as multiracial.

‡In 2023, 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 days during the past 30 days.

||In 2023, 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 days during the past 30 days.

Source: Data derived from Park-Lee et al.<sup>3</sup>

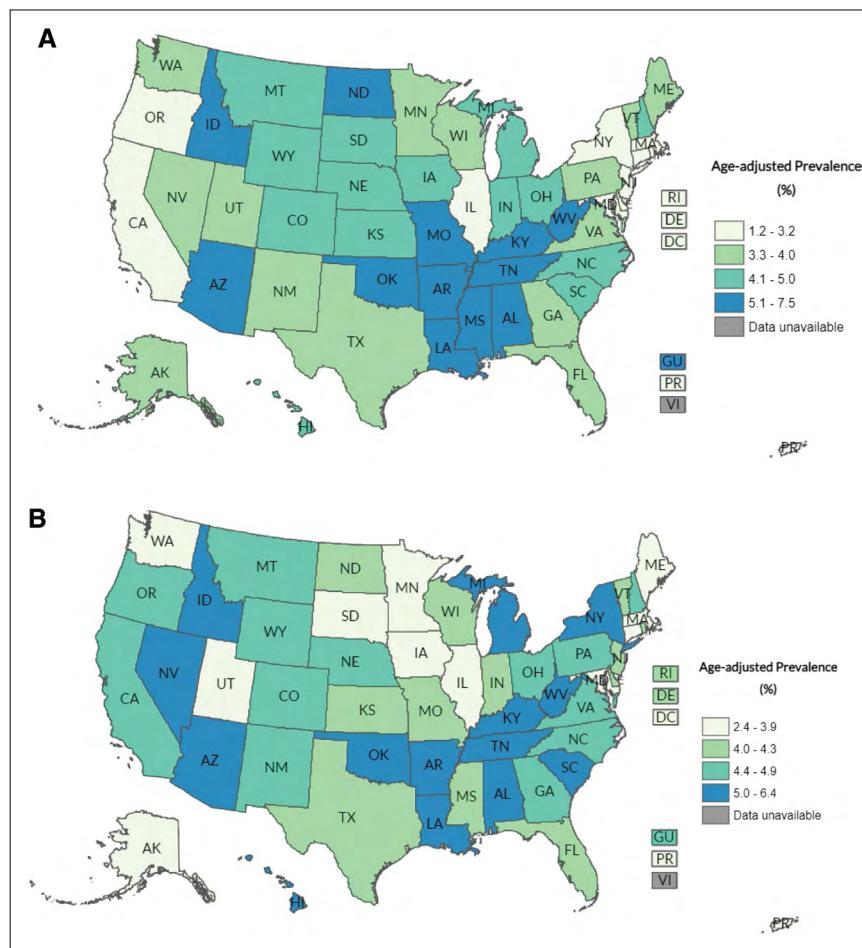


**Chart 3-2. Age-adjusted prevalence (percent) of current cigarette smoking for US adults by state (BRFSS, 2022).**

White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.

BRFSS indicates Behavior Risk Factor Surveillance System.

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

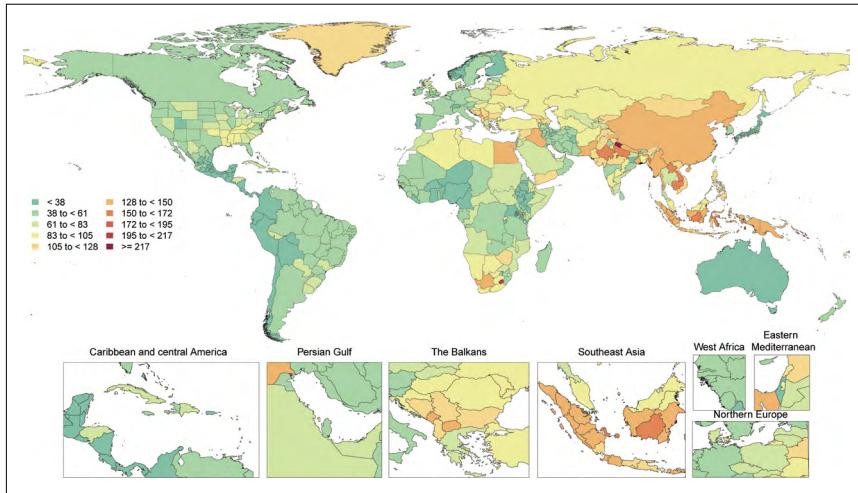


**Chart 3-3. Prevalence (age-adjusted) of current electronic cigarette use (every day and some days), United States (BRFSS, 2022).**

**A**, Everyday use. **B**, Some days use. White space between the map and legend has been removed. Icons and drop-down menus for interactive tools have been removed.

BRFSS indicates Behavior Risk Factor Surveillance System.

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



**Chart 3-4. Age-standardized global mortality rates attributable to tobacco per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>141</sup>

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## 4. PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR

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

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### Definition

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 that a lack of PA was a risk factor for the development of CHD.<sup>1</sup> Since then, an abundance of research has firmly established a lack of PA 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. The 2019 CVD primary prevention clinical practice guidelines<sup>4</sup> support the aerobic recommendations. For most 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 aerobic PA guideline recommendations is one of the AHA's Life's Essential 8 components of ideal CVH for both children and adults.<sup>5</sup> An AHA scientific statement published in 2023 updated the substantial evidence of cardiovascular benefits from meeting resistance training guidelines among individuals with and without CVD.<sup>6</sup>

Globally, the 2020 WHO guidelines also recommend moderate- to vigorous-intensity aerobic PA along with muscle-strengthening activities across all age groups and abilities.<sup>7</sup> Increasing moderate-intensity PA and replacing sedentary behavior with light-intensity PA can provide health benefits.<sup>3,7</sup> The WHO guidelines for PA also include recommendations for those living with a disability,<sup>8</sup> supporting research on wheelchair users.<sup>9,10</sup>

The 2025 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 2025. 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.

Sedentary behavior is defined as "any waking behavior characterized by an energy expenditure  $\leq 1.5$  METs while in a sitting, reclining, or lying posture."<sup>11</sup> Sedentary behavior is a distinct risk factor from PA, characterized by both posture (sitting, lying, or reclined) and intensity (low), and includes activities such as driving/riding in a vehicle, using a screen (eg, watching television, playing video games, using a computer), or reading. The 2018 Physical Activity Guidelines for Americans recommend that 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>7</sup>

PA is characterized by several dimensions (eg, frequency, duration, and intensity) and domains or types (eg, occupational, domestic, transportation, and leisure). Measurement of PA in population studies can be defined by 2 broad assessment methods: (1) self-reported methods that use questionnaires, diaries, or logs and (2) device-based methods that use wearable devices (eg, pedometers, accelerometers). Sedentary behavior can be characterized by similar dimensions (eg, frequency, duration) and domains or types (eg, occupational, leisure, transportation) and can also be assessed with both self-reported and device-based methods.

### Prevalence and Secular Trends

#### Youth PA

(See Charts 4-1 and 4-2)

- According to parental report, in 2022, the nationwide percentage of youths 6 to 17 years of age who were active for  $\geq 60$  minutes every day of the week was 18.9% (95% CI, 18.1%–19.7%).<sup>12</sup> The percentage was higher for youths 6 to 11 years of age (25.2% [95% CI, 24.0%–26.6%]) compared with youths 12 to 17 years of age (12.9% [95% CI, 12.0%–13.8%]; Chart 4-1) and higher for males (22.0% [95% CI, 20.8%–23.3%]) compared with females (15.6% [95% CI, 14.6%–16.6%]). The percentage varied by race and ethnicity of the child: 13.4% (95% CI, 11.1%–16.2%) for NH Asian children, 14.5% (95% CI, 12.4%–16.8%) for NH Black children, 16.2% (95% CI, 14.4%–18.2%) for Hispanic children, 20.6% (95% CI, 18.1%–23.4%) for NH other children, and 21.8% (95% CI, 20.8%–22.8%) for NH White children. The percentage was higher among English-speaking households (19.6% [95% CI, 18.8%–20.5%]) compared with households with a primary language other than English (14.1% [95% CI, 11.8%–16.8%]). Considering the highest education in the household, the percentage was 18.2% (95% CI, 14.8%–22.3%) for those with less than a high school education, 20.7% (95% CI, 18.6%–22.9%) for those with a high school education or passing a General Educational Development

Test, 19.0% (95% CI, 17.4%–20.7%) for those with some college or technical school, and 18.3% (95% CI, 17.4%–19.3%) for those with a college degree or higher.

- The 2021 nationwide percentage of high school students who engaged in ≥60 minutes of PA on all 7 days of the week was 23.9% (95% CI, 22.8%–25.0%).<sup>13</sup> The percentage was lower with each higher grade, from 25.6% (95% CI, 23.7%–27.7%) in ninth grade to 20.8% (95% CI, 18.9%–23.0%) in 12th grade. The percentage was higher in males (31.7% [95% CI, 30.2%–33.2%]) than females (15.7% [95% CI, 14.1%–17.4%]). The percentage varied by race and ethnicity: Hispanic, 18.9% (95% CI, 17.3%–20.5%); NH Asian, 19.4% (95% CI, 14.6%–25.3%); NH Black, 19.7% (95% CI, 17.5%–22.0%); Native Hawaiian or Other Pacific Islander, 23.2% (95% CI, 16.1%–32.2%); NH White, 27.7% (95% CI, 25.1%–30.4%); and American Indian/Alaska Native, 40.0% (95% CI, 22.5%–60.3%).
- In 2021, the percentage of high school students who participated in muscle-strengthening activities (such as push-ups, sit-ups, or weight lifting) on ≥3 d/wk was 44.9% (95% CI, 42.5%–47.2%) nationwide and was lower in the 12th grade (40.4% [95% CI, 37.6%–43.3%]) compared with the ninth grade (48.1% [95% CI, 44.8%–51.4%]).<sup>13</sup> More high school males (56.6% [95% CI, 54.4%–58.8%]) than females (32.3% [95% CI, 29.7%–35.1%]) reported participating in muscle-strengthening activities on ≥3 d/wk. The percentage varied by race and ethnicity: NH Black, 40.7% (95% CI, 36.1%–45.4%); NH Asian, 41.7% (95% CI, 35.2%–48.5%); Native Hawaiian or Other Pacific Islander, 43.2% (95% CI, 31.6%–55.6%); Hispanic, 44.2% (95% CI, 41.9%–46.5%); NH White, 47.0% (95% CI, 43.3%–50.6%); and American Indian/Alaska Native, 54.8% (95% CI, 39.2%–69.5%).
- The percentage of high school students who were physically active for ≥60 minutes on all 7 d/wk decreased over the past decade from 28.7% (95% CI, 27.1%–30.3%) in 2011 to 23.9% (95% CI, 22.8%–25.0%) in 2021. The percentage of high school students participating in muscle-strengthening activities on ≥3 d/wk decreased over the past decade from 55.6% (95% CI, 53.6%–57.5%) in 2011 to 44.9% (95% CI, 42.5%–47.2%) in 2021 (Chart 4-2).<sup>13</sup>
- The 2021 nationwide percentage of high school students who met both PA recommendations (were both physically active for ≥60 minutes on all 7 d/wk and participated in muscle-strengthening activities on ≥3 d/wk) was 16.0% (95% CI, 14.2%–17.9%).<sup>14</sup> Males were more likely to meet both PA recommendations (22.9% [95% CI, 20.5%–25.4%]) compared with females (8.8% [95% CI, 7.3%–10.6%]). There were also significant differences across race

and ethnicity: Black, 10.8% (95% CI, 8.4%–13.7%); Asian, 13.5% (95% CI, 7.9%–22.1%); multiracial, 13.5% (95% CI, 10.5%–17.1%); Hispanic or Latino, 13.5% (95% CI, 11.8%–15.4%); Native Hawaiian or Other Pacific Islander, 15.0% (95% CI, 10.9%–20.4%); White, 18.6% (95% CI, 15.8%–21.8%); and American Indian or Alaska Native, 29.9% (95%, 15.1%–50.5%). The percentage of students meeting both recommendations remained stable between 2019 and 2021.

- Wrist-worn accelerometry data from 6030 youths 3 to 19 years of age in the NHANES National Youth Fitness Survey 2012 and NHANES 2011 to 2014 indicated that the median daily total volume of PA (measured by MIMS units) peaked at 6 years of age for both males and females.<sup>15</sup> In contrast, the lowest median daily total volume of PA occurred at 17 years of age in males and 18 years of age in females. Generally, for both males and females, total PA volume was successively higher from 3 to 6 years of age, declined from 6 to ≈15 years of age, and then plateaued through 19 years of age.

### Youth Physical Education Classes

- In 2021, 19.0% (95% CI, 15.7%–22.7%) of high school students attended physical education classes in school daily (males, 21.1% [95% CI, 17.2%–25.6%]; females, 16.7% [95% CI, 13.4%–20.6%]).<sup>13</sup> Daily physical education class attendance was higher in the ninth grade (29.0% [95% CI, 23.5%–35.2%]) than in the 12th grade (11.8% [95% CI, 8.6%–15.9%]). Daily physical education varied by race and ethnicity: Asian, 9.6% (95% CI, 5.7%–15.6%); Native Hawaiian or Other Pacific Islander, 15.9% (95% CI, 8.4%–28.2%); White, 19.0% (95% CI, 15.0%–23.6%); Black, 19.6% (95% CI, 13.9%–27.0%); Hispanic, 21.0% (95% CI, 17.4%–25.2%); and American Indian/Alaska Native, 23.0% (95% CI, 14.7%–34.2%).
- Nationwide, over the past decade, the percentage of high school students who reported attending physical education classes at least once per week (on an average week while in school) was stable at 51.8% (95% CI, 46.0%–57.6%) in 2011 and 46.8% (95% CI, 39.7%–54.0%) in 2022.<sup>13</sup> However, the percentage of high school students who reported attending physical education classes on all 5 days of the week decreased from 31.5% (95% CI, 26.1%–37.4%) in 2011 to 19.0% (95% CI, 15.7%–22.7%) in 2021 (Chart 4-2).

### Youth Organized Sports

- According to parental report, in 2022, the nationwide percentage of youths 6 to 17 years of age participating in a sports team or sports lessons after school or on weekends was 53.8% (95% CI, 52.8%–54.9%).<sup>12</sup> The percentage was higher for youths 6

to 11 years of age (55.7% [95% CI, 54.2%–57.3%]) compared with youths 12 to 17 years of age (52.1% [95% CI, 50.5%–53.6%]) and higher for males (58.1% [95% CI, 56.6%–59.6%]) compared with females (49.4% [95% CI, 47.9%–50.9%]). The percentage varied by race and ethnicity of the child: 42.1% (95% CI, 39.6%–44.7%) for Hispanic children, 45.0% (95% CI, 41.6%–48.5%) for NH Black children, 50.1% (95% CI, 45.8%–54.4%) for NH Asian children, 59.9% (95% CI, 56.8%–62.9%) for NH other children, and 62.2% (95% CI, 61.0%–63.3%) for NH White children. The percentage was higher among English-speaking households (57.4% [95% CI, 56.4%–58.5%]) compared with households with a primary language other than English (32.5% [95% CI, 29.5%–35.7%]). Considering the highest education in the household, the percentage of youths participating on a sports team was 25.9% (95% CI, 21.7%–30.6%) from households with less than high school education, 36.4% (95% CI, 33.9%–39.0%) from households with high school or passing a General Educational Development Test, 47.1% (95% CI, 44.9%–49.4%) from households with some college or technical school, and 68.0% (95% CI, 66.7%–69.1%) from households with a college degree or higher.

- In 2021, about half (49.1% [95% CI, 46.3%–51.8%]) of high school students played on at least 1 school or community sports team in the previous year (46.4% [95% CI, 43.4%–49.4%] of females and 52.0% [95% CI, 49.1%–55.0%] of males); this number was lower in the 12th grade (43.7% [95% CI, 40.0%–47.4%]) compared with the ninth grade (53.2% [95% CI, 49.4%–57.0%]).<sup>13</sup> The percentage varied by race and ethnicity: Hispanic, 39.4% (95% CI, 36.7%–42.1%); Asian, 45.0% (95% CI, 33.7%–56.8%); Black, 47.2% (95% CI, 43.1%–51.3%); Native Hawaiian or Other Pacific Islander, 50.6% (95% CI, 32.6%–68.4%); American Indian/Alaska Native, 52.8% (95% CI, 41.8%–63.6%); and White, 55.3% (95% CI, 51.4%–59.2%).
- The percentage of high school students playing on ≥1 team sport in the past year decreased over the past decade, from 58.4% (95% CI, 56.0%–60.7%) in 2011 to 49.1% (95% CI, 46.3%–51.8%) in 2021 (Chart 4-2).<sup>13</sup>
- From the 2018 to 2019 National Survey of Children's Health, sports participation was higher among youths 12 to 17 years living in metropolitan areas compared with those in nonmetropolitan areas.<sup>16</sup>

### Youth Sedentary Behavior

#### (See Chart 4-3)

- According to parental report, in 2022, the nationwide percentage of youths 0 to 17 years of age spending ≥4 h/d in front of a television, computer,

cell phone, or other electronic device watching programs, playing games, accessing the internet, or using social media (not including schoolwork) on most weekdays was 22.0% (95% CI, 21.5%–22.9%).<sup>12</sup> The percentage was higher for increasing age groups: 0 to 5 years of age, 7.9% (95% CI, 7.1%–8.8%); 6 to 11 years of age, 18.3% (95% CI, 17.1%–19.6%); and 12 to 17 years of age, 37.9% (95% CI, 36.5%–39.3%). The percentage was 23.0% (95% CI, 22.0%–24.1%) for males and 21.4% (95% CI, 20.4%–22.4%) for females. The percentage varied by race and ethnicity of the child: 18.5% (95% CI, 17.8%–19.3%) for NH White children, 21.2% (95% CI, 19.2%–23.3%) for NH other children, 21.5% (95% CI, 18.4%–25.0%) for NH Asian children, 24.5% (95% CI, 22.8%–26.4%) for Hispanic children, and 32.4% (95% CI, 29.8%–35.2%) for NH Black children (Chart 4-3). The percentage was similar among English-speaking households (22.1% [95% CI, 21.4%–22.9%]) compared with households with a primary language other than English (22.4% [95% CI, 20.0%–25.0%]). Considering the highest education in the household, the percentage was 26.0% (95% CI, 22.2%–30.2%) with less than high school education, 26.2% (95% CI, 24.3%–28.2%) with high school or passing a General Educational Development Test, 26.5% (95% CI, 24.8%–28.3%) with some college or technical school, and 18.6% (95% CI, 17.8%–19.4%) with a college degree or higher.

### Neighborhood Environment Among Youth

#### (See Chart 4-4)

- According to parental report, in 2022, 36.5% (95% CI, 35.7%–37.3%) of children 0 to 17 years of age lived in neighborhoods containing all 4 activity-promoting features (parks, recreation centers, sidewalks, and libraries).<sup>12</sup> Chart 4-4 displays the percentages of children living in neighborhoods with 1, 2, 3, or 4 neighborhood activity-promoting features. The percentage of children having all 4 neighborhood activity-promoting amenities did not vary substantially by age group (36.6% [95% CI, 35.3%–38.1%] for 0–5 years, 36.4% [95% CI, 34.9%–37.8%] for 6–11 years, and 36.6% [95% CI, 35.2%–38.0%] for 12–17 years) or sex (36.1% [95% CI, 34.9%–37.2%] for males and 37.0% [95% CI, 35.9%–38.2%] for females). The percentage varied by race and ethnicity of the child: 33.5% (95% CI, 32.6%–34.3%) for NH White children, 36.8% (95% CI, 34.9%–38.8%) for Hispanic children, 37.2% (95% CI, 34.8%–39.6%) for NH other children, 41.4% (95% CI, 38.4%–44.4%) for NH Black children, and 52.3% (95% CI, 48.9%–55.8%) for NH Asian children. The percentage was similar

among English-speaking households (36.8% [95% CI, 36.0%–37.6%]) and households with a primary language other than English (34.5% [95% CI, 31.9%–37.3%]). With respect to differences in highest level of education in the household, the percentage of youths living in a neighborhood with all 4 neighborhood activity-promoting features varied, with 23.5% (95% CI, 19.9%–27.5%) in households with less than high school education, 28.6% (95% CI, 26.7%–30.6%) in households with high school degree or passing a General Educational Development Test, 32.5% (95% CI, 30.8%–34.4%) in households with some college or technical school, and 42.7% (95% CI, 41.7%–43.7%) in households with a college degree or higher.

- According to parental report, in 2022, 3.9% (95% CI, 3.9%–4.6%) of youths 0 to 17 years of age nationwide lived in a neighborhood with litter or garbage on the street or sidewalk, poorly kept or rundown housing, and vandalism such as broken windows and graffiti, whereas 76.5% (95% CI, 75.8%–77.3%) lived in a neighborhood with none of these detracting elements (Chart 4-4).<sup>12</sup>

### Adult PA

#### (See Charts 4-5 and 4-6)

- According to NHIS, the percentage of adults meeting the aerobic and muscle-strengthening Physical Activity Guidelines for Americans has changed little from 2020 to 2022 (Chart 4-5).<sup>17</sup> The percentage reporting engaging in ≥150 min/wk of moderate-intensity aerobic activity, 75 min/wk of vigorous-intensity aerobic activity, or an equivalent combination was 47.9% in 2020 and 48.1% in 2022. The percentage reporting engaging in muscle-strengthening activities of at least moderate intensity and including all major muscle groups ≥2 d/wk was 31.9% in 2020 and 31.5% in 2022. The percentage of adults meeting both aerobic PA and muscle-strengthening guidelines was 25.2% in 2020 and 25.3% in 2022. It is important to note that each of these population prevalence estimates remains below the goals set by Healthy People 2030, which are 52.9% of adults meeting aerobic PA guidelines, 36.6% of adults meeting muscle-strengthening guidelines, and 29.7% of adults meeting both guidelines.
- According to NHIS 2020, the percentage of adults reporting meeting both the aerobic PA and muscle-strengthening guidelines was lower with older age for both men and women.<sup>18</sup> For males, the percentage meeting both guidelines was 41.3% for 18 to 34 years of age, 29.4% for 35 to 49 years of age, 21.6% for 50 to 64 years of age, and 15.3% for ≥65 years of age; for women, the percentage meeting both guidelines was 28.7% for 18 to 34 years of age, 22.7% for 35 to 49 years of age, 17.6% for 50

to 64 years of age, and 10.8% for ≥65 years of age. The percentage varied by race and ethnicity for men (23.5% for Hispanic, 29.7% for NH Black, 30.2% for NH Asian, 30.5% for NH White) and women (18.0% for Hispanic, 16.5% for NH Black, 16.7% for NH Asian, 24.3% for NH White). The percentage meeting both guidelines was higher with higher income among men (16.1% at <100% of the FPL, 20.0% at 100%–199% of the FPL, and 32.4% at ≥200% of the FPL) and women (9.9% at <100% of the FPL, 13.6% at 100%–199% of the FPL, and 25.9% at ≥200% of the FPL). The percentage was higher with higher urbanicity: 16.1% nonmetropolitan, 22.3% medium/small metropolitan, 26.9% large fringe metropolitan, and 27.8% large central metropolitan.<sup>19</sup> From BRFSS 2022, across all US states, the District of Columbia, and territories, the median percentage of physical inactivity (defined as self-report of not participating in any PA in the past month) was 23.5%. This age-adjusted prevalence of inactivity varied by state or territory of residence, ranging from the lowest in the District of Columbia (15.6%), Colorado (16.5%), and Utah (17.0) to the highest in Arkansas (30.0%), Mississippi (30.7%), and Puerto Rico (42.2%; Chart 4-6).<sup>20</sup>

- In the PROPASS Consortium, an international research collaboration including 6 studies from Europe and Australia, 15 253 adults spent, on average, 1.3 h/d in moderate- to vigorous-intensity PA, 1.5 h/d in light-intensity PA, and 3.1 h/d standing, as measured by thigh-worn accelerometry.<sup>21</sup>
- According to 1 week of wrist-worn accelerometry data from 8675 participants ≥20 years of age in NHANES 2011 to 2014, the median daily total volume of PA (measured by MIMS units) peaked at 20 years of age for males and 36 years of age for females.<sup>15</sup> For both males and females, total volume of PA was the lowest at 80 years of age.
- From a systematic review of 20 studies applying an intervention to increase PA, ≈70% of all studies found evidence for a positive association between the PA-promoting attributes of the built environment (walkability, density, green space) and PA.<sup>22</sup>
- A 2023 AHA scientific statement<sup>23</sup> highlighted strong, consistent evidence that adults with obesity, hypertension, and diabetes and of older age were less active than their counterparts without these conditions or of younger age, respectively. Other factors associated with lower PA levels in at least 1 large observational study included female sex, Black race, lower SES, having a mobility disability, living in the South or Midwest regions, living in rural communities, less walkable infrastructure, and air pollution/extreme weather. The statement concluded that promoting PA in these groups could help to reduce CVH inequities.

### **Adult Sedentary Behavior**

- According to NHANES, self-reported mean daily sitting time increased by 19 min/d from 2007 to 2008 (332 min/d) to 2017 to 2018 (351 min/d).<sup>24</sup>
- In the PROPASS Consortium (N=15 253) including 6 studies from Europe and Australia,<sup>21</sup> adults spent an average of 10.4 h/d (equating to 43.2% of the 24-hour day) in sedentary behavior as measured by thigh-worn accelerometry, which is the best practice method<sup>11</sup> for assessing time spent sedentary. Sedentary behavior encompassed the greatest proportion of the 24-hour day in adults, followed by sleep (31.9%), standing (13.0%), light-intensity PA (6.4%), and moderate- to vigorous-intensity PA (5.5%).

### **Genetics and Family History**

- Genetic factors have been shown to contribute to the propensity to exercise.<sup>25</sup>
- A systematic review of GWASs for PA and sedentary behavior revealed that variants in 9 candidate genes (*ACE*, *CASR*, *CYP19A*, *FTO*, *DRD2*, *CNR1*, *LEPR*, *MC4R*, and *NPC1*) were associated with PA or sedentary behavior in greater than a single study.<sup>26</sup>
- A GWAS of 91 105 individuals with device-measured PA and sedentary behavior in the UK Biobank identified 7 significant loci, including 3 for overall activity (*SKIDA1*, *KANSL1-AS1*, and *SYT4*) and 4 for sedentary time (*MEF2C-AS2*, *EFNA5*, *LOC105377146*, and *CALN1*).<sup>27</sup> Together, these loci accounted for 0.06% of the activity duration variation in the sample.
- A follow-up study in the UK Biobank identified an additional 3 novel loci (*SEC13*, *RN7SKP16*, and *PDXDC2P*) in a GWAS evaluating associations with device-measured PA metrics in 88 411 individuals.<sup>28</sup> The novel loci were associated with active to sedentary transition probability, moderate- to vigorous-intensity PA involving the central nervous system, and total log acceleration (6–8 AM) involving the blood/immune and digestive systems.
- A GWAS of self-reported sedentary behaviors in 422 218 individuals of European ancestry from the UK Biobank yielded 145, 36, and 4 loci associated with leisure television watching, leisure computer use, and driving behavior, respectively.<sup>29</sup> A mendelian randomization analysis established the causal role of television watching in the risk of CAD in which each 1.5-hour increase in television watching was associated with greater odds of CAD (OR, 1.44 [95% CI, 1.25–1.66]).<sup>29</sup>
- A meta-analysis of 51 studies consisting of 703 901 multiancestry individuals identified 99 significant loci associated with self-reported moderate- to

vigorous-intensity PA, leisure screen time, or sedentary behavior at work.<sup>30</sup>

### **Prevention**

#### ***PA, Sedentary Behavior, and Cardiovascular Prevention Among Youth and Adults***

- A meta-analysis based on 19 prospective cohort studies estimated that high compared with low sedentary behavior (defined individually within each study) was associated with an increased risk of fatal CVD (pooled RR, 1.27 [95% CI, 1.19–1.36]) and nonfatal CVD (RR, 1.30 [95% CI, 1.18–1.43]).<sup>31</sup> Among 4 of these studies, the pooled effect of isotemporally increasing light-intensity PA and decreasing sedentary behavior by 1 hour was estimated to reduce the risk of nonfatal CVD by 16% (RR, 0.84 [95% CI, 0.73–0.97]).
- A meta-analysis of 15 studies characterized a beneficial, inverse dose-response association between PA and incidence of AF among 1.8 million females. A nonlinear association was identified in which a greater risk reduction was observed up to 20 MET-h/wk and a less steep slope from 20 to 50 MET-h/wk ( $P<0.0001$ ). The estimated RR of AF was reduced by 16% (RR, 0.84 [95% CI, 0.80–0.88]) at 50 MET-h/wk compared with 0 MET-h/wk.<sup>32</sup> The dose-response relationship above 50 MET-h/wk could not be determined because of low sample size.
- A meta-analysis of 15 studies found that engaging in a PA program during pregnancy reduced the incidence of HDP (RR, 0.44 [95% CI, 0.30–0.66]) but not the incidence of preeclampsia (RR, 0.81 [95% CI, 0.59–1.11]).<sup>33</sup>
- A systematic review of 28 studies in children and adolescents concluded that reallocation of sedentary behavior to moderate- to vigorous-intensity PA was consistently associated with lower adiposity (12 of 14 studies), greater cardiorespiratory fitness (5 of 6 studies), and more favorable cardiometabolic biomarkers (3 of 5 studies) in cross-sectional studies.<sup>34</sup> Reallocation of sedentary behavior to light-intensity PA was not consistently associated with CVH outcomes in cross-sectional studies. Few studies were prospective or evaluated reallocation of sedentary behavior bouts, limiting conclusions.
- A systematic review including 26 studies and 89 405 participants investigated the relationship between PA and CAC. The review found widely varied results: 4 studies with a positive association, 6 studies with a negative association, 2 studies with a U-shaped association, and 9 studies with null or varied subgroup findings.<sup>35</sup> Although the adverse relationship between high PA and incidence of CAC was more frequently observed in large studies and

studies of athletes, the nature of the relationship between PA and CAC remained unclear.

- A meta-analysis including 7 prospective cohort studies in adults found that high compared with low PA (defined within individual study populations) was associated with a reduced risk of vascular cognitive impairment (HR, 0.68 [95% CI, 0.54–0.86]), especially among 4 studies evaluating vascular dementia (HR, 0.53 [95% CI, 0.38–0.74]).<sup>36</sup>
- In the PROPASS Consortium, among 15 253 adults, a cross-sectional compositional data analysis estimated that replacing less intense activities such as sedentary time, standing, and light-intensity PA with 4 to 12 min/d of moderate-to vigorous-intensity PA was associated with cardiometabolic health benefits.<sup>21</sup> For example, the minimum reallocation associated with a statistically significant reduction in BMI was replacing 7 min/d of sedentary behavior with moderate- to vigorous-intensity PA. In addition, replacing 4 min/d of light-intensity PA with moderate- to vigorous-intensity PA was associated with a statistically significantly lower HbA1c.

### **Primary Prevention Using Self-Reported PA and Sedentary Behavior**

- A meta-analysis including 94 cohorts and >30 million participants found that higher leisure-time PA or combinations of nonoccupational PA were associated with a lower risk of all-cause mortality (RR, 0.69 [95% CI, 0.65–0.73]) and CVD mortality (RR, 0.71 [95% CI, 0.66–0.77]) at 8.75 marginal MET-h/wk.<sup>37</sup>
- In contrast, a systematic review and meta-analysis of 31 articles indicated that occupational activity was generally not associated with CVD mortality for both males and females.<sup>38</sup> There are multiple possible explanations for the apparent paradox between leisure-time (beneficial) and occupational (not beneficial) activity and CVD and mortality, including that occupational PA may be of lower intensity but longer duration, may have static and constrained postures/activities, and may have insufficient recovery compared with leisure-time PA.<sup>39</sup>
- A cohort study of 481 688 adults from Taiwan found that, compared with mostly not sitting while at work, those who mostly sat at work had a 16% (95% CI, 11%–20%) higher risk of mortality and a 34% (95% CI, 22%–46%) higher risk of CVD over 12.85 years of follow-up.<sup>40</sup> In a further joint analysis with leisure PA, high occupational sitting remained associated with higher all-cause mortality risk in individuals with no, low, or medium levels of leisure PA. However, high occupational sitting was not associated with additional risk of CVD in the high or very high leisure PA group (accumulating ≥60 minutes of leisure PA per day).

• A meta-analysis of 7 studies found that any resistance training was associated with a lower RR of mortality (0.85 [95% CI, 0.79–0.93]), CVD (0.83 [95% CI, 0.73–0.93]), and diabetes (0.83 [95% CI, 0.77–0.89]).<sup>41</sup> Yet, a further dose-response analysis indicated a J-shaped risk curve in which the incidence of CVD and mortality was lowest with 40 to 60 min/wk of resistance training and increased to above baseline beyond 130 to 140 min/wk of resistance training. Based on this and other literature, an expert review concluded that only small doses of resistance training should be recommended and that the potential adverse effects of higher doses of resistance training on mortality and CVD should be further investigated.<sup>42</sup> This review postulated that higher doses of resistance training may result in inflammation and arterial stiffness, which could explain the elevated risk estimates with ≥2 hours of resistance training per week.

- A study from Korea of 5075 adults, with an average 8-year follow-up period during which 50.1% of the population developed hypertension, found that meeting guidelines for aerobic PA was associated with a lower hazard of incident hypertension (HR, 0.68 [95% CI, 0.62–0.74]).<sup>43</sup> Adding resistance training was not associated with a lower hazard among those not meeting aerobic PA guidelines (HR, 1.29 [95% CI, 0.85–1.97]), but individuals meeting both aerobic PA and resistance training guidelines had the lowest hazard of incident hypertension (HR, 0.61 [95% CI, 0.51–0.74]).

### **Primary Prevention Using Device-Measured PA and Sedentary Behavior**

- In 86 657 adults 40 to 79 years of age who were enrolled in the UK Biobank cohort study and followed up over 6 years, those with an accelerometer-determined chronoactivity pattern in which more relative PA was accumulated in the late morning (peaking from about 9–11 AM) had a reduced hazard of CAD (HR, 0.84 [95% CI, 0.77–0.92]), stroke (0.83 [95% CI, 0.70–0.98]), and ischemic stroke (HR, 0.79 [95% CI, 0.64–0.97]) compared with those with a more typical population chronoactivity pattern in which PA peaked from 11 AM to 5 PM.<sup>44</sup> A chronoactivity pattern with greater relative activity in the early morning (peaking from about 7–9 AM) was also associated with lower hazard of CAD (HR, 0.89 [95% CI, 0.80–0.99]) compared with the average chronoactivity pattern but was not associated with stroke.
- Also from the UK Biobank cohort study, in 81 717 adults 42 to 78 years of age, greater accelerometer-measured PA was associated with reduced relative hazard of hospitalization for 9 of the 25 most common reasons.<sup>45</sup> Among 6 cardiometabolic

conditions included, 1-SD higher PA was associated with a decreased risk of hospitalization for VTE (HR, 0.82 [95% CI, 0.75–0.90]), ischemic stroke (HR, 0.85, [95% CI, 0.76–0.95]), and diabetes (HR, 0.79 [95% CI, 0.74–0.84]) but not IHD (HR, 0.95 [95% CI, 0.90–1.00]) or AF (HR, 1.00 [95% CI, 0.92–1.07]).

- Among 16031 WHS participants ≥62 years of age, those in the highest quartile for moderate- to vigorous-intensity PA (>120 min/d) had a 38% (95% CI, 18%–54%) lower hazard for CVD compared with those in the lowest quartile (≤60 min/d).<sup>46</sup> Those in the lowest quartile for sedentary behavior (<7.4 h/d) had a 33% (95% CI, 11%–49%) lower hazard of CVD compared with those in the highest quartile (≥9.5 h/d).
- 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>47</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>48</sup> 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>49</sup>

### **Primary Prevention Using Device-Measured Steps**

- Step counting is recommended as an effective method for translating PA guidelines and monitoring PA levels because of its simplicity and the increased availability of step-counting devices.<sup>50,51</sup> A meta-analysis of 17 cohort studies and including 226889 adults found a linear, inverse relationship between steps per day and all-cause mortality (HR, 0.85 [95% CI, 0.81–0.91] per 1000-step increment) and CVD mortality (HR, 0.93 [95% CI, 0.91–0.95] per 500-step increment).<sup>52</sup> Stratified analyses revealed that benefits were similar by sex and climate groups (ie, temperate, subtropical, subpolar, and mixed zone) but also found that older adults needed fewer steps to achieve similar risk reductions compared with younger adults.
- In a harmonized meta-analysis of 15 international cohort studies that included 47 471 adults and 3013 deaths, the HR for all-cause mortality was as follows (compared with the lowest quartile of average steps per day): 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>53</sup>
- In a harmonized meta-analysis of 8 international cohort studies that included 20 152 adults and 1523 CVD events (CHD, stroke, HF), the HR for those ≥60 years of age was as follows (compared

with the lowest quartile of average steps per day): quartile 2 HR, 0.80 (95% CI, 0.69–0.93); quartile 3 HR, 0.62 (95% CI, 0.52–0.74); and quartile 4 HR, 0.51 (95% CI, 0.41–0.63).<sup>54</sup> For those <60 years of age, quartile of steps was not associated with CVD events: compared with the lowest quartile of average steps per day, quartile 2 HR, 0.79 (95% CI, 0.46–1.35); quartile 3 HR, 0.90 (95% CI, 0.64–1.25); and quartile 4 HR, 0.95 (95% CI, 0.61–1.48).

### **Secondary Prevention by PA and Sedentary Behavior**

- In a population-based study of 20 653 post-MI patients in China, moderate PA (3000–4500 MET-min/wk) and high PA (>4500 MET-min/wk) were associated with lower all-cause mortality in the year after the event (moderate PA HR, 0.59 [95% CI, 0.40–0.88]; high PA HR, 0.63 [95% CI, 0.43–0.88]) compared with insufficient PA <3000 MET-min/wk.<sup>55</sup> Beyond 1 year after MI, moderate PA was no longer protective (HR, 0.83 [95% CI, 0.66–1.05]), although high PA remained associated with reduced all-cause mortality (HR 0.69 [95% CI, 0.56–0.86]).
- In the HAPIEE cohort study, adults 45 to 72 years of age with preexisting IHD had a reduced risk of IHD mortality over a mean 10.55 years of follow-up if they engaged in moderate (middle tertile: HR, 0.54 [95% CI, 0.37–0.81]) or high (highest tertile: HR, 0.48 [95% CI, 0.31–0.74]) levels of PA compared with low PA (lowest tertile).<sup>56</sup>
- An AHA scientific statement on supervised exercise training for chronic HFpEF concluded that these patients have similar or better improvement in symptoms and exercise capacity compared with patients with HFrEF.<sup>57</sup> The statement called for more research on optimal implementation of supervised exercise training in patients with HFpEF.

### **Estimated Population-Level Benefits of Increasing PA**

- According to accelerometry data from NHANES 2003 to 2006, if US adults ≥40 years of age increased their moderate- to vigorous-intensity PA by ≈10 min/d, an estimated 110 000 deaths per year could be prevented.<sup>58</sup>
- Increasing population levels of PA could increase productivity, particularly through presenteeism, and lead to substantial economic gains.<sup>59</sup> Engaging in at least 150 minutes of moderate-intensity PA per week, as per the lower limit of the range recommended by the 2020 WHO guidelines, would lead to an increase in global GDP of 0.15%/y to 0.24%/y by 2050, worth up to US \$314 to \$446 billion per

year and US \$6.0 to \$8.6 trillion cumulatively over the 30-year projection horizon (in 2019 prices). The results vary by country because of differences in baseline levels of PA and GDP per capita.

## Global Burden

### (See Table 4-1 and Chart 4-7)

- The Global Matrix 4.0 on PA for youths 5 to 17 years of age compiles PA around the world and provides letter grades from A (best) to F (worst).<sup>60</sup> The 2022 report summarized across 57 countries and ranked global PA with a grade D, school with a grade C+, community/environment with a grade C+, active transportation with a grade C–, and sedentary behavior with a grade D+.
- A 2023 report of the Global Matrix of Para Report Cards on Physical Activity for Children and Adolescents With Disabilities included 14 countries or jurisdictions and evaluated 10 indicators (overall PA, organized sport, active play, active transport, physical fitness, sedentary behavior, family and peers, schools, community and environment, and government) to produce Para Report Cards. The highest average ranking was for government with a grade of C+ and the lowest average rankings were for overall PA, organized sport and PA, and sedentary behavior with grades of D–.<sup>61</sup> Greater participation in Para Report Cards on PA by more countries in future reports is strongly encouraged.
- The Global Observatory for Physical Activity monitors trends in PA surveillance, policy, and research in 164 countries.<sup>62</sup> Compared with 2015, progress by 2020 in all 3 areas was modest. It was estimated

that 88.2% of the world's population lives in countries where PA capacity could be improved.

- In an analysis including 168 countries, the prevalence of inactivity was found to be highest in high-income countries (36.8% [95% CI, 35.0%–38.0%]), followed by middle-income countries (26.0% [95% CI, 22.6%–31.8%]) and then low-income countries (16.2% [95% CI, 14.2%–17.9%]). Globally, the PAR associated with inactivity for all-cause mortality rate was 9.3%, 6.8%, and 4.3% in high-, middle-, and low-income countries, respectively, with similar estimates for CVD mortality. The PAR for cardiovascular events such as CHD and stroke ranged from 3.0% in low-income countries to 6.5% in high-income countries.<sup>63</sup>
- An analysis of global trends from 1990 to 2019 found that the estimated age-standardized CVD mortality rate attributable to low PA has decreased at a rate of 1.44% per year (95% CI, –1.50% to –1.38%). Yet, age-standardized mortality rates from CVD were consistently higher than the global average in Northern Africa and the Middle East.<sup>64</sup> Furthermore, trends over time indicated that rates of age-standardized mortality from CVD and type 2 diabetes attributable to low PA were increasing more quickly among younger adults 25 to 44 years of age in higher-income countries.
- In 2021, based on 204 countries and territories, mortality rates attributable to low PA among regions were highest for southern sub-Saharan Africa, North Africa and the Middle East, and Oceania. Mortality rates were lowest for high-income Asia Pacific and southern Latin America (Chart 4-7). Low PA caused an estimated 0.66 (95% UI, 0.28–1.06) million total deaths in 2021, an increase of 91.86% (95% UI, 73.49%–112.26%) since 1990 (Table 4-1).<sup>65</sup>

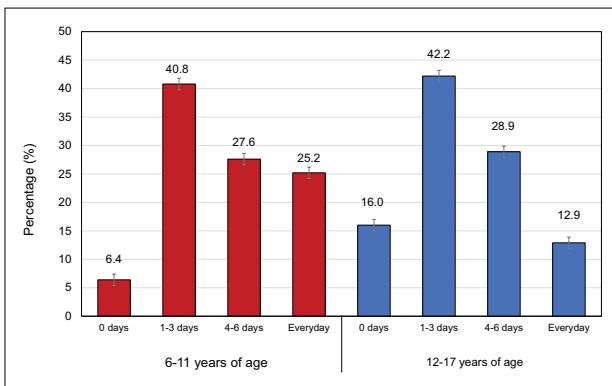
**Table 4-1. Deaths Caused by Low PA Worldwide, by Sex, 2021**

	Deaths		
	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total number (millions), 2021	0.66 (0.28 to 1.06)	0.25 (0.11 to 0.40)	0.41 (0.17 to 0.68)
Percent change (%) in total number, 1990–2021	91.86 (73.49 to 112.26)	112.24 (79.78 to 149.62)	81.31 (60.35 to 107.50)
Percent change (%) in total number, 2010–2021	30.74 (21.64 to 40.52)	36.22 (21.73 to 53.42)	27.63 (18.11 to 39.87)
Rate per 100 000, age standardized, 2021	7.99 (3.38 to 12.98)	6.96 (3.05 to 11.47)	8.74 (3.63 to 14.46)
Percent change (%) in rate, age standardized, 1990–2021	–23.06 (–31.33 to –11.40)	–15.46 (–28.57 to 0.61)	–25.38 (–34.33 to –13.29)
Percent change (%) in rate, age standardized, 2010–2021	–7.49 (–13.92 to –0.34)	–4.50 (–15.26 to 8.42)	–8.67 (–15.42 to 0.25)
PAF (%), all ages, 2021	0.97 (0.40 to 1.54)	0.66 (0.28 to 1.05)	1.36 (0.56 to 2.18)
Percent change (%) in PAF, all ages, 1990–2021	30.28 (18.46 to 44.98)	39.68 (21.30 to 63.74)	27.82 (13.76 to 45.40)
Percent change (%) in PAF, all ages, 2010–2021	2.20 (–4.06 to 8.82)	4.96 (–5.12 to 16.57)	1.54 (–5.02 to 9.31)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; PA, physical activity; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>65</sup>

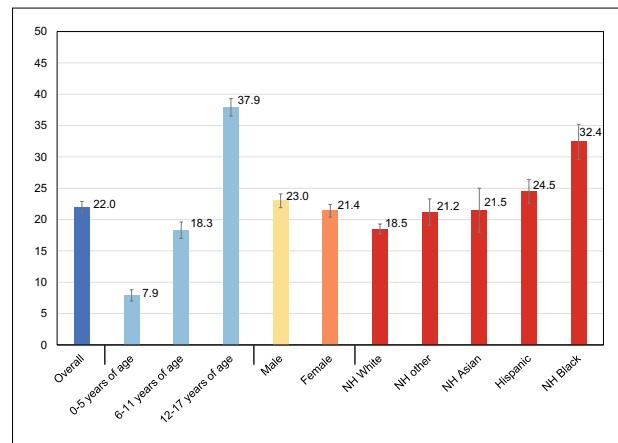


**Chart 4-1. Percentage of US youths 6 to 11 and 12 to 17 years of age who were physically active for at least 60 minutes from 0 to 7 d/wk, 2022.**

Error bars represent 95% CIs.

From the 2018 Physical Activity Guidelines for Americans, the aerobic guidelines recommend that youths 6 to 17 years of age should engage in at least 60 minutes of physical activity each day (7 d/wk).

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

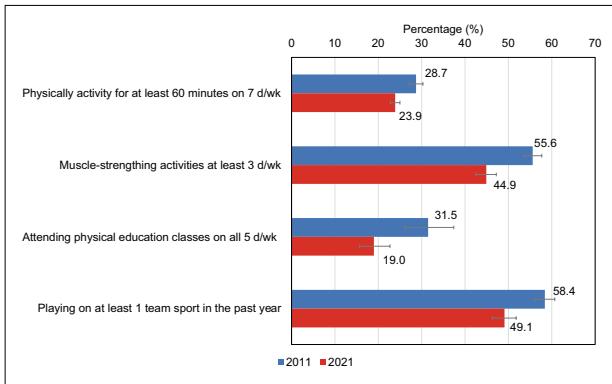


**Chart 4-3. Percentage of US children 0 to 17 years of age who spent ≥4 h/d in front of a television, computer, cell phone, or other electronic device on most weekdays (not including schoolwork), overall and by age group, sex, and race and ethnicity, 2022.**

Error bars represent 95% CIs.

NH indicates non-Hispanic.

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

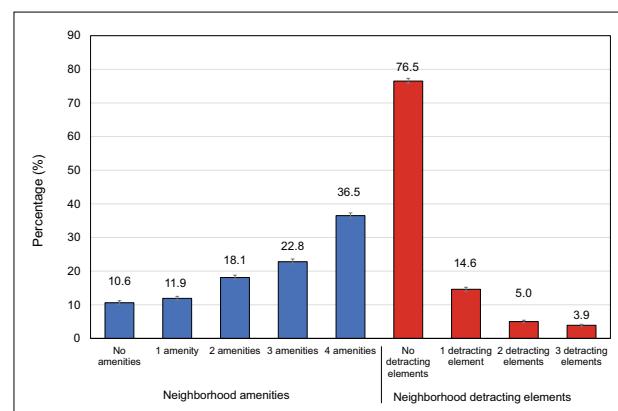


**Chart 4-2. Ten-year changes in the percentage of US youths in grades 9 through 12 who met aerobic PA and muscle-strengthening recommendations, attended physical education classes 5 d/wk, and played on a sports team (2011–2021).**

PA indicates physical activity.

From the 2018 Physical Activity Guidelines for Americans, the guidelines recommend that youths aged 6-17 years should engage in at least 60 min/d of PA and muscle-strengthening activities on 3 or more d/wk.

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

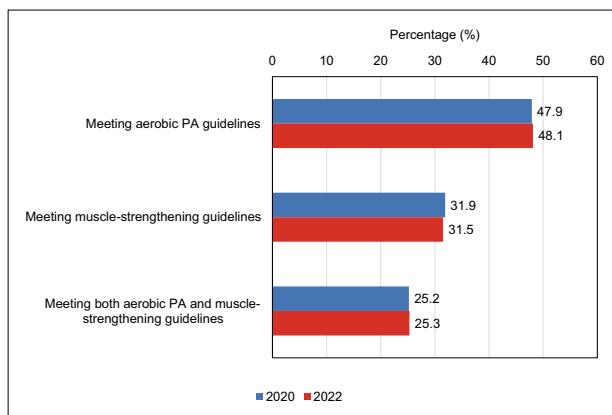


**Chart 4-4. Percentage of US youths 0 to 17 years of age living in neighborhoods with health-promoting amenities and detracting elements, 2022.**

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.

Error bars represent 95% CIs.

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

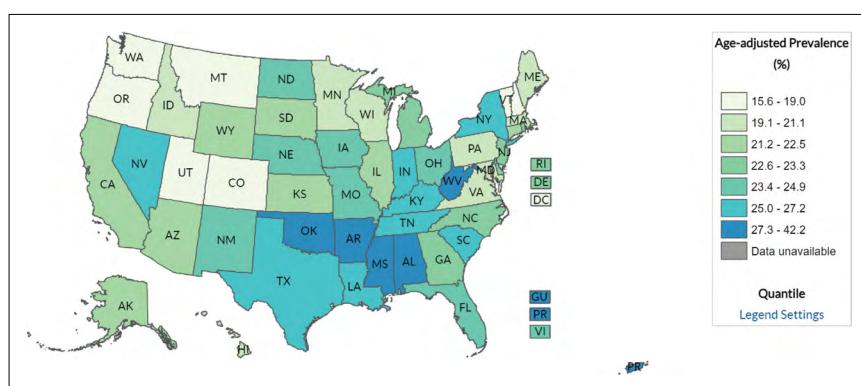


**Chart 4-5. Percentage meeting guidelines for aerobic PA, muscle strengthening, or both among US adults  $\geq 18$  years of age in 2020 and 2022.**

From the 2018 Physical Activity Guidelines for Americans, the aerobic guidelines recommend engaging in moderate leisure-time PA for  $\geq 150$  min/wk, vigorous activity for  $\geq 75$  min/wk, or an equivalent combination. The muscle-strengthening guidelines recommend activities of moderate or greater intensity involving all major muscle groups on  $\geq 2$  d/wk. The updated prevalence reflects the best, up-to-date estimate from the Centers for Disease Control and Prevention's ongoing PA surveillance efforts for Healthy People 2030.

PA indicates physical activity.

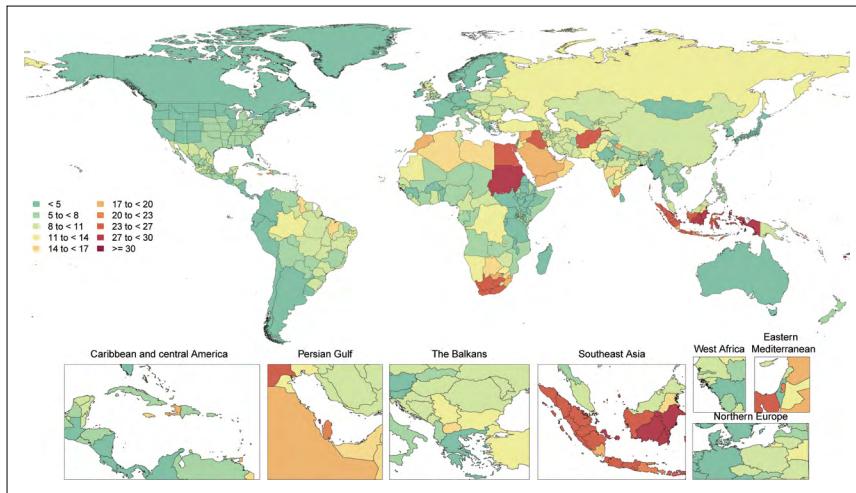
Source: Data derived from Healthy People 2030.<sup>17</sup>



**Chart 4-6. Percentage of self-reported physical inactivity among US adults  $\geq 18$  years of age, by state and territory, 2022.**

Age-adjusted prevalence of reporting no participation in any PA in the past month. PA indicates physical activity.

Source: Reprinted from Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System.<sup>20</sup>



**Chart 4-7. Age-standardized global mortality rates attributable to low PA per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and PA, physical activity.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>65</sup>

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## 5. NUTRITION

See Tables 5-1 through 5-5 and Chart 5-1

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This chapter highlights national dietary intake and habits with a focus on key foods, nutrients, diet patterns, food systems, 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 equitably improve dietary habits in relation to CVH.

### Prevalence and Trends in the AHA's Life's Essential 8's Healthy Diet Metrics

(See Tables 5-1 through 5-3)

On June 29, 2022, the AHA debuted Life's Essential 8 in a presidential advisory, an updated algorithm for quantifying CVH.<sup>1</sup> This update was in response to extensive evidence giving insights into the strengths and limitations of the original approach to quantifying CVH (Life's Simple 7). In AHA's 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 2022 presidential advisory to the AHA acknowledges disparities by personal and environmental factors and the need for innovation in systems and structures to correct current deleterious impacts on health.<sup>1</sup> A call for action focused on the food systems is made in the AHA science advisory covering favorable innovations to create healthy and

sustainable outcomes at every level of our very complex food system.<sup>2</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>3</sup> representing 201 728 000 adults, and 74 435 000 children.

This cross-sectional analysis of data from the NHANES 2013 to 2018 survey cycles revealed that 1 in 5 people in the United States has a CVH score indicative of optimal heart health and that there are differences across age and sociodemographic groups.<sup>3</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 (females, 67.0; males, 62.5), and racial and ethnic group (range, 59.7–68.5).<sup>3</sup> Diet was among the 4 metrics with the lowest scores; ranging from 23.8 to 47.7 for adults depending on the demographic group. 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

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>4</sup> They concluded that the core elements of a healthy dietary pattern are (1) vegetables of all types; (2) fruits, especially whole fruits; (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.

#### Adults

(See Table 5-4)

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) serving/d.

The 2025 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 2025. 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 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 ≥4 servings/wk.
- Consumption of processed meats was lowest among Mexican American females (1.0 servings/wk) and highest among NH White males (≈2.5 servings/wk). Between 59% (NH White males) and 87% (Mexican American females) of adults consumed ≤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 (≈10 servings/wk). The proportions of adults meeting guidelines of <36 oz/wk were ≈61% for NH White adults, 48% for Mexican American adults, and 41% for NH Black adults.
- Consumption of sweets and bakery desserts ranged from 4.5 servings/wk among Mexican American males to 3.3 servings/wk among NH Black males.
- 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 ≤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 ≥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/d.

- 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 ≥2.5 ranged from 11.2% in NH White males to 40.6% in NH Black females.
- Only ≈5% of NH White adults, ≈4% of Black adults, and ≈15% of Mexican American adults consumed ≥28 g dietary fiber/d.
- The average daily sodium consumption for Americans ≥1 year of age is >3400 mg, and the top 10 food categories accounted for 40% of sodium consumed.<sup>5</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>6</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>7</sup>:

- Whole grain consumption was low with an estimated average intake of 0.95 serving/d (95% CI, 0.88–1.03) among US youths 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 youths and those of other races, including multiracial youths, had the highest intake of whole fruit, followed by NH White youths, other Hispanic youths, Mexican American youths, and NH Black youths. 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 youths had the lowest intake of fruit juice, followed by NH Asian youths and youths of other races, including multiracial youths, Mexican American youths, other Hispanic youths, and NH Black youths.
- 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 youths had the highest intake of fish and shellfish, followed by NH Asian youths and youths of other races, including multiracial youths, NH Black youths, Mexican American youths, and NH White youths.
- 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 youths had the highest intake of nuts and seeds, followed by NH Asian youths and youths of other races, including multiracial youths, other Hispanic youths, NH Black youths, and Mexican American youths. The consumption pattern of nuts and seeds increased with higher parental education and parental income.
- Consumption of unprocessed red meats was 0.31 serving/d (95% CI, 0.27–0.34) with intakes inversely related to parental educational attainment.
- 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 youths had the highest intake of processed meat, followed by NH Black youths, Mexican American youths, NH Asian youths, and those of other races, including multiracial youths and other Hispanic youths.
- Consumption of SSBs was 1.0 serving/d (95% CI, 0.89–1.11) on average among US youths. The consumption pattern of SSBs increased with age. NH Black youths had the highest intake of SSBs, followed by Mexican American youths, NH White youths, other Hispanic youths, NH Asian youths, and those of other races, including multiracial youths.
- Consumption of sweets and bakery desserts contributed to an average of 6.07% of calories (95% CI, 5.55%–6.60%) among US youths 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 youths and those of other races, including multiracial youths, had the highest intake of EPA and DHA, followed by other Hispanic youths, Mexican American youths, NH White youths, and NH Black youths.
- Consumption of SFAs was ≈12.1% of calories (95% CI, 11.8%–12.4%) among US youths. Consumption of dietary cholesterol was 254 mg/d (95% CI, 244–264) with NH White youths having the lowest intake (238 mg/d [95% CI, 226–250]) and Mexican American youths 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 youths 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 youths. The consumption pattern increased with age. NH Asian youths and those of other races, including multiracial youths, had the highest intake of sodium, followed by NH Black youths, Mexican American youths, and NH White youths.

## Secular Trends

The Dietary Guidelines for Americans are published every 5 years, and adherence to them is measured with the HEI.<sup>4</sup>

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.

Trends in diet quality among youths in the United States were characterized in a study using 9 NHANES data cycles.<sup>7</sup> The primary outcomes were the survey-weighted, energy-adjusted mean consumption of dietary components and proportion meeting targets of the AHA 2020 continuous diet score (range, 0–50; based on total fruits and vegetables, whole grains, fish and shellfish, SSBs, and sodium). Other outcomes were the AHA secondary score (range, 0–80; adding nuts, seeds, and legumes; processed meat; and saturated fat) and HEI-2015 score (range, 0–100). 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>7</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). Based on 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%).

Based on 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 youths 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 youths 2 to 5 years of age, 49.2 (95% CI, 47.9–50.6) for youths 6 to 11 years of age, and 47.4 (95% CI, 46.0–48.8) for youths 12 to 19 years of age.

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> Relative to the other food sources, schools provided the best mean diet quality. More specifically, schools had the largest improvement in diet quality, with the percentage of the population having poor diet quality decreasing from 55.6% to 24.4% ( $P_{\text{trend}} < 0.001$ ).

### Trends in Dietary Supplement Intake

Use of dietary supplements is common in the United States among both adults and children. Data from NHANES 2007 to 2018 revealed that dietary supplement use increased from 50% in 2007 to 56% in 2018 in individuals  $\geq$ 1 year of age.<sup>10</sup> The use of micronutrient-containing supplements increased from 46% in 2007 to 49% in 2018; use of single-nutrient supplements also increased ( $P < 0.001$ ). In children 1 to 18 years of age, the use of dietary supplements in any form remained stable (38%) over this time frame. However, use of micronutrient-containing supplements increased in children who experience food insecurity, from 24% to 31% ( $P = 0.03$ ). In adults, use of dietary supplements in any form increased (54% to 61%), and use of micronutrient-containing supplements increased (49% to 54%). Dietary supplement use increased, especially in those who identify as male, NH Black, Hispanic, and low income.

### Social Determinants of Dietary Intake/Health Equity

- Household food insecurity, child diet quality, and child weight status at 5 years of age are associated

with duration of participation in WIC.<sup>11</sup> Longer duration of participation in WIC was associated with lower odds of household food insecurity (OR, 0.69 [95% CI, 0.51–0.95]), higher total dietary quality as measured by the HEI-2015 ( $\beta$ , 0.73 [95% CI, 0.21–1.25]), and higher obesity odds (OR, 1.20 [95% CI, 1.05–1.37]) in multivariable-adjusted regression models.

- 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 CVH.<sup>12</sup>
- An analysis of the 4 major outlets where food is obtained (stores, quick-serve restaurants, full-service restaurants, and schools) using 24-hour dietary recall data from 8 cycles of NHANES showed that Americans are not consuming foods that align with the Dietary Guidelines for Americans.<sup>13</sup> The HEI-2015 score for schools (65/100 points) and stores (62/100 points) was significantly higher than those for full-service (51/100 points) and quick-service (39/100 points) restaurants ( $P < 0.0001$ ).

### Genetics/Family History

- Genetic factors may contribute to food preferences and liking and modulate the association between dietary components and adverse CVH outcomes.<sup>14–16</sup> Nutrigenetics may also contribute to variation in the metabolism of specific dietary components such as carbohydrates, amino acids, and fatty acids across individuals or ethnic and racial groups.<sup>17</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>18,19</sup>
- Ancillary studies from the POUNDS Lost trial, a 2-year randomized clinical trial including 811 overweight or obese adults examining the role of dietary interventions in weight loss, demonstrated that the weight loss and changes in BP, cholesterol, and blood glucose in response to dietary interventions were modified by DNA methylation levels at *NFATC2IP*, *CPT1A*, *TXNIP*, and *LINC00319*.<sup>20</sup>
- However, a randomized trial of 609 participants with overweight/obesity and without diabetes demonstrated that, compared with 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>21</sup>
- A comprehensive GWAS of 85 single-food intake and 85 dietary patterns derived from food

frequency questionnaires including 44210 individuals identified 814 loci associated with single food intake and 136 loci associated with dietary patterns.<sup>22</sup> Furthermore, 84.1% of dietary habits assessed in the GWAS were found to be significantly heritable.<sup>22</sup>

- A recent GWAS identified 26 loci associated with dietary carbohydrate, fat, and protein intake.<sup>16</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.
- The interactions between a GRS composed of 97 BMI-associated variants and 3 diet-quality scores were examined in a pooled analysis of 30904 participants from the Nurses' Health Study, the HPFS, and the Women's Genome Health Study. Higher diet quality was found to attenuate the association between GRS and BMI ( $P$  for interaction terms  $<0.005$  for AHEI-2010 score, Alternative Mediterranean Diet score, and DASH diet score).<sup>23</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>24</sup>

## Impact on Mortality

- Nationally representative data from 37233 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, 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>25</sup>
- Higher intakes of fruit and vegetables are associated with lower mortality. Specifically, data from 66719 females from the Nurses' Health Study (1984–2014) and 42016 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>26</sup>

- NHANES III (1988–1994) data from 3733 adults (20–90 years of age) with overweight/obesity ( $BMI \geq 25 \text{ kg/m}^2$ ) were analyzed to assess the relationship between the DII score and mortality.<sup>27</sup> DII scores of metabolically unhealthy individuals with obesity/overweight were associated with increased mortality risk ( $HR_{\text{tertile 3 versus tertile 1}}^{*}$ , 1.44 [95% CI, 1.11–1.86];  $P_{\text{trend}}=0.008$ ;  $HR_{\text{1-SD increase}}^{*}$ , 1.08 [95% CI, 0.99–1.18]) and, more specifically, CVD-related mortality ( $HR_{\text{T3 versus T1}}^{*}$ , 3.29 [95% CI, 2.01–5.37];  $P_{\text{trend}}<0.001$ ;  $HR_{\text{1-SD increase}}^{*}$ , 1.40 [95% CI, 1.18–1.66]). These associations were not observed among adults with metabolically healthy obesity, and no cancer mortality risk was observed for either metabolically unhealthy individuals with obesity/overweight or metabolically healthy individuals with obesity. The SUN study, which began in 1999 (N=18566), and the PREDIMED study, which began in 2003 in Spain (N=6790), similarly analyzed the DII score in relation to mortality. Significant associations were found in differences between the highest and lowest quartiles of the DII score and mortality in both SUN (HR, 1.85 [95% CI, 1.15–2.98];  $P_{\text{trend}}=0.004$ ) and PREDIMED (HR, 1.42 [95% CI, 1.00–2.02];  $P_{\text{trend}}=0.009$ ).<sup>28</sup>
- Several studies examined the relationship between sugar intake and all-cause and cause-specific mortality. A 6-year cohort study of 13440 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>29</sup> In 2 Swedish studies (MDCS, N=24272; and NSHDS, N=24475), both higher consumption (>20% energy intake: HR, 1.30 [95% CI, 1.12–1.51]) and lower consumption (<5% energy intake: HR, 1.23 [95% CI, 1.11–1.35]) were associated with higher mortality risk.<sup>30</sup>
- A systematic review of 18 cohort studies (N=251497) examined the relationship of glycemic index and glycemic load with risk of all-cause mortality and CVD and found no associations. However, a positive association was found with all-cause mortality among females with the highest (versus lowest) glycemic index (RR, 1.17 [95% CI, 1.02–1.35]).<sup>31</sup> Using data from 137851 participants between 35 and 70 years of age living in high-, middle-, and low-income countries across 5 continents with a median follow-up of 9.5 years, the international PURE study reported that a high glycemic index was associated with an increased risk of a major cardiovascular event or death among participants with (HR, 1.51 [95% CI, 1.25–1.82]) and

- without (HR, 1.21 [95% CI, 1.11–1.34]) preexisting CVD at baseline.<sup>32</sup>
- In an assessment of the relationship between dairy intake and mortality, data from 3 large prospective cohort studies with 217 755 US adults showed a dose-response relationship in which 2 daily servings of dairy were associated with the lowest CVD mortality and higher intake was linked to higher mortality, especially cancer mortality. Compared with other subtypes of dairy (eg, skim/low-fat milk, cheese, yogurt, ice cream/sherbet), whole milk (and additional 0.5 serving/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 compared with nonconsumers.
  - A European study examined the relationship between dietary protein and protein sources and mortality among 2641 Finnish males. Higher meat intake (HR, 1.23 [95% CI, 1.04–1.47]) and higher ratio of animal to plant protein (HR, 1.23 [95% CI, 1.02–1.49]) were associated with higher mortality. This relationship was more pronounced among those with a history of CVD, cancer, and type 2 diabetes.<sup>33–35</sup> In addition, several meta-analyses of prospective cohort studies have consistently reported that higher plant protein intake is inversely associated with total and CVD mortality, lending support for dietary recommendations to replace foods high in animal protein with plant protein sources.<sup>36–38</sup>
  - The association between nut and peanut butter consumption and mortality has also been assessed. In a large prospective cohort study of 566 398 US adults (50–71 years of age at baseline) with a median follow-up of 15.5 years, nut consumption was inversely related to mortality (HR, 0.78 [95% CI, 0.76–0.81];  $P\leq 0.001$ ) and was associated with reductions in cancer, CVD, and infectious, respiratory, and liver and renal disease mortality (but not 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>39</sup>
  - Moderate egg consumption and all-cause and cause-specific<sup>40</sup> mortality were investigated in a large cohort of 40 621 adults (29–69 years of age) in the EPIC-Spain prospective cohort study across 18 years. Mean egg consumption was 22 g/d (SD,

15.8 g/d) in females and 30.9 g/d (SD, 23.1 g/d) in males, and no association was found between the highest and lowest quartiles of egg consumption and all-cause mortality (HR, 1.01 [95% CI, 0.91–1.11];  $P=0.96$ ) or cancer and CVD mortality. However, egg consumption appears to be inversely associated with deaths resulting from other causes (HR, 0.76 [95% CI, 0.63–0.93];  $P=0.003$ ), specifically nervous system-related deaths (HR, 0.59 [95% CI, 0.35–1.00];  $P=0.036$ ).<sup>40</sup>

- The association between dietary choline and overall- and cause-specific mortality was examined in a large, nationally representative study of 20 325 US adults (mean, 47.4 years of age). Higher choline consumption was found to be associated with worse lipid profiles, poorer glycemic control, and lower CRP levels (all comparisons,  $P<0.001$ ). Those with the highest compared with lowest consumption had increased risk of total (RR, 1.23 [95% CI, 1.09–1.38]), stroke (RR, 1.30 [95% CI, 1.02–1.66]), and CVD (RR, 1.33 [95% CI, 1.19–1.48]) mortality (all comparisons  $P<0.001$ ).<sup>41</sup> A subsequent meta-analysis confirmed these results and found choline to be linked to higher mortality risk (RR, 1.12 [95% CI, 1.08–1.17];  $P=2.9$ ) and CVD mortality risk (RR, 1.28 [95% CI, 1.17–1.39];  $P=9.6$ ).<sup>41</sup> Major contributors of choline to the American diet are meat, poultry, dairy foods, pasta, rice, and egg-based dishes.<sup>42</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>43</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>43</sup> without changes in body weight.<sup>44</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 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>45</sup>

- In a meta-analysis of 20 prospective cohort studies, the RR for each 4-point increment of the Mediterranean diet score was 0.84 (95% CI, 0.81–0.88) for unspecified stroke, 0.86 (95% CI, 0.81–0.91) for ischemic stroke, and 0.83 (95% CI, 0.74–0.93) for hemorrhagic stroke.<sup>46</sup>
- In another systematic review, a meta-analysis of 3 RCTs showed a beneficial effect of the Mediterranean diet on total CVD incidence (RR, 0.62 [95% CI, 0.50–0.78]) and total MI incidence (RR, 0.65 [95% CI, 0.49–0.88]).<sup>47</sup>
- Another meta-analysis of 38 prospective cohort studies showed that the RR for the highest versus the lowest categories of Mediterranean diet adherence was 0.79 (95% CI, 0.77–0.82) for total CVD mortality, 0.73 (95% CI, 0.62–0.86) for CHD incidence, 0.83 (95% CI, 0.75–0.92) for CHD mortality, 0.80 (95% CI, 0.71–0.90) for stroke incidence, 0.87 (95% CI, 0.80–0.96) for stroke mortality, and 0.73 (95% CI, 0.61–0.88) for MI incidence.<sup>47</sup>
- 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>48</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>48</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>49</sup> Support for BP effects of a healthy pattern with reduced sodium was seen in a dose-response meta-analysis of experimental studies including 85 clinical trials in participants with hypertension, without hypertension, or a combination. Analyses showed a linear relationship between sodium intake and reduction in SBP and DBP across the entire range of dietary sodium exposure (0.4–7.6 g/d).<sup>50</sup> The difference in 24-hour sodium excretion that was achieved between the intervention and control groups was equivalent to 0.1 to 7.1 g sodium/d with a median difference of 1.8 g sodium/d.<sup>50</sup> Over the range of sodium exposure, the overall BP difference was >15 mmHg for SBP and ≈10 mmHg for DBP. Linear regression analyses resulted in a lower mean SBP of 5.6 mmHg (95% CI, −4.52 to −6.6) and a lower mean DBP of 2.3 mmHg (95% CI, −1.7 to −3.0) for every 100–mmol/d reduction in urinary sodium excretion.
- 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: The 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 pescatarians. This association remained after adjustment for BMI among the lacto-ovo vegetarians.<sup>51</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>52</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>53</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>54</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>55</sup>

### Fats and Carbohydrates

- In a randomized trial of 609 participants without diabetes with a BMI of 28 to 40 kg/m<sup>2</sup> that compared the effects of healthy low-fat and healthy low-carbohydrate weight loss diets, weight loss at 12 months did not differ between groups.<sup>21</sup> A meta-analysis of 12 randomized studies confirmed the benefit of consuming low-carbohydrate healthy diets for multiple CVD risk factors, although the effects appear modest in general and the sustainability is uncertain.<sup>56</sup> For body weight, the change was −1.58 kg (95% CI, −1.58 to −0.75); for <6 months of intervention, this change was −1.14 kg

(95% CI, −1.65 to −0.63); and for 6 to 11 months of intervention, the change was −1.73 kg (95% CI, −2.7 to −0.76). For triglycerides, the change was −0.15 mmol/L (95% CI, −0.23 to −0.07). However, interventions that lasted <6 months were associated with a decrease of −0.23 mmol/L (95% CI, −0.32 to −0.15), whereas those low-carbohydrate interventions that lasted 12 to 23 months were associated with a decrease of −0.17 mmol/L (95% CI, −0.32 to −0.01). There were modest changes in plasma LDL-C of 0.11 mmol/L (95% CI, 0.02–0.19); SBP changed −1.41 mmHg (95% CI, −2.26 to −0.56); and DBP changed −1.71 mmHg (95% CI, −2.36 to −1.06). The change in plasma HDL-C levels was 0.1 mmHg (95% CI, 0.08–0.12); and the change in serum TC was 0.13 mmol/L (95% CI, 0.08–0.19). There was a nonsignificant change in fasting blood glucose level of 0.03 mmol/L (95% CI, −0.05 to 0.12).

- 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 intake (HR, 0.94 [95% CI, 0.89–0.99]) 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>57</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 relationship 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>58</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>59</sup>
- In the WHI RCT (N=48835), a 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>60</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>61</sup>

- In a study using NHANES 2007 to 2014 data (N=18 434 participants), ORs for newly diagnosed hypertension comparing dietary intakes from the highest and lowest tertiles were 0.60 (95% CI, 0.50–0.73) for 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>62</sup>
- In a prospective study of 3042 CVD-free adults followed up for a mean of 8.4 years, the consumption of olive oil exclusively (no other fats/oils) 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>63</sup>
- 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.<sup>64</sup> The same meta-analysis also reported increased risk of type 2 diabetes with higher glycemic index or glycemic load in US and Asian studies.
- Gut microbiota is associated with the risk of obesity, type 2 diabetes, and many other cardiometabolic diseases. In a 6-month randomized controlled feeding trial of 217 healthy young adults with BMI <28 kg/m<sup>2</sup>, the high-fat diet (fat, 40% energy) had overall unfavorable effects on gut microbiota: increased *Alistipes* ( $P=0.04$ ) and *Bacteroides* ( $P<0.001$ ) and decreased *Faecalibacterium* ( $P=0.04$ ). The low-fat diet (fat, 20% energy) appeared to have beneficial effects on gut microbiota: increased  $\alpha$ -diversity assessed by the Shannon index ( $P=0.03$ ) and increased abundance of *Blautia* ( $P=0.007$ ) and *Faecalibacterium* ( $P=0.04$ ).<sup>65</sup>

### 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 (RR<sub>CHD</sub>, 0.95 [95% CI, 0.92–0.98]; RR<sub>HP</sub>, 0.96 [95% CI, 0.95–0.97]), vegetables and fruits (RR<sub>CHD</sub>, 0.97 [95% CI, 0.96–0.99]

and 0.94 [95% CI, 0.90–0.97]; RR<sub>stroke</sub>, 0.92 [95% CI, 0.86–0.98] and 0.90 [95% CI, 0.84–0.97]), nuts (RR<sub>CHD</sub>, 0.67 [95% CI, 0.43–1.05]), and fish (RR<sub>CHD</sub>, 0.88 [95% CI, 0.79–0.99]; RR<sub>stroke</sub>, 0.86 [95% CI, 0.75–0.99]; RR<sub>HP</sub>, 0.80 [95% CI, 0.67–0.95]).<sup>66</sup> In contrast, the risk of these conditions was positively associated with consumption of egg (RR<sub>HP</sub>, 1.16 [95% CI, 1.03–1.31]), red meat (RR<sub>CHD</sub>, 1.15 [95% CI, 1.08–1.23]; RR<sub>stroke</sub>, 1.12 [95% CI, 1.06–1.17]; RR<sub>HP</sub>, 1.08 [95% CI, 1.02–1.14]), processed meat (RR<sub>CHD</sub>, 1.27 [95% CI, 1.09–1.49]; RR<sub>stroke</sub>, 1.17 [95% CI, 1.02–1.34]; RR<sub>HP</sub>, 1.12 [95% CI, 1.05–1.19]), and SSBs (RR<sub>CHD</sub>, 1.17 [95% CI, 1.11–1.23]; RR<sub>stroke</sub>, 1.07 [95% CI, 1.02–1.12]; RR<sub>HP</sub>, 1.08 [95% CI, 1.05–1.12]).

- 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 of 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>67</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>68</sup>
- In a meta-analysis of 22 RCTs, whole grain oats improved TC (SMD, 0.54 [95% CI, −0.95 to −0.12]) and LDL-C (SMD, 0.57 [95% CI, −0.84 to −0.31]), whole grain rice improved triglycerides (SMD, 0.22 [95% CI, −0.44 to −0.01]), and whole grains of all types improved HbA1c (SMD, −0.33 [95% CI, −0.61 to −0.04]) and CRP (SMD, −0.22 [95% CI, −0.44 to −0.00]).<sup>69</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>70</sup>
- A meta-analysis reported a 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>71</sup>
- An analysis of data from 6 prospective cohort studies in the United States in which baseline data were collected from 1985 to 2002 showed that higher intake of processed meat (aHR, 1.07 [95% CI, 1.04–1.11]), unprocessed red meat (aHR, 1.03 [95% CI, 1.01–1.06]), and poultry (aHR, 1.04 [95% CI, 1.01–1.06]), but not fish, was significantly associated with an increased risk of incident CVD.<sup>72</sup>

Higher intake of processed meat (aHR, 1.03 [95% CI, 1.02–1.05]) and unprocessed red meat (aHR, 1.03 [95% CI, 1.01–1.05]), but not poultry or fish, was significantly associated with an increased risk of all-cause mortality.

- In a network meta-analysis of RCTs of walnuts, pistachios, hazelnuts, cashews, and almonds on typical lipid profiles, the pistachio-enriched diets compared with other nut-enriched diets lowered triglycerides, LDL-C, and TC.<sup>73</sup>
- An umbrella review of 41 meta-analyses with 45 unique health outcomes concluded that milk consumption was more beneficial than harmful; for example, in dose-response analyses, an increment of 200 mL ( $\approx$ 1 cup) milk intake per day was associated with a lower risk of common cardiometabolic diseases such as CVD, stroke, hypertension, type 2 diabetes, MetS, and obesity.<sup>74</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 (OR, 0.87 [95% CI, 0.80–0.94]) and yogurt (OR, 0.78 [95% CI, 0.67–0.89]).<sup>75</sup>
- In a crossover RCT (N=25 individuals with normocholesterolemia and 27 with moderate hypercholesterolemia), 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>76</sup>
- In a cross-sectional study of 12 285 adults, for males, consumption of >30 g/d alcohol 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>77</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>78</sup> In females, consumption of 10.1 to 15.0 g/d alcohol was associated only with a higher risk of elevated blood glucose (OR, 1.65 [95% CI, 1.14–2.38]) compared with nondrinking.<sup>77</sup> Compared with nondrinkers, consumption of 0.1 to 10.0 g/d alcohol 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>78</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 SBP/DBP ≤131/78 mmHg: 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>79</sup> The effects of sodium reduction on BP appear to be stronger in individuals who are older, are Black, and have hypertension.<sup>80</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>81</sup>
- In a meta-analysis of 133 RCTs with 12 197 participants, interventions with reduced sodium versus usual sodium resulted in a mean reduction of 130 mmol (95% CI, 115–145) in 24-hour urinary sodium, 4.26 mmHg (95% CI, 3.62–4.89) in SBP, and 2.07 mmHg (95% CI, 1.67–2.48) in DBP.<sup>82</sup> 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 who are not White, and those with higher baseline SBP levels.
- A meta-analysis of 20 studies including a total of 616 905 adults showed that individuals with high sodium intake had a higher adjusted risk of CVD compared with individuals with low sodium intake (rate ratio, 1.19 [95% CI, 1.08–1.30]).<sup>83</sup> For every 1-g increase in dietary sodium intake, the risk of CVD increased 6%.
- In a secondary analysis of the PREMIER trial, changes in phosphorus intake were not significantly associated with changes in BP. Phosphorus type (plant, animal, or added) significantly modified this association, with only added phosphorus associated with increases in SBP (mean coefficient, 1.24 mmHg/100 mg [95% CI, 0.36–2.12]) and DBP (0.83 mmHg/100 mg [95% CI, 0.22–1.44]). An increase in urinary phosphorus excretion was significantly associated with an increase in DBP (0.14 mmHg/100 mg [95% CI, 0.01–0.28]).<sup>84</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>85</sup>

### Dietary Supplements

- 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>86</sup>
- A meta-analysis of 38 RCTs of omega-3 fatty acids, stratified by EPA monotherapy and EPA+DHA therapy, with 149 051 participants showed that omega-3 fatty acids reduced cardiovascular mortality and improved cardiovascular outcomes.<sup>87</sup> EPA monotherapy was associated with more cardiovascular risk reduction than with EPA+DHA. Omega-3 fatty acids were associated with reducing cardiovascular mortality (RR, 0.93 [95% CI, 0.88–0.98];  $P=0.01$ ), nonfatal MI (RR, 0.87 [95% CI, 0.81–0.93];  $P=0.0001$ ), CHD events (RR, 0.91 [95% CI, 0.87–0.96];  $P=0.0002$ ), MACEs (RR, 0.95 [95% CI, 0.92–0.98];  $P=0.002$ ), and revascularization (RR, 0.91 [95% CI, 0.87–0.95];  $P=0.0001$ ). There were also higher RR reductions with EPA monotherapy (0.82 [95% CI, 0.68–0.99]) than with EPA+DHA (0.94 [95% CI, 0.89–0.99]) for cardiovascular mortality, nonfatal MI (EPA, 0.72 [95% CI, 0.62–0.84]; EPA+DHA, 0.92 [95% CI, 0.85–1.00]), CHD events (EPA, 0.73 [95% CI, 0.62–0.85]; EPA+DHA, 0.94 [95% CI, 0.89–0.99]), and MACEs and revascularization. Incident AF was increased with omega-3 fatty acids (RR, 1.26 [95% CI, 1.08–1.48]). EPA monotherapy was associated with a higher risk of total bleeding (RR, 1.49 [95% CI, 1.20–1.84]) and with AF (RR, 1.35 [95% CI, 1.10–1.66]).
- 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). 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>88</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]), triglyceride (−9.422 mg/dL [95% CI, −15.514 to −3.330]), and LDL-C (−4.206 mg/dL [95% CI, −7.260 to −1.151]) concentrations.<sup>89</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>90</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>91</sup> A similar study, a post hoc analysis of the Effect of Vitamin D on Mortality in Heart Failure 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>92</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>93</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 [95% CI, 0.66–1.28] in the lowest versus highest subgroup). 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 estrogen (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>94</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>95</sup> Another review article similarly reported that vitamin D supplementation had no beneficial effects on SBP and DBP in children and adolescents.<sup>96</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>97</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>98</sup>

### Eating Patterns

- 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,  $-0.54 \text{ kg}$  [95% CI,  $-1.05$  to  $-0.03 \text{ kg}$ ]) but a modest increase in LDL-C (WMD,  $9.24 \text{ mg/dL}$  [95% CI,  $2.18$ – $16.30 \text{ mg/dL}$ ]).<sup>99</sup> Another meta-analysis of 23 RCTs with 1397 participants reported that fasting and energy-restricting diets resulted in significant reductions in SBP (WMD,  $-1.88 \text{ mmHg}$  [95% CI,  $-2.50$  to  $-1.25$ ]) and DBP (WMD,  $-1.32 \text{ mmHg}$  [95% CI,  $-1.81$  to  $-0.84$ ]), and the SBP-lowering effects were stronger with fasting (WMD,  $-3.26 \text{ mmHg}$  [95% CI,  $-5.88$  to  $-0.69$ ]) than energy restriction (WMD,  $-1.09 \text{ mmHg}$  [95% CI,  $-1.70$  to  $-0.47$ ] ).<sup>100</sup>

- Data from the French longitudinal study NutriNet-Santé (103 389 participants, 79% females, 42.6 years of age followed up for a median time of 7.2 years) reported 2036 incident cases of CVD.<sup>101</sup> Each 1-hour delay in the time of the first meal of the day was associated with higher risk of CVD (HR,  $1.06$  [95% CI,  $1.01$ – $1.12$ ]). Time of last meal was not associated with CVD risk (HR,  $1.13$  [95% CI,  $0.99$ – $1.29$ ]). Each additional hour of nighttime fasting was associated with reduced risk of cerebrovascular disease (HR,  $0.93$  [95% CI,  $0.87$ – $0.99$ ]) but not risk of CVD or CHD. Overall, findings were stronger in females than in males.
- Data from the NHANES 1999 to 2014, with 185 398 PY of follow-up, assessed associations between meal frequency, meal skipping, and meal intervals and CVD mortality.<sup>102</sup> Compared with eating 3 meals per day, eating 1 meal per day was associated with higher all-cause (HR,  $1.30$  [95% CI,  $1.03$ – $1.64$ ]) and CVD (HR,  $1.83$  [95% CI,  $1.26$ – $2.65$ ]) mortality in fully adjusted models. Eating  $>3$  meals per day was not significantly associated with all-cause and CVD mortality. Skipping breakfast compared with not skipping breakfast was associated with increased risk of CVD mortality (HR,  $1.40$  [95% CI,  $1.09$ – $1.78$ ]). Skipping breakfast (HR,  $1.11$  [95% CI,  $0.98$ – $1.26$ ]), lunch (HR,  $1.12$  [95% CI,  $1.01$ – $1.24$ ]), and dinner (HR,  $1.16$  [95% CI,  $1.02$ – $1.32$ ]) was associated with increased risk of all-cause mortality.

## Cost

The US Department of Agriculture reported that the food-at-home prices will increase by 2.9% (prediction interval, 0.5%–5.3%) in 2024. This is a deceleration relative to the reported increase of 8.6% (prediction interval, 5.6%–11.8%) in 2023.<sup>103</sup> The retail price of eggs increased 1.8% in January 2024 after an increase of 8.9% in December 2023, albeit 28.6% below prices seen in January 2023. The price for fresh vegetables increased by 2.9% in January 2024 but was almost 1% lower than prices seen in January 2023, at which time the prices remained elevated after a peak in December 2022.

Historically, in the first quarter of each year, fresh vegetables experience a seasonal peak in prices. The prices for fresh vegetables are predicted to increase 1.9% in 2024 (prediction interval, –3.0% to 7.0%). Data from Euromonitor International show that in 2023 consumers' most desired attribute in a food or beverage product globally is "low price" followed by "health properties." In 2021, consumers' most desired attribute in a food or beverage product globally was "health properties" followed by "low price."<sup>104</sup> Consumer desire for attributes such as taste, branding, and sustainable positioning was lower in 2023 than in 2021.

## Cost of a Healthy Diet

- A systematic review of studies published between 2000 and 2019 found moderate- to good-quality evidence supporting the use of pricing incentives to increase consumption or purchases of fruits and vegetables.<sup>105</sup> Providing incentives electronically on  $>1$  occasion for  $\geq 24$  weeks and allowing redemption in stores are associated with successful programs.

## 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 in the United States of \$31.5 (range, \$23.9–\$38.9) billion.<sup>106</sup> 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 (range, \$6.7–\$25.4) billion.<sup>106</sup> 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).
- 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.<sup>108</sup> 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

10000 (95% CI, 22084–22510) 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 −188919) for the cash intervention and −\$93 182 per DALY averted (95% CI, −93 707 to −92 503) for the CSA intervention.

### **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>109</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 (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 (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 (95% UI, \$12–\$31) billion. This highlights that potential health benefits and cost savings are greater than the costs associated with sodium reformulation.<sup>110</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>111</sup> In the United States, a validated microsimulation model (CVD PREDICT) was used to assess cost-effectiveness, CVD reductions, and QALYs gained from 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) compared with 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 of the proposed SSB tax).<sup>112</sup>

### **Global Trends in Key Dietary Factors**

Several 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>113</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>114</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>115</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>116</sup> Another global trend is the mean sodium intake among adults worldwide documented as 3950 mg/d in 2010.<sup>117</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. Successful population-level sodium initiatives tend to use multiple strategies and include 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>118</sup> along with concurrent decreases in BP (3.0/1.4 mm Hg) in patients not taking antihypertensive medication, stroke mortality (42%), and CHD mortality (40%;  $P<0.001$  for all comparisons). These findings remained statistically significant after adjustment for changes in demographics, BMI, and other dietary factors.

## Global Burden

### (See Table 5-5 and Chart 5-1)

- Based on 204 countries and territories in 2021, among regions, age-standardized mortality rates attributable to dietary risks were highest for central Asia and lowest for high-income Asia Pacific (Chart 5-1). There were 7.22 (95% UI, 1.96–10.77) million total deaths attributed to dietary risks in 2021. The age-standardized mortality rate of dietary risks was 86.26 (95% UI, 23.35–128.98) per 100 000 (Table 5-5).
- A report from the GBD Study 2019 estimated the impact of 15 dietary risk factors on mortality and DALYs worldwide using a comparative risk assessment approach.<sup>119</sup> 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 in 2019. The leading dietary risk factors were high sodium intake (1.9 [95% UI, 0.5–4.2] million deaths), low whole grain intake (1.8 [95% UI, 0.9–2.3] million deaths), and low legume intake (1.1 [95% UI, 0.3–1.8] million deaths).
  - Countries with low-middle SDI and middle SDI 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 SDI scores had the lowest age-standardized rates of diet-related deaths (56 [95% UI, 47–69] deaths per 100 000 population).

**Table 5-1.** Population-Level Measurement of Diet in the AHA's Life Essential 8 for CVH

Domain	CVH metric	Method of measurement	Quantification of CVH metric: adults (≥20 y of age)	Quantification of CVH metric: children* (2–19 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>120,121</sup> (populations); MEPA <sup>122</sup> (individuals)	Quantiles of DASH-style diet adherence or HEI-2015 (population) Scoring (population): <table> <thead> <tr> <th>Points</th> <th>Quantile</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>≥95th 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> <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	≥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)	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 <a href="#">Supplemental Material</a> for younger ages) Scoring (population): <table> <thead> <tr> <th>Points</th> <th>Quantile</th> </tr> </thead> <tbody> <tr> <td>100</td> <td>≥95th 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> <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	≥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)	Points	MEPA score (points)	100	9–10	80	7–8	50	5–6	25	3–4	0	0–2
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AHA indicates American Heart Association; CVH, 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 ≥95th 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 quantiles. In children, a modified MEPA is suggested on the basis of 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 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](#).

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

**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 Quintile 1 is lowest consumption; quintile 5 is highest consumption
Vegetables	All vegetables except potatoes and legumes		
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 in that higher quintiles represent less ideal intake Quintile 1 is lowest consumption; quintile 5 is highest consumption
Red and processed meats	Beef, pork, lamb, deli meats, organ meats, hot dogs, bacon		
Sweetened beverages	Carbonated and noncarbonated sweetened beverages		

The DASH diet score is assessed and points scored using the methods of Fung et al.<sup>123</sup> Quintiles of point score should be assigned using the most recent or most relevant NHANES data, appropriate to the question being addressed.

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

Source: Reproduced with permission from Fung et al.<sup>123</sup> Copyright © 2008, American Medical Association. All rights reserved, including those for text and data mining, artificial intelligence training, and similar technologies.

**Table 5-3. Scoring Criteria for the Mediterranean Eating Pattern for Americans\***

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)?	≥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 servings 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	
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	

\*The Mediterranean Eating Pattern for Americans screener is successful at capturing several components of the Mediterranean style pattern.<sup>122</sup>

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**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

(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
Fish and shellfish, servings/wk	1.0±1.8	15.0	1.5±4.2	21.6	1.5±3.8	19.3	1.1±1.5	21.2	1.9±3.8	33.7	1.2±3.2	18.0
Nuts and seeds, servings/wk	5.8±6.7	36.0	4.0±11.1	21.9	3.6±8.2	22.5	6.1±6.0	37.9	3.5±9.8	21.0	3.4±6.5	33.2
Unprocessed red meats, servings/wk	3.6±2.5	NA	2.9±4.1	NA	4.2±4.3	NA	2.6±1.9	NA	1.7±3.0	NA	2.6±3.3	NA
Processed meat, servings/wk	2.4±1.8	58.8	2.0±3.2	66.6	2.1±2.8	68.0	1.7±1.4	68.6	1.8±3.1	68.3	1.0±1.9	87.1
SSBs, servings/wk	7.3±7.3	55.6	9.8±12.4	38.6	9.9±10.7	37.9	6.4±6.7	66.7	8.6±13.6	44.1	6.5±12.8	57.3
Sweets and bakery desserts, servings/wk	4.2±4.0	51.9	3.3±6.4	65.2	4.5±6.8	58.6	3.8±3.2	53.7	4.0±8.0	58.9	4.4±6.1	53.1
Refined grain, servings/d	5.1±1.5	7.9	5.1±2.8	7.1	6.6±2.9	1.3	5.1±1.6	10.4	5.1±2.7	9.2	6.5±3.0	7.2
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 vs between-person variation. All values are energy adjusted by individual regressions or percent energy, and for comparability, means and proportions are reported for a 2000-kcal/d diet. To obtain actual mean consumption levels, the group means for each food or nutrient can be multiplied by the group-specific total calories (kilocalories per day) divided by 2000 kcal/d. The calculations for foods use the US Department of Agriculture Food Patterns Equivalent Database on composition of various mixed dishes, which incorporates partial amounts of various foods (eg, vegetables, nuts, processed meats) in mixed dishes; in addition, the characterization of whole grains is now derived from the US Department of Agriculture database instead of the ratio of total carbohydrate to fiber.

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; MUFA, monounsaturated fatty acid; NA, not available; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; and 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>124</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. 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>125</sup>

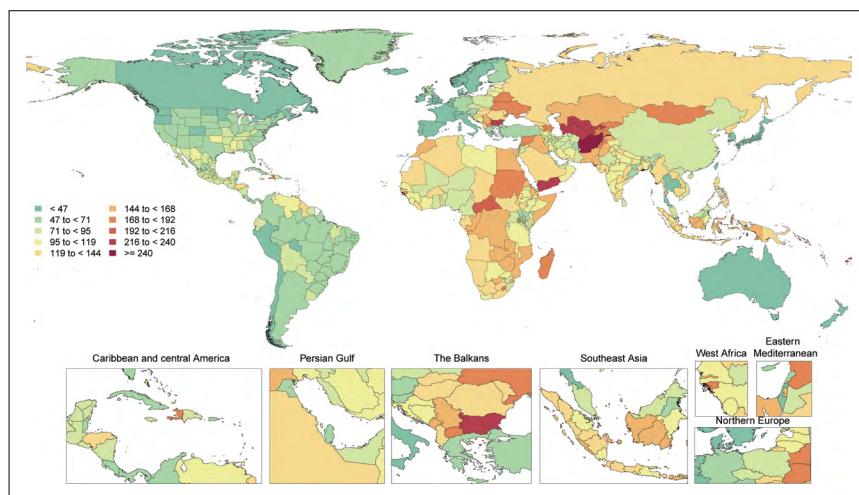
**Table 5-5. Deaths Caused by Dietary Risks Worldwide, by Sex, 2021**

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	7.22 (1.96 to 10.77)	3.98 (1.05 to 5.84)	3.24 (0.90 to 4.92)
Percent change (%) in total number, 1990–2021	50.76 (39.27 to 61.68)	57.07 (41.67 to 70.99)	43.66 (31.08 to 55.33)
Percent change (%) in total number, 2010–2021	18.78 (12.36 to 24.66)	18.90 (10.41 to 28.14)	18.63 (11.53 to 26.43)
Rate per 100,000, age standardized, 2021	86.26 (23.35 to 128.98)	106.00 (28.65 to 156.32)	69.49 (19.44 to 105.66)
Percent change (%) in rate, age standardized, 1990–2021	-35.68 (-39.86 to -31.47)	-33.03 (-38.80 to -27.03)	-38.89 (-43.40 to -33.88)
Percent change (%) in rate, age standardized, 2010–2021	-13.85 (-18.15 to -9.63)	-13.51 (-19.27 to -6.98)	-14.25 (-19.24 to -8.76)
PAF (%), all ages, 2021	10.63 (2.90 to 15.94)	10.57 (2.83 to 15.68)	10.71 (3.01 to 16.34)
Percent change (%) in PAF, all ages, 1990–2021	2.39 (-5.39 to 7.73)	3.43 (-5.49 to 10.18)	1.26 (-5.80 to 7.02)
Percent change (%) in PAF, all ages, 2010–2021	-7.16 (-10.23 to -4.12)	-8.39 (-12.22 to -4.70)	-5.64 (-9.00 to -1.67)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and PAF, population attributable fraction.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>126</sup>



### Chart 5-1. Age-standardized global mortality rates attributable to dietary risks per 100 000, both sexes, 2021.

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>126</sup>

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## 6. OVERWEIGHT AND OBESITY

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

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### Classification of Overweight/Obese

- BMI is calculated as weight in kilograms divided by height in meters squared. In adults, obesity is defined as a BMI  $\geq 30.0 \text{ kg/m}^2$  and severe obesity as a BMI  $\geq 40 \text{ kg/m}^2$ .<sup>1,2</sup> Overweight in adults is defined as BMI  $\geq 25.0$  but  $< 30 \text{ kg/m}^2$ .<sup>3</sup>
- Obesity in adults can be further subdivided into class 1 (BMI 30– $< 35 \text{ kg/m}^2$ ) and class 2 (BMI 35– $< 40 \text{ kg/m}^2$ ); severe obesity is classified as class 3 (BMI  $\geq 40 \text{ kg/m}^2$ ).<sup>1,2</sup>
- For children and adolescents, obesity is defined as BMI  $\geq 95$ th percentile and severe obesity as BMI  $\geq 120\%$  of the 95th percentile.<sup>4</sup> Overweight in children is defined as BMI  $\geq 85$ th but  $< 95$ th percentile.
- Abdominal obesity is also defined as a WC  $\geq 102 \text{ cm}$  (40 in) in males and  $\geq 88 \text{ cm}$  (35 in) in females.<sup>5</sup>
- Lower BMI thresholds have been recommended for Asian adults, with overweight defined as  $\geq 23$  to  $< 27.5 \text{ kg/m}^2$  and obesity as  $\geq 27.5 \text{ kg/m}^2$ .<sup>5</sup> Accordingly, the American Diabetes Association has lowered the BMI cut point for diabetes screening in Asian adults to  $\geq 23 \text{ kg/m}^2$ .<sup>6</sup> For individuals of South Asian, Japanese, and Chinese descent, the respective WC cut points associated with disease risk are  $\geq 90 \text{ cm}$  in males and  $\geq 80 \text{ cm}$  in females.<sup>5</sup>
- It should be noted that the risk for CVDs and diabetes conferred by an elevated BMI is not uniform across racial and ethnic groups, and risk may overestimated among Black adults and underestimated in Asian people.<sup>3</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>3,7</sup>

The 2025 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 2025. 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 Secular Trends

#### Youths

##### Prevalence in Children/Adolescents

(See Table 6-1)

- According to NHANES data from 2017 until March 2020 (before the COVID-19 pandemic), among US children and adolescents 2 to 19 years of age, the prevalence of obesity was 19.7% overall, 20.9% for males, and 18.5% for females.<sup>8</sup> Obesity prevalence increased with age, being 12.7% for those 2 to 5 years of age, 20.7% for those 6 to 11 years of age, and 22.2% for those 12 to 19 years of age (Table 6-1).<sup>8</sup>
- There were significant racial and ethnic disparities in obesity.<sup>8</sup> The highest prevalence of obesity was seen among Hispanic male and NH Black female youths. According to NHANES data from 2017 to March 2020, the prevalence of obesity among children and adolescents 2 to 19 years of age was 17.6% and 15.4% for NH White males and females, 18.8% and 30.8% for NH Black males and females, 13.1% and 5.2% for NH Asian males and females, and 29.3% and 23.0% for Hispanic males and females, respectively (Table 6-1).<sup>8</sup>
- Among youths, percent body fat was not consistent by BMI categories. In NHANES data from 2011 to 2018 in youths 8 to 19 years of age, percent body fat was highest among Hispanic females (35.7%) and males (28.2%).<sup>9</sup> There was no significant difference in percent body fat between NH Black females, White females, and Asian females (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 youths with obesity, NH Asian females had lower percent body fat (40.5%) than NH White females (42.8%;  $P=0.0072$ ).<sup>9</sup>
- There are regional/geographic differences in prevalence of obesity in youths across the United States. An analysis of pooled data from 25 cohorts of children and adolescents ( $N=14313$ ) found BMI  $z$  scores to be higher in the Midwest and lower in the South and West compared with the Northeast after adjustment for sociodemographic characteristics.<sup>10</sup>
- According to data from the National Survey of Children's Health from 2021 to 2022, 17% of youths 10 to 17 years of age had obesity, with 7 states having youths obesity rates significantly above the national average exceeding 20% (ie, West Virginia, Kentucky, New Mexico, Mississippi, Louisiana, Texas, and Tennessee).<sup>11</sup>

#### Youth Secular Trends

(See Chart 6-1)

- 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% in 1971 to 1974 to 16.1%, 19.3%, and 6.1%, respectively, in 2017 to 2018 (Chart 6-1).<sup>12</sup> 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>13</sup>

- Comparing NHANES data from 1999 to 2006 to 2011 to 2018 shows that the percent body fat among youths 8 to 19 years of age increased from 25.6% to 26.3% ( $P < 0.01$ ) among males and from 33.0% to 33.7% ( $P = 0.01$ ) among females.<sup>14</sup>
- Another analysis using NHANES data examined the change in prevalence of obesity in children and adolescents (2–19 years of age) between the 2011 to 2012 and 2021 to March 2020 periods and found that obesity prevalence increased significantly from 16.7% to 20.9% for male youths ( $P_{\text{trend}} = 0.0084$ ) but not significantly for female youths ( $P_{\text{trend}} = 0.35$ ). This study also reported that the prevalence of obesity increased significantly in children 2 to 5 years of age but not in children 6 to 11 years of age or adolescents 12 to 19 years of age.<sup>15</sup>

## Adults

### Prevalence in Adults

#### (See Tables 6-2 and 6-3 and Chart 6-2)

- According to NHANES data from 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%.<sup>8</sup> The prevalence of obesity was 41.9% and was similar for males (41.8%) and females (41.8%; Table 6-2).
- This prevalence of obesity by age categories for adults  $\geq 20$  years of age from this same time frame (2017–March 2020) was 39.8% in younger adults 20 to 39 years of age, 44.3% in middle-aged adults 40 to 59 years of age, and 41.5% in adults  $\geq 60$  years of age (Table 6-2).<sup>8</sup>
- There were significant disparities by racial and ethnic groups with the highest prevalence of obesity among NH Black females. Among adults  $\geq 20$  years of age, according to data from NHANES 2017 through March 2020 (before the pandemic), the prevalence of obesity for males and females was 43.1% and 39.6% for NH White adults, 40.4% and 57.9% for NH Black adults, 17.6% and 14.5% for NH Asian adults, and 45.2% and 45.7% for Hispanic adults, respectively (Table 6-2).<sup>8</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 9.2% with greater prevalence in females (11.7%) than males (6.6%; Table 6-3).<sup>8</sup> Significant disparities were noted by racial and ethnic groups with the greatest prevalence of severe obesity among Black females (19.1%).

- In that same time frame (2017–March 2020), the age-adjusted prevalence of severe obesity stratified by age groups was 9.7% for individuals 20 to 39 years of age, 10.7% for those 40 to 59 years of age, and 6.1% for individuals  $\geq 60$  years of age (Table 6-3).<sup>8</sup>
- Using 2022 data from the BRFSS (Chart 6-2), the CDC reported that all US states had an obesity prevalence  $> 20\%$  (ie, 1 in 5 adults), 22 states had an obesity prevalence between 30% and 35%, 19 states had an obesity prevalence of 35% to 40%, and 3 states had an obesity prevalence  $\geq 40\%$ .<sup>16</sup> There were regional differences with the Midwest and South having the highest prevalence of obesity in the United States followed by the Northeast and the West. These data are striking because 10 years ago no state had an adult obesity prevalence  $> 35\%$ .<sup>16</sup> By state, the highest prevalence of obesity was in West Virginia (41.3%) and the lowest in Colorado (24.9%) and the District of Columbia (24.8%; unpublished NHLBI tabulation using BRFSS<sup>16</sup>).

### Secular Trends in Adults

#### (See Chart 6-3)

- The age-adjusted trends in overweight, obesity, and severe obesity in US adults from 1960 to 1962 to 2017 to 2018 using NHANES data are shown in Chart 6-3.<sup>19</sup>
- Comparing NHANES data from 1999 to 2000 with data from 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. The increase in obesity biennially was greater among Mexican American males (3%) than NH White males (1.4%;  $P < 0.001$ ).<sup>20</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 females and NH Black females, whereas Mexican American females experienced a rise in obesity, but severe obesity increased only after 2009 to 2010.<sup>20</sup>

- An analysis using BRFSS data of US adults found that the prevalence of obesity increased 3%, along with a 0.6% increase in BMI, in the COVID-19 pandemic period of March 2020 to March 2021 compared with the prepandemic period of January 2019 to March 2020.<sup>21</sup>
- A recent analysis from the AHA modeling risk factor trends using NHANES data from January 2015 to March 2020 forecasted that if current rates continue the prevalence of obesity in US adults will rise from 43.1% in 2020 to 60.6% by 2050.<sup>22</sup> The highest prevalence and projected growth of obesity were in the 20 to 44 and 45 to 64 year of age groups.

## Social Determinants of Health and Health Equity

### Urbanization

- There are differences in obesity prevalence by urbanization status. Children and adolescents from rural locations had a 30% higher odds of being overweight or obese compared with children and adolescents living in urban locations (OR, 1.30 [95% CI, 1.11–1.52]) according to survey data from 2019 through 2020.<sup>23</sup> An analysis of preschoolers also found that indexed BMI was higher among children living in rural areas than children living in urban areas ( $\beta$ , 0.13 [95% CI, 0.09–0.42]), suggesting that the rural-urban disparity may begin as early as 3 to 4 years of age.<sup>24</sup>
- Also among US adults, obesity prevalence is higher in rural compared with urban counties (OR, 1.035 [95% CI, 1.03–1.04]).<sup>25</sup> Using BRFSS data from 2016, the CDC reported that the prevalence of obesity in adults was higher among nonmetropolitan county residents compared with those living in metropolitan areas (34.2% versus 28.7%;  $P<0.001$ ).<sup>26</sup>
- Rurality may further moderate Black and White racial disparities in obesity with a higher odds of obesity for Black adults compared with White adults living in rural areas (OR, 2.03 [95% CI, 1.71–2.4]) versus the odds of Black adults compared with White adults living in urban areas (OR, 1.83 [95% CI, 1.78–1.88], race-rural interaction,  $P<0.05$ ).<sup>25</sup>
- In contrast, a recent analysis reported that obesity-related cardiovascular mortality in the United States from 1999 through 2020 was greater among Black adults who lived in urban communities than those living in rural communities (6.8 versus 5.9 per 100 000 population), whereas the reverse was true for all of the other racial and ethnic groups (rural: range, 2.2–5.4 per 100 000 population; urban: range, 0.9–3.5 per 100 000 population).<sup>27</sup>

### Income and Education

#### (See Tables 6-1 through 6-3)

- There were significant differences in the prevalence of obesity in the United States by SES with the lowest prevalence of obesity in the highest education (college degree or above) and income (>350% FPL) groups according to NHANES data for adults ≥20 years of age from 2017 through March 2020 (before the pandemic).<sup>8</sup> In terms of education, the prevalence of obesity was 40.1% for those with less than a high school diploma, 46.4% for individuals with a high school diploma or some college, and 34.2% for individuals with a college degree or above. In terms of family income relative to FPL, the prevalence of obesity was 43.9% for those with income ≤130% FPL, 46.5% for those with income >130% to 350% FPL, and 39% for individuals with income >350% FPL (Table 6-2).
- Similar patterns of disparity by education and income were seen for the prevalence of severe obesity (Table 6-3).<sup>8</sup>
- According to 2022 BRFSS data, the prevalence of obesity among US adults was highest among those with incomes of <\$15 000 (38.2%) and \$15 000 to <\$25 000 (38.4%) and then steadily fell across income groups to a prevalence of 34.1% for those with income ≥\$75 000.<sup>28</sup> That same 2022 BRFSS data showed that the prevalence of obesity also decreased with higher education with prevalences of 37.6% for less than high school, 35.7% for high school graduate, 35.9% for some college or technical school, and 27.2% for college graduate.<sup>28</sup>
- There was also significant disparity by SES among youths and adolescents. According to data from NHANES 2017 through March 2020, the prevalence of obesity among children and adolescents 2 to 19 years of age was greatest among those with low family income. Prevalence of obesity was 25.8%, 21.2%, and 11.5% for those with a family income level of ≤130% FPL, >130% to 350% FPL, and >350% FPL, respectively (Table 6-1).<sup>8</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 such as economic stability; neighborhood, physical environment, and social cohesion; community and social context; food insecurity; education; and health care system 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>29</sup>

## Family History and Genetics

- Genetic variation contributes to overweight and obesity,<sup>30</sup> with heritability estimates ranging from 40% to 70%.<sup>31</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>32</sup> Monogenic obesity inherited in a mendelian pattern is generally rare and associated with other organ-specific abnormalities.
- Polygenic obesity has a heritability pattern similar to that of complex diseases.<sup>33</sup> Numerous GWASs have identified >1100 independent loci associated with polygenic obesity.<sup>33</sup> These GWASs have estimated that common genetic variants may account for >20% of the variation in BMI.<sup>34</sup>
- In a GWAS of African ancestral populations, only <30% of BMI and waist-to-hip loci identified in European ancestral populations were also associated in African ancestry.<sup>35</sup>
- One GWAS 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>36</sup>
- FTO* (first intron of fat mass and obesity) was one of the first GWAS-identified BMI loci<sup>37</sup> and is relatively common among individuals of European ancestry with a minor allele frequency of 40% to 45%.<sup>33,38</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 with BMI was similar in populations of African or Asian ancestry but less prevalent in these populations compared with European ancestry.<sup>33,38</sup> This locus has been replicated in diverse populations and across different age groups.<sup>38–42</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>37</sup>
- Large-scale exome sequencing projects have complemented GWASs, given their ability to capture rare coding variants. For example, in N=645 626 predominantly European ancestral populations, novel associations were identified for genes that encode G protein-coupled receptors, the largest human genome drug target class.<sup>43</sup> A rare predicted loss-of-function variant in *GPR75* also was identified. Carriers of this variant had, on average, 12-lb lower body weight.
- A GRS 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>44</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>44</sup>

- In another analysis, GRS explained 5.2% of BMI variance, and gene-by-environment interaction explained an additional 1.9%.<sup>45</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, demonstrating considerable uncertainty.<sup>46</sup>
- In the Bogalusa Heart Study with >40 years of follow-up, a GRS performed in childhood was found to be modestly associated with mid-life BMI (correlation coefficient, 0.27;  $P=1.94\times10^{-8}$ ) and associated with a 26% higher risk of later life obesity ( $P=3.50\times10^{-6}$ ) in White participants.<sup>47</sup> However, the GRS did not independently predict later-life cardiometabolic health in Black adults, emphasizing the need to develop GRS in more diverse populations.
- Polygenic risk associated with higher BMI is associated with increased risk for CAD, HF, and mortality.<sup>38</sup> A mendelian randomization study has shown that a high-BMI GRS is associated with shorter life span, defined as a younger age at death compared with the reference group in the UK Biobank (HR per 1-SD BMI GRS for increase in mortality, 1.07 [95% CI, 1.05–1.09]).<sup>48</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>49</sup>
- Genetic variants may also influence responsiveness to weight loss interventions.<sup>50</sup> A GWAS (N=1166) conducted in a low-calorie diet intervention trial identified 2 loci, *NKX6.3/MIR486* and *RBSG4*, that were associated with degree of weight loss. Both loci were replicated in a second low-calorie diet intervention study (N=789).<sup>50</sup>

- Genetic variants also may affect weight loss or weight gain in the context of a behavioral intervention. For example, the *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>51</sup>
- Environmental exposures may interact with common variants to affect obesity traits. In a study of >500 000 predominantly European ancestral populations, 4 significant loci were identified that modified the effect of current smoking on obesity traits: *INPP4B*, *CHRN B4*, *VEGFA*, and *RSPO3*.<sup>52</sup> *INPP4B* was previously identified in obesity<sup>53</sup> and smoking<sup>54</sup> GWASs, whereas *VEGFA* lead variants were identified in a gene-by-smoking study of rheumatoid arthritis.<sup>55</sup>

## Behavioral/Technology Interventions for Obesity Prevention

- A Cochrane systematic review and meta-analysis of studies from 2015 through 2021 was conducted to evaluate the effectiveness of obesity prevention interventions for children 6 to 18 years of age. Among 140 RCTs (183 063 participants), this meta-analysis found a small beneficial effect on BMI reduction for school-based interventions (SMD, -0.03 kg/m<sup>2</sup> [95% CI, -0.05 to -0.01]) but not interventions that were after-school programs or community or home based.<sup>56</sup>
- Another meta-analysis of technology-based interventions in youths (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 the treatment and comparator groups.<sup>57</sup>
- Another systematic review and meta-analysis of RCTs examined the effectiveness of technology-based interventions for weight loss maintenance (duration, 3–30 months) in adults and found that those interventions were similar to usual care but less effective than in-person interventions with 1.36-kg (95% CI, 0.29–2.43) higher weight regain.<sup>58</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>59</sup>
- A subanalysis from the Look AHEAD trial demonstrated that participants (with baseline BMI ≥25 kg/

m<sup>2</sup>) in an intensive lifestyle intervention group who lost at least 10% of their body weight had a 20% lower risk for a cardiovascular event over a 10-year follow-up (HR, 0.80 [95% CI, 0.65–0.99]) compared with those who gained or lost ≤2% body weight.<sup>60</sup>

- 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>61</sup>

## Obesity Treatment

### Surgery

- Bariatric surgery is effective for weight loss, but there are differences by surgery type. In a large meta-analysis of >65 000 patients 20 to 79 years of age with BMI ≥35 kg/m<sup>2</sup> who had undergone bariatric surgery, the average total weight loss at 5 years was 25.5% (95% CI, 25.1%–25.9%) for the Roux-en-Y gastric bypass, 18.8% (95% CI, 18.0%–19.6%) for the sleeve gastrectomy, and 11.7% (95% CI, 10.2%–13.1%) for the adjustable gastric banding procedure; however Roux-en-Y gastric bypass was associated with more adverse events.<sup>62</sup>
- Another meta-analysis including studies with >10 years of 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>63</sup>
- The weight reduction with bariatric surgery is associated with improved clinical outcomes. 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>64</sup>
- A meta-analysis of 39 observational studies with follow-up ranging from 2 to 24 years found that bariatric surgery was associated with reduced risk for all-cause mortality (HR, 0.55 [95% CI, 0.49–0.62]) and CVD mortality (HR, 0.59 [95% CI, 0.47–0.73]) compared with nonsurgical control.<sup>65</sup> In addition, bariatric surgery was associated with reduced risk of HF (HR, 0.50 [95% CI, 0.38–0.66]), MI (HR, 0.58 [95% CI, 0.43–0.76]), and stroke (HR, 0.64 [95% CI, 0.53–0.77]) with a nonsignificant favorable trend for reduction in AF (HR, 0.82 [95% CI, 0.64–1.06]).

## 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>66</sup>
- The older FDA-approved antiobesity medications orlistat, naltrexone-bupropion, phentermine-topiramate, and liraglutide have been shown to confer a placebo-corrected weight reduction of  $\approx 5\%$  to  $10\%$ .<sup>67</sup>
- SGLT-2 inhibitor medications can confer modest weight loss. In a recent meta-analysis of 116 RCTs, including patients with and without type 2 diabetes, SGLT-2 inhibitors conferred a mean weight reduction of  $-1.79 \text{ kg}$  (95% CI,  $-1.93$  to  $-1.66$ ) compared with placebo.<sup>68</sup> This effect was seen for all SGLT-2 inhibitor drugs and across diabetes status.
- Among patients with type 2 diabetes, systematic reviews and meta-analyses have shown that GLP1-RAs have conferred weight loss, but there are differences among the specific types and doses of GLP1-RAs (mean weight loss difference ranging from  $-0.48\%$  to  $-6.2\%$ ).<sup>69</sup>
- It is notable that among patients with type 2 diabetes and obesity, GLP1-RAs also significantly reduce MACEs (RR, 0.88 [95% CI, 0.81–0.96]).<sup>70</sup>
- More recently, GLP1-RAs have emerged as effective pharmacological options for weight loss with cardiovascular safety among patients with overweight/obesity but without type 2 diabetes,<sup>71–73</sup> as well as cardiovascular benefit among those with obesity and established CVD.<sup>74</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 at 68 weeks.<sup>71</sup> Similar weight loss results were seen with other phase 3 trials of semaglutide in the STEP 2 through 8 trials.<sup>75</sup> In all trials, there were more gastrointestinal side effects in the GLP1-RA-treated group, but most gastrointestinal side effects were mild to moderate and transient.
- 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 ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) or overweight ( $\text{BMI} \geq 27 \text{ kg/m}^2$ ) with a history of weight-related comorbidities and showed that this drug achieved significant weight loss in a dose-dependent manner.<sup>73</sup> The highest dose of tirzepatide (15 mg subcutaneous weekly) conferred an average 17.8% greater weight reduction compared with placebo, with a mean weight loss of 23.6 kg (52.0 lb) at 72 weeks.
- Newer GLP1-RAs have been recently studied in phase 3 trials. Retatrutide, a triple agonist for the glucose-dependent insulinotropic peptide, glucagon-like peptide 1, and glucagon receptors, was demonstrated to confer a 22.1% greater reduction in body weight at 48 weeks compared with placebo in individuals with overweight or obesity at its highest dose of 12 mg subcutaneous weekly.<sup>76</sup> Orforglipron, a daily oral nonpeptide GLP1-RA, was shown to confer 12.4% greater weight reduction compared with placebo at 36 weeks among individuals with overweight/obesity.<sup>77</sup> These agents are not yet approved by the FDA but are moving forward for additional study in phase 3 trials.
- Currently, liraglutide, semaglutide, and tirzepatide are the GLP1-RA agents approved by the FDA for long-term weight management in adults with obesity or with  $\text{BMI} \geq 27 \text{ kg/m}^2$  in the setting of at least 1 weight-related condition such as type 2 diabetes, hypertension, or dyslipidemia, in conjunction with a reduced-calorie diet and increased PA.
- It should be noted that GLP1-RAs are a treatment for weight management, not a cure. Weight regain is common after cessation of therapy. In the STEP 1 trial, 1 year after the discontinuation of the subcutaneous semaglutide 2.4 mg/wk, participants regained two-thirds of their prior weight loss.<sup>78</sup> Similar regain of lost weight was seen after cessation of tirzepatide in the SURMONT-4 trial compared with those who continued treatment.<sup>79</sup>
- GLP1-RAs have also been shown to reduce cardiovascular events among individuals with overweight or obesity but without diabetes. A meta-analysis of 9 weight-loss RCTs of patients with overweight and obesity but without diabetes demonstrated that cardiovascular events were fewer in individuals treated with GLP1-RAs compared with placebo (8.7% versus 11.2%; RR, 0.81 [95% CI, 0.70–0.92]).<sup>80</sup>
- Furthermore, the SELECT trial was a dedicated cardiovascular outcome trial evaluating semaglutide that enrolled patients with overweight or obesity and established CVD but without diabetes.<sup>74</sup> SELECT demonstrated that semaglutide compared with placebo reduced MACEs by 20% in this population (HR, 0.80 [95% CI, 0.72–0.90]) while conferring an  $\approx 9\%$  weight loss (estimated treatment difference,  $-8.51\%$  [95% CI,  $-8.75\%$  to  $-8.27\%$ ]). Although data did not meet hierarchical testing for superiority, a 19% reduction in all-cause mortality was also

demonstrated with semaglutide (HR, 0.81 [95% CI, 0.71–0.93]).<sup>74</sup> The weight loss with semaglutide in SELECT was more modest than in the previous weight loss trials with a reduction of –8.5% (95% CI, –8.8 to –8.3) compared with placebo. Furthermore, subgroup analysis of SELECT demonstrated no interaction of baseline BMI category with the MACE reduction conferred by semaglutide, with a significant MACE reduction seen even for those with a BMI of  $\geq 27$  to  $< 30 \text{ kg/m}^2$  (HR, 0.74 [95%, CI, 0.60–0.91]).<sup>74</sup> These findings suggest that the cardiovascular reduction conferred by semaglutide may not be entirely explained by only its weight reduction effects. After SELECT, the FDA has added a new indication for semaglutide to reduce the risk of cardiovascular events among adults with overweight and obesity and CVD but without diabetes.

- The STEP-HFpEF trials evaluated patients with  $\text{BMI} \geq 30 \text{ kg/m}^2$  and HFpEF with and without diabetes and demonstrated that semaglutide conferred a weight reduction of –8.4% (95% CI, –9.2 to –7.5), as well as significant improvement in symptoms (change in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, 7.5 points [95% CI, 5.3–9.8]). A reduction in time to first HF event (HR, 0.27 [95% CI, 0.12–0.56]) was also noted, although the trial was not specifically powered for clinical outcomes.<sup>81</sup>
- GLP1-RAs have also been evaluated for treatment of obesity-related conditions such as MASLD. Among patients with type 2 diabetes and MASLD, 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>82</sup> Furthermore, another recent meta-analysis evaluating GLP1-RA in patients with MASLD or metabolic dysfunction-associated steatohepatitis found that semaglutide conferred a significant improvement in liver fat content (mean difference, –4.97% [95% CI, –6.65% to –3.29%]), as well as an improvement in liver enzymes.<sup>83</sup> In addition, the dual-agonist tirzepatide was found to be more effective than placebo for resolution in metabolic dysfunction-associated steatohepatitis without worsening of fibrosis (difference, 53 percentage points [95% CI, 37–69];  $P < 0.001$ ).<sup>84</sup>
- GLP1-RAs have also been evaluated for treatment in youths with obesity. 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 kg [95% CI, –2.50 to –0.50]), showing efficacy and safety in youths with obesity.<sup>85</sup>

## Mortality

- Obesity-related cardiovascular deaths increased 3-fold in the United States between 1999 to 2020, with AAMR rising from 2.2 to 6.6 per 100 000 population.<sup>27</sup> The age-adjusted obesity-related cardiovascular mortality was noted to be highest among Black individuals (6.7 per 100 000 population), followed by American Indian individuals or Alaska Native individuals (3.8 per 100 000 population), and lowest among Asian individuals or Pacific Island individuals (0.9 per 100 000 population).<sup>27</sup>
- According to data from the NHIS from 1999 through 2018, there was a 21% to 108% increase in mortality for  $\text{BMI} \geq 30 \text{ kg/m}^2$  (HR, 1.21 for  $\text{BMI} 30\text{--}34.9 \text{ kg/m}^2$ ; HR, 1.44 for  $\text{BMI} 35.0\text{--}39.9 \text{ kg/m}^2$ ; and HR, 2.08 for  $\text{BMI} \geq 40 \text{ kg/m}^2$ ) compared with a BMI of 22.5 to 24.9  $\text{kg/m}^2$ .<sup>86</sup> For older adults  $\geq 65$  years of age, there was no significant increase in mortality for  $\text{BMI}$  of 22.5 to 34.9  $\text{kg/m}^2$ , whereas in younger adults, this lack of mortality increase was limited to  $\text{BMI}$  of 22.5 to 27.4  $\text{kg/m}^2$ . An increase in mortality was also seen for underweight individuals ( $\text{BMI} < 18.5 \text{ kg/m}^2$ ).
- Findings were similar to those of a previous large population study of 3.6 million UK adults that demonstrated a J-shaped association of BMI with all-cause mortality with lowest mortality risk in the BMI range of 21 to 25  $\text{kg/m}^2$ .<sup>87</sup> The association of BMI and mortality was greater among young adults and weaker among older adults. Life expectancy from 40 years of age associated with obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) was 4.2 years shorter in males and 3.5 years shorter in females; for underweight ( $\text{BMI} < 18.5 \text{ kg/m}^2$ ), it was 4.3 years shorter in men and 4.5 years shorter in females.
- 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>88</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) for 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.
- Another meta-analysis of 35 studies and 923 295 participants also found a J-shaped relationship of body fat with mortality, with the lowest mortality risk seen for body fat percent of 25% and fat mass of 20 kg. For every 10% increase in body fat percent, there was an 11% increase risk in all cause-mortality (HR, 1.11 [95% CI, 1.02–1.20]).<sup>89</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 being normal weight in a meta-analysis of >10 studies.<sup>90</sup>
- When US data from 2016 were modeled, excess weight ( $\text{BMI} \geq 25 \text{ kg/m}^2$ ) was attributed to 1300 excess deaths per day, nearly 500 000 excess deaths per year, and a loss of life expectancy of 2.4 years compared with a BMI 20 to 25  $\text{kg/m}^2$ ; this was a higher excess mortality than for smoking.<sup>91</sup> This relative excess in mortality attributed to increased weight was twice as high for females compared with males (21.9% versus 13.9%) and higher for Black NH adults compared with White NH adults (22.8% versus 17.0%).
- According to GBD data, deaths attributed to elevated BMI ( $\geq 25 \text{ kg/m}^2$ ) in Asia increased 265% from 1990 to 2019.<sup>92</sup> In 1990, the death burden attributed to elevated BMI was higher in females than males, but the burden in males has surpassed that in females since 1995.

## Complications of Obesity

### **Cardiovascular Disease**

- Obesity is associated with increased risk of adverse cardiovascular outcomes. An umbrella review examined 12 systematic reviews including 53 meta-analyses, >500 cohort studies, and 12 mendelian randomization studies.<sup>93</sup> This study found that for every 5- $\text{kg/m}^2$  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. Mendelian randomization analyses suggest that obesity is causally related to CVD: for each 5- $\text{kg/m}^2$  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.<sup>93</sup>
- 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>94</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>94</sup>

- In a meta-analysis of individuals with type 2 diabetes, there was a linear association between BMI and risk of CVD incidence with an RR of 1.12 (95% CI, 1.04–1.20) for each 5-unit increase in BMI.<sup>95</sup>

### **Coronary Heart Disease**

- Mendelian randomization studies among participants of predominantly European ancestry 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>96</sup> After these potential cardiovascular risk mediators were accounted for, the OR for CAD per 1-SD increase in genetically predicted BMI was attenuated to 1.14 (95% CI, 1.04–1.26). Another recent mendelian randomization study came to a similar conclusion with an OR for CAD attributed to genetically predicted BMI of 1.27 (95% CI, 1.18–1.37).<sup>97</sup>
- In a meta-analysis of 80 observational cohort studies, the HR for CHD was 1.15 (95% CI, 1.12–1.20) for each 5-unit increase in BMI.<sup>93</sup>

### **Stroke**

- In a meta-analysis of 13 observational cohort studies, the RR for ischemic stroke was 1.36 (95% CI, 1.25–1.47) for each 5-unit increase in BMI.<sup>93</sup>
- In the HUNT cohort of 14 139 individuals who had their BMI measured 4 times over a 42-year period, overweight and obesity over adulthood were associated with a higher risk for ischemic stroke (HR, 1.29 [95% CI, 1.11–1.48] and 1.27 [95% CI, 0.96–1.67], respectively) compared with normal weight over adulthood.<sup>98</sup>
- However, a prior mendelian randomization study in 694 649 subjects of primarily European descent did not find an association between genetically predicted BMI and cerebrovascular disease but did find an association between genetically predicted waist-hip-ratio and both ischemic and hemorrhagic stroke.<sup>99</sup>

### **Heart Failure**

- In a meta-analysis of 32 observational cohort studies, the RR for HF was 1.41 (95% CI, 1.32–1.50) for each 5-unit increase in BMI.<sup>93</sup>
- Another recent systematic review and meta-analysis of 35 studies including >1 million participants found that the RR of HF was 1.42 (95% CI, 1.40–1.42) for each 5- $\text{kg/m}^2$  higher BMI, 1.28 (95% CI, 1.26–1.31) for each 10-cm higher WC, and 1.33 (95% CI, 1.28–1.37) per each 0.1-unit higher waist-to-hip ratio.<sup>100</sup> The association of adiposity with HF was higher for HFpEF than for HFrEF; per 5- $\text{kg/m}^2$  higher BMI, the RR of HFpEF was 1.42 (95% CI, 1.33–1.51) and the RR for HFrEF was 1.13 (95% CI, 1.05–1.22).

- 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>101</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 LA size ( $P=0.02$ ) and improvement in LV diastology ( $P<0.0001$ ).<sup>101</sup>
- A pooled analysis across 10 cohorts examined the lifetime risk of HF.<sup>94</sup> 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. There was a stronger association of higher BMI with incident HF compared with other CVD subtypes.<sup>94</sup> For example, for severe obesity (BMI  $\geq 40$  kg/m $^2$ ) compared with normal weight, the HR for incident HF was 5.26 (95% CI, 3.65–7.57) for males and 4.32 (95% CI, 3.39–5.19) for females, whereas the HRs for MI and stroke were 1.98 (95% CI, 1.42–2.78) and 0.75 (95% CI, 0.35–1.60) and 1.80 (95% CI, 1.41–2.30) and 1.01 (95% CI, 0.73–1.39) for MI and stroke in males and females, respectively. Greater risk for HF compared with MI and stroke events was also seen for the overweight (BMI, 25.0–29.9 kg/m $^2$ ) and obesity (BMI, 30.0–39.9 kg/m $^2$ ) categories as well.
- 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 (45–84 years of age).<sup>102</sup> Even after accounting for present weight at later adulthood, higher BMI per 5 kg/m $^2$  (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>102</sup>
- Regionality of fat distribution influences HF risk.<sup>103</sup> Visceral adipose tissue, but not subcutaneous adipose tissue, was associated with incident HFpEF in the MESA cohort. For each 1-SD increment in visceral adipose tissue, the HR was 2.24 (95% CI, 1.44–3.49), and for subcutaneous adipose tissue, the HR was 1.30 (95% CI, 0.79–2.12).<sup>104</sup>
- Another recent meta-analysis found that both visceral fat (RR, 1.08 [95% CI, 1.04–1.12]) and pericardial fat (RR, 1.08 [95% CI, 1.06–1.10]) were associated with incident HF.<sup>100</sup>
- MASLD, 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>105</sup>
- Despite the increased risk of incident HF associated with obesity, many studies have demonstrated an “obesity paradox” wherein the short-term outcomes of patients with HF and overweight or obesity are more favorable compared with outcomes of individuals with HF with normal BMI (18.5 to <25 kg/m $^2$ ). In a primary care cohort including 47 531 individuals with HF, there was a U-shaped relationship between BMI and mortality with an increased mortality risk for those with underweight (HR, 1.59 [95% CI, 1.45–1.75]) and with class III obesity (HR, 1.23 [95% CI, 1.17–1.29]) compared with healthy weight, with a decrease risk of mortality associated with overweight and class I or class II obesity.<sup>106</sup>

## Atrial Fibrillation

- Obesity is a strong risk factor for AF; it is associated with incident AF and persistent AF.<sup>107</sup>
- Mendelian randomization studies support a causal relationship between BMI and AF risk. Genetically determined central adiposity from the UK Biobank (European ancestry) was associated with increased risk of AF, with an OR of 1.63 (95% CI, 1.26–2.12) for WC, 1.36 (95% CI, 1.11–1.67) for WHR, and 1.43 (95% CI, 1.34–1.53) for percent truncal fat.<sup>108</sup>
- Similar associations have been seen for measured BMI in observational studies. In a meta-analysis of 31 observational cohort studies, the RR for AF was 1.23 (95% CI, 1.17–1.30) for each 5-unit increase in BMI.<sup>93</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>109</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 $^2$  (HR, 1.09 [95% CI, 1.04–1.13]) compared with 20 to 22.5 kg/m $^2$  (reference) also had an increased risk, with the greatest risk of AF seen for a BMI  $\geq 40$  kg/m $^2$  (HR, 3.45 [95% CI, 2.56–4.64]).
- Weight reduction may prevent AF. In a meta-analysis of 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]). The reduced risk of AF after ablation was seen predominantly among patients who lost  $\geq 10\%$  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]).<sup>110</sup> There was also a lower risk of recurrent AF among patients who lost weight before the ablation procedure.

- Weight loss of  $\geq 5\%$  after treatment with an SGLT-2 inhibitor has been associated with reduced risk of new-onset AF in patients with type 2 diabetes (HR, 0.39 [95% CI, 0.22–0.68]).<sup>111</sup>
- GLP1-RAs, which confer weight reduction, have been shown to reduce AF risk in individuals with type 2 diabetes compared with other glucose-lowering medications (OR, 0.17 [95% CI, 0.04–0.61] versus metformin; OR, 0.23 [95% CI, 0.07–0.73] versus sulfonylurea; OR, 0.20 [95% CI, 0.07–0.86] versus insulin, and OR, 0.18 [95% CI, 0.04–0.66] versus nonsulfonylureas in a network meta-analysis).<sup>112</sup> However, whether GLP1-RA treatment in individuals with overweight/obesity but without diabetes can prevent AF warrants further investigation.
- For patients with overweight/obesity and AF, current AHA guidelines recommend a  $\geq 10\%$  reduction in weight, a BMI  $< 27 \text{ kg/m}^2$ , and at least a 2-MET increase in PA. Bariatric surgery could be considered in appropriate candidates.<sup>107</sup>

### **COVID-19**

- Obesity is a risk factor for severe COVID-19 and COVID-19-associated mortality.<sup>113</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  $< 30 \text{ kg/m}^2$  with an increased risk of death of 1.12 (95% CI, 1.08–1.18) for every 5-kg/ $\text{m}^2$  increase in BMI.<sup>114</sup> This relationship was J shaped with the lowest risk of COVID-19-associated mortality around a BMI of 22 to 24 kg/ $\text{m}^2$ .
- In the AHA COVID-19 registry, obese patients were more likely to be hospitalized with COVID-19 than non-obese patients and had greater multivariable-adjusted risk for the composite outcome of in-hospital death or mechanical ventilation (OR for class 1, 2, and 3 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).<sup>115</sup> There was a significant interaction with age, with severe obesity being associated with a greater risk of in-hospital death only for individuals  $\leq 50$  years of age (HR, 1.36 [95% CI, 1.01–1.84]). Obese patients also had greater risk of VTE (HR, 1.81 [95% CI, 1.22–2.98]).
- The STOP-COVID registry of 5133 patients admitted to critical care units with COVID-19 during March to July 2020 found that CVD risk factors rather than preexisting CVD were the major contributors to 28-day CVD events and mortality, with BMI ranking second (only after age) as the strongest predictor of risk.<sup>116</sup>

### **Complications in Youths**

- Overweight and obesity in youths frequently track into adulthood. In a meta-analysis including

$>200\,000$  participants, children and adolescents with obesity were  $\approx 5$  times more likely to have obesity in adulthood. Approximately 55% of children (7–11 years of age) with obesity will have obesity in adolescence (12–18 years of age), and  $\approx 80\%$  of adolescents with obesity will still have obesity in adulthood ( $\geq 20$  years of age), with  $\approx 70\%$  remaining obese after 30 years of age.<sup>117</sup>

- Children who had parents with obesity on average were at overweight status at 6 years of age (95% CI, 5–7), which is 19 years earlier than those who had parents with normal weight, who on average had overweight status at 25 years of age (95% CI, 24–27).<sup>118</sup>
- In the prospective the i3C Consortium, which examined childhood risk factors at 3 to 19 years of age with risk of future adult cardiovascular events after a mean follow-up of 35 years, elevated BMI was associated with adult CVD risk (HR, 1.45 [95% CI, 1.38–1.53]) per 1-z score increase in childhood BMI.<sup>119</sup> By categories, compared with low-normal weight in childhood, high-normal BMI status (HR, 1.19 [95% CI, 1.01–1.41]), overweight status (HR, 1.92 [95% CI, 1.62–2.27]), and obese status (HR, 3.39 [95% CI, 2.73–4.21]) were all associated with increased risk of adult CVD events.
- In another meta-analysis of 22 studies including  $>5$  million youths 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>120</sup> The associations did not change significantly after adjustment for SES or differ by sex.
- A mendelian randomization study determined that genetically predicted childhood obesity was associated with mild obesity-related diabetes in adulthood (OR, 7.30 [95% CI, 4.17–12.78]) and severe insulin-resistant diabetes in adulthood (OR, 2.76 [95% CI, 1.60–4.74]).<sup>121</sup>
- A recent cohort study assessed 801019 youths 3 to 17 years of age in a health care system in Southern California and found that even high-normal body weight between the 60th and 84th percentiles of BMI for age was associated with incident hypertension (HR, 1.26 [95% CI, 1.20–1.33]) over 5 years compared with youths in the 40th to 59th percentile.<sup>122</sup> Risk of incident hypertension was even greater for overweight (85th–94th percentile: HR, 1.91 [95% CI, 1.81–2.00]), moderately obese (95th–96th percentile: HR, 2.77 [95% CI, 2.61–2.94]), and severely obese ( $\geq 97$ th percentile: HR, 4.94 [95% CI, 4.72–5.18]).
- In an NHANES analysis, obesity in youths (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>123</sup>

## 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 individuals with obesity compared with individuals with normal weight.<sup>124</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 >30 kg/m<sup>2</sup> was associated with an additional \$253 (95% CI, \$167–\$347) cost per year per person.
- 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>124</sup>
- Medical expenditures associated with higher BMI were greater among females.<sup>124</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.
- In another MEPS 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>125</sup>

## Global Burden of Disease

### (See Tables 6-4 and 6-5 and Charts 6-4 and 6-5)

- According to WHO statistics, in 2022, it was estimated that among adults ≥18 years of age globally, 16% (890 million) were obese and 43% (2.5 billion) were overweight, with the worldwide prevalence of obesity doubling between 1990 and 2022.<sup>126</sup>
- In 2022, an estimated 37 million children <5 years of age were overweight and >390 million youths 5 to 19 years of age were overweight, including 160 million (8%) living with obesity.<sup>126</sup>
- The World Obesity Federation's 2024 Obesity Atlas reported that in 2020, 42% of adults globally had overweight or obesity, and this was projected to rise to 54% by 2023. In 2020, 1.39 billion and 0.81 billion adults had overweight ( $\geq 25$ –30 kg/m<sup>2</sup>) and obesity ( $\geq 30$  kg/m<sup>2</sup>), respectively, and this was projected to increase to 1.77 billion and 1.53 billion, respectively, by 2023.<sup>127</sup>
- The prevalence of obesity is increasing more rapidly in lower-income countries. In this same report, it was further estimated that 79% of adults and 88% of children with overweight and obesity will live in low- and middle-income countries by 2035.<sup>127</sup>

- Globally, the GBD Study 2021 reported that elevated BMI ranked 7 (ie, in the top 10) of modifiable risk factors attributable to the burden of CVD, accounting for 95 (95% CI, 1.12–2.91) million deaths attributable to CVD and 3.7 (95% CI, 1.97–5.49) million deaths resulting from any cause.<sup>128</sup> That same year (2021), the DALYs from all causes attributable to high BMI were 1560 per 100000 (95% CI, 711–2380 per 100000).
- Data from the GBD Study indicated that obesity ( $\geq 25$  kg/m<sup>2</sup>) related DALYs rose at a rate of 0.48% annually from 2000 to 2019 (Table 6-4) and were predicted to increase by 39.8% between the years 2020 and 2030. The highest obesity-related DALYs were observed in Eastern Mediterranean and middle-SDI countries.<sup>129</sup> High-SDI countries had the lowest obesity-related death rate (Table 6-4).
- Based on 204 countries and territories in 2021, age-standardized mortality rates attributable to high BMI among regions were lowest for high-income Asia Pacific and highest for southern sub-Saharan Africa, North Africa and the Middle East, and Oceania (Chart 6-4). Globally, high BMI was attributed to 3.71 (95% UI, 1.85–5.66) million total deaths in 2021, an increase of 154.13% (95% UI, 138.15%–170.49%) compared with 1990 (Table 6-5).
- Trends in global CVD attributable to high BMI per 100 000 by measure from 1990 to 2022 for YLDs, YLLs, mortality, and DALYs from the GBD Study are shown in Chart 6-5.<sup>130</sup>
- 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>127</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>131</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.
- Overweight and obesity contribute to significant economic costs globally. A recent analysis estimated that the negative economic impact of overweight and obesity in 2019 across 161 countries was 2.2% of the global GDP.<sup>132</sup> Furthermore, if these trends continue at same rate, the economic impact of overweight and obesity is estimated to rise to 3.3% of the global GDP by 2060, with the largest increases being concentrated in lower-resource countries.
- The World Obesity Federation estimated that the economic impact of an elevated BMI could reach as much as \$4.32 trillion annually by 2035, which is ≈3% of the GDP, an increase from \$1.96 trillion or 2.4% of the global GDP in 2020.<sup>127</sup>

**Table 6-1.** Prevalence of Children and Adolescents 2 to 19 Years of Age With Obesity, by Demographic Characteristics: United States, 2017 to March 2020

Characteristic	Both sexes		Males		Females	
	Sample size, n	Prevalence percentage (95% CI)	Sample size, n	Prevalence percentage (95% CI)	Sample size, n	Prevalence percentage (95% CI)
Total	4749	19.7 (17.9–21.6)	2410	20.9 (18.9–22.9)	2339	18.5 (16.3–21.0)
Age group, y						
2–5	1141	12.7 (10.8–14.8)	566	13.6 (10.8–16.8)	575	11.8 (9.3–14.8)
6–11	1765	20.7 (17.9–23.7)	894	22.9 (19.5–26.5)	871	18.5 (15.2–22.1)
12–19	1843	22.2 (19.7–24.8)	950	22.6 (19.7–25.7)	893	21.7 (18.1–25.7)
Race and ethnicity						
NH White	1471	16.6 (13.7–19.8)	743	17.6 (14.8–20.7)	728	15.4 (11.2–20.5)
NH Black	1270	24.8 (21.6–28.1)	662	18.8 (15.9–22.1)	608	30.8 (26.0–35.8)
NH Asian	420	9.0 (6.5–12.2)	208	13.1 (8.8–18.4)	212	5.2 (2.3–9.9)
Hispanic	1143	26.2 (22.4–30.2)	562	29.3 (23.1–36.0)	581	23.0 (19.6–26.6)
Family income relative to FPL, %						
≤130	1748	25.8 (22.8–29.1)	864	26.4 (22.4–30.8)	884	25.2 (22.3–28.3)
130–350	1514	21.2 (18.5–24.0)	789	20.7 (17.6–24.1)	725	21.7 (18.3–25.3)
>350	956	11.5 (8.9–14.5)	471	15.1 (11.1–19.8)	485	8.2 (5.0–12.5)

Obesity is defined as a body mass index greater than or equal to the age- and sex-specific 95th percentile of the 2000 Centers for Disease Control and Prevention growth charts. Children and adolescents were included and categorized into age categories based on age at examination in months. Pregnant females were excluded from the analysis.

FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al<sup>8</sup> using National Health and Nutrition Examination Survey.<sup>133</sup>

**Table 6-2.** Prevalence of Adults ≥20 Years of Age With Obesity, by Demographic Characteristics: United States, 2017 to March 2020

Characteristic	Both sexes		Males		Females	
	Sample size, n	Prevalence percentage (95% CI)	Sample size, n	Prevalence percentage (95% CI)	Sample size, n	Prevalence percentage (95% CI)
Total (age adjusted)	8295	41.9 (39.4–44.3)	4051	41.8 (37.7–45.9)	4244	41.8 (39.3–44.4)
Total age (crude)	8295	41.9 (39.4–44.3)	4051	41.6 (37.4–45.8)	4244	42.1 (39.6–44.8)
Age group, y						
20–39	2489	39.8 (35.3–44.3)	1177	39.9 (33.1–47.0)	1312	39.6 (34.9–44.3)
40–59	2765	44.3 (41.3–47.4)	1320	45.9 (41.0–50.9)	1445	42.8 (38.7–47.1)
≥60	3041	41.5 (38.4–44.7)	1554	38.4 (32.9–44.1)	1487	44.2 (40.5–47.9)
Race and ethnicity						
NH White	2866	41.4 (37.9–44.9)	1432	43.1 (37.4–48.9)	1434	39.6 (36.2–43.0)
NH Black	2213	49.9 (47.2–52.6)	1058	40.4 (36.3–44.6)	1155	57.9 (54.0–61.7)
NH Asian	1014	16.1 (13.6–18.9)	466	17.6 (13.7–22.2)	548	14.5 (11.4–18.1)
Hispanic	1806	45.6 (42.9–48.2)	880	45.2 (41.7–48.8)	926	45.7 (42.4–49.1)
Family income relative to FPL, %						
≤130	2019	43.9 (41.7–46.1)	892	38.6 (33.6–43.8)	1127	47.9 (44.0–51.7)
130–350	2815	46.5 (43.6–49.4)	1400	43.9 (40.5–47.3)	1415	48.8 (44.5–53.0)
>350	2312	39.0 (34.2–43.9)	1189	42.4 (34.9–50.2)	1123	35.1 (31.1–39.3)
Education						
Less than high school diploma	1538	40.1 (36.5–43.8)	803	35.3 (30.4–40.6)	735	45.3 (41.0–49.7)
High school diploma or some college	4709	46.4 (44.0–48.9)	2259	45.9 (41.9–50.0)	2450	46.8 (43.9–49.8)
College degree or above	2037	34.2 (30.1–38.5)	984	36.3 (29.0–44.1)	1053	32.2 (28.5–36.1)

Obesity is defined as a body mass index ≥30 kg/m<sup>2</sup>. Except when reported as crude estimates, estimates were age adjusted by the direct method to the projected US Census 2000 population using the age groups 20 to 39, 40 to 59, and ≥60 years. Statistical comparisons were not performed on crude estimates. Pregnant individuals were excluded from the analysis.

FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al<sup>8</sup> using National Health and Nutrition Examination Survey.<sup>133</sup>

**Table 6-3.** Prevalence of Adults ≥20 Years of Age With Severe Obesity, by Demographic Characteristics, United States, 2017 to March 2020

Characteristic	Both sexes		Males		Females	
	Sample size, n	Prevalence percentage (95% CI)	Sample size, n	Prevalence percentage (95% CI)	Sample size, n	Prevalence percentage (95% CI)
Total (age adjusted)	8295	9.2 (8.0–10.6)	4051	6.6 (5.3–8.1)	4244	11.7 (10.0–13.7)
Total age (crude)	8295	9.0 (7.8–10.3)	4051	6.4 (5.1–8.0)	4244	11.4 (9.7–13.3)
Age group, y						
20–39	2489	9.7 (7.7–12.0)	1177	7.0 (4.7–10.1)	1312	12.4 (9.8–15.3)
40–59	2765	10.7 (8.9–12.8)	1320	8.1 (5.5–11.5)	1445	13.2 (10.0–16.9)
≥60	3041	6.1 (5.2–7.2)	1554	3.5 (2.6–4.5)	1487	8.3 (6.8–10.0)
Race and ethnicity						
NH White	2866	9.5 (7.9–11.3)	1432	6.8 (5.1–8.9)	1434	12.0 (9.8–14.6)
NH Black	2213	14.0 (11.9–16.3)	1058	7.9 (6.3–9.7)	1155	19.1 (16.0–22.6)
NH Asian	1014	1.8 (1.0–2.8)	466	2.4 (0.9–5.1)	548	1.1 (0.2–3.3)
Hispanic	1806	7.4 (6.1–8.9)	880	6.0 (4.2–8.4)	926	8.8 (7.0–10.9)
Family income relative to FPL, %						
≤130	2019	10.9 (8.2–13.9)	892	7.4 (5.3–9.9)	1127	13.5 (10.0–17.7)
130–350	2815	11.8 (10.1–13.6)	1400	8.8 (7.1–10.8)	1415	14.5 (11.8–17.4)
>350	2312	6.9 (5.4–8.6)	1189	4.6 (2.9–6.8)	1123	9.5 (7.0–12.4)
Education						
Less than high school diploma	1538	7.6 (5.8–9.6)	803	3.3 (2.0–5.1)	735	12.2 (9.6–15.3)
High school diploma or some college	4709	11.3 (10.3–12.4)	2259	9.0 (7.2–11.0)	2450	13.5 (11.6–15.7)
College degree or above	2037	6.1 (4.3–8.5)	984	3.3 (1.9–5.4)	1053	8.5 (5.7–12.2)

Severe obesity is defined as a body mass index  $\geq 40 \text{ kg/m}^2$ . Except when reported as crude estimates, estimates were age adjusted by the direct method to the projected US Census 2000 population using the age groups 20 to 39, 40 to 59, and  $\geq 60$  years. Statistical comparisons were not performed on crude estimates. Pregnant individuals were excluded from the analysis.

FPL indicates federal poverty level; and NH, non-Hispanic.

Source: Adapted from Stierman et al<sup>8</sup> using National Health and Nutrition Examination Survey.<sup>133</sup>

**Table 6-4.** DALYs and Mortality of Individuals With Obesity From the GBD Study 2019

	DALYs				Mortality			
	n (Year 2019)	Age-standardized DALYs per 100 000 in 2019	Annual percentage change 2000–2019	P value	n (Year 2019)	Age-standardized death rate per 100 000 in 2019	Annual percentage change 2000–2019	P value
Overall	160 265 357 (105 969 034–218 870 439)	1933 (1277–2640)	0.48 (0.38–0.58)	<0.001	5019 360 (3223 364–7110)	62.59 (39.92–89.13)	-0.01 (−0.13 to 0.11)	0.881
Sex								
Male	82 840 928 (52 774 866–115 149 374)	2070 (1312–2889)	0.74 (0.63–0.85)	<0.001	2477 387 (1515 677–3568 860)	66.55 (39.76–97.21)	0.33 (0.15–0.52)	<0.001
Female	77 424 429 (53 176 344–104 577 664)	1790 (1229–2417)	0.25 (0.17–0.34)	<0.001	2541 973 (1683 590–3561 055)	58.14 (38.53–81.39)	-0.27 (−0.38 to −0.16)	<0.001
WHO region								
Africa	12 324 913 (8 371 480–16 578 508)	2221 (1486–3025)	0.87 (0.80–0.95)	<0.001	361 539 (237 293–499 448)	79.20 (50.92–111.98)	0.86 (0.78–0.94)	<0.001
Eastern Mediterranean	17 923 202 (12 584 59–23 768 056)	3721 (2591–4954)	1.04 (0.92–1.15)	<0.001	522 392 (352–707 166)	130.97 (87.38–179.78)	1.01 (0.87–1.14)	<0.001

(Continued)

**Table 6-4.** Continued

	DALYs				Mortality			
	n (Year 2019)	Age-standardized DALYs per 100 000 in 2019	Annual percentage change 2000–2019	P value	n (Year 2019)	Age-standardized death rate per 100 000 in 2019	Annual percentage change 2000–2019	P value
Europe	32 474 360 (22 183 037–43 473)	2206 (1519–2946)	−0.90 (−1.10 to −0.70)	<0.001	1 243 937 (810 492–1 717 794)	75.41 (49.74–103.02)	−1.16 (−1.41 to −0.89)	<0.001
Region of Americas	30 395 450 (21 207 720–39 622 411)	2457 (1725–3200)	0.17 (0.09–0.26)	<0.001	940 265 (625 116–1 268 476)	72.83 (48.62–97.90)	−0.27 (−0.44 to −0.10)	0.002
Southeast Asia	33 558 095 (20 816 783–46 899 343)	1786 (1096–2513)	2.63 (2.48–2.77)	<0.001	918 795 (550 880–1 327 038)	53.60 (31.54–78.85)	2.37 (1.93–2.81)	<0.001
Western Pacific	33 058 032 (16 759 032–52 761 895)	1229 (624–1963)	1.22 (0.98–1.46)	<0.001	1 015 716 (483 041–1 701 367)	38.38 (18.10–64.89)	0.87 (0.48–1.26)	<0.001
SDI								
High	26 809 080 (18 213 631–36 348 663)	1631 (1121–2198)	−0.14 (−0.19 to −0.09)	<0.001	901 712 (573 462–1 289 616)	45.65 (29.76–63.76)	−1.02 (−1.20 to −0.84)	<0.001
High-middle	39 587 645 (26 141 026–54 009 607)	1982 (1312–2706)	−0.91 (−1.09 to −0.73)	<0.001	1 376 628 (877 166–1 953 869)	69.14 (44.00–98.24)	−1.21 (−1.44 to −0.99)	<0.001
Middle	55 465 889 (36 710 764–75 810 218)	2119 (1388–2920)	1.26 (1.18–1.35)	<0.001	1 647 (1 051 542–2 333 137)	68.92 (43.02–99.26)	1.05 (0.92–1.19)	<0.001
Low-middle	28 007 122 (17 469 919–39 227 162)	1892 (1174–2682)	2.41 (2.18–2.63)	<0.001	804 748 (490 930–1 158 654)	60.34 (36.27–88.37)	2.07 (1.79–2.36)	<0.001
Low	10 276 830 (6 088 926–14 897 027)	1698 (990–2492)	1.87 (1.79–1.94)	<0.001	285 468 (162 714–429 330)	55.55 (31.38–85.09)	1.68 (1.59–1.78)	<0.001

Data in the parentheses are 95% uncertainty intervals.

DALY indicates disability-adjusted life-year; GBD, Global Burden of Disease; SDI, sociodemographic index; and WHO World Health Organization.

Source: Reprinted from Chong et al.<sup>129</sup> Copyright © 2023 The Authors. Published by Elsevier Ltd. This is an open access article under the terms of the Creative Commons CC BY-NC-ND License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

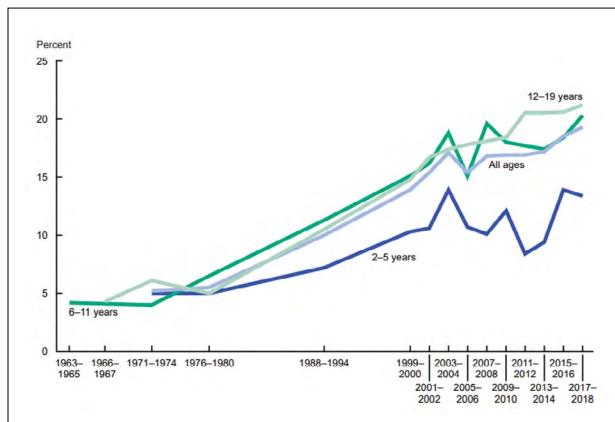
**Table 6-5.** Deaths Caused by High BMI Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	3.71 (1.85 to 5.66)	1.70 (0.86 to 2.64)	2.01 (0.98 to 3.08)
Percent change (%) in total number, 1990–2021	154.13 (138.15 to 170.49)	168.61 (148.95 to 187.41)	143.08 (125.70 to 162.94)
Percent change (%) in total number, 2010–2021	42.81 (36.71 to 48.87)	43.79 (36.29 to 51.45)	41.99 (34.92 to 49.16)
Rate per 100,000, age standardized, 2021	44.23 (22.01 to 67.64)	44.90 (23.01 to 70.17)	43.26 (21.08 to 66.05)
Percent change (%) in rate, age standardized, 1990–2021	8.15 (1.37 to 15.14)	15.06 (6.35 to 22.98)	4.06 (−3.28 to 11.93)
Percent change (%) in rate, age standardized, 2010–2021	3.38 (−0.84 to 7.83)	4.85 (−0.20 to 10.42)	2.60 (−2.47 to 8.09)
PAF (%), all ages, 2021	5.46 (2.74 to 8.27)	4.50 (2.29 to 6.83)	6.67 (3.22 to 10.14)
Percent change (%) in PAF, all ages, 1990–2021	72.59 (62.49 to 83.38)	76.83 (66.55 to 88.24)	71.39 (60.75 to 83.63)
Percent change (%) in PAF, all ages, 2010–2021	11.66 (8.11 to 15.42)	10.82 (7.45 to 14.61)	12.99 (8.99 to 17.10)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; PAF, population attributable fraction; and UI, uncertainty interval.

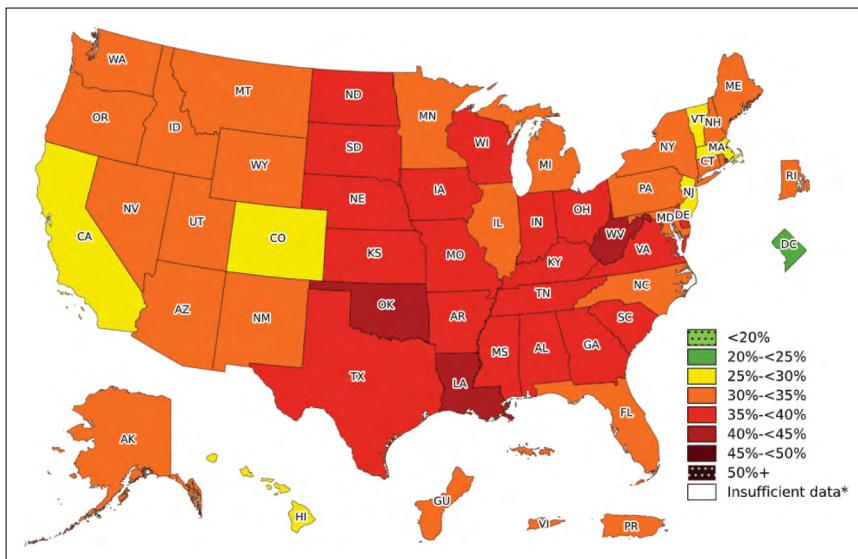
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>134</sup>



**Chart 6-1. Trends in obesity among children and adolescents 2 to 19 years of age, by age, United States, 1963 to 1965 through 2017 to 2018.**

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

Source: Reprinted from Fryar et al<sup>12</sup> using National Health and Nutrition Examination Survey.<sup>133</sup>

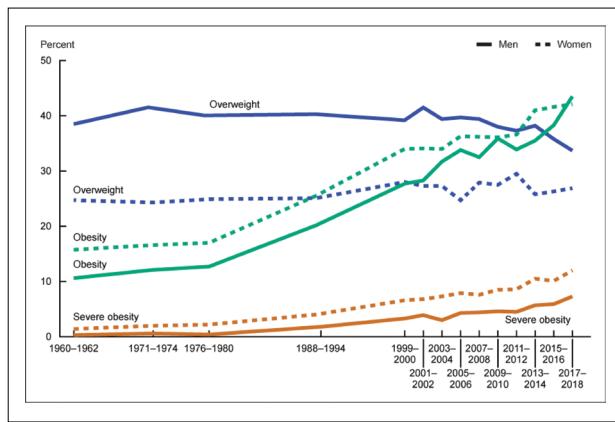


**Chart 6-2. Prevalence of self-reported obesity among US adults by state and territory, BRFSS, 2022.**

BRFSS indicates Behavioral Risk Factor Surveillance System.

\*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

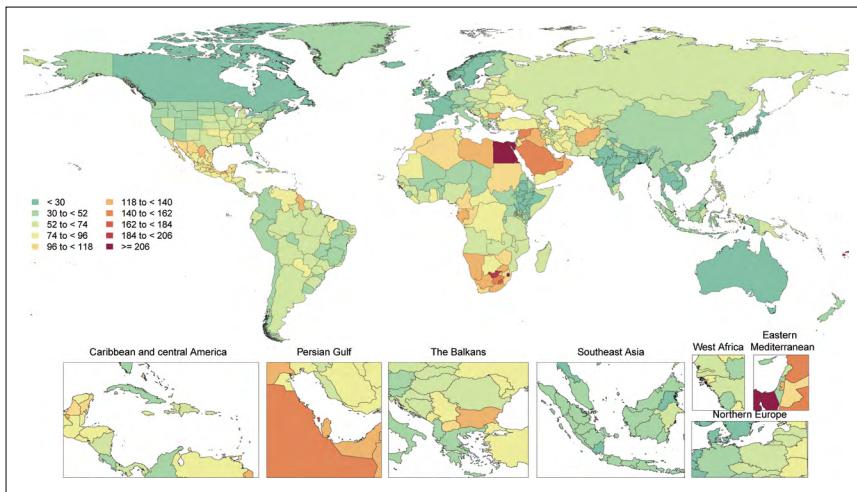
Source: Reprinted from Centers for Disease Control and Prevention Obesity Prevalence Map using BRFSS.<sup>16</sup>



**Chart 6-3. Age-adjusted trends in overweight, obesity, and severe obesity among males and females 20 to 74 years of age: United States, 1960 to 1962 through 2017 to 2018.**

Data are age adjusted by the direct method to US Census 2000 estimates using age groups 20–39, 40–59, and 60–74. Overweight is body mass index of 26.0–29.9 kg/m<sup>2</sup>. Obesity is body mass index at or above 30.0 kg/m<sup>2</sup>. Severe obesity is body mass index at or above 40.0 kg/m<sup>2</sup>. Pregnant women are excluded from the analysis.

Source: Reprinted from Fryar et al<sup>19</sup> using National Health and Nutrition Examination Survey.<sup>133</sup>

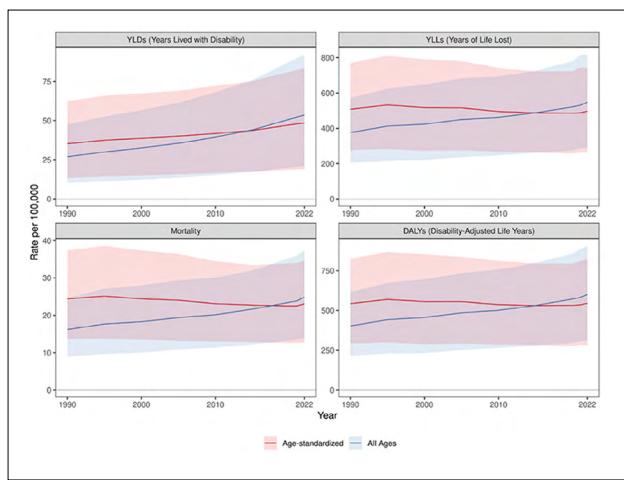


**Chart 6-4. Age-standardized mortality rates attributable to high BMI per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>134</sup>



**Chart 6-5. Global CVD attributable to high BMI estimates per 100 000 by measure with shaded 95% uncertainty, trends from 1990 to 2022 for YLD, YLL, mortality, and DALYs for all ages and age standardized.**

BMI indicates body mass index; CVD, cardiovascular disease; DALY, disability-adjusted life year; YLD, years of life lived with disability or injury; and YLL, years of life lost to premature mortality.

Source: Reprinted from Mensah et al.<sup>130</sup> Copyright © 2023, with permission from the American College of Cardiology Foundation.

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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 a primary causal risk factor for the development of atherosclerosis and CVD. TC levels in the blood have traditionally been 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. More recently, AHA's Life's Essential 8 has adopted non-HDL-C (TC minus HDL-C) as a key metric to assess lipid health.<sup>1</sup> However, 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 causally linked to ASCVD based on data from epidemiological, mendelian randomization, and GWASs. The multisociety 2018 Cholesterol Clinical Practice Guideline and the 2019 CVD Primary Prevention Clinical Practice Guidelines focus predominantly on the use of LDL-C-lowering therapy to reduce ASCVD risk.<sup>2,3</sup> The 2022 ACC expert consensus decision pathway discusses the role of nonstatin therapy in the management of ASCVD risk.<sup>4</sup>

### Prevalence of High TC

#### Youths

**(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>5</sup>):

The 2025 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 2025. 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 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
  - 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>5</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 youths 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 youths 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>6</sup>

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

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

- Among adults  $\geq$ 20 years of age, the mean TC level in 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>5</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 TC  $\geq$ 200 mg/dL and  $\geq$ 240 mg/dL among US adults  $\geq$ 20 years of age in 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>5</sup>) is shown overall and by sex and race and ethnicity in Table 7-1 and Charts 7-3 and 7-4.

- The US Department of Health and Human Services Healthy People 2030 target is a mean population TC level of 186.4 mg/dL for adults,<sup>7</sup> which was 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>5,7</sup>

## Prevalence of Abnormal Levels of Lipid Subfractions

### **LDL-C**

#### *Youths*

*See Chart 7-1*

- 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>5</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). Further specification of NH Asian subgroups is not available.
- LDL-C levels  $\geq 130$  mg/dL were present in 5.0% of male adolescents and 4.6% of female adolescents during 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>5</sup>).

#### *Adults*

*(See Table 7-1)*

- In 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>5</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) in US adults was 25.5% (unpublished NHLBI tabulation using NHANES<sup>5</sup>; Table 7-1).

- Among adults who reported CAD between 2015 and 2020, the age-adjusted mean LDL-C was 94.4 mg/dL (95% CI, 90.3–98.5).<sup>8</sup> In these adults, 73.5% (95% CI, 68.2%–78.8%) had an LDL-C  $\geq 70$  mg/dL, and 88.1% (95% CI, 83.6%–92.6%) had an LDL-C  $\geq 55$  mg/dL.

## **Lipoprotein(a)**

Lipoprotein(a) is an LDL-like particle, an apolipoprotein(a) covalently bound to apolipoprotein B<sub>100</sub> by disulfide bonds. Some professional societies recommend screening of lipoprotein(a) in individuals with a personal or family history of ASCVD or who are at high risk of ASCVD. An update to the 2019 US National Lipid Association scientific statement on the use of lipoprotein(a) in clinical practice recommended that lipoprotein(a) be measured once in every adult for risk stratification and to guide early, more intensive risk factor management.<sup>9</sup>

- 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 risk of CHD, stroke, valvular aortic stenosis, and even HF and AF.
- Among  $\approx 460\,000$  middle-aged adults in the UK Biobank enrolled between 2006 and 2010, median serum lipoprotein(a) concentration was 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, as well as 19 nmol/L in White adults, 31 nmol/L in South Asian adults, 75 nmol/L in Black adults, and 16 nmol/L in Chinese adults.<sup>10</sup>
- Among 16 117 participants in the HCHS/SOL, overall median lipoprotein(a) molar concentration was 19.7 nmol/L, with significant heterogeneity ranging from 12 nmol/L in Mexican participants to 41 nmol/L in those with a Dominican background.<sup>11</sup>
- In the INTERHEART study, median lipoprotein(a) levels and proportions with lipoprotein(a)  $> 50$  mg/dL were 7.8 mg/dL and 3.0% in China, 9.6 mg/dL and 13.0% in Europe, 10.2 mg/dL and 7.0% in Southeast Asia, 11.5 mg/dL and 15.0% in Latin America, 13.8 mg/dL and 9.0% in South Asia, 15.3 mg/dL and 12.0% in the Middle East, and 27.2 mg/dL and 27.0% in Africa.<sup>12</sup>

## **HDL Cholesterol**

#### *Youths*

*(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>5</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) were present in 5.9% of males and 8.9% of females in 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>5</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>5</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) were present in 19.3% of male adolescents and 8.6% of female adolescents in 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>5</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>5</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 males.

### *Triglycerides*

#### *Youths*

#### *(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>5</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
- Elevated triglycerides (≥90 mg/dL) occurred in 20.8% of male adolescents and 23.5% of female adolescents during 2017 to 2020 (unpublished NHLBI tabulation using NHANES<sup>5</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>13</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>5</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>5</sup>).

### *Secular Trends in TC and Lipid Subfractions*

#### *Youths*

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

- Between 1999 and 2016, trends in mean levels of TC, HDL-C, and non-HDL-C among youths 6 to 19 years of age demonstrated improved levels. Levels of LDL-C, triglycerides, and apolipoprotein B also improved among adolescents 12 to 19 years of age

over a similar period (data not available for younger children; Chart 7-1).

- The proportion of youths 6 to 19 years of age with ideal levels of 3 cholesterol measures (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 ideal levels of 6 cholesterol measures (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 (Chart 7-1).

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

#### *(See Chart 7-2)*

- Mean age-adjusted TC levels decreased in the US population from 197 mg/dL in 2007 to 2008 to 189 mg/dL in 2017 to 2018.<sup>14</sup> In females, mean TC decreased from 199 mg/dL in 2007 to 2008 to 192 mg/dL in 2017 to 2018. In males, mean TC decreased from 195 mg/dL in 2007 to 2008 to 185 mg/dL in 2017 to 2018.
- The prevalence of high TC ( $\geq 240$  mg/dL) has decreased over time, from 18.3% (95% CI, 16.3%–20.3%) of adults in 1999 to 2000 to 10.5% (95% CI, 9.7%–11.3%) in 2017 to 2018.<sup>15</sup>
  - From 1999 to 2020, mean serum TC for adults  $\geq 20$  years of age decreased across all subgroups of race and ethnicity (Chart 7-2).
  - Declines in mean TC levels were also observed among adults receiving lipid-lowering medication, from 206 mg/dL in 2005 to 2006 to 187 mg/dL in 2015 to 2016.<sup>16</sup>
  - Among adults 20 to 44 years of age in the United States, prevalence of hyperlipidemia (defined as TC  $\geq 200$  mg/dL or a health care diagnosis of high cholesterol) decreased from 40.5% in 2009 to 2010 to 36.1% in 2017 to 2020.<sup>17</sup>
  - In  $\approx 350\,000$  patients who were 40 to 79 years of age in the Kaiser Permanente Southern California health system with lipid information before (March 2019–March 2020) and during (December 2020–December 2021) the COVID-19 pandemic, the proportion with elevated TC  $\geq 240$  mg/dL increased from 9.9% to 10.8%.<sup>18</sup>
- Age-adjusted mean LDL-C decreased among US adults from 116 mg/dL in 2007 to 2008 to 111 mg/dL in 2017 to 2018, with similar patterns in females and males.<sup>14</sup>

- 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>5</sup>).
- Mean HDL-C levels increased statistically significantly between 2007 to 2008 and 2017 to 2018 in female (from 57 to 58 mg/dL;  $P_{trend} = 0.002$ ) and male (from 46 to 48 mg/dL;  $P_{trend} = 0.001$ ) adults in the United States.<sup>14</sup>
- The prevalence of low HDL-C ( $< 40$  mg/dL) among US adults declined from 22.2% in 2007 to 2008 to 16.0% in 2017 to 2018.<sup>15</sup>
- Geometric mean triglyceride levels decreased between 2007 to 2008 and 2017 to 2018 in female (from 104 to 86 mg/dL) and male (from 122 to 98 mg/dL) adults in the United States.<sup>14</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>19</sup>

### **Family History and Genetics**

- GWASs in hundreds of thousands of individuals of diverse ancestry, in addition to the 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>20–24</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>25</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>25,26</sup>
- With the use of whole-genome sequencing across diverse ancestries in 66 000 individuals, 428 million variants were interrogated, and a rare noncoding variant model for blood lipids was characterized.<sup>27</sup> Novel associations were replicated in 45 000 independent samples with array-based genotyping.
- 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>28</sup>

- Furthermore, CAD risk conferred by LDL-C is modulated polygenically. One study showed that among individuals with high polygenic risk (defined as the highest decile of PRS), the increase in the point estimate of the HR for each LDL-C bin was almost double compared with individuals in the intermediate PRS group (defined as the second to ninth PRS deciles).<sup>29</sup> Relative to LDL-C <100 mg/dL, individuals with high PRS and LDL-C 130 to <160 mg/dL showed an increased risk (HR, 2.23 [95% CI, 1.08–4.59]) comparable to the risk in those with intermediate PRS and LDL-C ≥190 mg/dL (HR, 2.34 [95% CI, 1.75–3.14]). Conversely, CAD risk in individuals in the low PRS group (lowest decile of PRS) did not follow the stepwise increase in risk relative to LDL-C <100 observed in the other PRS groups.
- 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>30</sup>
- Mendelian randomization studies: These studies support a causal link between LDL-C, triglycerides, non-HDL-C, apolipoprotein B, and cardiovascular CVD. However, there is no clear evidence for a causal role of HDL-C or apolipoprotein A1.<sup>31–36</sup>

## Familial Hypercholesterolemia

- FH is an autosomal codominant genetic disorder associated with pathogenic variants in *LDLR*, *APOB*, *LDLRAP1*, and *PCSK9*, which affect LDL-C uptake and clearance.<sup>37,38</sup> Fewer than 10% of patients with FH have actually been diagnosed.<sup>39</sup>
- According to a meta-analysis 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>40</sup>
- Individuals with the FH phenotype (LDL-C ≥190 mg/dL) experience an acceleration in CHD risk by 10 to 20 years in males and 20 to 30 years in females.<sup>41</sup> However, individuals with LDL-C ≥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 ≥190 mg/dL without pathogenic variants.<sup>37</sup>
  - Compared with individuals with LDL-C <130 mg/dL and no pathogenic variant, those with both LDL-C ≥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 increased 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 18300 PY of follow-up) compared with the total Norwegian population (24 incident cases compared with 3.1 expected cases).<sup>42</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>43</sup> Among participants with a pathogenic variant associated with FH compared with those without a pathogenic variant associated with FH, the 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>44</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 of cardiovascular events (1% versus 26%) and death resulting from cardiovascular causes (0% versus 7%) by 39 years of age compared with affected parents.<sup>45</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>46</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>47</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 a 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>48</sup> These figures are similar to the medians reported for 8 European countries, although there is substantial variation between countries.<sup>49</sup>
- Cascade screening, meaning cholesterol testing for all first-degree relatives of patients with FH, can effectively identify affected family members who would benefit from therapeutic intervention.<sup>50</sup> A systematic review of 10 studies of cascade testing for FH identified that the average yield [diagnostic yield=positive cases (n)/total tested (n)×100] was 44.8%, and the mean number of new cases per index case was 1.65.<sup>51</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>52</sup>
- In a report of 24 pediatric patients with biallelic (homozygous or compound heterozygous) FH in Germany, the mean age at diagnosis was 6.3 years (SD, 3.4 years), and the mean LDL-C at diagnosis was 752 mg/dL (SD, 193 mg/dL). Twenty-one 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 of 510 mg/dL (SD, 201 mg/dL). In contrast, 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 (no ASCVD events or interventions) over a mean follow-up of 17.2 years (SD, 5.6 years).<sup>53</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 as high as 14%. Familial combined hyperlipidemia has a heterogeneous clinical presentation within families and individuals, including fluctuating elevations in LDL-C or triglycerides, as well as elevated apolipoprotein B levels. Environmental interactions are essential in familial combined hyperlipidemia, and metabolic comorbidities are common. Familial combined hyperlipidemia remains underdiagnosed.<sup>54</sup>

## Screening

- According to BRFSS 2021, the median crude prevalence of adults reporting that they had their blood cholesterol checked within the past 5 years across all states and the District of Columbia was 85.2%. In addition, 10.8% reported that they never had it checked, and 3.5% 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 (90.1%) and Puerto Rico (93.5%), whereas the state with the lowest percentage was Maine (64.7%).<sup>55</sup>
- From 2017 to 2018, the proportion of US adults with cholesterol levels screened in the preceding 5 years was 65.8% for Hispanic adults, 75.0% for NH Asian adults, 70.7% for NH Black adults, and 74.1% for NH White adults.<sup>56</sup>
- Among US adults with severe dyslipidemia (LDL-C >190 mg/dL), 78.0% (SE, 4.8%) reported cholesterol evaluation in the preceding 5 years, with no significant change in screening rates between 2011 to 2012 and 2017 to March 2020.<sup>57</sup>
- In the United States, universal cholesterol screening with a lipid profile 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>2,58</sup>
  - In a survey of 472 clinicians in the United States, 64.8% of pediatricians and 34.1% of family medicine physicians reported completing lipid screening of eligible pediatric-age patients within the preceding year.<sup>59</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>60</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>61</sup>
- Screening for lipoprotein(a) is uncommon, with region- and system-level variation. An analysis of health claims data for  $>9000$  patients in the United States showed that only 0.6% of primary prevention and 0.7% of secondary prevention patients with laboratory data had lipoprotein(a) levels measured.<sup>62</sup> Among 5 553 654 adults who received care across 6 medical centers in the University of California health system between 2012 to 2021, 0.3% had lipoprotein(a) testing done.<sup>63</sup> Those tested were more likely to be older, male, and White and to have a greater burden of CVD. Lipoprotein(a) testing was performed in 1.8% of patients who had a lipid panel checked, but lipoprotein(a) testing was still  $<5\%$  even in those with a personal or family history of ASCVD, with little improvement in testing over the past decade. In comparison, among 2 412 020 patient charts in the Hartford Health network in Connecticut from 2017 to 2022, 0.25% had lipoprotein(a) measured; those who had a measurement were more likely to be younger and NH.<sup>64</sup> Among patients in the Optum Clininformatics database receiving lipid-lowering treatment and with lipid measures, only 0.7% of secondary prevention and 0.6% of primary prevention patients had lipoprotein(a) test results.<sup>62</sup>
- In the Mass General Brigham health care system in the Northeast United States between 2000 and 2023, lipoprotein(a) testing was done in 5.8% of 465 814 patients with CHD, with Black patients and female patients having lower rates of testing.<sup>65</sup> Among  $\approx 65\,000$  adults without CHD who

had a 10-year ASCVD risk between 5% and  $<20\%$  between 2010 and 2012, only 4.4% underwent lipoprotein(a) testing.

## Awareness

- According to BRFSS 2021 data, 35.6% of US adults report having been told that they have high cholesterol (although objective lipid levels are not available for comparison in this sample).<sup>55</sup> The age-adjusted percentage of adults reporting that they have been told they have high cholesterol was highest in Puerto Rico (36.9%), West Virginia (34.1%), and Virginia (34.1%) and lowest in Montana (25.1%).
- Among 73 771 Latino immigrants in the United States evaluated between 2010 and 2018 in the NHIS, the adjusted prevalence of self-reported high cholesterol (reflecting cholesterol awareness) was 34.1% in Puerto Rican adults, 33.5% in Mexican adults, 30.9% in Cuban adults, 29.5% in Dominican adults, 25.4% in South American adults, and 24.7% in Central American adults.<sup>66</sup>
- 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>16</sup>
- Awareness of hypercholesterolemia among US adults with severe dyslipidemia ( $\text{LDL-C} > 190 \text{ mg/dL}$ ) remained stable from 2011 to 2012 (48.1% [SE, 5.5%]) to 2017 to March 2020 (51.9% [SE, 5.8%]).<sup>57</sup>
- In US adults in NHANES from 1999 to 2020 among those with  $\text{LDL-C} 160$  to  $189 \text{ mg/dL}$ , the proportion who were unaware and untreated declined from 52.1% (95% CI, 41.0%–63.0%) in 1999 to 2000 to 42.7% (95% CI, 33.6%–52.3%, representing 6.1 million people) in 2017 to 2020.<sup>67</sup> For adults with  $\text{LDL-C} \geq 190 \text{ mg/dL}$ , this proportion declined from 40.8% (95% CI, 26.9%–56.3%) in 1999 to 2000 to 26.8% (95% CI, 12.6%–48.2%, representing 1.4 million people) in 2017 to 2020.
- Among young adults in the United States who were 20 to 39 years of age with  $\text{LDL-C}$  at least  $130 \text{ mg/dL}$ , 23.3% were aware of having high cholesterol in NHANES 2015 to 2020.<sup>68</sup>
- Among US adults assessed in NHANES 2007 to 2016, awareness of high blood cholesterol (defined as being told by a health care professional that they had high blood cholesterol) was 25.2% in heterosexual females, 26.2% in lesbian females, 14.5% in bisexual females, and 18.9% in females who reported another sexual identity, as well as 27.1% in heterosexual males, 28.2% in gay males, 19.0% in bisexual males, and 8.4% in males who reported another sexual identity.<sup>69</sup>

## 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>7</sup>
- In an analysis of 5218 adults with ASCVD in NHANES 1999 to 2020, there was a significant increase in the use of lipid-lowering medications among all racial and ethnic subgroups between 1999 and 2020 (Black, 18.31%; Hispanic or Latino, 26.02%; and White, 23.50%). Compared with White individuals, the use of lipid-lowering medications between 2017 and 2020 remained significantly lower among Black individuals ( $-24.07\%$ ;  $P<0.001$ ) and Hispanic and Latino individuals ( $-17.56\%$ ;  $P=0.005$ ).<sup>70</sup>
- Within the Optum Clininformatics database between 2015 and 2018 among patients with ASCVD (N=1424 893), only 43.7% had at least 1 LDL-C measurement at baseline, and during the 31-month follow-up, about one-quarter of the patients did not receive any lipid treatment; among those treated, 89.5% received statins and 10.5% received nonstatin lipid-lowering therapy.<sup>71</sup> Fewer than half (47.6%) of the patients were adherent to the index treatment during the 12-month follow-up.
- In a study of lipid-lowering therapy after 81 372 events in US adults in the Veterans Affairs Health System, lipid-lowering therapy intensification was most common (82.5%) among those not taking lipid-lowering therapy before the coronary event.<sup>72</sup> Having higher baseline LDL-C, having lipid levels checked, and attending a cardiology visit after the event were associated with a greater likelihood of intensification of lipid-lowering therapy.
- Among US adults with diabetes who were 40 to 75 years of age, statin use increased from 48.5% in 2011 to 2014 to 53.0% in 2015 to 2018.<sup>73</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>16</sup>
- In US adults without a history of CVD at borderline (5%–7.5%) or intermediate (7.5%–20%) 10-year ASCVD risk, 55% and 53%, respectively, had at least 1 ASCVD risk-enhancing factor, as defined by the 2019 CVD Primary Prevention Clinical Practice Guidelines.<sup>3,74</sup> Among those with any risk-enhancing factors, only 23% were on a statin for primary prevention. Compared with White adults (27.4% statin use), statin use was lower in Black adults (20.0%) and Hispanic adult (15.4%) and comparable in Asian adults (25.5%), a pattern similar across ASCVD risk strata.<sup>75</sup>
- In 3 232 153 patients with a history of ASCVD between 2017 and 2018 in the Cerner electronic health record database of 92 US health systems, 76.1% were on statin medications.<sup>76</sup> Patients with PAD (OR, 0.40 [95% CI, 0.37–0.42]) and cerebrovascular disease (OR, 0.75 [95% CI, 0.70–0.80]) had lower odds of using high-intensity statins compared with patients with CAD. Nonstatin lipid-lowering therapy use was low (ezetimibe, 4.4%; PCSK9 inhibitors, 0.7%).
- Among US adults assessed in NHANES 2007 to 2016, use of lipid-lowering medication was 7.7% in heterosexual females, 0% in lesbian females, 1.1% in bisexual females, and 5.5% in females who reported another sexual identity, as well as 9.6% in heterosexual males, 8.5% in gay males, 9.6% in bisexual males, and 0% in males who reported another sexual identity.<sup>69</sup>
- In  $\approx 350 000$  patients who were 40 to 79 years of age in the Kaiser Permanente Southern California health system with lipid information before (March 2019–March 2020) and during (December 2020–December 2021) the COVID-19 pandemic, statin use increased from 37.7% to 42.4%.<sup>18</sup>
- In an analysis of adults in NHANES from 2017 to 2020 examining statin use in different ASCVD risk groups, the proportion not on statin therapy was highest in those with LDL-C  $\geq 190$  mg/dL (92.8%) and those with intermediate ASCVD risk plus risk-enhancing factors (74.6%), followed by those with high ASCVD risk (59.4%), those with diabetes (54.8%), and those with established ASCVD (41.5%).<sup>77</sup>
- Among 81 332 participants with diabetes in the All of Us Program, 49.8% were not on statin therapy.<sup>78</sup> Only 18.2% of those with diabetes and ASCVD were on high-intensity statins. Overall, 5.1% were using ezetimibe and 0.6% were using PCSK9 inhibitors. Overall, 1.9% of participants with triglycerides  $\geq 150$  mg/dL were on icosapent ethyl.
- In the PROMINENT trial of  $>10 000$  patients with type 2 diabetes, mild to moderate hypertriglyceridemia (200–499 mg/dL), and HDL-C  $\leq 40$  mg/dL; on guideline-directed lipid-lowering therapy; or with adverse reactions to statins who were randomized to receive pemetrisib or placebo, there was no significant difference between groups in the primary outcome of MACEs (HR, 1.03 [95% CI, 0.91–1.15]). The group receiving pemetrisib showed an increase in LDL-C and apolipoprotein B levels.<sup>79</sup>
- In an open-label 4-year extension of the ORION-1 trial (ORION-3), twice-yearly inclisiran resulted in a 4-year averaged LDL-C reduction of 44% (95% CI, 41%–47%).<sup>80</sup>
- In a patient-level analysis of 3655 patients in the ORION-9, -10, and -11 trials who had heterozygous

FH, ASCVD, or ASCVD risk equivalent on maximally tolerated statin therapy randomized to receive inclisiran versus placebo, over 18 months, the participants on inclisiran had a lower likelihood of MACEs (7.1% versus 9.4% receiving placebo; OR, 0.74 [95% CI, 0.58–0.94]), although there was no significant difference in incidence of fatal and nonfatal MI (1.8% versus 2.3%) or fatal and nonfatal stroke (0.7% versus 0.8%).<sup>81</sup>

- In the CLEAR Outcomes trial of 13970 patients who had or were at high risk for CVD, who were unable to take statins, or who were statin intolerant randomized to receive bempedoic acid or placebo, the incidence of MACEs was lower among patients who received bempedoic acid (11.7%) compared with placebo (13.3%; HR, 0.87 [95% CI, 0.79–0.96]), although no significant differences in fatal or nonfatal stroke, death resulting from cardiovascular causes, or all-cause mortality were observed.<sup>82</sup>
- In a prespecified subgroup analysis of 4206 primary prevention patients in the CLEAR Outcomes trial, participants who were randomized to receive bempedoic acid had a lower risk of MACEs (5.3%) compared with participants who received placebo (7.6%; aHR, 0.70 [95% CI, 0.55–0.89]) including MI, cardiovascular death, and all-cause mortality.<sup>83</sup> There was no significant difference between groups in stroke or coronary revascularization.
- In the LODESTAR randomized trial of 4400 patients with CAD at 12 centers in South Korea, a treat-to-target strategy of lowering LDL-C to a goal between 50 and 70 mg/dL was not significantly different from a strategy of using high-intensity statin for the rate of a 3-year composite end point of death, MI, stroke, or coronary revascularization (8.1% versus 8.7%).<sup>84</sup> In the 2×2 factorial design of this trial, there was no difference in rate of the primary outcome between participants who received rosuvastatin (8.7%) and those who received atorvastatin (8.2%; HR, 1.06 [95% CI, 0.86–1.30]).<sup>85</sup>
- In a systematic review and meta-analysis of randomized trials evaluating the effect of a fixed-dose combination polypill that included at least 1 lipid-lowering medication and 1 BP-lowering medication, studies of mostly primary prevention patients demonstrated that the polypill (versus comparator) was associated with a lower risk of all-cause mortality by 11% (5.6% versus 6.3%; RR, 0.89 [95% CI, 0.78–1.00]) and lower risk of fatal and nonfatal ASCVD events by 29% (6.1% versus 8.4%; RR, 0.71 [95% CI, 0.63–0.79]).<sup>86</sup>

## Control

- Among US adults receiving statin therapy, age-adjusted rates of lipid control (TC ≤200 mg/dL) did

not significantly change over time, from 78.5% in 2007 to 2008 to 79.5% in 2017 to 2018, with similar patterns by sex.<sup>14</sup> Between 2007 to 2008 and 2017 to 2018, lipid control statistically significantly improved among Mexican American adults (73.0% to 86.5%) but did not significantly change among Black adults (67.4% to 73.1%), White adults (79.9% to 82.0%), or Asian adults (78.5% in 2011 to 2012 to 75.2% in 2017 to 2018).

- Among 5391 adults with diagnosed ASCVD from NHANES 1999 to 2018, there was an increase in the proportion achieving non-HDL-C<100 mg/dL from 7.0% in 1999 to 2002 to 26.4% in 2015 to 2018 ( $P_{\text{trend}} < 0.001$ ).<sup>87</sup> The proportion taking statins increased from 40.1% in 1999 to 2002 to 63.4% in 2011 to 2014 but plateaued thereafter ( $P_{\text{trend}} < 0.001$ ). Ezetimibe use rose to 7.0% in 2007 to 2010 but declined to 1.6% in 2015 to 2018.
- Between 1999 and 2020 among US adults with diagnosed diabetes, non-HDL-C control (<130 mg/dL) increased from 26.6% in 1999 to 2002 to 58.6% in 2015 to 2020.<sup>88</sup> A trend of increasing non-HDL-C control was observed in adults with diabetes across all obesity categories (Proportion with non-HDL-C control in 2015 to 2020 was 66.5% in normal-weight adults, 58.7% in adults with overweight, 55.9% in adults with obesity class I, 58.0% in adults with obesity class II, and 56.9% in adults with obesity class III).

## Mortality and Complications

- Among 18288 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>89</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 middle adulthood (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 middle adulthood, 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]; middle adulthood 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>90</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 ( $\geq$ 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>91</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>35</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>92</sup>
- A meta-analysis of 21 RCTs of lipid-lowering therapies, including statins, ezetimibe, and PCSK9 inhibitors, comprising 184 012 patients with mean 4.4 years of follow-up showed greater RR reduction of major vascular events with increasing duration of treatment: each 1 mmol/L of LDL-C lowered was associated with a 12% (95% CI, 8%–16%) RR reduction for year 1, 20% (95% CI, 16%–24%) reduction for year 3, 23% (95% CI, 18%–27%) reduction for year 5, and 29% (95% CI, 14%–42%) reduction for year 7.<sup>93</sup>
- Among 20 490 adults who had an MI or coronary revascularization in Stockholm, Sweden, between 2012 and 2018 and initiated lipid-lowering therapy, the risk of MACEs was significantly lower for each 10% increase in 1-year adherence (HR, 0.94 [95% CI, 0.93–0.96]), intensity (HR, 0.92 [95% CI, 0.88–0.96]), and adherence-adjusted intensity (HR, 0.91 [95% CI, 0.89–0.94]).<sup>94</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 individuals, 1.10 (95% CI, 1.04–1.16) in South Asian individuals, and 1.07 (95% CI, 1.00–1.15) in Black individuals.<sup>10</sup> Lipoprotein(a)  $\geq$ 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.
- In an analysis among >435 000 adults in the UK Biobank, each 50-nmol/L higher lipoprotein(a) was associated with a higher risk of AF (HR, 1.03 [95% CI, 1.02–1.04]).<sup>95</sup> Only 39% (95% CI, 27%–73%) of the lipoprotein(a)-associated risk was mediated through ASCVD, suggesting that lipoprotein(a) may increase risk of AF independently of its effect on ASCVD risk.
- In a systematic review and meta-analysis of 43 studies comprising data from 957 253 participants, lipoprotein(a) in the top (versus bottom) tertile was associated with a higher risk of all-cause mortality in the general population (HR, 1.09 [95% CI, 1.01–1.18]) and in patients with CVD (HR, 1.18 [95% CI, 1.04–1.34]).<sup>96</sup> There was a linear dose-response relationship indicating that each 50-mg/dL higher lipoprotein(a) was associated with a 31% higher risk of death in the general population.
- 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>97</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]).
- A meta-analysis of individual participant-level data from RCTs of statin therapy participating in the Cholesterol Treatment Trialists' Collaboration evaluated the risk of diabetes associated with statin treatment.<sup>98</sup> Compared with placebo, randomization to low- or moderate-intensity statin resulted in a 10% proportional increase in new-onset diabetes (1.3% versus 1.2% per year; rate ratio, 1.10 [95% CI, 1.04–1.16]), and randomization to high-intensity statin resulted in a 36% proportional increase in new-onset diabetes (4.8% versus 3.5% per year; rate ratio, 1.36 [95% CI, 1.25–1.48]). Among participants who had a baseline measure of glycemia,  $\approx$ 62% of new-onset diabetes cases were in the top 25% of the baseline glucose distribution (mean fourth quartile HbA1c, 6.2% in the low- to moderate-intensity statin trials and 6.1% in the high-intensity statin trials).
- In an analysis of 27 756 adults from 5 US prospective studies of CVD (ARIC, CARDIA, Framingham

Offspring, JHS, and MESA) with a mean follow-up of 21.1 years, lipoprotein(a) level  $\geq$ 90th percentile (averaging 53 mg/dL; compared with  $<$ 50th percentile) was associated with an increased risk of ASCVD events (HR, 1.46 [95% CI, 1.33–1.59]), including MI (HR, 1.66 [95% CI, 1.44–1.90]) and revascularization (HR, 1.69 [95% CI, 1.48–1.91]).<sup>99</sup> The risk of ASCVD events was almost 2 times higher among those with preexisting diabetes (HR, 1.92 [95% CI, 1.50–2.45]). Associations were similar by sex, race and ethnicity, and baseline LDL-C levels.

- In the Copenhagen General Population study of 108 146 individuals followed up for a median of 7.4 years, those with lipoprotein(a)  $\geq$ 99th percentile (versus  $<$ 50th percentile) had higher risks of developing PAD (RR, 2.99 [95% CI, 2.09–4.30]), AAA (RR, 2.22 [95% CI, 1.21–4.07]), and major adverse limb events (RR, 3.04 [95% CI, 1.55–5.98]).<sup>100</sup>
- Among 6086 cases of first MI and 6857 controls from the INTERHEART study, which included individuals of African, Chinese, Arab, European, Latin American, South Asian, and Southeast Asian descent, lipoprotein(a) concentrations  $>$ 50 mg/dL were associated with a higher risk of MI (OR, 1.48 [95% CI, 1.32–1.67]).<sup>102</sup> The association was strongest in South Asian individuals (OR, 2.14 [95% CI, 1.59–2.89]).

## Cost

- In an analysis of 2016 US health care spending, hyperlipidemia ranked the 35th most expensive health condition, with estimated spending of \$26.4 (95% CI, \$24.3–\$29.4) billion overall.<sup>101</sup> Costs were split relatively evenly between younger and older adults (51.0% for 20–64 years of age, 48.4% for  $\geq$ 65 years of age, 0.6% for  $<$ 20 years of age), were higher for public compared with 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 the 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>102</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>103</sup>
- Based on 204 countries and territories, among regions, age-standardized mortality rates attributable to high LDL-C were highest for eastern Europe followed by Central Asia and North Africa and the Middle East in 2021 (Chart 7-5). There were 3.65 (95% UI, 2.13–5.26) million total deaths attributable to high LDL-C in 2021. The PAF was 5.37% (95% UI, 3.12%–7.77%; Table 7-2).
- Among  $>$ 10.7 million adults across 31 provinces of China between 2017 and 2020, the prevalence of dyslipidemia (TC  $\geq$ 200 mg/dL, triglycerides  $\geq$ 150 mg/dL, LDL-C  $\geq$ 130 mg/dL, HDL-C  $<$ 40 mg/dL, or use of dyslipidemia medication) was 58.4%, with mean TC of 191 mg/dL, triglycerides of 123 mg/dL, LDL-C of 109 mg/dL, and HDL-C of 52 mg/dL.<sup>104</sup>
- Among Korean adults  $\geq$ 20 years of age evaluated in the 2007 to 2020 Korean National Health and Nutrition Examination Survey, the prevalence of triglycerides  $\geq$ 150 mg/dL was 38.5% in males and 20.5% in females. In 2020,  $\approx$ 10% of Korean adults were using lipid-lowering medications.<sup>105</sup>

**Table 7-1.** High TC and LDL-C and Low HDL-C, United States ( $\geq 20$  Years of Age), 2017 to 2020

Population group	Prevalence of TC $\geq 200$ mg/dL	Prevalence of TC $\geq 240$ mg/dL	Prevalence of LDL-C $\geq 130$ 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  $\geq 200$  mg/dL includes people with TC  $\geq 240$  mg/dL. In adults, levels of 200 to 239 mg/dL are considered borderline high, and levels of  $\geq 240$  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>106</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>5</sup> applied to 2020 population estimates.

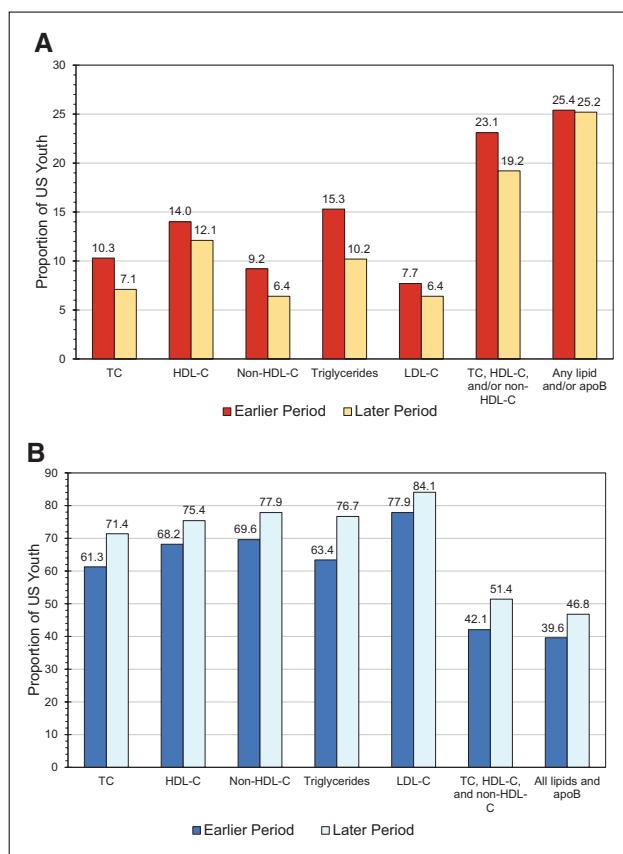
**Table 7-2.** Deaths Caused by High LDL-C Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	3.65 (2.13 to 5.26)	2.01 (1.21 to 2.85)	1.64 (0.91 to 2.46)
Percent change (%) in total number, 1990–2021	48.69 (40.45 to 56.94)	57.63 (46.33 to 69.75)	39.02 (30.18 to 48.20)
Percent change (%) in total number, 2010–2021	17.41 (11.77 to 22.99)	18.52 (10.86 to 26.48)	16.08 (9.59 to 23.38)
Rate per 100 000, age standardized, 2021	43.67 (25.33 to 63.43)	53.15 (31.05 to 76.26)	35.12 (19.69 to 52.58)
Percent change (%) in rate, age standardized, 1990–2021	−38.06 (−41.08 to −34.70)	−33.91 (−38.25 to −28.96)	−42.36 (−45.58 to −38.40)
Percent change (%) in rate, age standardized, 2010–2021	−14.68 (−18.40 to −10.83)	−13.11 (−18.43 to −7.46)	−16.25 (−20.84 to −10.94)
PAF (%), all ages, 2021	5.37 (3.12 to 7.77)	5.33 (3.23 to 7.51)	5.42 (3.01 to 8.06)
Percent change (%) in PAF, all ages, 1990–2021	0.98 (−3.30 to 4.92)	3.76 (−1.69 to 9.35)	−1.98 (−7.10 to 2.72)
Percent change (%) in PAF, all ages, 2010–2021	−8.21 (−10.60 to −5.72)	−8.68 (−11.59 to −5.77)	−7.62 (−10.87 to −4.72)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; LDL-C, low-density lipoprotein cholesterol; PAF, population attributable fraction; and UI, uncertainty interval.

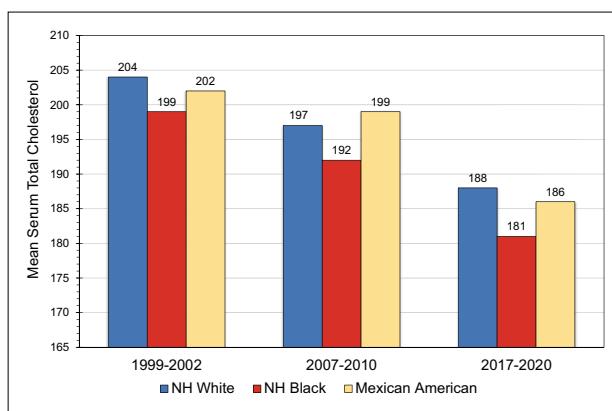
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>107</sup>



**Chart 7-1. Proportions of US youths 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 youths 6 to 19 years of age, and triglycerides, LDL-C, and any or all lipids plus apoB are shown for fasting adolescents 12 to 19 years of age. **A**, For high (or, for HDL-C, low) lipid levels, the earlier and later periods shown for each lipid are as follows: 1999 to 2006 and 2009 to 2016 for TC; 2007 to 2010 and 2013 to 2016 for HDL-C; 2007 to 2010 and 2013 to 2016 for non-HDL-C; 1999 to 2006 and 2007 to 2014 for triglycerides; 1999 to 2006 and 2007 to 2014 for LDL-C; 2007 to 2010 and 2013 to 2016 for any of TC, HDL-C, or non-HDL-C; and 2007 to 2010 and 2011 to 2014 for any lipid or apoB. **B**, For acceptable lipid levels, the earlier and later periods shown for each lipid are as follows: 1999 to 2000 and 2015 to 2016 for TC; 2007 to 2008 and 2015 to 2016 for HDL-C; 2007 to 2008 and 2015 to 2016 for non-HDL-C; 1999 to 2000 and 2013 to 2014 for triglycerides; 1999 to 2000 and 2013 to 2014 for LDL-C; 2007 to 2008 and 2015 to 2016 for TC, HDL-C, and non-HDL-C; and 2007 to 2008 and 2013 to 2014 for all lipids and apoB. High (or, for HDL-C, low) and acceptable levels were defined according to the 2011 National Heart, Lung, and Blood Institute pediatric guideline<sup>58</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>6</sup>



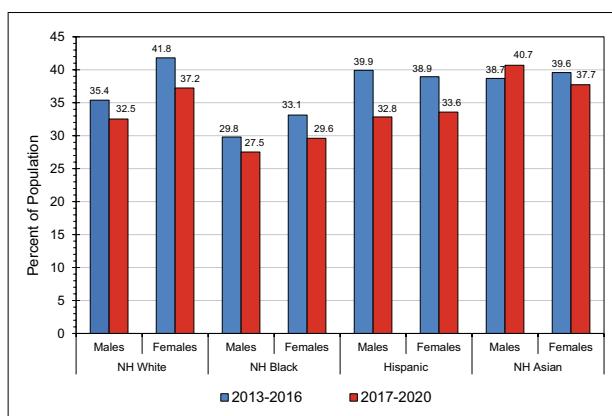
**Chart 7-2. Age-adjusted trends in mean serum TC among US adults  $\geq 20$  years of age, by race and ethnicity and survey year (NHANES 1999-2002, 2007-2010, and 2017-2020).**

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>106</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>5</sup>

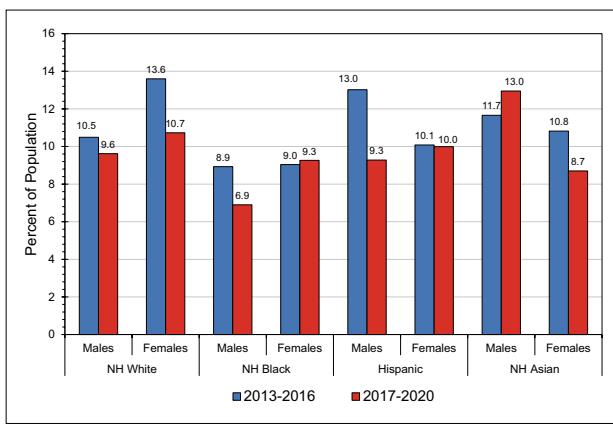


**Chart 7-3. Age-adjusted trends in the prevalence of serum TC  $\geq 200$  mg/dL in US adults  $\geq 20$  years of age, by race and ethnicity, sex, and survey year (NHANES 2013-2016 and 2017-2020).**

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>106</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>5</sup>

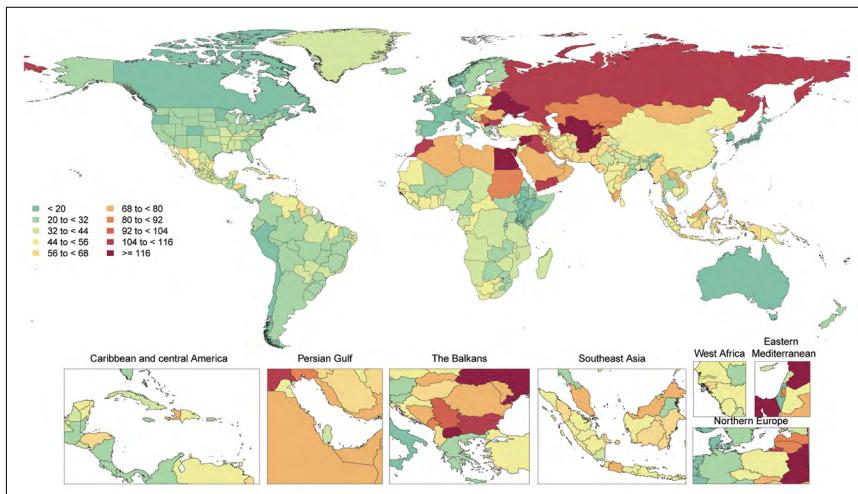


**Chart 7-4. Age-adjusted trends in the prevalence of serum TC  $\geq 240$  mg/dL in US adults  $\geq 20$  years of age, by race and ethnicity, sex, and survey year (NHANES 2013–2016 and 2017–2020).**

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>106</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>5</sup>



**Chart 7-5. Age-standardized global mortality rates attributable to high LDL-C per 100,000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and LDL-C, low-density lipoprotein cholesterol.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>107</sup>

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## 8. HIGH BLOOD PRESSURE

**ICD-9 401 to 404; ICD-10 I10 to I15. See Tables 8-1 through 8-3 and Charts 8-1 through 8-6**

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HBP is a major risk factor for CHD, HF, and stroke.<sup>1,2</sup> The AHA has identified untreated BP <90th percentile (for children) and <120/<80 mmHg (for adults ≥20 years of age) as 1 of the 8 components of ideal CVH.<sup>3</sup>

### 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 hypertension has been proposed for surveillance<sup>4</sup>:
  - SBP ≥130 mmHg, DBP ≥80 mmHg, 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 who have hypertension (62.8 million males and 59.6 million females; Table 8-1).

The 2025 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 2025. 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.

- In NHANES 2017 to 2020,<sup>5</sup> the prevalence of hypertension 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>5</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 hypertension in adults ≥20 years of age is presented by both age and sex in Chart 8-1.
- Data from NHANES 2017 to 2020<sup>5</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 2022, the prevalence of HBP in US adults was highest in Mississippi (40.2%) and lowest in Colorado (24.6%; unpublished NHLBI tabulation using BRFSS<sup>6</sup>).
- In a meta-analysis of 42 studies and 71 353 patients with apparent treatment-resistant hypertension, the overall pooled prevalence of nonadherence was 37% (95% CI, 27%–47%).<sup>7</sup> The prevalence was higher with direct methods of assessment (eg, direct observed therapy test or therapeutic drug monitoring) at 46% (95% CI, 40%–52%) than with indirect methods (pill counts or questionnaires) at 20% (95% CI, 11%–35%).

### Children and Adolescents

- According to the 2017 guidelines from the American Academy of Pediatrics,<sup>8</sup> hypertension in children and adolescents is defined as follows:
  - Elevated BP as ≥90th to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower) for children 1 to <13 years of age and 120/<80 to 129/<80 mmHg for those ≥13 years of age
  - Stage 1 hypertension as ≥95th to <95th percentile+12 mmHg or 130/80 to 139/89 mmHg (whichever is lower) for children 1 to <13 years of age and 130/80 to 139/89 mmHg for those >13 years of age
  - Stage 2 hypertension as ≥95th percentile+12 mmHg or ≥140/90 mmHg (whichever is lower) for children 1 to <13 years of age and ≥140/90 mmHg for those ≥13 years of age
- In NHANES 2015 to 2016, 13.3% (SE, 1.3%) of children and adolescents 8 to 17 years of age had elevated BP, and 4.9% (SE, 0.7%) had hypertension (defined according to the 2017 guidelines from the

American Academy of Pediatrics<sup>8</sup>). Rates of elevated BP were higher among youths 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 youths at younger ages, with a prevalence of 4.4% among youths 13 to 17 years of age and 5.3% in youths 8 to 12 years of age.<sup>9</sup>

- In NHANES 2015 to 2016, among youths 8 to 17 years of age, hypertension (defined according to the 2017 guidelines from the American Academy of Pediatrics<sup>8</sup>) was more common among males (5.9%) than females (3.8%) and among Mexican American youths (9.0%) compared with NH Black youths (4.7%) and NH White youths (2.7%). Having elevated BP was more common among males (16.9%) than females (9.8%). In addition, Mexican American youths (16.9%) and NH Black youths (16.4%) were more likely to have elevated BP than NH White youths (10.7%).<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 youths and Indigenous youths (referring to the indigenous populations of North America) having the highest prevalence of all racial and ethnic groups (Pacific Islander youths, 26.7% [95% CI, 14.5%–40.7%]; Indigenous youths, 26.5% [95% CI, 17.3%–36.7%]; White youths, 21.0% [95% CI, 12.7%–30.6%]; Black youths, 19.0% [95% CI, 12.0%–27.2%]; Hispanic/Latino youths, 15.1% [95% CI, 6.6%–26.3%]; Asian youths, 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 mmHg, the prevalence was higher at 27% and 13% for SBP and DBP, respectively.
- In a 2022 systematic review of 53 studies of pediatric populations from Africa, hypertension prevalence ranged from 0.2% to 38.9%.<sup>12</sup> In the meta-analysis, which included 41 studies and 52918 participants 3 to 19 years of age from 10 countries, the pooled prevalence for hypertension (SBP or DBP  $\geq$ 95th percentile) was 7.5% (95% CI, 5.3%–9.9%) and elevated BP (SBP or DBP  $\geq$ 90th and  $<$ 95th percentile) was 11.4% (95% CI, 8.0–15.3) with a high degree of statistical heterogeneity ( $I^2 > 99$ ).

- A meta-analysis from 2022 of secondary hypertension in children included 19 prospective studies and 7 retrospective studies with 2575 children with hypertension.<sup>13</sup> The overall pooled prevalence of secondary hypertension was 8.0% (95% CI, 4.0%–13.0%) among otherwise healthy youths with hypertension. Studies conducted in primary care or school settings reported a lower prevalence of secondary hypertension (pooled prevalence, 3.7% [95% CI, 1.2%–7.2%]) compared with studies conducted in referral clinics (pooled prevalence, 20.1% [95% CI, 11.5%–30.3%]).
- A retrospective analysis of medical records from 9 tertiary children's hospitals in China during 2010 to 2020 included 5847 pediatric inpatients (<18 years of age) with a diagnosis of hypertension.<sup>14</sup> The proportion of those with diagnosed secondary hypertension increased from 51.2% during the period of 2010 to 2015 to 59.8% during the period of 2016 to 2020. Compared with primary hypertension, secondary hypertension was more common in girls (43.1% versus 23.3%) and children  $<$ 5 years of age (32.2% versus 2.1%). Among those with primary hypertension, obesity and obesity-related comorbidities were noted in 85.2% of individuals.
- A systematic review and meta-analysis of 136 studies with 28612 individuals (4–25 years of age) to estimate the prevalence and complications of masked hypertension showed that the pooled prevalence of masked hypertension was 10.4% (95% CI, 8.0%–12.8%).<sup>15</sup> Compared with the general pediatric population, the prevalence of masked hypertension was higher in the presence of coarctation of the aorta (RR, 1.91 [95% CI, 1.53–2.38]), solid-organ or stem-cell transplantation (RR, 2.34 [95% CI, 2.16–2.54]), CKD (RR, 2.44 [95% CI, 2.29–2.59]), and sickle cell disease (RR, 1.33 [95% CI, 1.06–1.69]). Masked hypertension was associated with greater subclinical cardiovascular outcomes compared with normotension, including higher LVH (OR, 2.44 [95% CI, 1.50–3.96]) and higher pulse wave velocity (WMD, 0.30 m/s [95% CI, 0.14–0.45 m/s]).

### Race and Ethnicity

#### (See Table 8-1 and Chart 8-2)

- Table 8-1 includes statistics on prevalence of HBP, mortality resulting 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>5</sup> the age-adjusted prevalence of hypertension among NH Black people was 55.8% among males and 56.9% among females (Chart 8-2).

- Data from the NHIS 2018 showed that Black adults ≥18 years of age were more likely (32.2%) to have been told on ≥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>16</sup>
- Data from the National Longitudinal Study of Adolescent to Adult Health (1994–1995, 11–18 years of age; 2007–2008, 24–32 years of age) show that older age, being NH Black or Asian, male sex, BMI, and current smoking were associated with higher incidence of hypertension (defined as SBP ≥140 or DBP ≥90 mm Hg).<sup>17</sup> At the individual level, compared with NH White students, NH Black students (OR, 1.21 [95% CI, 1.03–1.42]) and Asian students (OR, 1.28 [95% CI, 1.02–1.62]) had higher odds of hypertension. At the school level, however, hypertension was associated with the percentage of NH White students (OR for 10% higher, 1.06 [95% CI, 1.01–1.09]). Parental education and neighborhood-level fixed effects were not associated with hypertension.

## Incidence and Lifetime Risk

- Data from 13 160 participants in cohorts in the Cardiovascular Lifetime Risk Pooling Project (ie, the Framingham Offspring Study, CARDIA, and ARIC) showed 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>18</sup>

## Secular Trends

- In 51 761 participants from NHANES, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure definition of hypertension (≥140/90 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 (≥130/80 mm Hg), 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>19</sup>

- With the use of the 2017 guidelines from the American Academy of Pediatrics, an 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>9</sup>
- In NHANES, among youths with underweight or normal weight (8–17 years of age), there was a statistically significant decline in the prevalence of elevated BP/hypertension and hypertension (defined according to the 2017 guidelines from the American Academy of Pediatrics<sup>8</sup>) between 2003 to 2004 and 2015 to 2016. There were no changes in the prevalence of elevated BP/hypertension or hypertension among youths with overweight during this time period; among youths with obesity, there was a decline in the prevalence of elevated BP/hypertension ( $P_{\text{trend}}=0.03$ ) but not hypertension. Among adolescents with underweight or normal weight, 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 of hypertension was 2.7% (SE, 1%) in 2015 to 2016 ( $P_{\text{trend}}=0.001$  and 0.002). Among youths with obesity, 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 prehypertension was 25.5% (SE, 2.4%) and that of hypertension was 11.6% (SE, 2.1%) in 2015 to 2016.<sup>9</sup>
- In NHDS data compiled by the CDC, chronic hypertension in pregnancy (defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg either before pregnancy or up to the first 20 weeks during pregnancy) increased >13-fold between 1970 and 2010. Black females had a persistent 2-fold higher rate of chronic hypertension compared with White females over the 40-year period.<sup>20</sup>
- In an observational study of 11 million Veterans Affairs patients between 2010 and 2019 who were 18 to 50 years of age with a diagnosis of chronic hypertension before a documented pregnancy, 8% had maternal chronic hypertension.<sup>21</sup> Of these, 60% had uncontrolled BP on at least 1 BP reading and 31% had uncontrolled BP on at least 2 BP readings in the year before pregnancy. The use of nonrecommended BP-lowering medications in pregnancy was observed in 16% of the veterans. CKD (OR, 3.2 [95% CI, 1.6–6.4]) and diabetes (OR, 2.3 [95% CI, 1.7–3.0]) were associated with a higher likelihood

of using nonrecommended BP-lowering medication during pregnancy.

## Risk Factors

- In NHANES 2015 to 2016, the prevalence of hypertension (defined according to the 2017 guidelines from the American Academy of Pediatrics<sup>8</sup>) was 11.6% among US adolescents with obesity ( $\text{BMI} \geq 120\%$  of 95th percentile of sex-specific BMI for age or  $\text{BMI} \geq 35 \text{ kg/m}^2$ ) compared with 2.7% among children with normal weight or underweight. The prevalence of elevated BP among youths with obesity compared with youths with normal weight or underweight was 16.2% compared with 8.7%.<sup>9</sup>
- In an analysis of the Australian Longitudinal Study on Women's Health, 9508 females were followed up for 145 159 PY, 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 PY) compared with females without (10 per 1000 PY). The incidence rate difference of hypertension was 4-fold higher (15.8 per 1000 PY versus 4.3 per 1000 PY) among females with obesity 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 an RR of hypertension of 1.13 (95% CI, 0.99–1.28) per 10-dB higher ambient noise.<sup>23</sup>
- In an analysis from DEBATS of 1244 adults living near 3 major French airports, a 10-dB increase in aircraft noise levels was associated with a higher incidence of hypertension (RR, 1.36 [95% CI, 1.02–1.82]).<sup>24</sup> Noise annoyance, or noise sensitivity, was not associated with higher incident hypertension.
- 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>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-mmHg (95% CI, 0.66–1.54) reduction in SBP and a 0.33-mmHg (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 ( $-3.33/-1.23 \text{ mmHg}$  in those  $\geq 65$  years of age compared with  $-0.39/-0.18 \text{ mmHg}$  in those  $<35$  years of age), individuals with higher baseline SBP ( $-2.97/-1.41 \text{ mmHg}$  in those with SBP  $>160 \text{ mmHg}$  compared with  $-0.39/-0.07 \text{ mmHg}$  in those with SBP  $<120 \text{ mmHg}$ ), and Black individuals ( $-4.07/-2.37 \text{ mmHg}$  compared with  $-1.60/-0.82 \text{ mmHg}$  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 the use of the salt substitute (RR, 1.04 [95% CI, 0.80–1.37]).
- In a population-based study from the Australian Longitudinal Study on Women's Health, which included 6599 middle-aged females 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>28</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 an analysis of the electronic FHS participants, higher daily habitual PA as measured by a smart-watch was associated with lower home BP. Every 1000-step increase in the average daily step count was associated with a 0.49-mmHg lower home SBP ( $P=0.004$ ) and 0.36-mmHg lower home DBP ( $P=0.003$ ) with no difference between males and females.<sup>29</sup>
- A systematic review of the relationship between screen time and hypertension in children and adolescents included 20 studies and 151 763 participants.<sup>30</sup> Screen time was defined on the basis of the use of digital video disks, tablets, smartphones, personal computers, and video games. Screen time in the highest category compared with the lowest category was associated with a higher odds of hypertension (OR, 1.15 [95% CI, 1.08–1.23];

$P<0.001$ ) although with significant heterogeneity ( $I^2=83.20\%$ ). High screen time was also associated with higher SBP (WMD, 1.89 mmHg [95% CI, 0.18–3.62];  $P=0.03$ ), again with significant heterogeneity ( $I^2=83.4$ ). Moreover, screen time in children and adolescents with hypertension was higher than in normotensive children and adolescents (WMD, 0.79 hours [95% CI, 0.02–1.56];  $P=0.046$ ) with significant heterogeneity ( $I^2=92.8$ ).

- In the JHS ancillary sleep study conducted from 2012 to 2016 among 913 participants, those with moderate or severe OSA had 2-fold higher odds (95% CI, 1.14–3.67) of resistant hypertension than participants without sleep apnea.<sup>31</sup>
- In a double-blind, placebo-controlled, crossover RCT, 110 individuals were randomized to receive 1 g acetaminophen 4 times daily or matched placebo for 2 weeks.<sup>32</sup> Use of acetaminophen resulted in a significant increase in mean daytime SBP with a placebo-corrected increase of 4.7 mmHg (95% CI, 2.9–6.6) and mean daytime DBP with a placebo-corrected increase of 1.6 mmHg (95% CI, 0.5–2.7).
- In a meta-analysis of 7 studies including 102 152 patients and 636 645 healthy individuals, male infertility was significantly associated with a slightly higher incidence of subsequent hypertension (RR, 1.08 [95% CI, 1.02–1.14]).<sup>33</sup> This risk persisted when only studies that adjusted for potential confounders were included (RR, 1.06 [95% CI, 1.03–1.09]).
- In the BWHS of 59 000 self-identified Black females from across the United States, a validated predicted vitamin D score relation to incident hypertension was reported.<sup>34</sup> Of the 42 239 participants who were free of CVD and cancer from 1995 to 2019, 19 505 incident cases of hypertension were identified during follow-up. An inverse dose-response association between predicted vitamin D score and hypertension risk was reported (HR, 0.66 [95% CI, 0.63–0.68]) for the highest quartile of predicted vitamin D relative to the lowest. This trend was mostly attenuated after controlling for potential confounders, including BMI, PA, and smoking status (HR, 0.91 [95% CI, 0.87–0.95]).
- A study including cross-sectional data on heterosexual couples from contemporaneous waves of the HRS (2016–2017, n=3989 couples), ELSA (2016–2017, n=1086), CHARLS (2015–2016, n=6514), and LASI (2017/2019, n=22 389) analyzed rates of concordant hypertension, defined as both husband and wife in a couple having hypertension.<sup>35</sup> The prevalence of concordant hypertension within couples was common across all countries, at 37.9% in the United States (95% CI, 35.8%–40.0%), 47.1% in England (95% CI, 43.2%–50.9%), 20.8% in China (95% CI, 19.6%–21.9%), and 19.8% in

India (95% CI, 19.0%–20.5%). Compared with wives married to husbands without hypertension as reference, wives married to husbands with hypertension were more likely to have hypertension in the United States (PR, 1.09 [95% CI, 1.01–1.17]), England (PR, 1.09 [95% CI, 0.98–1.21]), China (PR, 1.26 [95% CI, 1.17–1.35]), and India (PR, 1.19 [95% CI, 1.15–1.24]). Within each country, similar associations were also observed for husbands.

## Social Determinants/Health Equity

- 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 compared with 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>36</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>37</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.
- 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 working  $\leq 40$  h/wk.<sup>38</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 mmHg [95% CI, 0.75–4.29] and 1.76 mmHg [95% CI, 0.41–3.12], respectively) compared with day workers was noted.<sup>39</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 mmHg [95% CI, 0.07–1.22] and 1.28 mmHg [95% CI, 0.18–2.39], respectively).
- In an analysis from NHANES 1999 to March 2020, of 20 761 middle-aged adults (40–64 years of age), adults with low income had an increase in hypertension over the study period (37.2% [95% CI, 33.5%–40.9%] to 44.7% [95% CI, 39.8%–49.5%]).<sup>40</sup>

However, adults with higher income did not have a change in hypertension. The treatment and control rates for hypertension were unchanged in both groups (>80%). Income-based disparities in hypertension persisted in more recent years even after adjustment for insurance coverage, health care access, and food insecurity.

## 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>41–51</sup>
- Nine genetic loci have been identified for BP traits in African-ancestry populations.<sup>52</sup> Large-scale genomic discovery effort in non-European ancestry populations is needed to comprehensively understand the genetic architecture of hypertension.
- 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>53</sup>
- In a recent study, the multiancestry SBP PRS was constructed with 1.08 million variants identified from SBP GWAS data from >400 000 individuals of pan-ancestry in the UK Biobank. The SBP PRS was applied to 21 987 multiancestry US individuals who underwent whole-genome sequencing. The SBP PRS was associated with increased 10-year risk of incident cardiovascular events by 7% after accounting for traditional cardiovascular risk factors. These associations were seen across all racial and ethnic groups.<sup>54</sup>
- GWASs for BP variability and longitudinal BP traits have led to the discovery of novel loci.<sup>55,56</sup> Furthermore, females were noted to have rapid progression of BP measures over a lifetime, which may indicate a sex-specific genetic burden for hypertension.<sup>57,58</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>59,60</sup> and sodium.<sup>61,62</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 multiancestry populations have not yet been conducted.

- A multistage analysis including 52 436 individuals of diverse ancestral backgrounds developed a hypertension PRS that combined 3 individual PRSSs (SBP, DBP, and hypertension).<sup>63</sup> The hypertension PRS was associated with prevalent hypertension (OR, 2.10 [95% CI, 1.99–2.21];  $P<1\times10^{-100}$ ), incident hypertension (OR, 2.10 [95% CI, 1.99–2.21];  $P<1\times10^{-100}$ ), CAD (OR, 1.13 [95% CI, 1.07–1.18];  $P<3.2\times10^{-6}$ ), ischemic stroke (OR, 1.15 [95% CI, 1.04–1.28];  $P<6.94\times10^{-3}$ ), and type 2 diabetes (OR, 1.19 [95% CI, 1.14–1.24];  $P<8.46\times10^{-15}$ ).
- A GWAS for preeclampsia and gestational hypertension including 20 064 cases and 703 117 controls with preeclampsia and 11 027 cases and 412 788 controls with gestational hypertension identified 18 genomic loci.<sup>64</sup> Among these 18 loci, novel loci included *MTHFR*–*CLCN6*, *WNT3A*, *NPR3*, *PGR*, *RGL3*, *PLCE1*, and *FURIN*. An independent GWAS including 16 743 women with prior preeclampsia and 15 200 with preeclampsia or other maternal hypertension during pregnancy reported 19 loci, of which 13 loci were novel.<sup>65</sup> Novel loci reported in the study included *NPPA*, *NPPB*, *NPR3*, *PLCE1*, *TNS2*, *FURIN*, *RGL3*, *PREX1*, *PGR*, *TRPC6*, *ACTN4*, *PZP*, and *FLT1*.<sup>65</sup>
- 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>66</sup> Pharmacogenomic studies in ethnically diverse populations have the potential to recognize potential adverse events and to inform personalized drug efficacy.<sup>67</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>5</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>5</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  $\geq 140/90$  mm Hg) in NHANES, the estimated age-adjusted proportion with controlled BP increased from 31.8% (95% CI, 26.9%–36.7%) in 1999 to 2000 to 48.5% (95% CI, 45.5%–51.5%) in 2007 to 2008, remained relatively stable at 53.8% (95% CI, 48.7%–59.0%) in 2013 to 2014, but declined to 43.7% (95% CI, 40.2%–47.2%) in 2017 to 2018.<sup>19</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).
- In the UK Biobank, among 99468 previously diagnosed, treated individuals with hypertension, 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/wk (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>68</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]).
- A longitudinal analysis of prospectively collected data from the UK Avon Longitudinal Study of Parents and Children cohort reported the association of self-reported alcohol intake and presence of hypertensive disorders in pregnancy.<sup>69</sup> Of the 8999 females in the study, 1490 (17%) had developed hypertensive disorders in pregnancy. Both maternal drinking and partner drinking were associated with decreased odds of hypertensive disorders in pregnancy (OR, 0.86 [95% CI, 0.77–0.96] and OR, 0.82 [95% CI, 0.70–0.97], respectively).
- A systematic review of longitudinal studies in healthy adults that reported the association between alcohol intake and BP included 7 studies with 19548 participants and a median follow-up of 5.3 years.<sup>70</sup> Usual SBP and DBP were 1.25 mm Hg (95% CI, 0.49–2.01) and 1.14 mm Hg (95% CI, 0.60–1.68) higher, respectively, for a 12-g/d greater daily consumption of alcohol compared with no alcohol consumption. The corresponding SBP and DBP differences for daily alcohol consumption of 24 g/d were 2.48 mm Hg (95% CI, 1.40–3.56) and 2.03 mm Hg (95% CI, 1.19–2.86) and for 48 g/d were 4.90 mm Hg (95% CI, 3.71–6.08) and 3.10 mm Hg (95% CI, 1.88–4.33). This was a linear positive association between baseline alcohol intake and changes over time in SBP and DBP, with no exposure-effect threshold.
- 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>71</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-mm Hg (95% CI, −1.64 to −1.29 mm Hg) lower SBP over time.
- In a meta-analysis of 15 RCTs and 7415 patients with hypertension of app-based behavioral self-monitoring interventions, a small but significant reduction in SBP was reported (WMD, 1.6 mm Hg [95% CI, 2.7–0.6]). App-based interventions were also associated with an increase in adherence behavior (SMD, 0.78 [95% CI, 0.22–1.34]) compared with usual care or minimal intervention.
- A meta-analysis of 16 cohort studies with 2769700 participants analyzed the association of adherence to BP-lowering medications and subsequent CVD events.<sup>72</sup> The pooled RR of CVD events was 0.66 (95% CI, 0.56–0.78) for the highest versus lowest BP-lowering drug adherence categories. A linear dose-response association of adherence and CVD events was also reported ( $P_{\text{nonlinearity}}=0.89$ ), and each 20% increase in adherence was associated with a 13% lower risk of CVD events (RR, 0.87 [95% CI, 0.83–0.92]).<sup>73</sup>
- A meta-analysis of 14 RCTs of renin-angiotensin system inhibitor continuation or initiation compared with no renin-angiotensin system inhibitor therapy included 11 trials and 1838 participants with a mean follow-up of 26 days.<sup>74</sup> There was no effect of renin-angiotensin system inhibitors compared with control on all-cause mortality (RR, 0.95 [95% CI, 0.69–1.30]) overall or in subgroups defined by COVID-19 severity or trial type. In a network meta-analysis, renin-angiotensin system inhibitor use was associated with a nonsignificant reduction in AMI (RR, 0.59 [95% CI, 0.33–1.06]) and a higher risk of acute kidney injury (RR, 1.82 [95% CI, 1.05–3.16]) in trials that initiated and continued renin-angiotensin system inhibitors.
- In a prospective RCT of 21104 participants who were enrolled to take all of their usual antihypertensive medications in either the morning (6–10 AM) or the evening (8 PM–midnight), the primary cardiovascular end-point event of vascular death or hospitalization for nonfatal MI or nonfatal stroke occurred in

362 participants (3.4%) assigned to evening treatment and 390 (3.7%) assigned to morning treatment (HR, 0.95 [95% CI, 0.83–1.10]), suggesting no benefit with taking antihypertensive medications in the evening.<sup>75</sup>

- A systematic review and meta-analysis of studies from January 2000 until April 2022 included 6 RCTs with 1550 participants comparing studies on pharmacist-led home BP telemonitoring with usual care.<sup>76</sup> The addition of pharmacist-led telemonitoring to usual care was associated with a significant decrease in SBP (WMD, −8.09 [95% CI, −11.15 to −5.04;  $P<0.001$ ]) and in DBP (WMD, −4.19 [95% CI, −5.58 to −2.81]) compared with usual care.
- A meta-analysis of RCTs to estimate the SBP reduction for team-based care strategies compared with usual care included 19 studies comprising 5993 participants.<sup>77</sup> Team-based care was defined as a team of  $\geq 2$  health care professionals working collaboratively toward a shared clinical goal. Team-based care strategies were stratified by the inclusion of a physician or a nonphysician team member who could titrate antihypertensive medications. The pooled analysis reported that the 12-month SBP change compared with usual care was −5.0 mmHg (95% CI, −7.9 to −2.2) for team-based care with physician titration and −10.5 mmHg (−16.2 to −4.8) for team-based care with nonphysician titration.
- A systematic review of the efficacy of polypills combining 3 or 4 BP-lowering medications included 18 trials and 14 307 participants.<sup>78</sup> The mean difference in SBP ranged from −9.8 to −20.6 mmHg for a polypill compared with −0.9 to −5.2 mmHg for placebo and −9.0 to −29.3 mmHg for a polypill compared with −2.0 to −20.6 mmHg for monotherapy or usual care. All trials reported similar rates of adverse events. Medication adherence was high (6 trials reported  $>95\%$  adherence) but was similar for polypills compared with controls.

## Mortality

### (See Table 8-1)

- According to data from the NVSS, in 2022,<sup>79</sup> 131 454 deaths were attributable primarily to HBP (Table 8-1). The 2022 age-adjusted death rate attributable primarily to HBP was 31.5 per 100 000. Death rates by sex, race, and ethnicity for 2022 are given in Table 8-1.
- From 2012 to 2022, the age-adjusted death rate attributable to HBP increased 63.2%, and the actual number of deaths attributable to HBP rose 93.0%. From 2018 to 2022, in NH White people, the HBP age-adjusted death rate increased 36.8%,

whereas the actual number of deaths attributable to HBP increased 39.7%. In NH Black people, the HBP death rate increased 17.9%, and the actual number of deaths attributable to HBP increased 25.8%. In Hispanic people, the HBP death rate increased 21.3%, and the actual number of deaths attributable to HBP increased 37.7% (unpublished NHLBI tabulation using CDC WONDER<sup>80</sup>).

- When any mention of HBP was present, the overall age-adjusted death rate in 2022 was 163.1 per 100 000. Death rates were 188.6 for NH White males, 299.8 for NH Black males, 111.9 for NH Asian males, 192.3 for Native Hawaiian or Other Pacific Islander males, 205.8 for NH American Indian or Alaska Native males (underestimated because of underreporting), and 160.0 for Hispanic males. In females, rates were 135.9 for NH White females, 198.7 for NH Black females, 81.2 for NH Asian females, 156.2 for NH Native Hawaiian or Other Pacific Islander females, 159.9 for NH American Indian or Alaska Native females (underestimated because of underreporting), and 111.8 for Hispanic females (unpublished NHLBI tabulation using CDC WONDER<sup>80</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>81</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>82</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>83</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  $\approx 10\%$ , regardless of previous diagnoses of CVD.<sup>84</sup> This effect was also seen at normal and high-normal BP values.

- 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>
- Among 27 078 Black individuals 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>85</sup>
- In an RCT of 8511 older Chinese patients with hypertension (60–80 years of age), randomizing to a BP target of 110 to <130 mmHg (intensive treatment) compared with a target of 130 to <150 mmHg (standard treatment) reduced MACEs (HR, 0.74 [95% CI, 0.60–0.92]).<sup>86</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 (defined as ≥130/80 per the 2017 Hypertension Clinical Practice Guidelines<sup>4</sup> compared with normotension) was almost 2-fold higher (HR, 1.91 [95% CI, 1.48–2.46]) for composite incident CVD and was 2.41 (95% CI, 1.59–3.66) for incident CHD, 2.20 (95% CI, 1.44–3.36) for incident stroke, and 1.52 (95% CI, 1.01–2.30) for incident HF.<sup>1</sup> The PAR associated with hypertension was 32.5% (95% CI, 20.5%–43.6%) for composite incident CVD, 42.7% (95% CI, 24.0%–58.4%) for incident CHD, 38.9% (95% CI, 19.4%–55.6%) for incident stroke, and 21.6% (95% CI, 0.6%–40.8%) for incident HF. For composite CVD, the PAR for hypertension was 54.6% (95% CI, 37.2%–68.7%) among NH people <60 years of age but was significantly lower, at 32% (95% CI, 11.9%–48.1%), among NH Black people ≥60 years of age.
- In 8022 individuals from SPRINT with hypertension but without AF at baseline, those in the intensive BP-lowering arm (target SBP <120 mmHg) had a 26% lower risk of developing AF over the 5.2 years of follow-up (28 322 PY) than those in the standard BP-lowering arm (target SBP <140 mmHg; HR, 0.74 [95% CI, 0.56–0.98];  $P=0.037$ ).<sup>87</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 mmHg) was also associated with an increased incidence of CVD events (HR, 1.53 [95% CI, 1.24–1.88]) after multivariable adjustment that included clinic BP. Adjusted findings were similar for nighttime SBP (HR, 1.48 [95% CI, 1.22–1.80]) per 15.5 mmHg, daytime DBP (HR, 1.25 [95% CI, 1.02–1.51]) per 9.3 mmHg, and nighttime DBP (HR, 1.30 [95% CI, 1.06–1.59]) per 9.5 mmHg.<sup>88</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>88</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 ESKD or 50% decline in eGFR (HR, 1.51 [95% CI, 1.14–1.97]), but not cardiovascular outcomes or mortality.
- 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>89</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 in coefficient of variation: HR, 1.23 [95% CI, 1.01–1.50];  $P=0.04$ ).
- In a subsample of 191 participants from CARDIA, higher cumulative SBP from baseline through year 30 was associated with slower walking speed ( $P=0.010$ ), smaller step length ( $P=0.011$ ), and worse cognitive function in the executive ( $P=0.021$ ), memory ( $P=0.015$ ), and global ( $P=0.010$ ) domains.<sup>90</sup> Associations between cumulative BP and both walking speed and step length were moderated by cerebral WMH burden ( $P_{\text{interaction}}<0.05$ ).
- 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>91</sup>
- A pooled individual participant data analysis of 5 RCTs from the Dementia Risk Reduction collaboration included 28 008 individuals recruited from 20 countries.<sup>92</sup> After a median follow-up of 4.3 years, there were 861 cases of incident dementia. The pooled mean BP difference between the antihypertensive and control arms was 9.6 mmHg for SBP and 3.7 mmHg for DBP. With multilevel logistic regression, BP-lowering treatment was associated with a lower risk of subsequent dementia (OR, 0.87 [95% CI, 0.75–0.99]).
- An analysis from the CRIC study examined the link between BP and incident cognitive impairment defined as a decline in modified MMSE score

to >1 SD below the cohort mean.<sup>93</sup> The analysis included 3048 participants who did not have cognitive impairment at baseline and with at least 1 follow-up modified MMSE score. Spline analyses showed that the relationship between baseline SBP and incident cognitive impairment was J shaped and significant only in those participants with eGFR >45 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> ( $P=0.02$ ). The aHR was 1.13 (95% CI, 1.05–1.22) per 10-mmHg higher SBP for incident cognitive impairment in those with eGFR >45 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>. Baseline DBP was not associated with incident cognitive impairment in any analyses.

- A meta-analysis included 5 cohort studies with a total of 183 874 females with and 230 9705 females without HDP to study the risk of subsequent dementia.<sup>94</sup> Any type of HDP was associated with a higher risk of subsequent dementia (HR, 1.38 [95% CI, 1.18–1.61]). For dementia subtypes, any HDP was associated with higher risk of vascular dementia (HR, 3.14 [95% CI, 2.32–4.24]).
- In a population-based cohort study, the Netherlands Perinatal Registry and the national death registry at the Dutch Central Bureau for Statistics were linked to analyze the association between cardiovascular mortality and HDP for women with a first birth during 1995 and 2015.<sup>95</sup> The registry included 2 462 931 deliveries and 1 625 246 women with a median follow-up time of 11.2 years, of whom 259 177 women (20.8%) had HDP. Of these, 45 482 women (3.7%) had preeclampsia, and 213 695 women (17.2%) had gestational hypertension; 984 713 women (79.2%) did not develop hypertension in their first pregnancy (reference group). Compared with the reference group, the risk of all-cause mortality was higher in women who had HDP (HR, 1.30 [95% CI, 1.23–1.37];  $P<0.001$ ), preeclampsia (HR, 1.65 [95% CI, 1.48–1.83];  $P<0.0001$ ), and gestational hypertension (HR, 1.23 [95% CI, 1.16–1.30];  $P<0.0001$ ). Compared with the reference group, women with preeclampsia (aHR, 3.39 [95% CI, 2.67–4.29]) and gestational hypertension (aHR, 2.22 [95% CI, 1.91–2.57]) had higher risk for subsequent cardiovascular mortality. For women with a history of HDP who also had PTB (gestational age <37 weeks) and birth weight ≤10th percentile, association with cardiovascular mortality was even higher (HR, 6.43 [95% CI, 4.36–9.47]) compared with the reference group. The highest DBP measured during pregnancy was strongly associated with cardiovascular mortality (for 80–89 mmHg: aHR, 1.47 [95% CI, 1.00–2.17]; for ≥130 mmHg: HR, 14.70 [95% CI, 7.31–29.52]) with reference group having DBP <70 mmHg.
- In an analysis of the ONTARGET study, the lowest risk of ESKD or doubling of serum creatinine

(707 events overall) was seen at an achieved SBP of 120 to <140 mmHg; 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>96</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>97</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 ARBs; HR, 0.98 [95% CI, 0.89–1.07] for β-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>98</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 ARBs; HR, 0.99 [95% CI, 0.89–1.11] for β-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).
- A prospective observational cohort study of 906 patients from Italy with hypertension and CKD reported outcomes associated with baseline ambulatory BP patterns.<sup>99</sup> The absence of nocturnal dipping (defined as nighttime:daytime SBP ratio of <0.9) was associated with higher rates of cardiovascular events (HR, 2.79 [95% CI, 1.64–4.75]) and kidney disease progression (HR, 2.40 [95% CI, 1.58–3.65]) in participants whose daytime ambulatory SBP was not at goal (SBP >135 mmHg). Similar results were also noted in those whose ambulatory daytime SBP was at goal (HR for cardiovascular events, 2.06 [95% CI, 1.15–3.68]; HR for kidney disease progression, 1.82 [95% CI, 1.17–2.82]).
- In an analysis of the FHS including 8198 participants with hypertension subtypes, the prevalence of nonhypertension (SBP <140 mmHg and DBP <90 mmHg) was 79%, isolated systolic hypertension (SBP ≥140 mmHg and DBP <90 mmHg) was 8%, isolated diastolic hypertension (SBP <140 mmHg and DBP ≥90 mmHg) was 4%, and systolic-diastolic hypertension (SBP ≥140 mmHg and DBP ≥90 mmHg) was 9%.<sup>100</sup> Over the median

5.5-year follow-up, compared with nonhypertension (referent), isolated diastolic hypertension was not associated with increased CVD risk (HR, 1.03 [95% CI, 0.68–1.57] in contrast to isolated systolic hypertension [HR, 1.57 (95% CI, 1.30–1.90)] and systolic-diastolic hypertension [HR, 1.66 (95% CI, 1.36–2.01)]).

- In an individual participant data meta-analysis of 23 cohorts and 53 172 participants, higher arm compared with lower arm BP reclassified 12% of participants at either 130– or 140-mm Hg SBP thresholds (both  $P<0.001$ ).<sup>101</sup> Higher arm BP models fitted better using Akaike information criteria for all-cause mortality, cardiovascular mortality, and cardiovascular events (all  $P<0.001$ ).
- In an analysis of data from 2 waves of the National Longitudinal Study of Adolescent to Adult Health, including participants who had measured BP at wave IV (2008–09) and a pregnancy that resulted in a singleton live birth between waves IV and V (2016–2018; n=2038), the prevalence of PTB was 12.6%.<sup>102</sup> A 1-SD increment in SBP (SD, 12.2 mm Hg) and DBP (SD, 9.3 mm Hg) was associated with a 14% (95% CI, 2%–27%) and 20% (95% CI, 4%–37%) higher risk of preterm delivery. Compared with normotension, stage I hypertension (defined as SBP 130–139 mm Hg or DBP 80–89 mm Hg; RR, 1.33 [95% CI, 1.01–1.74]) and stage II hypertension (defined as SBP  $\geq$ 140 mm Hg or DBP  $\geq$ 90 mm Hg; RR, 1.34 [95% CI, 0.89–2.00]) were also associated with increased subsequent risk of preterm delivery.
- In a meta-analysis of 86 articles with 18 775 387 patients with COVID-19 from 18 countries, hypertension was associated with in-hospital mortality (OR, 1.36 [95% CI, 1.28–1.45]) and other adverse outcomes (OR, 1.32 [95% CI, 1.24–1.41]).<sup>103</sup> The analysis by mean age at a study level reported that in-hospital mortality was higher in studies with mean age <49 or >70 years compared with a mean age of 50 to 59 and 60 to 69 years ( $P<0.001$ ).
- A systematic review and meta-analysis analyzed the association of a simultaneously measured interarm SBP difference and all-cause mortality and cardiovascular mortality. The study included 10 cohort studies with 15 320 individuals published before April 2023.<sup>104</sup> An interarm SBP difference of  $\geq$ 15 mm Hg compared with an interarm SBP difference <15 mm Hg was associated with higher all-cause mortality (pooled HR, 1.28 [95% CI, 1.02–1.61]) and higher cardiovascular mortality (pooled HR, 1.93 [95% CI, 1.24–2.99]). In a subgroup analysis, the association with cardiovascular mortality was stronger in studies of younger patients (pooled HR, 9.03 [95% CI, 2.00–40.82]) than in studies of older patients (pooled HR, 1.67 [95% CI, 1.06–2.64]),

with the difference between groups being statistically significant ( $P=0.04$ ).

- A systematic review and meta-analysis including studies published through April 2022 examined the relationship between orthostatic hypertension, defined as a rise in SBP or DBP on standing, and subsequent cardiovascular outcomes.<sup>105</sup> The analysis included 20 studies with 61 669 participants and a median follow-up of 7.9 years. Orthostatic hypertension was associated with a higher risk of all-cause mortality (pooled HR, 1.21 [95% CI, 1.05–1.40]), cardiovascular mortality (pooled HR, 1.39 [95% CI, 1.05–1.84]), and stroke (pooled HR, 1.94 [95% CI, 1.52–2.48]).
- In a study of the association between invasive aortic BP and outcomes, data on all patients undergoing cardiac catheterization in Western Denmark from 2003 to 2016 who were registered in the Western Denmark Heart Registry were linked to outcome data in the Danish National Patient Registry, the Danish National Prescription Registry, and the Danish Civil Registration System with a median follow-up of 7.2 years.<sup>106</sup> The mean difference between cuff-based brachial SBP and invasive aortic BP was –1.6 mm Hg (95% CI, –1.8 to –1.3) for patients without CKD and –2.4 mm Hg (95% CI, –2.9 to –1.8) for patients with CKD. Office SBP and aortic SBP were associated with stroke in patients without CKD (HR per 10 mm Hg, 1.08 [95% CI, 1.05–1.12] and 1.06 [95% CI, 1.03–1.09], respectively) and with MI in patients with CKD (aHR, 1.08 [95% CI, 1.03–1.13] and 1.08 [95% CI, 1.04–1.12], respectively). However, office SBP and aortic SBP were similar for prediction of outcomes when adjusted models were compared by C statistics.
- An observational study of all males in late adolescence who were conscripted into the military in Sweden from 1969 to 1997 included 1 366 519 males with a mean age of 18.3 years and a median follow-up of 35.9 years.<sup>107</sup> The baseline BP at the time of conscription was classified as elevated (defined as SBP 120–129 mm Hg and DBP  $<$ 80 mm Hg) for 28.8% of participants and hypertensive ( $\geq$ 130/80 mm Hg) for 53.7%. Elevated BP was associated with a higher risk of the composite outcome of cardiovascular death or first hospitalization for MI, HF, ischemic stroke, or ICH (aHR, 1.10 [95% CI, 1.07–1.13]) during follow-up.
- A reanalysis from the Spanish Ambulatory Blood Pressure Registry included clinic and ambulatory BP data obtained from 2004 to 2014 from 223 primary care centers from the Spanish National Health System in all 17 regions of Spain.<sup>108</sup> Over a median follow-up of 9.7 years, these records were linked to the vital registry of the Spanish National Institute of Statistics for outcome data. Overall, 24-hour

SBP was more strongly associated with all-cause mortality (HR, 1.41 per 1-SD increment [95% CI, 1.36–1.47]) than clinic SBP (HR, 1.18 [95% CI, 1.13–1.23]). Twenty-four-hour BP was associated with all-cause mortality after adjustment for clinic BP (HR, 1.43 [95% CI, 1.37–1.49]); however, the association between clinic BP and all-cause mortality was attenuated when adjusted for 24-hour BP (HR, 1.04 [95% CI, 1.00–1.09]). Relative to normal BP, elevated all-cause mortality risks were observed for masked hypertension (HR, 1.24 [95% CI, 1.12–1.37]) and sustained hypertension (HR, 1.24 [95% CI, 1.15–1.32]) but not white-coat hypertension. Similarly, higher cardiovascular mortality risks were observed for masked hypertension (HR, 1.37 [95% CI, 1.15–1.63]) and sustained hypertension (HR, 1.38 [95% CI, 1.22–1.55]) but not white-coat hypertension.

## Health Care Use: Hospital Discharges/ Ambulatory Care Visits

- Beginning in 2016, a code for hypertensive crisis (*ICD-10-CM*116) was added to the HCUP inpatient database. For 2016, hypertensive crisis is included in the total number of inpatient hospital stays for HBP. From 2011 to 2021, the number of inpatient discharges from short-stay hospitals with HBP as the principal diagnosis increased from 296 253 to 1 311 528. The number of discharges with any listing of HBP increased from 16 112 764 to 17 160 070 in that same time period.
- In 2021, there were 7090 principal diagnosis discharges for essential hypertension (HCUP,<sup>109</sup> unpublished NHLBI tabulation).
- In 2021, there were 8827 938 all-listed discharges for essential hypertension (HCUP,<sup>109</sup> unpublished NHLBI tabulation).
- In 2019, 56 795 000 of 1 036 484 000 physician office visits had a primary diagnosis of essential hypertension (*ICD-9-CM* 401; NAMCS,<sup>110</sup> unpublished NHLBI tabulation). There were 779 438 ED discharges with a principal diagnosis of essential hypertension in 2021 (HCUP,<sup>109</sup> unpublished NHLBI tabulation).
- A matched observational study emulating a cluster RCT design compared changes in outcomes from 2019 to 2021 for patients with hypertension at high remote patient monitoring practices with those at matched control practices with little remote patient monitoring.<sup>111</sup> The study matched 192 high remote patient monitoring practices including 19 978 patients with hypertension to 942 low remote patient monitoring control practices including 95 029 patients with hypertension. Compared with patients with hypertension at matched control

practices, patients with hypertension at high remote patient monitoring practices had a 3.3% (95% CI, 1.9%–4.8%) increase in hypertension medication fills, a 1.6% (95% CI, 0.7%–2.5%) increase in days' supply of medication, and a 1.3% (95% CI, 0.2%–2.4%) increase in unique medications received. However, these patients also saw increases in primary care physician outpatient visits (7.2% [95% CI, –0.1% to 14.6%]) and a \$274 [95% CI, \$165–\$384] increase in total hypertension-related spending.

## Cost

- The estimated direct and indirect cost of HBP for 2020 to 2021 (annual average) was \$49.0 billion (unpublished NHLBI tabulation using MEPS<sup>112</sup>).
- Estimated US health care expenditures for hypertension in 2016 were \$79 (95% CI, \$72.6–\$86.8) billion. Of 154 health conditions, hypertension ranked 10th in health care expenditures.<sup>113</sup>
- In a systematic review of 33 studies reporting cost of care with hypertension from sub-Saharan Africa, only 25% of the countries were represented.<sup>114</sup> The included studies reported costs from the public sector or used a mixed approach including private, nongovernmental, or missionary facilities. Medication costs were accountable for most of the monthly expenditures with a range from \$1.7 to \$97.1 from a patient perspective and \$0.1 to \$193.6 from a health care professional perspective (per patient per month). Other patient costs reported included transportation, time, and wages lost as a result of hypertension treatment and laboratory costs. At a geographic level, macroeconomic costs ranged from \$1.6 million annually for the full population of patients ≥25 years of age living with hypertension on the Seychelles to \$397.6 million for direct costs for hypertensive treatment in the sub-Saharan population with SBP ≥115 mm Hg.
- A meta-analysis of RCTs to estimate the SBP reduction for team-based care strategies compared with usual care included 19 studies comprising 5993 participants.<sup>77</sup> The validated BP Control Model–Cardiovascular Disease Policy Model was used to project the expected BP reductions out to 10 years and to simulate CVD events, direct health care costs, QALYs, and cost-effectiveness of team-based care with physician and nonphysician titration. Relative to usual care at 10 years, team-based care with nonphysician titration was estimated to cost \$95 (95% UI, -\$563 to \$664) more per patient and gain 0.022 (95% UI, 0.003–0.042) QALYs, costing \$4400 per QALY gained. Team-based care with physician titration was

estimated to cost more and gain fewer QALYs and was dominated by team-based care with nonphysician titration.

## Global Burden

### (See Chart 8-6 and Table 8-3)

- 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>115</sup>
- Based on 204 countries and territories in 2021, age-standardized mortality rates attributable to high SBP among regions were highest for central Asia, followed by eastern Europe, central sub-Saharan Africa, and North Africa and the Middle East (Chart 8-6). High SBP was attributed to 10.85 (95% UI, 9.22–12.54) million total deaths in 2021. The PAF was 15.99% (95% UI, 13.52%–18.19%; Table 8-3).<sup>116</sup>
- It has been estimated that 7.834 million deaths and 143.037 million DALYs in 2015 could be attributed to SBP  $\geq$ 140 mmHg.<sup>117</sup> In addition, 10.7 million deaths and 211 million DALYs in 2015 could be attributed to SBP of  $\geq$ 110 mmHg.
- Between 1990 and 2015, the number of deaths related to SBP  $\geq$ 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>117</sup>
- In a cross-sectional study of 12926 individuals from the Bangladesh Demographic and Health Survey conducted over 2017 to 2018, the overall prevalence of hypertension was 27.4%, being higher in females (28.4%) than males (26.2%). Of those with hypertension, 42.4% ( $n=508$ ) of people were aware of being hypertensive.<sup>118</sup>
- In a 2021 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>119</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 data from the 2017 to 2019 baseline wave, the estimated hypertension prevalence among adults  $\geq$ 45 years of age was 45.9% (95% CI, 45.4%–46.5%).<sup>120</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.

- In a 2021 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>121</sup> The pooled prevalence was 29% in children with obesity compared with 7% in children with normal weight.
- A systematic review and meta-analysis included observational studies from January 1, 2010, to December 31, 2021, of adolescents 10 to 19 years of age residing in sub-Saharan African countries to examine the prevalence of hypertension.<sup>122</sup> Thirty-six studies comprising 37 926 participants 10 to 19 years of age from 10 of 49 sub-Saharan African countries were included. The reported prevalence of elevated BP ranged from 0.2% to 25.1% in the individual studies. The pooled prevalence was 9.9% (95% CI, 7.3%–12.5%) although with significant heterogeneity ( $I^2=99.2\%$ ;  $P<0.0001$ ).
- In an analysis from the CROOLE study, which included 721 Black people from sub-Saharan Africa between 30 and 79 years of age with uncontrolled hypertension and a baseline 24-hour ambulatory BP monitoring, the prevalence of a nondipping pattern was 78%.<sup>123</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>124</sup> In Japan, the corresponding rates also declined from 63.7 and 24.7 in males and from 35.9 and 8.9 in females.
- In a 2022 meta-analysis of 147 studies involving 1312 244 general population participants from Middle East and North Africa, the prevalence of hypertension was 26.2% (95% CI, 24.6%–27.9%).<sup>125</sup> The prevalence of hypertension awareness was only 51.3% (95% CI, 47.7%–54.8%), and the prevalence of hypertension treatment was also low at 47.0% (95% CI, 34.8%–59.2%). The prevalence of BP control among treated patients was 43.1% (95% CI, 38.3%–47.9%). There was a high degree of statistical heterogeneity ( $I^2>99\%$ ) in all the analyses. The year of study publication and mean age of patients at the study-level were associated with a higher prevalence and contributed to the heterogeneity in the univariate meta-regression.

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

Population group	Prevalence, 2017–2020, ≥20 y of age	Mortality,* 2022, all ages	Age-adjusted mortality rates per 100 000 (95% CI),* 2022
Both sexes	122 400 000 (46.7%) (95% CI, 44.2%–49.3%)	131 454	31.5 (31.3–31.7)
Males	62 800 000 (50.4%)	63 901 (48.6%)‡	35.4 (35.2–35.7)
Females	59 600 000 (43.0%)	67 553 (51.4%)‡	27.6 (27.4–27.8)
NH White males	48.9%	44 028	33.3 (33.0–33.6)
NH White females	42.6%	49 115	26.8 (26.5–27.0)
NH Black males	57.5%	11 665	67.3 (66.0–68.6)
NH Black females	58.4%	10 647	44.7 (43.8–45.5)
Hispanic males	50.3%	5 132	28.0 (27.2–28.9)
Hispanic females	35.3%	4 694	20.4 (19.8–20.9)
NH Asian males	50.2%	1 861§	20.7 (19.7–21.6)§
NH Asian females	37.6%	2 146§	17.0 (16.3–17.7)§
NH American Indian/Alaska Native people	...	861	34.4 (32.0–36.7)
NH Native Hawaiian or Pacific Islander people	...	182	31.5 (26.8–36.2)

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>128</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 that there were 103.3 million noninstitutionalized US adults with hypertension.<sup>127</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 people, American Indian or Alaska Native people, 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 decedents, Asian and Pacific Islander decedents, 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 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 using Agency for Healthcare Research and Quality Prevention Quality Indicator 08, heart failure admission rate.

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

§Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.<sup>5</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 estimates. Mortality (for underlying cause of HBP): Unpublished NHLBI tabulation using National Vital Statistics System<sup>79</sup> and CDC WONDER.<sup>80</sup> These data represent underlying cause of death only.

**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>126</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>5</sup>

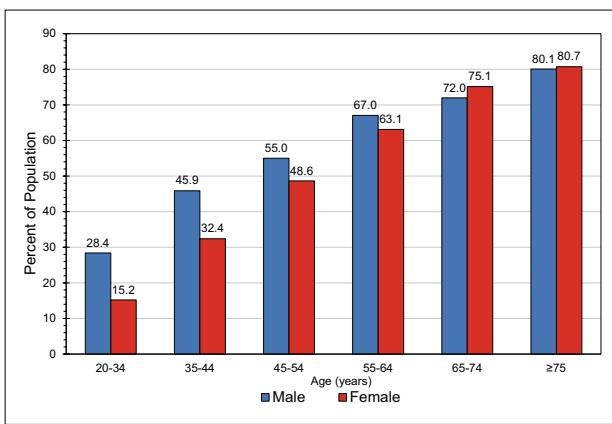
**Table 8-3. Deaths Caused by High SBP Worldwide, by Sex, 2021**

	Deaths		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	10.85 (9.22 to 12.54)	5.55 (4.63 to 6.48)	5.30 (4.41 to 6.16)
Percent change (%) in total number, 1990–2021	65.31 (54.16 to 77.29)	77.93 (61.83 to 94.92)	53.89 (41.50 to 66.50)
Percent change (%) in total number, 2010–2021	20.50 (14.29 to 27.17)	22.32 (13.82 to 32.26)	18.65 (11.09 to 26.26)
Rate per 100 000, age standardized, 2021	131.10 (111.63 to 151.57)	151.95 (126.65 to 176.70)	113.21 (94.17 to 131.42)
Percent change (%) in rate, age standardized, 1990–2021	-32.32 (-36.69 to -27.64)	-27.70 (-33.87 to -21.13)	-36.46 (-41.29 to -31.33)
Percent change (%) in rate, age standardized, 2010–2021	-13.63 (-18.07 to -8.97)	-12.26 (-18.35 to -5.49)	-14.94 (-20.29 to -9.49)
PAF (%), all ages, 2021	15.99 (13.52 to 18.19)	14.73 (12.40 to 16.91)	17.56 (14.64 to 20.14)
Percent change (%) in PAF, all ages, 1990–2021	12.28 (6.24 to 18.10)	17.15 (10.45 to 25.31)	8.50 (1.07 to 15.06)
Percent change (%) in PAF, all ages, 2010–2021	-5.79 (-9.17 to -2.55)	-5.75 (-9.79 to -1.31)	-5.57 (-9.86 to -1.83)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

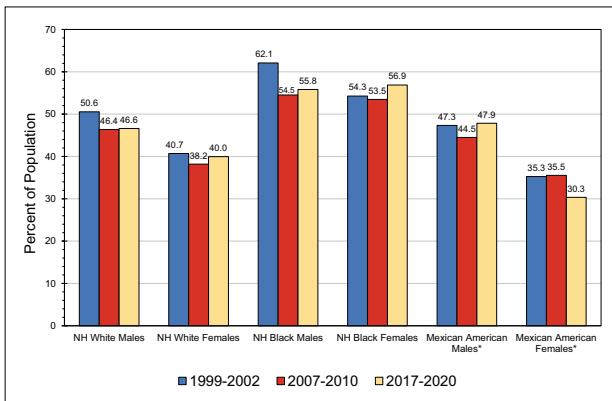
GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; PAF, population attributable fraction; SBP, systolic blood pressure; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>116</sup>



**Chart 8-1. Prevalence of hypertension in US adults ≥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>126</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, 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>5</sup>

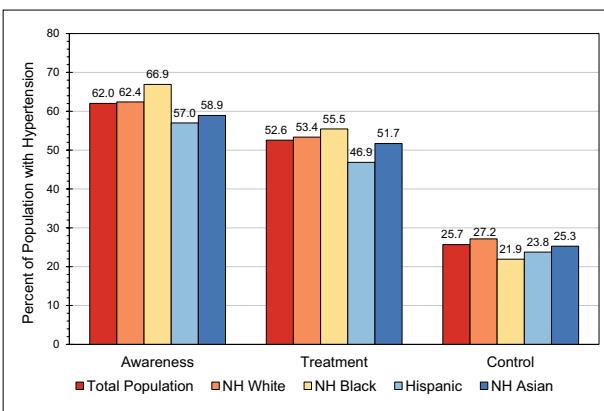


**Chart 8-2. Age-adjusted prevalence trends for hypertension in US adults ≥20 years of age, by race and ethnicity, sex, and survey year (NHANES 1999–2002, 2007–2010, and 2017–2020).**

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>126</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; 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.

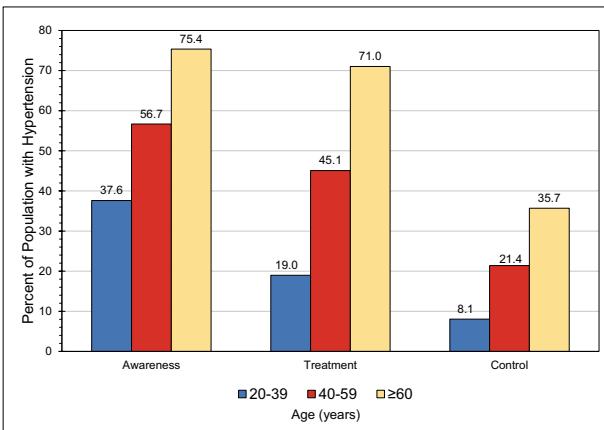
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>5</sup>



**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>126</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.

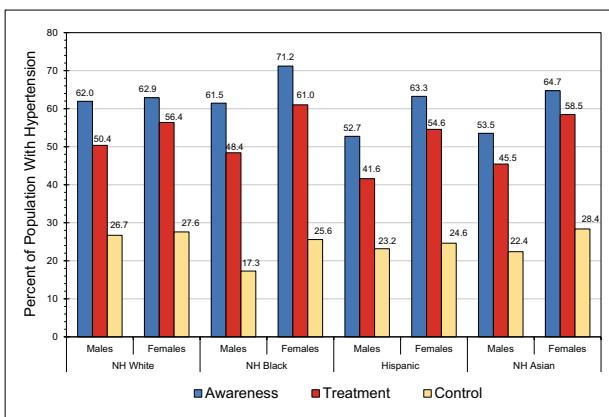
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>5</sup>



**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>126</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.

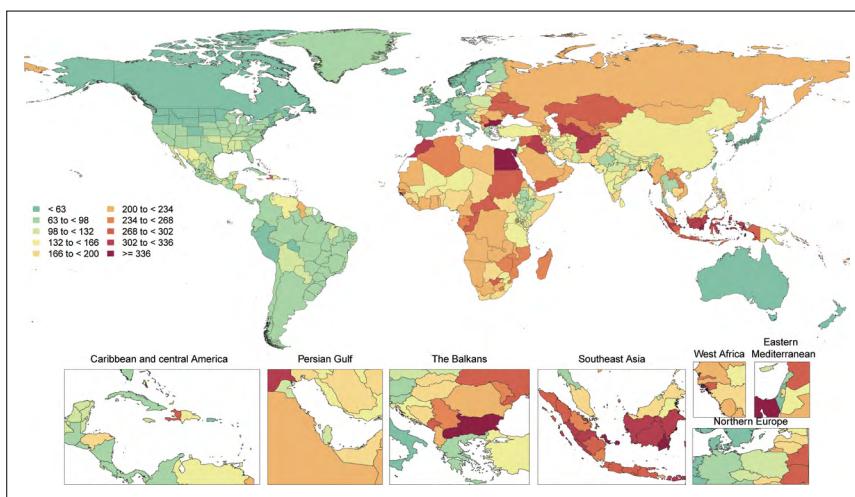
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>5</sup>



**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>126</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>5</sup>



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## 9. DIABETES

**ICD-9 250; ICD-10 E10 to E11. See Tables 9-1 through 9-3 and Charts 9-1 through 9-9**

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Diabetes is a heterogeneous condition 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 8 components of ideal CVH.<sup>4</sup>

### Prevalence

#### Youth

- In 2021, 352 000 children and adolescents  $<20$  years of age, or 35 per 10 000 US youths, had diagnosed diabetes. This includes 304 000 with type 1 diabetes.<sup>1</sup>
- Among US adolescents 12 to 18 years of age in 2005 to 2016, the prevalence of prediabetes was

The 2025 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 2025. 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.

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>5</sup>

- A mathematical prediction model from the SEARCH for Diabetes in Youth study suggests that the number of youths with diabetes will increase from 213 000 (type 1 diabetes, 185 000; type 2 diabetes, 28 000) in 2017 to 239 000 (type 1 diabetes, 191 000; type 2 diabetes, 48 000) in 2060 if the incidence remains constant as observed in 2017, which corresponds to relative increases of 3% for type 1 diabetes and 69% for type 2 diabetes.<sup>6</sup> But if one bases this estimate on increasing trends in incidence observed between 2002 and 2017, the projected number of youths with diabetes will be 526 000 (type 1 diabetes, 306 000; type 2 diabetes, 220 000), corresponding to relative increases of 65% for type 1 diabetes and 673% for type 2 diabetes.

#### Adults

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

- On the basis of NHANES 2017 to 2020 data,<sup>7</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>7</sup> data for people  $\geq 20$  years of age indicate that the prevalence of diagnosed diabetes varied by race and sex and was lowest in NH Asian females and NH White females and highest in NH Asian males and Hispanic males (Table 9-1 and Chart 9-1).
- On the basis of US Indian Health Service data from 2018 to 2019, the age-adjusted prevalence of diagnosed diabetes among American Indian/Alaska Native people was 14.4% for males and 14.7% for females.<sup>1</sup>
- On the basis of NHANES 2017 to 2020 data,<sup>7</sup> the age-adjusted prevalence of diagnosed diabetes in adults  $\geq 20$  years of age varied 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).
- Geographic variations in diabetes prevalence have been reported in US adults:
  - From state-level data from BRFSS<sup>8</sup> 2022, Guam (21.3%), Puerto Rico (14.9%), and West Virginia (14.4%) had the highest age-adjusted prevalence of diagnosed diabetes, and Vermont (7.0%) had the lowest prevalence (Chart 9-3).

## Incidence

### Youth

- During 2017 to 2018, an estimated 18 169 people <20 years of age in the United States were diagnosed with incident type 1 diabetes, and 5293 individuals 10 to 19 years of age were newly diagnosed with type 2 diabetes annually.<sup>1</sup>
- On the basis of SEARCH 2002 to 2018 data among youths <20 years of age from 5 centers across Arizona, California, Colorado, New Mexico, Ohio, South Carolina, and Washington in 2017 to 2018, the annual incidence of type 1 diabetes was 22.2 per 100 000 and that of type 2 diabetes was 17.9 per 100 000, indicating that the gap is closing between type 1 and type 2 diabetes, with type 2 diabetes in youths poised to possibly become more prevalent than type 1 diabetes in the future.<sup>9</sup>
  - For type 1 diabetes, the incidence rate (per 100 000) was 7.8 for American Indian youths, 9.4 for Asian or Pacific Islander youths, 22.1 for Black youths, 17.7 for Hispanic youths, and 26.4 for White youths.<sup>10</sup>
  - For type 2 diabetes, the incidence rate (per 100 000) was 46.0 for American Indian youths, 16.6 for Asian or Pacific Islander youths, 50.1 for Black youths, 25.8 for Hispanic youths, and 5.2 for White youths.

### Adults

#### (See Table 9-1)

- Approximately 1.2 million US adults ≥18 years of age were diagnosed with incident diabetes in 2021 (Table 9-1). This included ≈620 000 males and 591 000 females, 52 000 NH Asian individuals, 185 000 NH Black individuals, 233 000 Hispanic individuals, and 721 000 NH White individuals.<sup>1</sup>
- During 2018 to 2019, adults with less than a high school education had a higher age-adjusted incidence rate for diagnosed diabetes (7.1 per 1000 [95% CI, 5.5–9.1]) than adults with more than a high school education (4.5 per 1000 [95% CI, 3.9–5.12]).<sup>1</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>11</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 2021 (5.8 per 1000 adults), with a decreasing trend noted since 2008 (8.4 per 1000 adults).<sup>1</sup>

- In the SEARCH study, the incidence rate of type 1 diabetes increased by 2.0% annually and the incidence of type 2 diabetes increased by 5.3% annually from 2002 to 2018.<sup>9</sup>
  - The annual increase in diabetes varied by race and ethnicity. For type 1 diabetes, the annual percent increase was 2.9% for Black youths, 4.1% for Hispanic youths, 4.8% for Asian or Pacific Islander youths, and 0.6% for White youths. For type 2 diabetes, the annual percent increase was 6.0% for Black youths, 7.2% for Hispanic youths, 3.5% for American Indian youths, 8.9% for Asian or Pacific Islander youths, and 1.8% for White youths (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 PY for FPG 100 to 125 mg/dL, 43.8 per 1000 PY for 2-hour postchallenge glucose 140 to 199 mg/dL, and 45.2 per 1000 PY for HbA1c of 5.7% to 6.4%.<sup>12</sup>
- In an analysis of NHANES over the years 2001 through 2018, the top predictors of early-onset type 2 diabetes (age at onset, <50.5 years) in males in multivariable logistic regression were NH Black ethnicity and race (OR, 2.97 [95% CI, 2.24–3.95]), tobacco smoking (OR, 2.79 [95% CI, 2.18–3.58]), and high education level (OR, 1.65 [95% CI, 1.27–2.14]); in females, the top predictors were tobacco smoking (OR, 2.59 [95% CI, 1.90–3.53]), Hispanic ethnicity (OR, 1.49 [95% CI, 1.08–2.05]), and obesity (OR, 1.30 [95% CI, 0.91–1.86]).<sup>13</sup>
- In the WHI, the risk of diabetes in females 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>14</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>15</sup>

- In a meta-analysis of 42 studies, total dairy and yogurt intake was associated with a dose-dependent 3% and 7% lower risk of developing type 2 diabetes per 200– and 50-g/d intake increase, respectively.<sup>16</sup>
- Higher levels of omega-3 polyunsaturated fat biomarkers are associated with lower risk of type 2 diabetes. Among 67 prospective studies comprising 310955 participants, a significant inverse relation of type 2 diabetes risk was observed across categories of  $\alpha$ -linolenic acid (RR, 0.89 [95% CI, 0.82–0.96]), EPA (RR, 0.85 [95% CI, 0.72–0.99]), and docosapentaenoic acid (RR, 0.84, [95% CI, 0.73–0.96]).<sup>17</sup>
- In 4468 adults from the Look AHEAD trial, body weight time in target range (per 1 SD) was associated with a decreased risk of adverse cardiovascular outcomes (HR, 0.84 [95% CI, 0.75–0.94]).<sup>18</sup>
- Data from mortality follow-up through 2019 from the NHANES surveys 1999 to 2018 showed that among 7101 patients with diabetes, in fully adjusted analyses, those in the highest compared with the lowest serum uric acid quintile had an HR of 1.28 (95% CI, 1.03–1.58) for all-cause mortality and 1.41 (95% CI, 1.03–1.94) for CVD mortality.<sup>19</sup>
- In a pooled analysis for the STEP diabetes subgroup and ACCORD-BP standard glycemic group involving 3989 patients who were randomized to intensive (110–<130 mmHg) compared with standard (130–<150 mmHg) SBP control, after 3.8 years, those in the intensive group had a lower risk of major cardiovascular events (HR, 0.77 [95% CI, 0.64–0.93]).<sup>20</sup>
- Among 8 485 539 Korean adults, in adjusted analysis, the upper quartiles of remnant cholesterol were associated with a higher risk of developing type 2 diabetes; multivariable-adjusted HRs were 1.25 (95% CI, 1.24–1.27), 1.51 (95% CI, 1.50–1.53), and 1.95 (95% CI, 1.93–1.97) for those in the second, third, and fourth quartiles compared with the lowest quartile.<sup>19</sup>
- In a post hoc analysis of the ACCORD trial, a higher time in target range of 110 to 130 mmHg for SBP was associated with a reduction in MACEs (HR, 0.54 [95% CI, 0.43–0.67]), including stroke (HR, 0.19 [95% CI, 0.10–0.36]), MI (HR, 0.67 [95% CI, 0.51–0.89]), HF (HR, 0.47 [95% CI, 0.33–0.66]), cardiovascular death (HR, 0.63 [95% CI, 0.42–0.93]), and all-cause mortality (HR, 0.70 [95% CI, 0.54–0.91]).<sup>21</sup>
- Among 9 cohort studies of 6 877 661 participants, the extent of glycemic variability was significantly

associated with incident AF both in those with (RR, 1.24 [95% CI, 1.03–1.50]) and in those without (RR, 1.13 [95% CI, 1.00–1.28]) diabetes.<sup>22</sup>

- Among 14 randomized controlled trials and 144 334 patients with type 2 diabetes, an intensive glucose-lowering treatment regimen compared with conventional therapy reduced the incidence of MI (OR, 0.90 [95% CI, 0.84–0.97]).<sup>23</sup>
- Among 27 articles evaluating sex differences in cardiovascular outcomes, females compared with males with diabetes had an increased risk of all-cause mortality (RR, 1.13 [95% CI, 1.07–1.19]), cardiac mortality (RR, 1.49 [95% CI, 1.11–2.00]), and CHD mortality (RR, 1.44 [95% CI, 1.20–1.73]).<sup>18</sup>
- A recent meta-analysis of 8 observational studies showed a 38% higher risk of developing diabetes among individuals in the bottom quintile of lipoprotein(a) (<3–5 mg/dL) compared with the top quintile of lipoprotein(a) (>27–55 mg/dL).<sup>24</sup> In a meta-analysis of 19 clinical trials of statin therapy among 123 940 participants, compared with placebo, low- to moderate-intensity statin allocation was associated with a 10% proportional increase in new-onset diabetes; for high-intensity statin therapy, this increase was 36%.<sup>25</sup> Sixty-two percent of the new-onset diabetes cases were among those in the top quartile of the HbA1c distribution (mean HbA1c, 6.14%–6.17%). Among those with prevalent diabetes, the excess risk for worsening glycemia was 10% (95% CI, 6%–14%) for low-intensity or moderate-intensity statin therapy and 24% (95% CI, 6%–44%) for high-intensity statin versus placebo.
- 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, with excess alcohol intake (RR, 1.12 [95% CI, 1.03–1.22]), physical inactivity (RR, 1.14 [95% CI, 1.07–1.22]), sedentary behavior (RR, 1.10 [95% CI, 1.04–1.16]), and unhealthy diet (RR, 1.26 [95% CI, 1.18–1.35]) contributing to higher risks for diabetes.<sup>26</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>27</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>28</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>39</sup>
  - In NHANES 2007 to 2014, the prevalence of gestational diabetes was 7.6%, with 19.7% of females with gestational diabetes having a subsequent diagnosis of type 2 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>30</sup>
  - In the Nurses' Health Study 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>31</sup>
  - Among 1956452 individuals with type 2 diabetes in the Korean National Health Insurance Service database, those in the highest quartile of remnant cholesterol level had a 28% significantly higher risk of MI and a 22% significantly higher risk of stroke.<sup>32</sup>
  - An analysis of 11 prospective studies of 355230 individuals recently showed highest dietary cholesterol intake to be associated with a 15% greater risk of developing type 2 diabetes, with relationships strongest in Western countries (United States, France, and Finland) compared with Eastern countries (China, Japan, and Korea).<sup>33</sup> In a meta-analysis of 9 observational studies, the risk of developing gestational diabetes was 49% greater for the highest compared with lowest categories of dietary cholesterol intake, with a 32% increase per 100-mg/d cholesterol intake.<sup>34</sup>
  - In a systematic review and meta-analysis of 24 prospective cohort studies, olive oil consumption was associated with a 22% lower risk for developing type 2 diabetes.<sup>35</sup>
  - Among 18908 Japanese participants with prediabetes in an observational cohort study of claims data, nonideal BMI, BP, and TC and the number of nonideal CVH metrics were associated with an increased risk of developing diabetes.<sup>36</sup>
  - Among 1890 studies, the development of type 2 diabetes was associated with unprocessed red meat (HR, 1.27 [95% CI, 1.16–1.39]) and processed red meat (HR, 1.44 [95% CI, 1.27–1.63]).<sup>37</sup>
  - Among participants in the FHS and HCHS/SOL, the risk of incident diabetes increased by ≈50% for each 10-year increment in age or 5-unit increment in BMI and was 50% to 70% higher in those with hypertension compared with those without hypertension.<sup>38</sup> Among 2829 Black adults in the JHS,
- in adjusted models, a higher HDL-C concentration was associated with a lower risk of diabetes (HR for highest versus lowest tertile of HDL-C, 0.56 [95% CI, 0.44–0.71]).<sup>39</sup>
- Among 83721 patients with type 2 diabetes from a multi-institutional diabetes registry in Singapore, with SBP at levels of 120 to 129 mmHg as the reference, levels ≥140 mmHg were associated with increased CVD mortality (HR, 1.27 [95% CI, 1.12–1.45]), and in those ≥65 years of age with DBP 70 to 79 mmHg as the reference, higher CVD mortality risks were seen in those with DBP ≥90 mmHg (HR, 1.55 [95% CI, 1.24–1.95]) and DBP <70 mmHg (HR, 1.19 [95% CI, 1.10–1.29]).<sup>40</sup>
  - Among 30 RCTs including 59934 patients with type 2 diabetes, the lowest risk of major cardiovascular events was found in those patients who achieved SBP levels of 120 to 124 mmHg (HR, 0.73 [95% CI, 0.52–1.02]) compared with 130 to 134 mmHg (HR, 0.60 [95% CI, 0.41–0.85]) and 140 to 144 mmHg.<sup>41</sup>
  - In a meta-analysis of 45 cohort studies, an SBP ≥140 mmHg (but not ≥130 mmHg) compared with below these numbers was associated with a greater risk of cardiovascular outcomes (HR, 1.56 [95% CI, 1.04–2.34]).<sup>42</sup> The risk was greater for each 10-mmHg increment in SBP (HR, 1.10 [95% CI, 1.04–1.18]).
  - In an analysis of 9307 participants from the ACCORD trial, cumulative HbA1c exposure measured as the AUC during exposure time was associated with an increased risk of cardiovascular events (HR, 1.32 [95% CI, 1.22–1.43]), all-cause mortality (HR, 1.33 [95% CI, 1.21–1.46]), and cardiovascular death (HR, 1.45 [95% CI, 1.27–1.67]).<sup>43</sup>

## Social Determinants of Health/Health Equity

- In NHIS 2013 to 2017, adults with diabetes who were <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%). Among adults with diabetes <65 years of age, the prevalence of cost-related medication nonadherence was 34.7%, and the prevalence of delayed medical care was 55.5%.<sup>44</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>45</sup>
- According to 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>46</sup>
- In the SEARCH study (Washington and South Carolina sites), the prevalence of food insecurity among individuals with type 1 diabetes was 19.5%. Youths 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>47</sup>
  - Data from the NHIS 2013 to 2018 for >170 000 adults demonstrate low versus high social cohesion to be associated with a higher adjusted prevalence of type 2 diabetes (PR, 1.17 [95% CI, 1.11–1.22]) after adjustment, with even stronger associations in those 31 to 49 years of age (PR, 1.36 [95% CI, 1.20–1.54]) and in Hispanic/Latino women 18 to 30 years (PR, 3.70 [95% CI, 1.40–9.80]).<sup>48</sup>
  - In a case-control study using Geisinger electronic health records (2008–2016), compared with people living in rural affordable residence tracts, higher odds of new-onset type 2 diabetes were found in those categorized as living in extreme poverty (OR, 1.11 [95% CI, 1.02–1.21]) or those categorized as multilingual working (OR, 1.07 [95% CI, 1.03–1.23]).<sup>49</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 risk is not equivalent to the risk in those with preexisting CVD, with only 19% of those with diabetes without CVD recently estimated to be a CVD risk equivalent.<sup>49</sup>
- Individuals with type 2 diabetes have a wide spectrum of risks that warrant comprehensive CVD risk assessment, including global risk scoring, consideration of risk enhancing factors, and, in subgroups, evaluation of subclinical atherosclerosis to inform treatment.<sup>50</sup>
- Currently, the US PCE 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>51</sup> However, this equation does not include diabetes-specific risk enhancers that can be used to inform the treatment decision, including (1) long duration ( $\geq 10$  years for type 2 diabetes or  $\geq 20$  years for type 1 diabetes), (2) albuminuria ( $\geq 30$   $\mu\text{g}$  albumin/mg creatinine), and (3) eGFR ( $< 60$   $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , retinopathy, neuropathy, and an ABI  $< 0.9$  if uncertain).<sup>52</sup> There is currently no available US-based pooled cohort risk score developed specifically in individuals with diabetes. However, the new AHA scientific statement on cardiovascular-kidney-metabolic health has

introduced the PREVENT risk score, which predicts the 10-year risk of total CVD and the components of ASCVD separately.<sup>53</sup> It requires input of eGFR and allows input of HbA1c, urine ACR, and zip code for further refinement of risk estimation, including among individuals with diabetes.

- In a recent analysis of 27 730 subjects with diabetes from 4 major US cohorts (ARIC, JHS, MESA, FHS Offspring), diabetes was identified as a CVD risk equivalent in only one-fifth of CVD-free adults with diabetes. A high HbA1c, long diabetes duration, and diabetes medication use were predictors of being a CVD risk equivalent. Moreover, diabetes was a CVD risk equivalent for women, White people, those of younger age, people with higher triglycerides or CRP, or people with reduced kidney function.<sup>49</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%/y for CAC scores of  $\geq 400$ , and CAC provided significant improvements in the C statistic beyond risk factors.<sup>54</sup> A subsequent report noted that a duration of diabetes of at least 10 years further stratified risk, especially at higher CAC scores.<sup>55</sup> Moreover, the 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>56</sup> More recently, in the Coronary Calcium Consortium, among 4503 adults with diabetes (32.5% women) 21 to 93 years of age, higher levels of CAC were more strongly related to CVD and total mortality in women compared with men.<sup>57</sup> For CVD mortality, HRs for CAC scores of 101 to 400 and  $> 400$  were 3.67 and 6.27, respectively, for women and 1.63 and 3.48, respectively, for men ( $P_{\text{interaction}} = 0.04$ ). For total mortality, HRs were 2.56 (CAC scores 101–400) and 4.05 (CAC scores  $> 400$ ) for women and 1.88 (CAC scores 101–400) and 2.66 (CAC scores  $> 400$ ;  $P_{\text{interaction}} = 0.01$ ) for men.
- CONFIRM recently showed baseline statin therapy to be associated with a reduction in MACEs in those with CAC scores  $\geq 100$  who also had a segment involvement score of  $\geq 3$  (HR, 0.24 [95% CI, 0.07–0.87]).<sup>58</sup>
- A recent report from the CLARIFY registry of 6462 patients with diabetes showed higher levels of CAC ( $> 400$  versus 0) to be associated with greater statin and high-intensity statin initiation and CAC scores of  $> 400$  compared with lower levels to be associated with reductions in SBP, TC, LDL-C, and triglycerides.<sup>59</sup>
- An analysis from MESA and MASALA studies among 7562 participants showed that CAC  $> 0$  and

CAC  $\geq 100$  in those with diabetes was highest in NH White adults (80% and 48%) and South Asian adults (72% and 41%).<sup>60</sup> South Asian adults and Chinese adults had the highest odds of CAC  $\geq 100$  (2.28 and 2.27, respectively;  $P < 0.01$ ). Fasting glucose and glycated hemoglobin were most strongly associated with CAC among South Asian adults.

- In an analysis from the CAC Consortium among 2246 individuals with a CAC score  $\geq 1000$ , both diabetes (HR, 2.04 [95% CI, 1.47–2.83]) and severe left main CAC (HR, 2.32 [95% CI, 1.51–3.55]) were associated with a similar risk of ASCVD mortality.<sup>61</sup> In a follow-up of the DPP Outcomes Study, in analyses adjusted for demographic, genetic, metabolic, vascular, and behavioral covariates, a CAC score  $> 300$  compared with 0 remained associated with greater decline in only Spanish English Verbal Learning Test Delayed Recall in women ( $\beta = -1.09$  [95% CI, -1.87 to -0.31]) but not men with prediabetes or diabetes.<sup>62</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 statistic, 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>63</sup>
- The updated version of the QDiabetes risk prediction algorithm had C statistics between 0.81 and 0.89.<sup>64</sup>
- Risk prediction algorithms for CVD among individuals with diabetes have also been developed.<sup>65–67</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>66</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>68</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>69</sup> Using the Steno Type 1 risk engine, a cross-sectional multicenter study of 2041 patients with type 1 diabetes estimated the 10-year CVD risk to be 15.4% overall, but it was significantly higher ( $P < 0.001$ ) in males than females before 55 years of age, after which the risk equalized between

sexes. Of note, 68% of males compared with 32% of females before 55 years of age had high 10-year CVD risk ( $P < 0.001$  comparing risk distribution between sexes).<sup>70</sup>

- A machine learning model for the prediction of HF in individuals with prediabetes or diabetes from NHANES 2007 to 2018 was developed and showed that age, poverty-to-income ratio, MI, CHD, chest pain, and glucose-lowering medication use were all independent predictors of HF, with the random forest model showing the best performance (AUC, 0.978).<sup>71</sup>
- The European SCORE2 diabetes risk score for prediction of cardiovascular events in individuals with diabetes was recently developed and incorporates conventional risk factors (ie, age, smoking, SBP, total, and HDL-C), as well as diabetes-related variables (ie, age at diabetes diagnosis, HbA1c, and creatinine-based eGFR).<sup>72</sup> External validation showed good discrimination and improvement over SCORE2 (C index change from 0.009 to 0.031).

## Family History and Genetics

- Diabetes is heritable. Twin and family studies have demonstrated a range of heritability estimates from 30% to 70%, depending on age at onset.<sup>73,74</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>75</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>76</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 children and adolescents with overweight and obesity with type 2 diabetes, 4.5% of individuals were found to have monogenic diabetes.<sup>77</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 a polygenic architecture and gene-gene and gene-environment interactions. Diabetes GWASs have identified  $> 500$  genetic variants associated with diabetes,<sup>78</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 per coded allele.<sup>79</sup>
- A common intronic variant in the *TCF7L2* (transcription factor 7 like 2) gene is the most consistently identified diabetes variant.<sup>80–83</sup> Together, common variants account for 18% of type 2 diabetes risk.<sup>79</sup>

Several of these variants have also been associated with gestational diabetes (see Chapter 11 [Adverse Pregnancy Outcomes]).<sup>84</sup>

- Few GWASs have examined type 2 diabetes in youths. 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>85</sup> *PHF2* may influence adipogenesis and fat storage through CCAAT-enhancer binding protein  $\alpha$  and peroxisome proliferator-activated receptor  $\gamma$  transcriptional regulation in adipose tissue.<sup>86</sup> The 6 known loci previously identified in adult populations that generalized to youths at genome-wide significant levels were *TCF7L2*, *MC4R*, *CDC123*, *KCNQ1*, *IGF2BP2*, and *SLC16A11*.
- Genetic studies in non-European ancestral populations have also identified significant risk loci for diabetes. For example, the DIAMANTE Consortium of n=180 834 cases and n=1 159 055 controls (48.9% European ancestry) identified 338 independent variants at 237 loci.<sup>87</sup> Population diversity was particularly valuable for fine mapping, in which 54.4% of associations were localized to a single variant with high posterior probability. Such efforts enable assessment of causal genes and molecular mechanisms.
- 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>88</sup> These loci include common and low-frequency variants, some of which may be population specific.<sup>89</sup>
- Postprandial or random glucose GWASs also have been published.<sup>90</sup> A multiancestry GWAS of 476 326 participants identified 120 loci. Of these loci, 13 demonstrated sex-dimorphic effects, and 44 were novel. Functional annotation supported a role of the intestine in glycemic regulation, which is consistent with diabetes resolution after gastric bypass surgery.
- A diabetes GRS composed of >6 million diabetes-associated variants was associated with incident diabetes in >130 000 individuals in the FINRISK study (HR, 1.74 [95% CI, 1.72–1.77];  $P<1\times10^{-300}$ ), with the GRS showing improved reclassification over a clinical model (net reclassification index, 4.5% [95% CI, 3.0%–6.1%]).<sup>91</sup> However, a GRS composed in European ancestral populations may not transfer to other ancestral populations, potentially requiring population-specific optimization.<sup>92</sup>
- A transancestry diabetes GRS developed in populations of European, African, and East Asian ancestry significant predicted type 2 diabetes in external

European populations, African populations, and Hispanic populations.<sup>93</sup> However, prediction accuracy remained highest for European populations (AUC, 0.66) and lowest for African populations (AUC, 0.58).

- Several studies have examined whether genetic risk modifies the effect of a poor lifestyle on diabetes incidence. In a study of the UK Biobank, high genetic risk and poor lifestyle together were associated with an HR of 15.5 (95% CI, 10.8–22.1) for diabetes compared with participants with an ideal lifestyle and in the group at low genetic risk.<sup>94</sup> However, no evidence of interaction between genetic risk and lifestyle factors was detected ( $P>0.3$ ). 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 reported 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>95</sup>
- Genetic variants associated with traits that are risk factors for diabetes have been shown to be associated with diabetes. For example, in a genome-wide study in the UK Biobank, a waist-specific GRS 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>96</sup> Providing additional evidence are studies examining coheritability or evidence of a shared genetic architecture between type 2 diabetes and cardiometabolic diseases. For example, a prior study reported significant positive genetic correlation between type 2 diabetes and BMI ( $rg=0.36$ ), extreme BMI ( $rg=0.34$ ), overweight ( $rg=0.38$ ), obesity ( $rg=0.34$ ), hip circumference ( $rg=0.27$ ), WC ( $rg=0.40$ ), glycemic traits ( $rg=0.58$ ), triglycerides ( $rg=0.31$ ), and CAD ( $rg=0.38$ ).<sup>97</sup> Conversely, inverse genetic correlations for type 2 diabetes were observed with HDL-C ( $rg=-0.45$ ) and birth weight ( $-0.37$ ).
- 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 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  $\geq 2$  experienced a 3-fold increase in risk (HR, 3.08 [95% CI, 1.82–5.21]).<sup>98</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  $\approx$ 50% of the genetic risk.<sup>99</sup> Other studies have identified additional loci, including rare variants at *STK39* and *LRP1B*.<sup>100</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>101</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  $\geq$ 0.9).<sup>102</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>103</sup>
  - Genetic variants have also been identified that increase the risk of CAD or dyslipidemia in patients with diabetes<sup>104,105</sup> and that are associated with end-organ complications in diabetes (retinopathy,<sup>106</sup> nephropathy,<sup>107</sup> and neuropathy<sup>108</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>78</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>109</sup> and incident type 2 diabetes risk. For example, a meta-analysis reported that every 1-SD increase in isoleucine, leucine, and valine was associated with type 2 diabetes ORs of 1.54 (95% CI, 1.36–1.74), 1.40 (95% CI, 1.29–1.52), and 1.40 (95% CI, 1.25–1.57), respectively.<sup>110</sup> Branched-chain amino acids also respond to weight loss interventions.<sup>111</sup> Circulating glycine levels are associated with lower diabetes risk (meta-analysis RR, 0.89 [95% CI, 0.81–0.96]).<sup>112</sup> Other metabolites associated with type 2 diabetes include complex lipid species such as triacylglycerols<sup>113</sup> and  $\alpha$  amino-adipic acid.<sup>114</sup>

**Prevention**

- Among adults without diabetes in NHANES 2007 to 2012, 37.8% met the moderate-intensity PA goal of  $\geq$ 150 min/wk, and 58.6% met the weight loss or maintenance goal for diabetes prevention. Adults with prediabetes were less likely to meet the PA and weight goals than adults with normal glucose levels.<sup>115</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>116</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>117</sup>
- Among 599 participants with prediabetes, a 12-month digital diabetes prevention program was shown to result in greater reductions (relative to education comparison control groups) in 10-year ASCVD risk, which were significant only at 4 months ( $-0.96\%$  [95% CI,  $-1.58\%$  to  $-0.34\%$ ]) but not at 12 months, indicating the need for additional interventions for a sustained effect.<sup>118</sup>
- Among older adults with diabetes, a meta-analysis of 16 RCTs showed mobile health interventions (including telemonitoring, telecommunication, online education programs, and wearable devices) to have significant benefits on reducing HbA1c ( $-0.24\%$  [95% CI,  $-0.44\%$  to  $-0.05\%$ ]) and postprandial blood glucose ( $-2.91$  mmol/L [95% CI,  $-4.78$  to  $-1.03$ ]) but not total cholesterol, LDL-C, or BP.<sup>119</sup>
- In a study of high-risk patients with prediabetes or diabetes assigned to a 15-week lifestyle intervention or usual care, there were improvements in BMI, HbA1c, total cholesterol, LDL-C, triglycerides, and BP, with significant reductions in the European Society of Cardiology–SCORE pre-post intervention from 8.07% to 6.33% ( $P < 0.001$ ) in the intent-to-treat group and 8.52% to 5.85% ( $P < 0.001$ ) in the per-protocol analysis group.<sup>120</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>121</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-1RAs have been shown to reduce cardiovascular outcomes<sup>122</sup> and are now currently recommended as first-line therapy 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, as well as reducing the progression of CKD.<sup>123</sup> Furthermore, aspirin therapy is recommended for those with both diabetes and ASCVD to reduce future ASCVD risk. Control of diabetes in most individuals includes a reduction of HbA1c to <7% (<8% may be appropriate for those with limited life expectancy or when harms outweigh benefits), BP reduction to <130/80 mmHg, and control of LDL-C with statin therapy. For those at highest risk, high-intensity statin is recommended with additional nonstatin therapy if LDL-C remains ≥55 mg/dL in those with ASCVD or LDL-C ≥70 mg/dL among those with additional risk factors after maximally tolerated statin therapy.<sup>123</sup> 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>124</sup>

### **Awareness**

- Of 38.1 million adults ≥18 years of age with diabetes in 2021, 8.7 million were not aware of or did not report having diabetes (undiagnosed diabetes), representing 22.8% of all US adults with diabetes.<sup>125</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>126</sup>

### **Treatment**

#### **(See Chart 9-6)**

- Among 1590 patients with ASCVD and diabetes from 107 sites/physicians in the United States followed up prospectively from December 2016 to July 2018, by the end of follow-up, 58% were on high-intensity statin, 87% were on antithrombotic therapy, 71% were on ACE inhibitor/ARB/angiotensin receptor/neprilysin inhibitor, and 17% were on SGLT-2 inhibitor or GLP-1RA, with 11% overall on comprehensive optimal medical therapy, which was a modest improvement from 8% at baseline ( $P=0.002$ ).<sup>127</sup> Patients treated by cardiologists were more likely to be on high-intensity lipid lowering but less likely to be on an SGLT-2 inhibitor/GLP1-RA and had lower rates of being on comprehensive optimal medical therapy. Older individuals were less

likely and those with private insurance or with coronary disease more likely to be on optimal medical therapy.

- Among 1 001 542 outpatients from 391 US sites within the Diabetes Collaborative Registry, the percentage of patients prescribed an SGLT-2 inhibitor or GLP-1RA increased over time (7.3% in 2013 to 28.8% in 2019), but only 18.3% of patients with ASCVD, HF, or CKD were on at least 1 of these medications at the last follow-up compared with 25.5% of patients without any of these comorbidities.<sup>128</sup>
- Among data from 324 706 patients with diabetes and established ASCVD in the National Patient-Centered Research Network studied during 2018, 58.6% were prescribed a statin, but only 26.8% were prescribed a high-intensity statin.<sup>129</sup> Only 3.9% were prescribed a GLP-1RA and 2.8% were prescribed an SGLT-2 inhibitor. 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 male or to have ASCVD.
- Among 321 304 patients with type 2 diabetes and ASCVD in 88 US health care systems, from January 2018 to March 2021, the use of SGLT-2 inhibitors increased from 5.8% to 12.9%, and the use of GLP1-RAs increased from 6.9% to 13.8% (and either agent from 11.4% to 23.2%).<sup>130</sup> Those taking either of these agents were younger, less likely to have been hospitalized in the past year, and more likely to be taking other secondary prevention medications.
- In the US Precision Medicine Initiative All of Us Research Program including >80 000 patients with diabetes studied during 2018 to 2022, among those with both diabetes and ASCVD, only 8.6% were on an SGLT-2 inhibitor and 11.9% were on a GLP1-RA, with <10% of those with HF or CKD on an SGLT-2 inhibitor.<sup>131</sup> Moreover, only 18.2% were on high-intensity statins, and use of ezetimibe and PCSK9 inhibitors was also low (5.1% and 0.6%, respectively). Among those with triglycerides >150 mg/dL, only 1.9% were taking icosapent ethyl.<sup>132</sup>
- A large meta-analysis of glucose-lowering agents showed GLP1-RAs and SGLT-2 inhibitors to be associated with significant reductions in all-cause mortality (OR, 0.88 [95% CI, 0.83–0.95] and 0.85 [95% CI, 0.79–0.91], respectively) and MACEs (OR, 0.89 [95% CI, 0.84–0.94] and 0.90 [95% CI, 0.84–0.96], respectively), with SGLT-2 inhibitors additionally associated with a reduced risk of HF hospitalizations (OR, 0.68 [95% CI, 0.62–0.85]).<sup>133</sup> Metformin and pioglitazone were also associated with a lower risk of MACEs (OR, 0.60 [95% CI, 0.47–0.80] and 0.85 [95% CI, 0.74–0.97], respectively), but pioglitazone was associated with a higher

risk of HF hospitalizations (OR, 1.30 [95% CI, 1.04–1.62]), and insulin secretagogues were associated with higher risks of both all-cause mortality (OR, 1.12 [95% CI, 1.01–1.24]) and MACEs (OR, 1.19 [95% CI, 1.02–1.39]).

- In the long-term 21-year follow-up of the DPP among 3234 participants with impaired glucose tolerance, neither lifestyle intervention nor metformin (compared with placebo) was associated with a reduction in the incidence of major cardiovascular events, despite the long-term prevention of diabetes.<sup>134</sup>
- In a recent analysis of 2 large US health insurance databases (Clininformatics and Medicare) examining adult patients with type 2 diabetes who initiated diabetes 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>135</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 2017 to 2018 data, 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>136</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  $\leq 5\%$  in the subgroup  $\geq 65$  years of age, regardless of ASCVD status.<sup>137</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 participants (HR, 0.81 [95% CI, 0.70–0.94]) and American Indian/Alaska Native participants (HR, 0.51 [95% CI, 0.26–0.99]), 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>138</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>139</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>140</sup>
- Continuous glucose monitoring allows more granular monitoring of glucose levels compared with a single glucose measurement.<sup>141</sup> In a meta-analysis of 22 studies of 2188 people with type 1 diabetes, continuous glucose monitoring was associated with a 2.46-mmol/mol mean decrease in HbA1c levels compared with single glucose monitoring ( $-0.23\%$ ).<sup>141</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% lower risk of CVD events, respectively, compared with having no risk factors at goal.<sup>142</sup> This study showed multivariable-adjusted risk reductions of 62% for CVD events and 60% for CHD events.
- Recent data from the All of Us Research Program (2018–2022) show that 73% of US adults with diabetes have an HbA1c <7%, with control slightly better in women (73.6%) than in men (69.8%) and in NH White individuals (78.3) and Asian individuals (76.3%) compared with NH Black individuals (65.1%) or Hispanic/Latino individuals (60.8%).<sup>131</sup> Overall, 50.6% of the participants had LDL-C levels <100 mg/dL, although only 16.0% had levels <70 mg/dL, and among those with diabetes and ASCVD, only 21.1% had LDL-C <70 mg/dL. Overall, 64.4% had triglyceride levels <150 mg/dL, and 31.6% had levels <100 mg/dL.<sup>132</sup>
- 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>143</sup>

- In a study of 1179 adults with type 2 diabetes (representing 19.7 million in the US population in 2013–2016), 56% of adults were at target control of HbA1c (<7% or <8% if with CVD), 51% for BP (<130/80 mm Hg), and 49% for LDL-C (<100 mg/dL or <70 mg/dL if with CVD); 84% were non-smokers.<sup>144</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 were a significant increase in the proportion of individuals with HbA1c <7% (59.8% for 1998–1994 versus 73.7% for 2009–2018) and decreases in mean HbA1c (7.0% versus 6.7%), mean BP (130.1/77.5 mm Hg versus 126.0/72.1 mm Hg), and mean TC (219.4 mg/dL versus 182.4 mg/dL). The proportion with HbA1c <7.0%, BP <140/90 mm Hg, and TC <240 mg/dL improved from 31.6% to 56.2%.<sup>145</sup>
- Among HCHS/SOL study participants with diabetes in 2008 to 2011, 43.0% had HbA1c <7.0%, 48.7% had BP <130/80 mm Hg, and 36.6% had LDL-C <100 mg/dL; 8.4% had reached all 3 treatment targets.<sup>146</sup>
- In a national cohort of 1 140 634 veterans with diabetes, in adjusted models, higher levels of HbA1c ( $\geq 8\%$  versus <7%) were more likely in NH Black people and Hispanic people than in White people (OR, 1.11 [95% CI, 1.09–1.14] for NH Black people and 1.36 [95% CI, 1.32–1.41] for Hispanic people).<sup>147</sup>
- Among those with type 1 diabetes in the SEARCH study, 60% reported having  $\geq 3$  HbA1c measurements in the past year. Other screening tests reported were as follows: 93% for BP assessment, 81% for eye examination, 71% for lipid level assessment, 64% for foot examination, and 63% for albuminuria screening.<sup>148</sup>
- In a decision analytical model, the BRAVO diabetes microsimulation model applied to adults with type 2 diabetes from NHANES (2015–2016) with linked short-term mortality data showed that improvements in BMI, SBP, LDL-C, and HbA1c were estimated to be associated with up to 3.9, 1.9, 0.9, and 3.8 years of gain in life expectancy, respectively.<sup>149</sup>

## Mortality

### (See Table 9-1)

- Diabetes was listed as the underlying cause of mortality for 101 209 people (57 557 males and 43 652 females) in the United States in 2022 (Table 9-1).<sup>150</sup>
- The 2022 overall age-adjusted death rate attributable to diabetes was 24.1 per 100 000 (unpublished NHLBI tabulation using CDC WONDER<sup>151</sup>).

Death rates by sex, race, and ethnicity are located in Table 9-1. In 2022, diabetes was the eighth leading cause of death in the United States.<sup>152</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 higher for 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>153</sup>
- From a systematic review and meta-analysis including 20 studies among individuals after MI, in adjusted analyses, diabetes was associated with increased short-term (males: RR, 1.16 [95% CI, 1.12–1.20]; females: RR, 1.29 [95% CI, 1.15–1.46]), midterm (males: RR, 1.39 [95% CI, 1.31–1.46]; females: RR, 1.38 [95% CI, 1.20–1.58]), and long-term (males: RR, 1.58 [95% CI, 1.22–2.05]; females: RR, 1.76 [95% CI, 1.25–2.47]) mortality.<sup>154</sup>

## Complications

### *Peripheral Artery Disease*

- In a cohort study of patients in Denmark undergoing coronary angiography, those with diabetes but not CAD had an increased risk of PAD (HR, 1.73 [95% CI, 1.51–1.97]) and lower-limb revascularization (HR, 1.73 [95% CI, 1.51–1.97]) compared with those with neither diabetes nor CAD.<sup>155</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>155</sup>
- In the Fremantle 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 PY to 4.5 (95% CI, 3.0–6.4) per 1000 PY.<sup>156</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 PY in 1998 to 2001 compared with 2.64 per 1000 PY in 2011 to 2013.<sup>157</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>158</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>159</sup>

- Reasons for stagnation or even slight increases in recent years in lower-extremity amputation rates could be explained by more comorbidities in patients with diabetes in recent years; shortcomings in prevention practices; reduced mortality resulting in longer duration of diabetes, affecting the risk of complications; and increasing costs of insulin and other therapies, which may result in patients cutting back on some therapies, leading them to greater risks of complications.<sup>160</sup>

### **Retinopathy**

- In the multicenter, population-based SEARCH study of youths and young adults <20 years of age with youth-onset type 1 diabetes (n=2519) and type 2 diabetes (n=447), diabetic retinopathy was found in 52% of those with type 1 diabetes and 56% of those with type 2 diabetes.<sup>161</sup> Higher baseline HbA1c (per 0.1 unit) was associated with retinopathy (aRR, 1.10 [95% CI, 1.05–1.15]), and increases in DBP and SBP were associated with the observation of diabetic retinopathy at follow-up for both diabetes types (among those with type 1 diabetes, change in SBP z score: aRR, 1.05 [95% CI, 1.01–1.09]; change in DBP z score: aRR, 1.08 [95% CI, 1.02–1.15]).
- In DCCT/EDIC, over >30 years of follow-up, the rates of ocular events per 1000 PY were 12 for proliferative diabetic retinopathy, 14.5 for clinically significant macular edema, and 7.6 for ocular surgeries.<sup>162</sup>
- Among US adults ≥18 years of age with diagnosed diabetes in 2021, 10.1% (95% CI, 9.6%–11.3%) reported severe vision difficulty or blindness.<sup>1</sup>
- Among American Indian and Alaska Native individuals with diabetes using primary care clinics of the US Indian Health Service, tribal, and urban Indian health care facilities, 17.7% had nonproliferative diabetic retinopathy, 2.3% had proliferative diabetic retinopathy, and 2.3% had diabetic macular edema.<sup>163</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>164</sup>
- Among patients with type 1 diabetes diagnosed before 35 years of age, after 32 years since diagnosis, the prevalence of proliferative diabetic retinopathy and macroalbuminuria increased with increasing

HbA1c levels, being highest (74% and 44%, respectively) in those who had HbA1c >9.5%.<sup>165</sup>

### **Chronic Kidney Disease**

- Among adults ≥18 years of age (37.4% were ≥65 years of age) 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 kidney function) was 5.4% (95% CI, 4.5%–6.4%), stage 4 CKD (severely decreased kidney function) 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>166</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%–9.9%).<sup>145</sup>
- According to data from 142 countries representing 97.3% of the world population, the global annual incidence of ESKD increased from 375.8 to 1016.0 per million with diabetes from 2000 to 2015. The percentage of individuals with ESKD with diabetes increased from 19.0% to 29.7% over this same period.<sup>167</sup>
- Among 4217 patients with type 1 diabetes from the FinnDiane Study, reduced eGFR was associated with increased risks for cardiovascular and diabetes-related mortality (HRs of 3.27 [95% CI, 1.76–6.08], 3.62 [95% CI, 1.69–7.73], and 4.03 [95% CI, 2.24–7.26], for eGFR categories grades 3, 4, and 5, respectively).<sup>168</sup>
- In a systematic review of 15 studies globally (most in North America and Europe) examining CKD outcomes in individuals diagnosed with type 2 diabetes before 20 years of age, incidence rates per 1000 PY varied from 12.4 to 114.8 for albuminuria, 10 to 35.0 for macroalbuminuria, 0.4 to 25.0 for end-stage kidney disease, and 1.0 to 18.6 for total mortality, being greatest in Australian Aboriginal populations and Pima Indian populations.<sup>169</sup>

### **Neuropathy**

- In the T1D Exchange Clinic Registry, from 2016 to 2018, the prevalence of self-reported diabetic peripheral neuropathy was 11%.<sup>170</sup>

### **CVD Complications**

- 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>171</sup>

- Data from a large clinical trial of youths 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>172</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.
- In the Look AHEAD study of 4095 participants with type 2 diabetes, microvascular disease in adults free of HF 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>173</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 1 325 493 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>174</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>175</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>176</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 individuals 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>177</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>178</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 Fremantle 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>179</sup>
- In MESA, 63% of participants with diabetes had a CAC score  $>0$  compared with 48% of those without diabetes.<sup>180</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>181</sup>
- In the Swedish National Diabetes Register from 2001 to 2013, the IRR for AF compared with diabetes and matched control subjects was 1.35 (95% CI, 1.33–1.36).<sup>182</sup> In another meta-analysis of 4 cohort studies, type 1 diabetes was shown to be associated with a higher risk of AF compared with controls (HR, 1.30 [95% CI, 1.15–1.47]).<sup>22</sup>
- From a 29-year follow-up of patients with type 1 diabetes among the combined DCCT and EDIC studies at 27 clinical centers in the United States and Canada, although females achieved BP <130/80 mm Hg (90% versus 77%;  $P<0.001$ ) and triglycerides <150 mg/dL (97% versus 91%;  $P<0.001$ ) targets more often than males, their use of cardio-protective medications (ACE inhibitors/ARBs [30% versus 40%;  $P=0.001$ ] and lipid-lowering medication [25% versus 40%;  $P<0.001$ ]) was less, and they did not have a lower burden of cardiovascular events.<sup>183</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>184</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>185</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>186</sup>

- In an analysis of ARIC 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>187</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>188</sup>
- Among patients in the ACCORD study, severe hypoglycemia was noted in 4% (n=365) of the 9208 participants; severe hypoglycemia requiring medical assistance was associated with a 38% higher risk of incident HF.<sup>189</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>190–193</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 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 (85%;  $P<0.001$ ).<sup>194</sup>
- In a meta-analysis of 158 observational studies of 270 212 of participants, patients with diabetes had a higher risk of COVID-19-related mortality (OR, 1.87 [95% CI, 1.61–2.17]), ventilator use (OR, 1.44 [95% CI, 1.20–1.73]), and severe or critical presentation (OR, 2.88 [95% CI, 2.29–3.63]).<sup>195</sup> Patients with diabetes had increased odds of ICU admissions (OR, 1.59 [95% CI, 1.15–2.18]); however, this was driven by studies from East Asia (OR, 1.94 [95% CI, 1.51–2.49]). In another meta-analysis of 145 original studies, the presence of diabetes was also associated with an increased risk of COVID-19 mortality (aRR, 1.43 [95% CI, 1.32–1.54]).<sup>196</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>197</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>198</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>199</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>200</sup>

## Health Care Use

- According to the 2020 US Nationwide Emergency Department Sample, the rate of ED visits was 716 per 1000 people with diabetes for diabetes as any listed diagnosis (16.8 million visits), 8.6 per 1000 people with diabetes for hypoglycemia (202 000 visits), and 11.4 per 1000 people with diabetes for hyperglycemia (267 000 visits).<sup>1</sup>
- In 2021, there were 682 279 principal diagnosis discharges for diabetes and 12 426 181 all-listed diagnosis discharges for diabetes (HCUP,<sup>201</sup> unpublished NHLBI tabulation).<sup>202</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>203</sup> From 2007 to 2018, list prices of branded insulins increased by 262% and of branded noninsulin antidiabetic agents by 165%.<sup>204</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>205</sup>
- In 2022 in the United States, the cost of diabetes was \$412.9 billion. Of this cost, \$306.6 billion was direct medical costs; medications and supplies accounted for 17% of these costs.<sup>206</sup> Indirect costs were \$106.3 billion, including reduced employment

due to disability (\$28.3 billion), presenteeism (\$35.8 billion), and lost productivity due to 338 526 premature deaths (\$32.4 billion). Medical costs for people diagnosed with diabetes were on average 2.6 times higher than what would be expected without diabetes. Women with diabetes spend more on average than men on annual health care expenditures. Of all racial and ethnic groups, Black individuals with diabetes have the greatest amount of direct health care expenditures from diabetes. After adjustment for inflation, the direct medical cost of diabetes increased by 7% between 2017 and 2022. In addition, US health care costs attributable to diabetes have increased by \$80 billion in the past 10 years, from \$227 billion in 2012 to \$307 billion in 2022. After adjustment for inflation, the total cost of insulin and other medications to manage blood glucose increased by 26% from 2017 to 2022.

- In an economic evaluation of manufacturing costs, estimated annual cost-based prices for treatment with insulin in a reusable pen device were as low as \$96 (human insulin) or \$111 (insulin analogs) for a basal-bolus regimen, \$61 using twice-daily injections of mixed human insulin, and \$50 (human insulin) or \$72 (insulin analogs) for a once-daily basal insulin injection (for type 2 diabetes), which included the cost of injection devices and needles.<sup>207</sup> Cost-based prices ranged from \$1.30 to \$3.45 per month for SGLT-2 inhibitors (except canagliflozin: \$25.00–\$46.79) and from \$0.75 to \$72.49 per month for GLP1-RAs. Current prices in the 13 countries surveyed were substantially higher than these cost-based prices.
- Informal care is estimated to cost \$1192 to \$1321 annually per person with diabetes.<sup>208</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>209</sup>
- In the United States, nearly one-third of the expenditures for people with CVD are attributable to diabetes.<sup>206</sup>

## Global Burden of Diabetes

### (See Tables 9-2 and 9-3 and Charts 9-7 through 9-9)

- Based on 204 countries and territories in 2021, high FPG caused an estimated 5.29 (95% UI,

4.49–6.11) million total deaths in 2021, an increase of 144.69% (95% UI, 130.26%–158.94%) since 1990 (Table 9-2).<sup>210</sup> The number of prevalent cases of diabetes increased by 285.80% (95% UI, 276.65%–295.92%) for males and 269.80% (95% UI, 262.61%–278.61%) for females between 1990 and 2021. Overall, 270.84 (95% UI, 252.69–291.09) million males and 254.81 (95% UI, 237.40–273.99) million females worldwide had diabetes. In 2021, 1.66 (95% UI, 1.54–1.76) million total deaths were attributable to diabetes (Table 9-3).

- In 2021, the age-standardized prevalence of diabetes among regions was estimated to be highest for Oceania, followed by North Africa and the Middle East, the Caribbean, and high-income North America (Chart 9-7).
- In 2021, age-standardized mortality rates attributable to high FPG among regions were highest for Oceania followed by southern and central sub-Saharan Africa and North Africa and the Middle East (Chart 9-8).
- In 2021, among regions, age-standardized mortality estimated for diabetes was highest for Oceania, followed by southern sub-Saharan Africa. Rates were lowest for high-income Asia Pacific (Chart 9-9).
- The global diabetes prevalence in those 20 to 79 years of age was estimated to be 10.5% (536.6 million people) in 2021 and expected to increase to 12.2% (783.2 million) by 2045 with a similar prevalence in males and females.<sup>211</sup> A higher prevalence in 2021 was seen in urban (12.1%) compared with rural (8.3%) areas and among higher-income (11.1%) compared with lower-income (5.5%) countries. Through 2045, a greater relative increase in the prevalence of diabetes is projected to be seen in middle-income countries (21.1%) than in high- (12.2%) and low- (11.9%) income countries. Global health care costs attributable to diabetes were estimated at US \$966 billion in 2021, projected to reach US \$1054 billion by 2045. 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>212</sup> The IDF atlas global prevalence estimate did not include all ages and used a different methodology from the GBD prevalence estimate reported here.

**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, 2021: ≥18 y of age	Mortality, 2022: all ages*	Age-adjusted mortality rates per 100 000 (95% CI),† 2022
Both sexes	29 300 000 (10.6%)	9 700 000 (3.5%)	115 900 000 (46.4%)	1 211 000	101 209	24.1 (23.9–24.2)
Males	16 400 000 (12.2%)	4 600 000 (3.5%)	63 500 000 (52.9%)	620 000	57 557 (56.9%)‡	30.5 (30.3–30.8)
Females	12 900 000 (9.1%)	5 100 000 (3.5%)	52 400 000 (40.0%)	591 000	43 652 (43.1%)‡	18.8 (18.6–18.9)
NH White males	11.5%	2.6%	57.2%	...	37 886	27.6 (27.3–27.9)
NH White females	7.7%	2.8%	38.8%	...	26 815	16.0 (15.8–16.2)
NH Black males	11.8%	5.6%	35.3%	...	9371	52.8 (51.7–53.9)
NH Black females	13.3%	3.2%	35.7%	...	8583	35.5 (34.8–36.3)
Hispanic males	14.5%	5.3%	50.7%	...	7033	34.7 (33.9–35.6)
Hispanic females	12.3%	4.5%	41.3%	...	5475	22.9 (22.3–23.5)
NH Asian males	14.4%	5.4%	51.6%	...	1982‡	21.5 (20.5–22.4)‡
NH Asian females	9.9%	5.2%	40.2%	...	1727‡	13.9 (13.2–14.5)‡
NH American Indian or Alaska Native	...	...	...	...	1219	47.7 (45.0–50.5)
NH Native Hawaiian or Pacific Islander					303	49.9 (44.2–55.7)

Undiagnosed diabetes is defined as those whose fasting glucose is  $\geq 126$  mg/dL but who did not report being told by a health care professional that they had diabetes. Prediabetes is a fasting blood glucose of 100 to  $<126$  mg/dL (impaired fasting glucose); prediabetes includes impaired glucose tolerance. 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>213</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 people, American Indian or Alaska Native people, Asian people, 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 decedents, Asian and Pacific Islander decedents, 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.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Prevalence of diagnosed and undiagnosed diabetes: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.<sup>7</sup> Percentages for sex and racial and ethnic groups are age adjusted for Americans  $\geq 20$  years of age. Incidence: Centers for Disease Control and Prevention, National Diabetes Statistics Report.<sup>1</sup> Mortality (for underlying cause of diabetes): Unpublished NHLBI tabulation using National Vital Statistics System<sup>150</sup> and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.<sup>151</sup> These data represent diabetes as the underlying cause of death only.

**Table 9-2.** Deaths Caused by High FPG Worldwide, by Sex, 2021

	Deaths		
	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total number (millions), 2021	5.29 (4.49 to 6.11)	2.69 (2.32 to 3.10)	2.60 (2.17 to 3.03)
Percent change (%) in total number, 1990–2021	144.69 (130.26 to 158.94)	152.74 (134.77 to 171.76)	136.87 (118.56 to 153.65)
Percent change (%) in total number, 2010–2021	37.09 (31.14 to 43.54)	37.34 (29.10 to 46.25)	36.83 (29.98 to 43.81)
Rate per 100 000, age standardized, 2021	63.73 (54.02 to 73.84)	73.86 (63.32 to 85.23)	55.63 (46.48 to 64.83)
Percent change (%) in rate, age standardized, 1990–2021	1.63 (−4.19 to 7.29)	2.62 (−4.21 to 9.60)	−0.31 (−7.74 to 6.73)
Percent change (%) in rate, age standardized, 2010–2021	−1.92 (−6.03 to 2.46)	−2.47 (−7.97 to 3.51)	−1.64 (−6.47 to 3.43)
PAF (%), all ages, 2021	7.80 (6.69 to 8.90)	7.15 (6.20 to 8.08)	8.61 (7.31 to 10.03)
Percent change (%) in PAF, all ages, 1990–2021	66.18 (57.43 to 73.73)	66.41 (58.33 to 74.52)	67.00 (55.43 to 76.63)
Percent change (%) in PAF, all ages, 2010–2021	7.19 (4.34 to 9.63)	5.85 (2.77 to 8.97)	8.89 (5.44 to 11.77)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

FPG indicates fasting plasma glucose; GBD, Global Burden of Diseases, Injuries, and Risk Factors; PAF, population attributable fraction; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study, Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>210</sup>

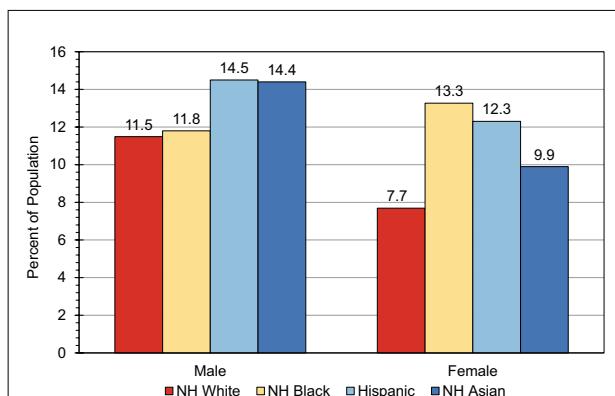
**Table 9-3. Global Prevalence and Mortality of Diabetes, 2021**

	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), 2021	1.66 (1.54 to 1.76)	525.65 (490.92 to 565.38)	0.80 (0.74 to 0.86)	270.84 (252.69 to 291.09)	0.86 (0.79 to 0.92)	254.81 (237.40 to 273.99)
Percent change (%) in total number, 1990–2021	146.52 (128.75 to 162.26)	277.88 (269.98 to 286.40)	160.14 (130.39 to 186.96)	285.80 (276.65 to 295.92)	135.12 (115.76 to 150.89)	269.80 (262.61 to 278.61)
Percent change (%) in total number, 2010–2021	41.13 (33.05 to 47.60)	61.17 (59.54 to 63.12)	41.17 (29.81 to 50.51)	61.35 (59.69 to 63.31)	41.10 (33.65 to 48.50)	60.99 (59.17 to 63.15)
Rate per 100 000, age standardized, 2021	19.61 (18.12 to 20.83)	6123.59 (5723.41 to 6585.82)	20.91 (19.33 to 22.54)	6530.75 (6101.93 to 7013.80)	18.57 (17.06 to 19.86)	5742.93 (5351.76 to 6184.65)
Percent change (%) in rate, age standardized, 1990–2021	7.95 (0.42 to 14.63)	90.43 (85.98 to 95.31)	11.66 (−0.53 to 22.99)	93.17 (88.64 to 98.20)	4.49 (−3.85 to 11.49)	87.13 (82.74 to 91.82)
Percent change (%) in rate, age standardized, 2010–2021	2.58 (−3.15 to 7.18)	26.44 (25.14 to 27.89)	1.72 (−6.30 to 8.40)	26.60 (25.27 to 28.06)	3.04 (−2.44 to 8.35)	26.13 (24.62 to 27.87)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

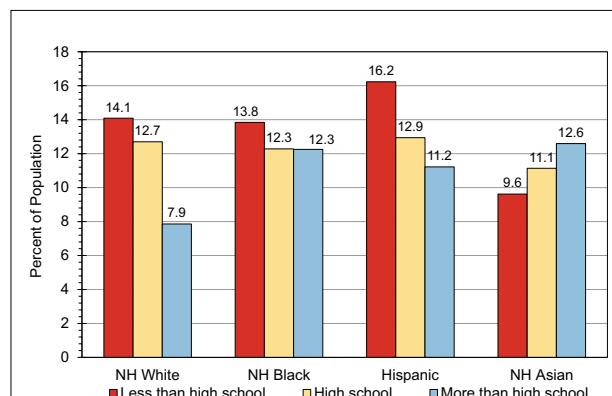
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>210</sup>



**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>213</sup>

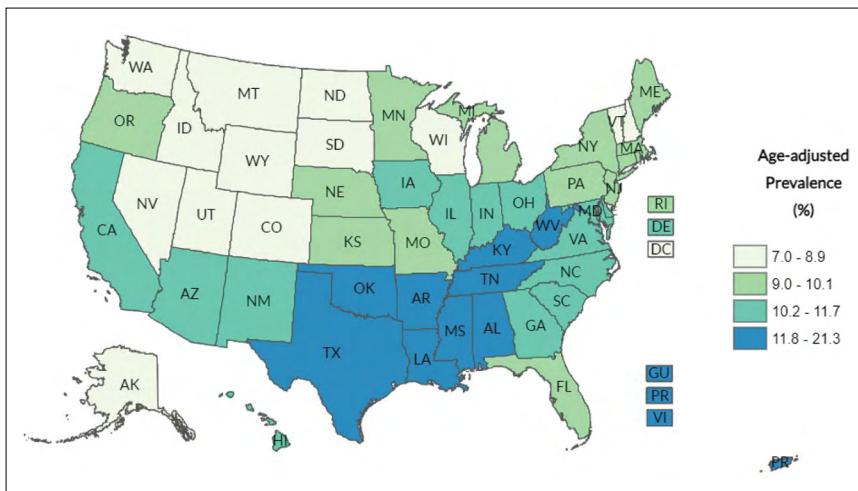
COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>7</sup>



**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>213</sup>

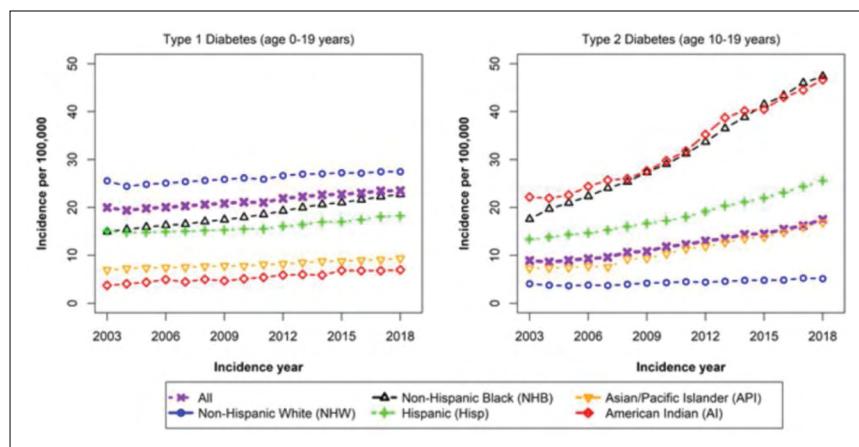
COVID-19 indicates coronavirus disease 2019; NH, non-Hispanic; and NHANES, National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>7</sup>



**Chart 9-3. Age-adjusted percentage of adults with diagnosed diabetes, US states and territories, 2022.**

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>8</sup>

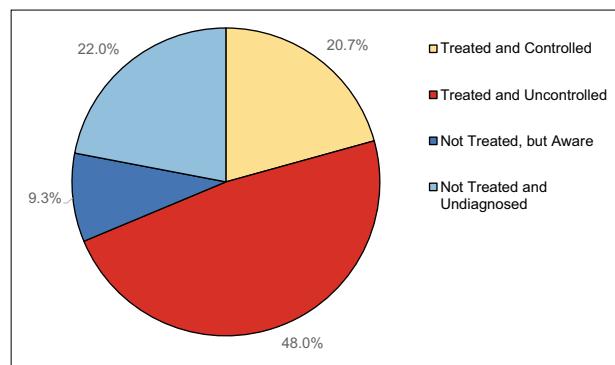
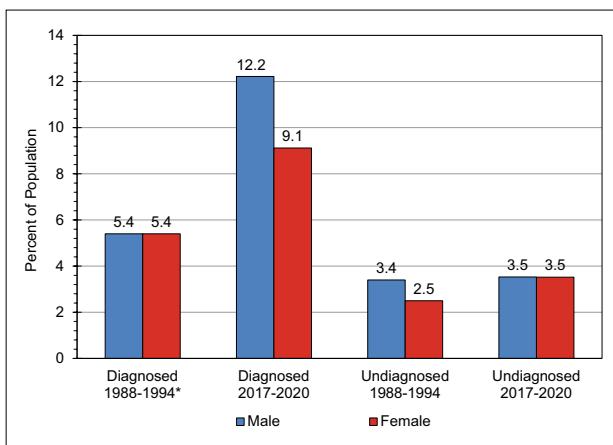


**Chart 9-4. Incidence of type 1 and type 2 diabetes, overall and by race and ethnicity, among US youths ≤19 years of age (SEARCH study, 2002–2015).**

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 primarily from 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; and SEARCH, Search for Diabetes in Youth.

Source: Reprinted from Wagenknecht et al,<sup>9</sup> *The Lancet*, Copyright © 2023, with permission from Elsevier.



**Chart 9-5. Prevalence of diagnosed and undiagnosed diabetes in US adults ≥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>213</sup>

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

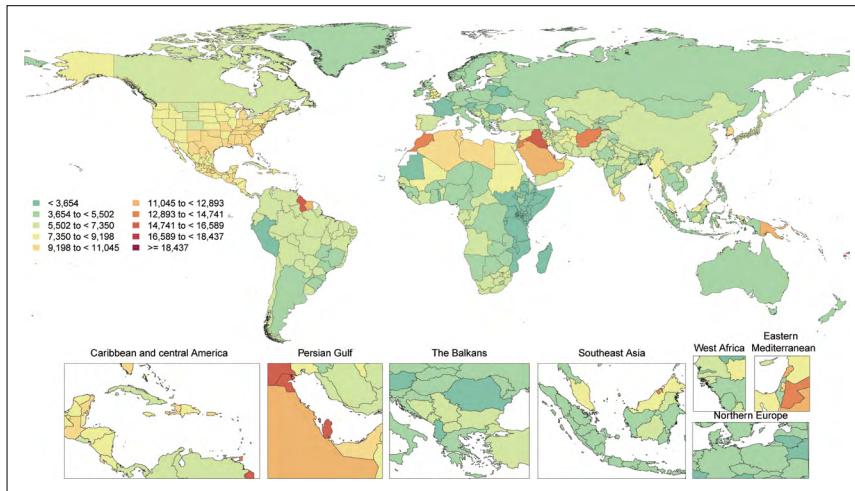
\*The definition of diabetes changed in 1997 (from glucose  $\geq 140$  to  $\geq 126$  mg/dL).

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>7</sup>

**Chart 9-6. Awareness, treatment, and control of diabetes in US adults ≥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>213</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.

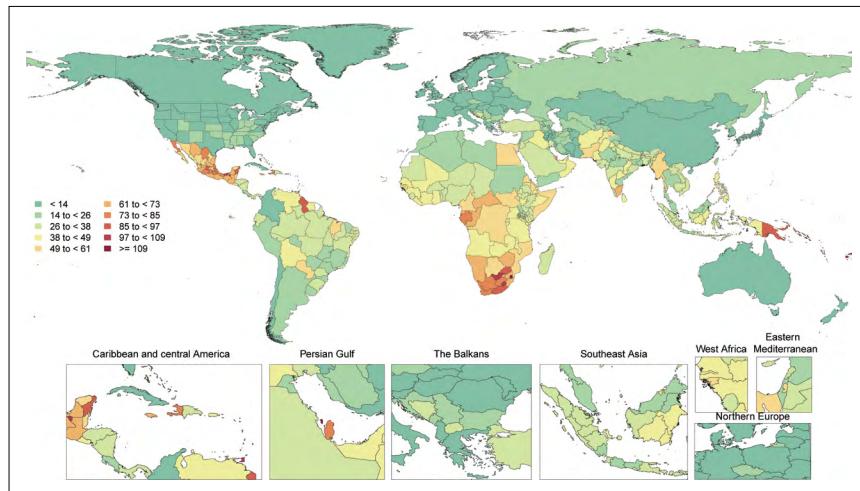
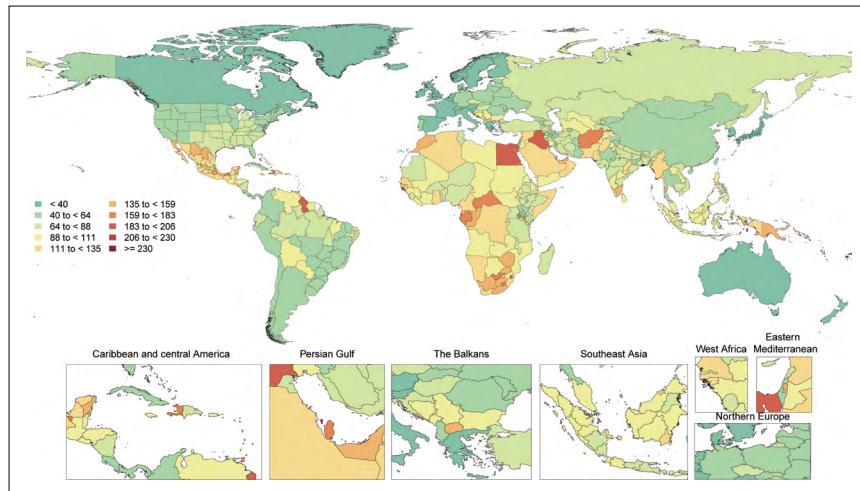
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>7</sup>



These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>210</sup>



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## 10. METABOLIC SYNDROME

See Charts 10-1 through 10-4

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### Definition

- MetS is a multicomponent risk factor for CVD and type 2 diabetes that reflects the clustering of individual cardiometabolic risk factors related to abdominal obesity and insulin resistance. MetS is a useful entity for communicating the nature of lifestyle-related cardiometabolic risk to both patients and clinicians. Although multiple definitions for MetS have been proposed, the IDF, NHLBI, AHA, and others recommended a harmonized definition for MetS based on the presence of any 3 of the following 5 risk factors<sup>1</sup>:
  - FPG  $\geq 100$  mg/dL or undergoing drug treatment for elevated glucose
  - HDL-C  $< 40$  mg/dL in males or  $< 50$  mg/dL in females or undergoing drug treatment for reduced HDL-C
  - Triglycerides  $\geq 150$  mg/dL or undergoing drug treatment for elevated triglycerides
  - WC  $> 102$  cm in males or  $> 88$  cm in females for people of most ancestries living in the United States. Ethnicity- and country-specific thresholds can be used for diagnosis in other groups, particularly Asian individuals and individuals of non-European ancestry who have resided predominantly outside the United States. Current recommendations for WC cut points also may overestimate MetS in US Hispanic/Latina females.<sup>2</sup>
  - SBP  $\geq 130$  mm Hg, 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 MASLD, sexual/reproductive dysfunction (erectile dysfunction in males and polycystic ovarian syndrome in females), OSA, certain forms of cancer,

The 2025 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 2025. 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, HbA1c  $\geq 6.5\%$ , or taking hypoglycemic medication, is a separate clinical diagnosis distinct from MetS; however, many individuals with type 2 diabetes also have MetS.

### Prevalence

#### Youths

(See Chart 10-1)

- According to NHANES 1999 to 2014 data, 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 than females across all regions (Chart 10-1). From NHANES 2011 to 2016, the prevalence of MetS according to the IDF definition 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 2001 to 2020, the prevalence of MetS among youths 12 to 18 years of age was 3.73% (95% CI, 3.05%–4.56%) for Hispanic youths, 1.58% (95% CI, 1.19%–2.10%) for NH Black youths, and 2.78% (95% CI, 2.25%–3.43%) for NH White youths.<sup>5</sup>
- Uncertainty remains concerning the definition of the abdominal obesity and hypertension component of MetS in the pediatric population because it is age dependent. Therefore, the use of WC and BP percentiles<sup>6</sup> has been suggested. The IDF definition<sup>7</sup> generally provided the lowest prevalence of 0.3% to 9.5% globally, whereas the classification of de Ferranti et al<sup>8</sup> yields the highest of 4.0% to 26.4%.<sup>9</sup>
- The prevalence of MetS varied by parental educational attainment, level of family income, and household food security status. For example, the prevalence of MetS among youths 12 to 19 years of age was 6.53% (95% CI, 4.89%–8.69%) for parental education of less than high school and 2.51% (95% CI, 1.39%–4.50%) for parental education of college degree or above according to data from NHANES 1999 to 2018.<sup>10</sup>
- The prevalence of MetS significantly differed by BMI category according to data from NHANES 1999 to 2018. The prevalence of MetS was 0.18% (95% CI, 0.05%–0.62%) for children with underweight and normal weight, 2.56% (95% CI, 1.65%–3.96%) for children with overweight, and 20.1% (95% CI, 17.0%–23.6%) for children with obesity.<sup>10</sup>

**Adults**

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

- 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>11</sup> The prevalence of MetS was higher with older age group, 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  $\geq 60$  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 including multiracial adults had 46.7% (95% CI, 41.9%–51.4%).<sup>12</sup>
- In 2017 to 2018, the prevalence of MetS was the lowest among adults who were college graduates or above at 39.3% (95% CI, 34.9%–43.6%).<sup>12</sup> In contrast, adults with lower educational attainment had a higher prevalence of MetS at 49.1% (95% CI, 44.7%–53.6%) for those less than high school graduates, 51.9% (95% CI, 47.5%–56.2%) for those who were high school graduates, and 50.2% (95% CI, 46.9%–53.4%) for those with some college.
- In 2017 to 2018, adults with a higher family income (ratio of family income to the FPL  $\geq 3.0$ ) had a lower prevalence of MetS at 44.2% (95% CI, 40.9%–47.6%) compared with those with lower family income (ratio  $<1.30$ ) with a prevalence of MetS at 50.6% (95% CI, 47.0%–54.2%).<sup>12</sup>
- A meta-analysis including 28 193 768 participants showed that the global MetS prevalence varied from 12.5% (95% CI, 10.2%–15.0%) to 31.4% (95% CI, 29.8%–33.0%) according to the definition used.<sup>13</sup> The prevalence was significantly higher in the Eastern Mediterranean region and Americas and was directly related to the country's level of income.
- The prevalence of MetS has been noted to be higher 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</sup>; HIV infection<sup>18</sup>; chronic obstructive pulmonary disease<sup>19</sup>; prior treatment for blood cancers<sup>17,20</sup>; systemic inflammatory disorders such as psoriasis,<sup>21</sup> ankylosing spondylitis,<sup>22</sup> and rheumatoid arthritis<sup>23</sup>; type 1 diabetes<sup>24,25</sup>; latent autoimmune diabetes in adults<sup>25</sup>; prior gestational diabetes<sup>26</sup>; prior HDP<sup>27</sup>; acne keloidalis nuchae<sup>28</sup>; periodontitis<sup>29,30</sup>; gallstones<sup>31</sup>; cerebral

palsy<sup>32</sup>; spinal cord injury<sup>33</sup> in veterans; and chronic opiate dependence,<sup>34</sup> as well as in individuals in select professions, including sedentary with high-SES occupations<sup>35</sup> and transportation workers.<sup>36,37</sup>

**Secular Trends****Youths**

- A recent NHANES analysis from 1999 to 2018 among youths 12 to 19 years of age reported that the prevalence of MetS remained stable at 4.36% (95% CI, 3.65%–5.20%) over the study period.<sup>10</sup>

**Adults****(See Chart 10-2)**

- Secular trends in MetS differed according to the definition used.<sup>38,39</sup> Chart 10-2 demonstrates trends using the harmonized MetS criteria in NHANES 2009 to 2010 until 2017 to 2018.
- Data from NHANES 2011 to 2016 showed that the prevalence of MetS increased significantly among those between 20 to 39 years of age (16.2% to 21.3%;  $P_{\text{trend}}=0.02$ ), women (31.7% to 36.6%;  $P_{\text{trend}}=0.008$ ), and Hispanic participants (32.9% to 40.4%;  $P_{\text{trend}}=0.01$ ).<sup>11</sup>
- According to data from NHANES 1999 to 2018, the overall MetS prevalence (according to the AHA/NHLBI definition) increased from 36.2% (95% CI, 33.2%–39.1%) to 47.3% (95% CI, 45.3%–49.3%;  $P_{\text{trend}}<0.001$ ).<sup>12</sup>

**Risk Factors****Youths**

- Early-life famine exposure and adulthood obesity aggravated the risk of MetS (OR, 17.52 [95% CI, 10.07–30.48]) compared with individuals without either condition.<sup>40</sup>
- A meta-analysis including 13 305 adolescents and children suggested that short sleep duration was not associated with MetS (OR, 0.92 [95% CI, 0.48–1.37]); however, long sleep duration was associated with lower risk of MetS (OR, 0.57 [95% CI, 0.38–0.76]).<sup>41</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>42</sup>
- A recent review summarized the evidence identifying obesity and weight gain among obese children as important risk factors for MetS among youths.<sup>43</sup>

**Respiratory Exposures**

- Exposure to parental smoking after birth was associated with increased risk of MetS among school

children 6 to 18 years of age (OR, 1.43 [95% CI, 1.11–1.85]) after adjustment for age, sex, pubertal stages, lifestyle factors, and family history.<sup>44</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- $\mu\text{m}$  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>45</sup>

### Diet and PA

- Daily intake of added and free sugar (incremented by quintiles) was associated with higher MetS score (defined<sup>46</sup> on the basis of BMI, HDL-C, triglycerides, glucose, SBP, and DBP) among adolescents ( $P_{\text{trend}}<0.01$ ).<sup>47</sup> Higher consumption of ultraprocessed foods was associated with greater prevalence of 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% greater prevalence of MetS (PR, 1.04 [95% CI, 1.02–1.07]).<sup>48</sup> Furthermore, compared with ultraprocessed food contribution <40% (first population quintile), the dietary contribution of ultraprocessed foods >71% (fifth population quintile) was associated with a 28% higher prevalence of MetS (40.4 versus 37.5; PR, 1.28 [95% CI, 1.09–1.50]).
- Among 6009 children and adolescents 9 to 18 years of age with device-based accelerometer data from the International Children's Accelerometry Database, total PA and moderate- to vigorous-intensity PA were directly associated with prevalent MetS according to the IDF definition.<sup>49</sup> The odds of MetS decreased by 17% (OR, 0.83 [95% CI, 0.76–0.91]) for every 100-count/min (total PA) increase in average total PA and by 9% (OR, 0.91 [95% CI, 0.84–0.99]) for every 10-min increase in moderate- to vigorous-intensity PA after adjustment for 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 6-fold higher odds of MetS compared with those in the highest tertile (OR, 6.02 [95% CI, 1.93–18.76]).<sup>50</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>51</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>52</sup> Total serum adiponectin, but not high-molecular-weight adiponectin, was inversely associated with MetS according to modified WHO criteria in Mexican children 8 to 11 years of age.<sup>53</sup>

## Adults

### Incident MetS

#### Diet

- Dietary habits have been directly associated with incident MetS, including a Western dietary pattern,<sup>54,55</sup> high inflammatory diet pattern,<sup>56–58</sup> and higher intake of SSBs or AABs,<sup>59</sup> carbohydrates,<sup>60</sup> total fat,<sup>61</sup> and meats (total, red, and processed but not white meat).<sup>62,63</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>64</sup>
- Restrained and emotional eating behaviors<sup>65</sup> and a problematic relationship with eating and food<sup>66</sup> were risk factors for incident MetS. In women, emotional eating behavior had 2.14 increased risk of incident MetS (95% CI, 1.50–3.06). In the CARDIA study, the risk of MetS was 25% higher per 1 problematic relationship to eating and food score increase through 5 years of follow-up (95% CI, 1.17–1.34).
- Dietary habits were also inversely associated with incident MetS, including fiber intake,<sup>67</sup> Mediterranean diet,<sup>68</sup> fruit consumption ( $\geq 4$  servings/d versus <1 serving/d),<sup>69</sup> dairy consumption,<sup>70</sup> coffee consumption,<sup>56,57,71</sup> vitamin D intake,<sup>72</sup> intake of tree nuts,<sup>73</sup> and intake of long-chain omega-3 PUFAs.<sup>74</sup>

### Physical Activity

- In a meta-analysis that included 76699 participants and 13871 incident cases of MetS, there was a negative linear relationship between leisure-time PA and the development of MetS.<sup>75</sup> With each 10 MET-h/wk of PA (equal to  $\approx 150$  min/wk of moderate-intensity PA), the risk of MetS was reduced by 10% (RR, 0.90 [95% CI, 0.86–0.94]).
- A meta-analysis that included 105239 participants suggested that high levels of sedentary behavior were associated with a higher risk of MetS (OR, 1.71 [95% CI, 1.43–2.04]), independently of PA,

and the pattern of association was stronger in females (OR for females, 2.10 [95% CI, 1.06–4.18]; OR for males, 1.75 [95% CI, 1.41–2.18]).<sup>76</sup>

- 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>77</sup> aerobic or resistance training,<sup>78</sup> and cardiorespiratory fitness (eg, maximal oxygen uptake).<sup>79</sup>
- Each 1000-step/d increase was associated with lower odds of having MetS (OR, 0.90 [95% CI, 0.83–0.98]) in American males.<sup>80</sup> The long-term meeting of step-based guidelines or an increase in daily steps was associated with a reduced risk of MetS from 39% to 12% over 7 years of follow-up among older European females.<sup>81</sup>

### Sleep

- The association between sleep duration and incident MetS appears U shaped, but compared with normal sleep duration (7–8 hours), only short duration of sleep was significantly associated with an increased risk of incident MetS (OR, 1.28 [95% CI, 1.07–1.53]); a long duration of sleep was not.<sup>82</sup>

### Blood Biomarkers

- In Chinese adults, greater 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>83</sup>
- Blood biomarkers<sup>84</sup> that were associated with incident MetS include higher triglyceride-glucose index (HR, 1.79 [95% CI, 1.61–2.00]; cutoff point, 8.51)<sup>85</sup>; lower adiponectin (OR, 2.24 [95% CI, 1.11–4.52] comparing lowest versus highest quartile)<sup>86</sup>; elevated CRP (OR, 1.23 [95% CI, 1.11–1.36] per 1-unit change in log-transformed plasma CRP)<sup>87</sup>; ferritin (OR, 1.73 [95% CI, 1.54–1.95] comparing highest and lowest quartiles)<sup>88</sup>;  $\gamma$ -glutamyltransferase (HR, 1.26 [95% CI, 1.18–1.35] per 1-SD increment log- $\gamma$ -glutamyltransferase)<sup>89</sup>; uric acid (RR, 1.30 [95% CI, 1.22–1.38] per 1-mg/dL increase)<sup>90</sup>; lower total (HR, 0.48 [95% CI, 0.32–0.72] comparing highest and lowest quartiles) and indirect (HR, 0.52 [95% CI, 0.35–0.77] comparing highest and lowest quartiles) bilirubin<sup>91</sup>; and lower follicle-stimulating hormone in postmenopausal females (OR, 2.39 [95% CI, 1.05–5.46] comparing lowest and highest quartiles).<sup>92</sup>

### Other

- Risk factors for incident MetS include smoking,<sup>93,94</sup> childhood MetS,<sup>95</sup> childhood cancer, and obesity- and lipid-related indices.<sup>96</sup>
- There was a bidirectional association between MetS and depression. A mendelian randomization study

indicated that depression was a risk factor for MetS (OR, 1.22 [95% CI, 1.09–1.37]) and its components (WC: OR, 1.08 [95% CI, 1.03–1.14]; hypertension: OR, 1.03 [95% CI, 1.02–1.04]; triglycerides: OR, 1.11 [95% CI, 1.06–1.16], and HDL-C: OR, 0.93 [95% CI, 0.89–0.98]).<sup>97</sup> Furthermore, individuals with depression in the United States (OR, 1.46 [95% CI, 1.16–1.84]) were at higher odds of MetS than those in Europe (OR, 1.46 [95% CI, 1.16–1.84]).<sup>98</sup> On the other hand, a cohort study suggested that individuals with 4 or 5 MetS components had an HR of incident depression of 1.16 (95% CI, 1.06–1.32) and 1.25 (95% CI, 1.10–1.54), respectively.<sup>99</sup>

- There was 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 for both males and females (pooled OR, 1.45 [95% CI, 1.27–1.66]).<sup>100</sup>
- In a meta-analysis, infant outcomes such as LBW (pooled OR, 1.79 [95% CI, 1.39–2.31]) and PTB (pooled OR, 1.72 [95% CI, 1.12–2.65]) were associated with greater odds of MetS.<sup>101</sup>
- A meta-analysis including a combined total of 18295 preterm and 294063 term-born adults showed that PTB was strongly associated with a number of components of MetS, including higher glucose (0.07 mmol/L [95% CI, 0.02–0.10]), fasting insulin (random mean difference, 16% [95% CI, 6%–26%]), and homeostasis model assessment of insulin resistance (random mean difference, 24% [95% CI, 0%–47%]) in adult life.<sup>102</sup>
- Among perimenopausal females (mean age, 55±5.4 years), >12 months of breastfeeding significantly reduced the odds of incident MetS in midlife (OR, 0.76 [95% CI, 0.60–0.95]).<sup>103</sup>
- In the National Health Insurance Service–National Sample Cohort in South Korea 2009 to 2015, the presence of MASLD was associated with a higher risk of incident MetS (HR, 2.10 [95% CI, 1.18–3.71]).<sup>104</sup> MASLD was an early predictor of metabolic dysfunction even in metabolically healthy populations.

### Prevalent MetS

#### Diet

- In cross-sectional studies, prevalent MetS was directly associated with a high dietary inflammatory index score,<sup>105</sup> high dietary acid load,<sup>106</sup> high insulin load or insulin index diet,<sup>107</sup> a long-chain food supply (compared with a short-chain food supply),<sup>108</sup> excessive dietary calcium (>1200 mg/d) in males,<sup>109</sup> and inadequate energy intake among patients undergoing dialysis.<sup>110</sup>

- Prevalent MetS is inversely associated with total antioxidant capacity from diet and dietary supplements,<sup>111</sup> animal-based oils such as butter and ghee,<sup>112</sup> organic food consumption,<sup>113</sup> and Mediterranean–DASH Intervention for Neurodegenerative Delay diet, identified as a new dietary pattern that combines the Mediterranean and DASH diets.<sup>114</sup>
- Longer eating duration and late meal intake, higher energy consumption in the evening, and skipped breakfast (but not dinner) were associated with higher odds of MetS and its key components.<sup>115</sup> Adults with a longer eating duration (>12 h) had a higher prevalence of abdominal obesity (IRR, 1.15 [95% CI, 1.03–1.28]) compared with those who ate their meals in a shorter eating duration (<12 h). Adults in the third tertile of the time of the last meal (mean, 10:03 PM) had a higher prevalence of abdominal obesity (IRR, 1.12 [95% CI, 1.01–1.25]) compared with adults in the first tertile. Another study showed that compared with the group with a lower proportion of energy intake in the evening, the group with the highest proportion of energy intake in the evening had an OR of 1.37 (95% CI, 1.17–1.61) for prevalent MetS.<sup>116</sup> Individuals who skipped breakfast had increased odds of MetS of 1.22 (95% CI, 1.04–1.43) for men and 1.18 (95% CI, 1.02–1.35) for women.<sup>117</sup>
- Compared with persistent light drinkers, individuals who increased alcohol intake to heavy levels had an elevated risk of MetS (OR, 1.45 [95% CI, 1.09–1.92]).<sup>118</sup> In contrast, heavy drinkers who became light drinkers had a reduced risk of MetS (OR, 0.61 [95% CI, 0.44–0.84]) compared with persistent heavy drinkers.

### Physical Activity

- In cross-sectional studies, prevalent MetS was directly associated with low cardiorespiratory fitness<sup>119</sup> and low levels of PA.<sup>120,121</sup> Prevalent MetS was inversely associated with “weekend warrior” and regular PA patterns,<sup>122</sup> any length of moderate-to vigorous-intensity PA,<sup>121</sup> and greater handgrip strength.<sup>123,124</sup>
- Higher leisure-time PA was associated with a lower risk of MetS in a dose-response manner, whereas no associations were found between occupational PA and the risk of MetS.<sup>125</sup>
- The relationship between PA and MetS might be moderated by lean muscle mass in males. Males and females with higher lean muscle mass had lower 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: OR, 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>126</sup>

### Sleep

- Associations between sleep duration and prevalent MetS were U shaped. Compared with normal sleep duration (7–8 hours), short durations of sleep were significantly associated with higher rates of prevalent MetS (OR, 1.36 [95% CI, 1.04–1.78] for <5 hours and 1.09 [95% CI, 1.01–1.16] for <6 hours), as were long durations of sleep (OR, 1.11 [95% CI, 1.02–1.21] for >9 hours and 1.31 [95% CI, 1.22–1.40] for >10 hours).<sup>82</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 ranged from 1.10–2.15).<sup>127</sup>

### Blood Biomarkers

- Blood biomarkers directly associated with prevalent MetS included proinflammatory cytokines such as interleukin-6 and tumor necrosis factor- $\alpha$ <sup>128</sup>; retinol binding protein 4<sup>129</sup>; cancer antigen 19-9<sup>130</sup>; serum liver chemistries, including alanine transaminase,<sup>131</sup> aspartate transaminase, alanine transaminase/aspartate transaminase ratio, alkaline phosphatase, and  $\gamma$ -glutamyl transferase<sup>132</sup>; serum vitamin levels,<sup>133</sup> including retinol and  $\alpha$ -tocopherol; serum thyrotropin in individuals with euthyroidism<sup>134</sup>; and erythrocyte parameters<sup>135</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 (OR, 2.10 [95% CI, 1.21–3.65]).<sup>130</sup>
- In cross-sectional studies, prevalent MetS was inversely associated with anti-inflammatory cytokines (interleukin-10),<sup>128</sup> ghrelin,<sup>128</sup> adiponectin,<sup>128</sup> and antioxidant factors (paraoxonase-1)<sup>128</sup> and anti-aging protein such as klotho.<sup>136</sup>
- Lower serum 25-hydroxyvitamin D level was associated with higher odd of MetS.<sup>119,137–139</sup> For example, results from NHANES show that individuals with a 25-hydroxyvitamin D level <30 nmol/L were almost 3 times more likely to have MetS (OR, 2.98 [95% CI, 2.14–4.16]) compared with those with 25-hydroxyvitamin D level >75 nmol/L.

### Other

- Prevalent MetS was also directly associated with elevated urine sodium<sup>140</sup> and high heavy metal exposure.<sup>141</sup>
- Current and former e-cigarette users were 30% (OR, 1.30 [95% CI, 1.13–1.50]) and 15% (OR, 1.15 [95% CI, 1.03–1.28]) more likely to have MetS than never e-cigarette users (48.5%, 40.2%, and 45.7%

with MetS for current, former, and never e-cigarette users, respectively).<sup>142</sup> The prevalence of MetS for dual users (using both combustible cigarette and e-cigarette) was 1.35-fold (95% CI, 1.15–1.58) higher than that for nonsmokers and 1.21-fold (95% CI, 1.00–1.46) higher than that for combustible cigarette-only users.

- In cross-sectional studies, prevalent MetS was inversely associated with the ratio of muscle mass to visceral fat in college students,<sup>143</sup> vacation frequency,<sup>144</sup> and substance use.<sup>145</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>146</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 association (OR, 1.22 [95% CI, 1.02–1.46]).
- In NHANES 2005 to 2018, the odds of depression in patients with MetS was 1.37 in the fully adjusted model (95% CI, 1.17–1.60) after propensity score matching.<sup>147</sup> In addition, an elevation in MetS component count was associated with a significant linear elevation in the mean score of Patient Health Questionnaire-9 ( $F=2.8356$ ,  $P<0.001$ ).
- In Korea NHANES 2013 to 2017, among 24 695 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>148</sup>

## Social Determinants of Health/Health Equity

- In HCHS/SOL, SES was inversely associated with prevalent MetS among Hispanic/Latino adults of diverse ancestry groups.<sup>149</sup> Higher versus lower income, higher versus lower education level, and full-time employment status versus unemployed status were associated with a 4%, 3%, and 24% decreased odds of having MetS, respectively. The association with income was significant only among females and those with current health insurance.
- In the JHS, subjective measures of social status were independently associated with MetS severity among Black adults ( $\beta=-0.05$ ,  $P=0.0007$ ).<sup>150</sup> Education level (objective measure of social status) was also independently associated with MetS severity ( $\beta=0.19$ ,  $P=0.0498$  for graduate/professional compared with below high school education). Subjective social status was a stronger predictor of MetS severity than subjective social status, particularly among women.
- 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 higher food security (OR, 1.43 [95% CI, 1.13–1.80] and 1.71 [95% CI, 1.31–2.24], respectively).<sup>151</sup>

- In the HELENA study among 1037 European adolescents 12.5 to 17.5 years of age, those with mothers with low education had a higher MetS risk ( $\beta$  estimate for the MetS score, calculated as the sum of sex- and age-specific z score of MetS components, 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>152</sup>
- According to data from the Korean National Health and Nutrition Examination Survey (2016–2018), high SES was inversely associated with the prevalence of MetS after adjustment for covariates (OR, 0.67 [95% CI, 0.50–0.89]).<sup>153</sup>
- Similar findings were reported around the world on the association of socioeconomic inequalities with MetS.<sup>154–156</sup> In a Spanish working population, the prevalence of MetS by ATP III criteria among males was 8.01% for social class I (highest), 8.72% for social class II, and 9.82% for social class III (lowest;  $P=0.004$ ); the values among females were 1.35%, 3.85%, and 4.6%, respectively. Individuals with no education or primary school education in the French West Indies had a higher risk of MetS (OR, 2.4 [95% CI, 1.3–4.4]) compared with those having equivalent to high school or higher than high school education.<sup>155</sup>

## Genetics and Family History

**(See also Chapter 6 [Overweight and Obesity], Chapter 8 [High Blood Pressure], and Chapter 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>157</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>158</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>159–162</sup> A recent multiancestry 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 interethnicity heterogeneity.<sup>163</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>164</sup>
- The minor G allele of the atrial natriuretic peptide genetic variant rs5068, which is associated with higher levels of circulating ANP, has been associated with lower prevalence of MetS in White people and Black people.<sup>165–167</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>168</sup>
- A UK Biobank study of 291 107 individuals performed GWASs for the clustering of MetS traits and found 3 loci associated with all 5 MetS components (near *LINC0112*, *C5orf67*, and *GIP*), of which *C5orf67* has been associated with individual MetS components.<sup>169</sup>
- Recently, 90 novel loci (cumulative 94 loci) have been identified for MASLD.<sup>170</sup> A total of 8 common genetic loci (*MTARC1*, *ADH1B*, *TRIB1*, *GPAM*, *MAST3*, *TM6SF2*, *APOE*, and *PNPLA3*) have also been identified for association with hepatic steatosis, a leading risk factor for cardiometabolic diseases.<sup>171</sup>
- A comprehensive GWAS, using the continuous parameters of MetS components such as fasting glucose, HDL-C, SBP, triglycerides, and WC, uncovered the shared genetic architecture of each component with MetS. This study identified 235 genomic loci, of which 174 loci were novel.<sup>172</sup> Among the loci identified, 53 (22.5%) overlapped with loci associated with  $\geq 2$  components of MetS.
- An epigenome-wide association study of MetS including 1187 individuals of European ancestry examining 468 809 methylation sites identified 12 sites associated with MetS and 33 sites associated with at least 1 component of MetS.<sup>173</sup> The cg19693031 methylation site in *TXNIP* was prioritized as a strong candidate for linking the individual components of MetS.
- A proteomics-based study of MetS including 1921 participants with prevalent MetS identified 116 proteins associated with prevalent MetS.<sup>174</sup> Mendelian

randomization analysis identified 3 causal proteins in MetS, including apolipoprotein E2, apolipoprotein B, and proto-oncogene tyrosine-protein kinase receptor.

## Prevention and Awareness of MetS

- Despite the high prevalence of MetS, the public's recognition of MetS was limited. A study showed that the average MetS Knowledge Scale score was  $36.7 \pm 18.8$  of a possible score of 100.<sup>175</sup>

## Morbidity and Mortality

### Adults

#### CVD Morbidity and Mortality

- MetS had been associated with incident AF,<sup>176,177</sup> HF,<sup>178</sup> and PAD.<sup>179</sup> The HR was 1.38 (95% CI, 1.36–1.39) for incident AF and 2.50 (95% CI, 1.68–3.40) for incident HF. The RR for incident PAD was 1.76 (95% CI, 1.05–2.92).
- MetS was associated with CVD morbidity and mortality. A meta-analysis of 87 studies comprising 951 083 subjects showed that MetS increased the risk of CVD (summary RR, 2.35 [95% CI, 2.02–2.73]), with significantly increased risks (RRs ranging from 1.6–2.9) for all-cause mortality, CVD mortality, MI, and stroke, even for those with MetS but without diabetes.<sup>180</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>181</sup>
- In the RIVANA Study, a Mediterranean population-based cohort of 3976 participants, individuals with MetS had an HR of 1.32 (95% CI, 1.01–1.74) with a rate advancement period (indicating prematurity of cardiovascular events occurrence) of 3.23 years (95% CI, 0.03–6.42 years) for MACEs and an HR of 1.64 (95% CI, 1.03–2.60) with rate advancement periods of 3.73 years (95% CI, 0.02–7.45 years) for cardiovascular mortality.<sup>182</sup>
- In the INTERHEART case-control study of 26 903 subjects from 52 countries, MetS was associated with an increased risk of MI, according to both the WHO (OR, 2.69 [95% CI, 2.45–2.95]) and IDF (OR, 2.20 [95% CI, 2.03–2.38]) definitions, with a PAR of 14.5% (95% CI, 12.7%–16.3%) and 16.8% (95% CI, 14.8%–18.8%), respectively. 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 IDF definition was used.<sup>183</sup>

- In the Three-City Study, among 7612 participants ≥65 years of age who were followed up for 5.2 years, MetS was associated with an increased risk of 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 risk beyond its individual components.<sup>184</sup>
  - Among 3414 patients with stable CVD and atherogenic dyslipidemia who were treated intensively with statins in the AIM-HIGH trial, neither the presence of MetS nor the number of MetS components was associated with cardiovascular outcomes, including coronary events, ischemic stroke, nonfatal MI, CAD death, or the composite end point.<sup>185</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 (OR, 1.92 [95% CI, 1.31–2.81]) but not in males (OR, 0.97 [95% CI, 0.61–1.55]).<sup>186</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.<sup>187</sup> 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 individuals 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 there was no significant interaction by sex and race.<sup>188</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 (HR, 1.70 [95% CI, 1.37–2.12];  $P<0.001$ ).<sup>189</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>190</sup>
- All-Cause Mortality**
- In patients with impaired LV systolic function (EF <50%) who underwent CABG, MetS was associated with increased risk of all-cause in-hospital mortality (OR, 5.99 [95% CI, 1.02–35.15]).<sup>191</sup>
  - In a meta-analysis of 20 prospective cohort studies that included 57 202 adults ≥60 years of age, MetS was associated with an 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>192</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, and definition of MetS and with 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>190</sup>
  - From the Taiwan NHIRD including 119 843 subjects, after propensity score matching, subjects with 3 to 4 MetS components had a significantly higher risk of all-cause mortality (HR, 1.13 [95% CI, 1.08–1.17]) than those with only 1 to 2 MetS components.<sup>193</sup> In addition, 3 to 4 MetS components (versus 1–2) led to greater all-cause mortality among those <65 years of age (OR, 1.35 [95% CI, 1.25–1.45]) in males (OR, 1.06 [95% CI, 1.01–1.12]) and females (OR, 1.20 [95% CI, 1.13–1.27]), individuals with (OR, 1.13 [95% CI, 1.06–1.20]) or without (OR, 1.13 [95% CI, 1.08–1.19]) CHD, those without CKD history (OR, 1.13 [95% CI, 1.09–1.18]), aspirin users (OR, 1.24 [95% CI, 1.17–1.31]) and nonusers (OR, 1.06 [95% CI, 1.00–1.12]), users of nonsteroidal anti-inflammatory drugs (OR, 1.18 [95% CI, 1.13–1.23]), and users of statins (OR, 1.54 [95% CI, 1.43–1.66]).
  - The impact of MetS on mortality had been shown to be modified by objective sleep duration.<sup>194</sup> According to data from the Penn State Adult Cohort, a prospective population-based study of 1344 males and females followed up for 16.6 years, the HRs of all-cause and CVD mortality associated with MetS were 1.29 (95% CI, 0.89–1.87) and 1.49 (95% CI, 0.75–2.97) for individuals who slept ≥6 hours and 1.99 (95% CI, 1.53–2.59) and 2.10 (95% CI, 1.39–3.16) for individuals who slept <6 hours.

## Complications

### Youths

- 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 >2.4-fold risk for adult MetS from 5 years of age onward.<sup>95</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 person-years; HR, 2.82 [95% CI, 1.41–5.64]) independently of baseline age and sex, adult BMI, and family history of diabetes.<sup>195</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>196</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>95</sup>

### Adults

#### CKM Syndrome

(See Chart 10-3)

- CKM syndrome was defined in an AHA presidential advisory in 2023 as a health disorder attributable to connections among obesity, diabetes, CKD, and CVD, including HF, AF, CHD, stroke, and PAD. CKM syndrome includes those at risk for CVD and those with existing CVD.<sup>197</sup> The advisory provided CKM syndrome staging that features the following: stage 0, no CKM risk factors; stage 1, excess or dysfunctional adiposity; stage 2, metabolic risk factors (hypertriglyceridemia, hypertension, diabetes, MetS) or moderate- to high-risk CKD; stage 3, subclinical CVD in CKM syndrome or risk equivalents (high predicted CVD risk or very high-risk CKD); and stage 4, clinical CVD in CKM syndrome (Chart 10-3).<sup>197</sup>
- In the NHANES 2011 to 2018 database, among individuals 20 to 44, 45 to 64, and ≥65 years of age, stage 0 CKM was present in 17.35%, 5.45%, and 1.80%, respectively, and risk factors and

subclinical CKM (stages 1–3) were present in 80.94%, 85.95%, and 72.03%, respectively.<sup>198</sup>

- A novel CVD risk prediction algorithm, PREVENT, was recommended by the AHA to assess the risk of CVD in the context of CKM syndrome.<sup>199</sup> PREVENT would serve a central role in the development of risk-based primary prevention strategies for individuals with CKM syndrome stages 0 to 3.

### MetS and Subclinical CVD

- In MESA, among 6603 adults 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>200,201</sup> There appears to be a synergistic relationship among MetS, MASLD, and prevalence of CAC,<sup>202</sup> as well as a synergistic relationship with smoking.<sup>203</sup>
- Individuals with MetS have a higher degree of endothelial dysfunction than individuals with a similar burden of traditional cardiovascular risk factors.<sup>204</sup> The OR 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>205</sup> MetS was associated with increased thrombosis, including increased resistance to aspirin<sup>206</sup> and clopidogrel loading.<sup>207</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 (SMD,  $0.28 \pm 0.06$  [95% CI, 0.16–0.40];  $P=0.00003$ ) and higher prevalence of carotid plaques (pooled OR, 1.61 [95% CI, 1.29–2.01];  $P<0.0001$ ).<sup>208</sup> Both cardio-ankle vascular index (OR, 1.34 [95% CI, 1.20–1.50] per 1.0-unit increase) and carotid IMT (OR, 1.31 [95% CI, 1.22–1.41] per 0.1-mm increase) were positively associated with the presence of MetS.<sup>209</sup>
- In modern imaging studies using echocardiography, MRI, cardiac CT, and positron emission tomography, MetS was closely related to increased epicardial adipose tissues<sup>210</sup>; increased visceral fat<sup>211</sup>; increased ascending aortic diameter<sup>212</sup>; high-risk coronary plaque features, including increased necrotic core<sup>213</sup>; impaired coronary flow reserve<sup>214</sup>; abnormal indexes of LV strain<sup>215</sup>; LV diastolic dysfunction<sup>216</sup>; LV dyssynchrony<sup>217</sup>; and subclinical RV dysfunction.<sup>218</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>210</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>219</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 below 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 percentiles, 1.29 (95% CI, 0.76–2.19) for the 50th to 75th percentiles, 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 percentiles, 4.00 (95% CI, 2.22–7.18) for the 50th to 75th percentiles, and 5.30 (95% CI, 2.73–10.29) for above the 75th percentile.
- In 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 (HR, 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 (HR, 1.28 [95% CI, 0.92–1.75]).<sup>220</sup> Similar findings were also reported in the Korean nationwide cohort study.<sup>221</sup> When the reference group was set as subjects having 4 to 5 components of MetS, subjects having ≤1 component of MetS had the lowest risk of incident type 2 diabetes (HR, 0.27 [95% CI, 0.266–0.271]), and the risk increased as components of MetS increased at baseline and the second visit.

### Kidney Disease

- Among 633 Chinese adults without diabetes receiving a first renal transplantation, presence of pretransplantation MetS was an independent predictor of prevalent (OR, 1.28 [95% CI, 1.04–1.51]) and incident (OR, 2.75 [95% CI, 1.45–6.05]) post-transplantation diabetes.<sup>222</sup>
- In RENIS-T6, which included 1627 people representative of the general population without baseline self-reported CKD, CVD, or diabetes, MetS was associated with a mean 0.30–mL/min per year (95% CI, 0.02–0.58) faster decline in glomerular filtration rate than in individuals without MetS during follow-up.<sup>223</sup>

### Cancer

- MetS was associated with increased risk of cancer (in particular breast, endometrial, prostate, pancreatic, hepatic, colorectal, and renal cancers)<sup>224–226</sup> and gastroenteropancreatic neuroendocrine tumors.<sup>227</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 aHR 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>228</sup> Another large, nested, case-control study among participants 18 to 64 years of age in the IBM MarketScan Commercial Database (2006–2015) suggested that MetS was associated with increased risk of early-onset (diagnosed before 50 years of age) colorectal cancer (OR, 1.25 [95% CI, 1.09–1.43]).<sup>229</sup>
- MetS was linked to poorer cancer outcomes, including increased risk of recurrence and overall mortality.<sup>230,231</sup> In a meta-analysis of 24 studies that included 132589 males with prostate cancer (17.4% with MetS), MetS was associated with worse oncological outcomes, including biochemical recurrence and more aggressive tumor features.<sup>232</sup> Among 94555 females free of cancer at baseline in the prospective NIH-AARP cohort, MetS was associated with increased risk of breast cancer mortality (HR, 1.73 [95% CI, 1.09–2.75]), particularly among postmenopausal females (HR, 2.07 [95% CI, 1.32–3.25]).<sup>233</sup>
- In a meta-analysis of 17 prospective longitudinal studies that included 602195 females and 15945 cases of breast cancer, MetS was associated with increased risk of incident breast cancer in postmenopausal females (RR, 1.25 [95% CI, 1.12–1.39]) but significantly reduced breast cancer risk in premenopausal females (RR, 0.82 [95% CI, 0.76–0.89]).<sup>234</sup> The association between MetS and increased risk of breast cancer was observed only among White females and Asian females, whereas there was no association in Black females.
- 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 patients with breast and prostate cancer, respectively).<sup>235</sup>
- In 25 038 Black individuals 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>224</sup> For those with all 5 MetS components present, the risk of cancer mortality

was 59% higher than for those with no 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>236</sup>

### Gastrointestinal

- MASLD, a spectrum of liver disease that ranges from isolated fatty liver to fatty liver plus inflammation (nonalcoholic steatohepatitis), was hypothesized to represent the hepatic manifestation of MetS. According to data from NHANES 2011 to 2014, the overall prevalence of MASLD among US adults was 21.9%.<sup>237</sup> The global prevalence of MASLD was estimated to be 25.2%.<sup>238</sup> In cross-sectional studies, an increase in the number of MetS components was associated with underlying nonalcoholic steatohepatitis and advanced fibrosis in MASLD in adults and children.<sup>237,239</sup>
- MetS has been associated with cirrhosis,<sup>240</sup> colorectal adenomas,<sup>241</sup> acute pancreatitis,<sup>242</sup> and Barrett esophagus.<sup>243</sup>

### Other

- Among 725 Chinese adults ≥90 years of age, MetS was associated with prevalent disability in activities of daily living (OR, 1.65 [95% CI, 1.10–3.21]) and instrumental activities of daily living (OR, 2.09 [95% CI, 1.17–4.32]).<sup>244</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>245</sup>
- MetS was associated with dementia<sup>246</sup> (particularly Alzheimer dementia<sup>247</sup>), cognitive decline,<sup>248</sup> and lower cognitive performance in older adults at risk for cognitive decline.<sup>249</sup> For example, during the mean follow-up of 4.9 years, the aHRs in a non-MetS group who progressed to having MetS compared with the sustained non-MetS 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>246</sup> The aHRs 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 aHRs 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 (95% CI, 1.32–1.44) for vascular dementia.

- MetS was 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>250,251</sup> Adolescents with excess weight and MetS exhibited significantly lower transformed bone mineral density and concentrations of bone alkaline phosphatase, osteocalcin, and carboxy-terminal telopeptide compared with the matched group, except for osteocalcin in male adolescents; thus, bone formation and resorption may be affected.<sup>252</sup>
- In males, MetS had been associated with decreased sperm total count, sperm concentration, sperm normal morphology, sperm progressive motility, sperm vitality, and semen quality and an increase in sperm DNA fragmentation and mitochondrial membrane potential, which may contribute to male infertility.<sup>253</sup>
- MetS and its components were associated with more severe infection with SARS-CoV-2 and high risk for poor outcomes in COVID-19 illness.<sup>254–257</sup>

### Cost and Health Care Use

- The medical costs of subjects with MetS for 5 years were 2.16 times higher than for those without MetS (\$15 699 versus \$7274;  $P<0.001$ ); medical costs were higher with a greater number of risk factors (\$2285, \$3154, \$4277, \$5888, \$7391, \$8466 for those with 0–6 MetS components;  $P<0.001$ ).<sup>258</sup>
- The presence of MetS increased 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>235,259–261</sup>

### Global Burden of MetS

#### (See Chart 10-4)

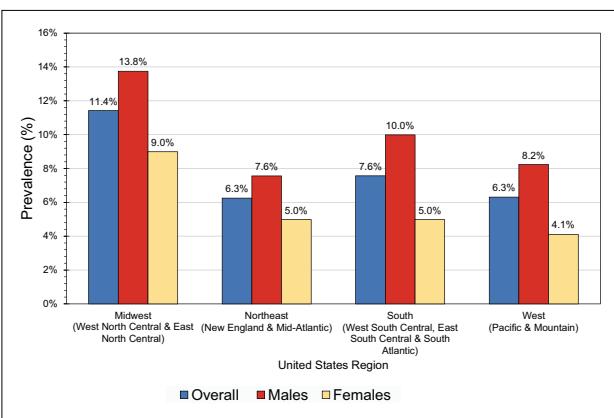
- MetS has become hyperendemic around the world. Published evidence has described the prevalence of MetS in Aruba,<sup>262</sup> India,<sup>263</sup> Bangladesh,<sup>264</sup> Iran,<sup>265,266</sup> Ghana,<sup>267</sup> the Gaza Strip,<sup>268</sup> Jordan,<sup>269</sup> and Ethiopia,<sup>270,271</sup> as well as many other countries. Chart 10-4 shows the prevalence of MetS by different definitions and by WHO region from a meta-analysis published in 2021.<sup>13</sup>
- Global prevalence of MetS in military personnel was estimated at 21% (95% CI, 17%–25%; N=37

studies: 15 in America, 13 in Europe, and 9 in Asia) between 2001 and 2017.<sup>272</sup>

- MetS among children and adolescents is an emerging public health challenge in low- to middle-income countries. In a meta-analysis including data from 76 studies with 142 142 children and adolescents residing in low- to middle-income countries, the pooled prevalence of MetS was 4.0% (IDF), 6.7% (ATP III), and 8.9% (de Ferranti et al<sup>8</sup>).<sup>273</sup> Among children and adolescents with obesity or overweight, pooled prevalence was estimated at 24.1%, 36.5%, and 56.3% with the IDF, ATP III, and de Ferranti et al criteria, respectively.
- A systematic review synthesized the prevalence of MetS using data published between 2014 and 2019 according to different definitions in the pediatric population across the world.<sup>9</sup> According to the IDF, 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, 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 meta-analysis of 10 191 participants 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>274</sup>



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

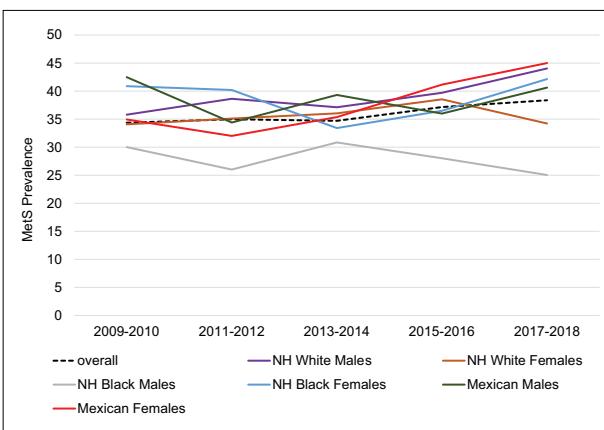
MetS indicates metabolic syndrome; and NHANES, National Health and Nutrition Examination Survey.

Source: Data derived from DeBoer et al.<sup>274</sup>

- The prevalence of MetS in Mexican adults according to the harmonized definition was 40.2% in 2006, 57.3% in 2012, 59.99% in 2016, and 56.31% in 2018 ( $P_{\text{trend}} < 0.0001$ ).<sup>275</sup>
- The prevalence of MetS in Brazil was 28% in 2005 to 2009, 35% in 2010 to 2014, and 31% in 2015 to 2019. The pooled prevalence was 34% in urban, 15% in rural, 28% in quilombola, and 37% in indigenous areas.<sup>276</sup> There were no statistically significant differences between these subgroups.

### **Asia and Middle East**

- The prevalence of MetS among Chinese adults  $\geq 20$  years of age in 2015 to 2017 was 31.1%, with a significantly higher prevalence in women than in men (32.3% versus 30.0%).<sup>277</sup> The highest prevalence was in participants  $\geq 75$  years of age (44.2%), and the lowest prevalence was in participants 20 to 44 years of age (23.3%). The prevalence in the north (35.9%) was higher than in the south (27.4%).
- 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 as high as 40.1% in the United Arab Emirates, depending on the time frame, country studied, and definition of MetS used. There was high heterogeneity among the 61 included studies.<sup>278</sup>

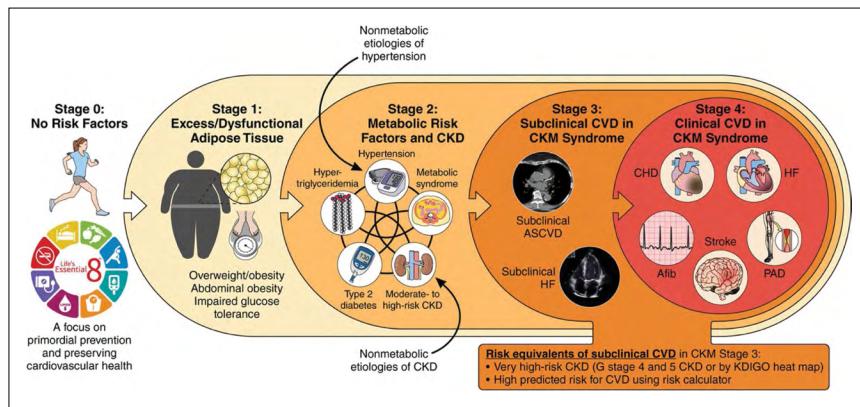


**Chart 10-2. Prevalence of MetS among US adults using the harmonized MetS criteria (NHANES 2009-2018).**

MetS was defined using the criteria agreed to jointly by the IDF; the NHLBI; the AHA; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity.

AHA indicates American Heart Association; IDF, International Diabetes Federation; MetS, metabolic syndrome; NH, non-Hispanic; NHANES, National Health and Nutrition Examination Survey; and NHLBI, National Heart, Lung, and Blood Institute.

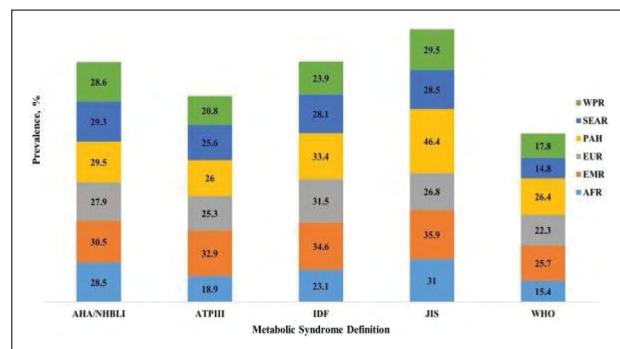
Source: Data courtesy of Junxiu Liu using NHANES.<sup>280</sup>



### Chart 10-3. Stages of CKM syndrome.

The CKM staging construct reflects the progressive pathophysiology and increasing absolute CVD risk along the spectrum of CKM syndrome. Stage 0 CKM includes individuals with normal weight, normal glucose, normal BP, normal lipids, normal kidney function, and no evidence of subclinical or clinical CVD; the focus in stage 0 CKM is primordial prevention and preserving CVH. Stage 1 CKM includes individuals with excess adipose tissue, dysfunctional adipose tissue, or both. Excess adiposity is identified by either weight or abdominal obesity, and dysfunctional adipose tissue is reflected by impaired glucose tolerance and hyperglycemia. Stage 2 includes individuals with metabolic risk factors (hypertriglyceridemia, hypertension, MetS, or type 2 diabetes), moderate- to high-risk CKD, or both. Although hypertension and CKD are usually downstream of metabolic risk factors, curved arrows represent individuals with nonmetabolic causes of these conditions; the risk implications and treatment approaches are similar. Stage 3 includes individuals with subclinical CVD with overlapping CKM risk factors (excess/dysfunctional adipose tissue, metabolic risk factors, or CKD) or those with the risk equivalents of very high-risk CKD or high predicted risk using the forthcoming CKM risk calculator. Stage 4 includes individuals with clinical CVD (CHD, HF, stroke, PAD, or Afib) overlapping with CKM risk factors. Afib indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CKM, cardio-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; MetS, metabolic syndrome; and PAD, peripheral artery disease.

Source: Reprinted from Ndumele et al.<sup>197</sup> Copyright © 2023 American Heart Association, Inc.



### Chart 10-4. Meta-analysis prevalence of MetS, by different definitions and by WHO region.

AFR indicates Africa region; AHA, American Heart Association; ATP-III, Adult Treatment Panel III of the National Cholesterol Education Program; EMR, Eastern Mediterranean Region; EUR, European Region; IDF, International Diabetes Federation; JIS, Joint Interim Statement; MetS, metabolic syndrome; NHBLI, National Heart, Lung, and Blood Institute; PAH, Region of the Americas; SEAR, South-East Asia Region; WHO, World Health Organization; and WPR, Western Pacific Region.

Source: Reprinted from Noubiap et al.<sup>13</sup> Copyright © 2022, with permission from Elsevier.

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## 11. ADVERSE PREGNANCY OUTCOMES

**See Tables 11-1 and 11-2 and Charts 11-1 through 11-8**

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[Click here to return to the Abbreviations](#)

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 birthing people.<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 birthing individuals and their offspring.<sup>2,3</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

The 2025 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 2025. 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.

Kawasaki Disease] for pregnancy-related risk factors for congenital HD).

### Classification of APOs

- HDP
  - Gestational hypertension: Gestational hypertension is de novo hypertension that develops after week 20 of pregnancy without protein in the urine or evidence of end-organ involvement.
  - Preeclampsia/eclampsia: Hypertension after week 20 of pregnancy, most often de novo, with protein in the urine or other evidence of end-organ involvement is defined as preeclampsia and may progress to the convulsive phase or eclampsia.
  - Chronic (ie, prepregnancy) hypertension is hypertension that is present before week 20 of pregnancy; note that preeclampsia/eclampsia can develop on top of chronic hypertension.
  - 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 for hypertension diagnosis 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>4</sup>
- Gestational diabetes: De novo diabetes that develops after week 20 of pregnancy is considered gestational diabetes. Gestational diabetes often initially resolves after delivery but is strongly associated with future type 2 diabetes risk.<sup>5</sup>
- PTB: PTB includes spontaneous or indicated delivery before 37 weeks' gestation.
- Infant with SGA: An infant with a birth weight  $\leq 10$ th percentile for gestational age is considered to be SGA. SGA is called intrauterine growth restriction during gestation.
- LBW is defined as a birth weight of  $< 2500$  g as per the WHO.<sup>6</sup>
- 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: Placental abruption is 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 globally.<sup>7</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>8</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>9</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 (aOR, 5.36 [95% CI, 3.76–7.64]), history of abortion (aOR, 2.92 [95% CI, 1.91–4.47]), multiple pregnancies (aOR, 3.60 [95% CI, 2.49–5.19]), and anemia during pregnancy (aOR, 3.41 [95% CI, 2.1–5.56]) were associated with PTB.
- In 24 369 females from 12 studies (case-control, 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>10</sup>

### Prevention

- In 15 509 females with 27 135 pregnancies from NHANES (mean maternal age, 35.1 years; 35.8% of pregnancies with  $\geq 1$  APO), most healthy lifestyle factors (defined as BMI 18.5–24.9 kg/m<sup>2</sup>, nonsmoking,  $\geq 150$  min/wk of moderate-to vigorous-intensity PA, healthy eating [top 40% of DASH score], no or low to moderate alcohol intake [ $< 15$  g/d], and use of multivitamins) were independently associated with lower risk of APOs.<sup>11</sup> High-quality diet (highest versus lowest quartile of DASH score, 0.85 [95% CI, 0.78–0.93]) and multivitamin supplementation

$\geq 6$  d/wk (OR 0.97 [95% CI, 0.92–1.03]) were most protective for APOs. Compared with healthy weight, overweight (OR, 1.42 [95% CI, 1.32–1.52]), stage 1 obesity (OR, 1.68 [95% CI, 1.52–1.86]), and stage 2 or higher obesity (OR 1.92 [95% CI, 1.69–2.18]) were associated with a higher risk of APOs. Avoiding harmful alcohol consumption and regular PA were not independently associated with lower risk of adverse pregnancy outcomes after mutual adjustment for other healthy lifestyle factors. The 6 healthy lifestyle factors had a PAR of 19% (95% CI, 13%–26%) with APOs.

- According to 21 systematic reviews and meta-analyses, and 54 RCTs, exercise interventions were more effective than standard prenatal care in decreasing gestational diabetes and gestational hypertension incidence by 39% and 47%, respectively.<sup>12</sup> Exercise interventions are particularly effective when they are supervised, have a low to moderate intensity level, and are initiated during the first trimester of pregnancy.

### Pregnancy-Related Complications: Mortality and CVD

#### Pregnancy-Related Mortality

#### (See Chart 11-2)

- The pregnancy-related mortality rate was 32.9 per 100 000 live births in 2021.<sup>13</sup> Maternal or pregnancy-related mortality is defined by the WHO as death while pregnant or within 42 days of the end of pregnancy; late maternal or pregnancy-related deaths occurring between 43 days and 1 year are not included as part of the definition.
- Maternal mortality rates have risen for all racial and ethnic groups since 2018. In 2021, maternal death rate per 100 000 live births was highest in NH Black females (69.9), followed by Hispanic females (28.0) and NH White females (26.6; Chart 11-2).<sup>13</sup>
- Pregnancy-related mortality rates were higher in older age groups for females  $\geq 40$  years of age compared with females  $< 25$  years of age (138.5 versus 20.4 per 100 000 live births) in 2021.<sup>13</sup>
- In a study of 712 284 birthing people in the Korean National Health Service, being below the 25th percentile for income was associated with a higher mortality within 6 weeks of delivery (aOR, 2.42 [95% CI, 1.65–3.53]) and within 1 year (aOR, 1.83 [95% CI, 1.47–2.28]).<sup>14</sup>
- Between 1999 and 2019 in the United States, median-state pregnancy-related mortality increased in all racial and ethnic groups, although disparities were seen.<sup>15</sup> Median mortality rates per 100 000 live births ranged from 14.0 (IQR, 5.7–23.9) to 49.2 (IQR, 14.4–88.0) among the American Indian and Alaska Native population; 26.7 (IQR, 18.3–32.9) to 55.4 (IQR, 31.6–74.5) among the Black population; 9.6 (IQR, 5.7–12.6) to 20.9 (IQR, 12.1–32.8)

among the Asian, Native Hawaiian, or Other Pacific Islander population; 9.6 (IQR, 6.9–11.6) to 19.1 (IQR, 11.6–24.9) among the Hispanic population; and 9.4 (IQR, 7.4–11.4) to 26.3 (IQR, 20.3–33.3) among the White population. In each year between 1999 and 2019, the Black population had the highest median rate, whereas the American Indian and Alaska Native population had the largest increase in these rates. In 2019, pregnancy-related mortality was lowest in the Northeast (33.6 [IQR, 5.8–206.0]) and highest in the South (94.2 [IQR, 45.4–193.4]).

- From 2017 to 2019, the maternal mortality rate was lowest (14.0 deaths per 100 000 live births) for women living in large fringe metro counties and highest (26.1 deaths per 100 000 live births) for women living in noncore counties (ie, those not in proximity to a metro core).<sup>16</sup> 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 26.6% of maternal deaths from 2017 to 2019; HDP contributed an additional 6.3% of maternal deaths.<sup>17</sup> In low- to middle-income countries, the second leading cause of death is HDP, accounting for 14% of maternal deaths.<sup>18</sup>

#### *Long-Term Mortality*

- The Collaborative Perinatal Project was a prospective cohort 48 197 pregnant females at 12 US clinical centers during the years 1959 to 1966 (45% were Black females and 46% were White females).<sup>19</sup> After a median of 52 years after pregnancy, the following APOs were associated with all-cause mortality: preterm spontaneous labor (HR, 1.07 [95% CI, 1.03–1.1]); premature rupture of membranes (HR, 1.23 [95% CI, 1.05–1.44]); gestational hypertension (HR, 1.09 [95% CI, 0.97–1.22]); preeclampsia or eclampsia (HR, 1.14 [95% CI, 0.99–1.32]) and superimposed preeclampsia or eclampsia (HR, 1.32 [95% CI, 1.20–1.46]) compared with normotension; and gestational diabetes or impaired fasting glucose (HR, 1.14 [95% CI, 1.00–1.30]) compared with normoglycemia. Preterm induced labor was associated with greater mortality risk among Black participants (HR, 1.64 [95% CI, 1.10–2.46]) compared with White participants (HR, 1.29 [95% CI, 0.97–1.73]).

#### *Associations With Cardiovascular Risk Factors and CVD*

- A cohort study of 2 195 989 Swedish females demonstrated a higher risk of hypertension within 10 years among those who had preterm delivery (gestational age <37 weeks; HR, 1.67 [95% CI, 1.61–1.74]) compared with those with full-term delivery (39–41 weeks' gestation).<sup>20</sup> There were

also elevated risks of hypertension among females who experienced extremely preterm (22–27 weeks' gestation; HR, 2.23 [95% CI, 1.98–2.5]) and moderately preterm (28–33 weeks' gestation; HR, 1.85 [95% CI, 1.74–1.97]) deliveries.

- Among 48 113 participants from the WHI, 13 482 (28.8%) reported ≥1 APOs (defined as HDP, gestational diabetes, PTB, LBW, and high birth weight).<sup>21</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 independently 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>22</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.
- In a registry of 26 024 menopausal women from Japan (4.6% had HDP), the aOR for the combined 6 CVD categories (angina/MI, cerebral infarction, cerebral hemorrhage, SAH, HF, and aneurysm/aortic dissection) was higher for those with HDP history and hypertension (OR, 4.11 [95% CI, 3.16–5.35]) compared with those with only hypertension (OR, 2.30 [95% CI, 2.02–2.63]) or only HDP (OR, 1.61 [95% CI, 1.03–2.53]).<sup>23</sup>

#### **Hypertensive Disorders of Pregnancy**

##### *Incidence, Prevalence, and Secular Trends (See Charts 11-3 and 11-4)*

- Rates of overall HDP are increasing. During 2017 to 2019, the prevalence of HDP among delivery hospitalizations increased from 13.3% to 15.9% (Chart 11-3). The highest prevalence was among females 35 to 44 and 45 to 55 years of age (18% and 31%, respectively) and those who were Black (20.9%) or American Indian and Alaska Native (16.4%).
- There is substantial geographic heterogeneity in rates of HDP across the United States (Chart 11-4). In 2019, the highest rate of HDP was observed in Louisiana at 116 per 1000 live births.
- Among 51 685 525 live births between 2007 and 2019, age-standardized HDP rates doubled (38.4 [95% CI, 38.2–38.6] to 77.8 [95% CI, 77.5–78.1] per 1000 live births).<sup>24</sup> An inflection point was observed in 2014, with an acceleration in the

rate of increase of HDP (from +4.1%/y [95% CI, 3.6%/y–4.7%/y] before 2014 to +9.1%/y [95% CI, 8.1%/y–10.1%/y] after 2014). Rates of PTB and LBW increased significantly when co-occurring in the same pregnancy with HDP. Absolute rates of APOs were higher in NH Black individuals and in older age groups. However, similar relative increases were seen across all age and racial and ethnic groups.

### 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>25</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' 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>26</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): >35 years of age (versus <35 years of age; 1.2 [95% CI, 1.1–1.3]); prior preeclampsia (8.4 [95% CI, 7.1–9.9]); chronic hypertension (5.1 [95% CI, 4.0–6.5]); prepregnancy diabetes (3.7 [95% CI, 3.1–4.3]); prepregnancy obesity ( $BMI >30 \text{ kg/m}^2$  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]). The PAF was highest for nulliparity (32.3% [95% CI, 27.4%–37.0%]), followed by prepregnancy  $BMI >25 \text{ kg/m}^2$  (23.8% [95% CI, 22.0%–25.6%]) and prior preeclampsia (22.8% [95% CI, 19.6%–26.3%]).<sup>27</sup>

### Weight Gain

- A review of 54 studies of >30 245 946 females in the obese weight category with singleton pregnancies showed that gestational weight gain less than recommended (by the current Institute of Medicine and the American College of Obstetricians and Gynecologists guidelines<sup>28</sup>) compared with weight gain within the guidelines was associated with higher odds of having an SGA neonate (OR, 1.30 [95% CI, 1.17–1.45]) and lower odds for preeclampsia (OR, 0.71 [95% CI, 0.63–0.79]).<sup>29</sup>
- 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<sup>30</sup> (12.5–18 kg for underweight [ $BMI <18.5 \text{ kg/m}^2$ ], 11.5–16 kg for normal weight [ $BMI, 18.5\text{--}24.9 \text{ kg/m}^2$ ], 7.0–11.5 kg for overweight [ $BMI, 25.0\text{--}29.9 \text{ kg/m}^2$ ], and 5.0–9.0 kg for obese [ $BMI >30.0 \text{ kg/m}^2$ ]) 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>31</sup>
- Among 8296 nulliparous females in the nuMoM2b study, higher HDP risks were observed for excess weight gain in midpregnancy (from 5–13 to 16–21 weeks' gestation; 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>32</sup>
- A meta-analysis of 61 studies showed that interpregnancy weight gain was associated with HDP (OR, 1.46 [95% CI, 1.12–1.91];  $P=94.9\%$ ) and preeclampsia (OR, 1.92 [95% CI, 1.55–2.37];  $P=93.6\%$ ).<sup>33</sup> In a meta-analysis of 12 studies, interpregnancy weight gain was associated with increased HDP risk; each 1-kg/m<sup>2</sup> increase in BMI from the start of one pregnancy to the next was associated with a 31% increase in OR for HDP (95% CI, 11%–53%).<sup>34</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>35</sup>

- 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 compared with a strategy of no treatment unless BP was severely elevated ( $\geq$ 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>36</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.
- In a retrospective cohort of 174 925 nulliparous women from Kaiser Permanente Northern California hospitals in 2009 to 2019 with measured BP trajectories in early pregnancy ( $\approx$ 4 measurements at  $\leq$ 20 weeks' gestation), the low-increasing, moderate-stable, and elevated-stable groups had higher odds for preeclampsia/eclampsia (OR, 3.25 [95% CI, 2.7–3.9]; OR, 5.3 [95% CI, 4.5–6.3]; and OR, 9.2 [95% CI, 7.7–11.1], respectively) and for gestational hypertension (OR, 6.4 [95% CI, 4.9–8.3]; OR, 13.6 [95% CI, 10.5–17.7]; and (OR, 30.2 [95% CI, 23.2–39.4], respectively) compared with the reference group with ultralow-declining BP trajectory.<sup>37</sup> The highest odds for preeclampsia/eclampsia were seen among Black women, followed by Hispanic women and Asian women, for all BP trajectories ( $P_{\text{interaction}} < 0.01$ ). As an example, the aOR for the elevated stable trajectory was 9.1 (95% CI, 6.4–13.1) for Black females, 8.4 (95% CI, 6.0–11.8) for Hispanic females, and 7.4 (95% CI, 5.2–10.5) for Asian females (referent White females with ultralow-declining BP).

#### Diet and Exercise

- Among 8507 females in the multiancestry (25% NH White, 47% Black, 28% Hispanic) 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>38</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>39</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>40</sup>

#### Race and Ethnicity

- 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]).
- In a nationwide sample spanning 15 years (2004–2019), among females with preeclampsia, Black females with high income (defined as 75th–100th percentile based on the median US income) still had worse maternal outcomes at delivery such as PPCM (aOR, 1.47 [95% CI, 1.16–1.86]), stroke (aOR, 2.05 [95% CI, 1.54–2.74]), HF (aOR, 1.63 [95% CI, 1.34–1.99]), cardiac arrhythmias (aOR, 1.43 [95% CI, 1.31–1.58]), and VTE (aOR, 2.37 [95% CI, 1.54–3.65]) compared with White females of low income (<25th percentile [ranging from <\$36 000 in 2002 to <\$48 000 in 2018]).<sup>41</sup>
- In a study of hospital discharge records among 45 204 Black California-born primiparous mothers (born 1982–1997) and their infants (born 1997–2011), early childhood and adulthood neighborhoods were categorized as deprived, mixed, or privileged based on the Index of Concentration at the Extremes (a measure of concentrated racial and economic segregation), yielding 9 life-course trajectories. Women living in deprived neighborhoods had the highest odds of HDP (mixed effect logistic regression, unadjusted OR, 1.26 [95% CI, 1.13–1.40]) compared with women living in privileged neighborhoods.<sup>42</sup> Among 2697 NH Black women in the Boston Birth Cohort (1998–2016), 40.5% were foreign born. Foreign-born women who had  $<$ 10 years of residence in the United States had lower odds of preeclampsia than those who were born in the US (OR, 0.73 [95% CI, 0.55–0.97]).<sup>43</sup> The odds of preeclampsia in foreign-born women with duration of US residence  $\geq$ 10 years was similar to that of US-born women.

**Other**

- Among 1964 females from the nuMoM2b-HHS, SDB (as reflected by an AHI  $\geq 5$ ) during pregnancy was associated with increased risk for hypertension 2 to 7 years after delivery (aRR, 2.02 [95% CI, 1.30–3.14]).<sup>44</sup> Risks of hypertension 2 to 7 years after delivery were greater for participants with an AHI  $\geq 5$  in pregnancy that persisted after delivery (aRR, 3.77 [95% CI, 1.84–7.73]).
- In a meta-analysis of 10 studies, air pollution (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>45</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>46</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>47</sup> Participants were enrolled in 43 institutions across 18 countries, and 725 (33.2%) had COVID-19. Pregnant females with COVID-19 were twice as likely to develop preeclampsia (8.1% versus 4.4%; aRR, 1.77 [95% CI, 1.25–2.52]) compared with pregnant females without COVID-19.
- Similarly, in a large nationally representative US sample of hospital deliveries from the pandemic year 2020, pregnant females with COVID-19 ( $n=46\,375$ ) had a greater odds of preeclampsia (aOR, 1.33 [95% CI, 1.29–1.37]) than pregnant females without COVID-19.<sup>48</sup>
- Other US nationwide analyses have identified the autoimmune disorders of systemic lupus erythematosus and rheumatoid arthritis to be associated with increased risk of preeclampsia. Among 12 789 722 deliveries, rheumatoid arthritis ( $n=11\,979$ ) was an independent risk factor for preeclampsia (aOR, 1.37 [95% CI, 1.27–1.47]) after adjustment for sociodemographic factors and comorbidities.<sup>49</sup> Similarly, among 63 115 002, pregnant females, systemic lupus erythematosus ( $n=77\,560$ ) was an independent risk factor for preeclampsia (aOR, 2.12 [95% CI, 2.07–2.17]).<sup>50</sup>
- In a nationwide analysis between 2016 and 2019, pregnant females from rural areas were at greater risk for maternal ICU admission (RR, 1.14 [95% CI, 1.04–1.20]) and maternal mortality (RR, 1.93 [1.71–2.17]) compared with their counterparts from urban areas.<sup>51</sup>

- Among 9 097 355 pregnant women in the HCUP NIS data from 2004 through 2014, anxiety was associated with increased odds of gestational hypertension (aOR, 1.32 [95% CI, 1.26–1.40]), preeclampsia (aOR, 1.52 [95% CI, 1.44–1.60]), and eclampsia (aOR, 1.81 [95% CI, 1.26–2.61]).<sup>52</sup> Maternal depression, bipolar disorder, and mood disorder were not associated with any HDP.

**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>32,53</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  $\approx 50\%$  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>54</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>55</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 SBP; aOR, 0.65 per 5-mmHg lowering of SBP;  $P_{\text{heterogeneity}} = 0.037$ ).<sup>55</sup>

**Genetic Variants**

- Large GWASs of preeclampsia and maternal hypertension during pregnancy are beginning to emerge. For example, a European consortium of 16 743 women with prior preeclampsia and 15 200 women with preeclampsia or other maternal hypertension

during pregnancy identified 19 loci.<sup>56</sup> Seven of the 13 novel loci were previously identified in BP GWASs. Other novel loci included genes with roles in placenta development (*PGR*, *TRPC6*, *ACTN4*), uterine spinal artery remodeling (*NPPA*, *NPPB*, *NPR3*, and *ACTN4*), kidney function (*PLCE1*, *TNS2*, *ACTN4*, and *TRPC6*), and maintenance of proteostasis (*PZP*).

- A multiancestry GWAS (78.0% European, 21.2% Asian, 0.5% admixed American and 0.3% African ancestry) of 20 064 preeclampsia cases and 11 027 gestational hypertension cases reported 18 loci, 12 of which were previously unidentified.<sup>57</sup> Consistent with other preeclampsia and gestational hypertension GWASs, identified loci contained genes with roles in angiogenesis, renal glomerular function, trophoblast development, and immune dysregulation. Authors also examined the utility of GRS to improve identification of pregnant women eligible for low-dose aspirin after 12 weeks' gestation to reduce preeclampsia risk. The sensitivity and positive predictive value of major risk factors to identify preeclampsia/eclampsia for low-dose aspirin eligibility were 17.5% and 12.8%, respectively. However, including women at the top 10% of a GRS composed of SBP and preeclampsia loci increased sensitivity to 30.4%, although a decline in the positive predictive value (11%) was noted.
- The role of variants associated with preeclampsia risk factors (eg, hypertension and BMI) in pre-eclampsia is supported by a study of 498 pre-eclampsia cases. An increasing burden of risk alleles for elevated DBP and BMI was associated with an increased risk of preeclampsia (OR for DBP, 1.11 [95% CI, 1.01–1.21]; OR for BMI, 1.10 [95% CI, 1.00–1.20]).<sup>58</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>59</sup>
- Motivated by high disease heterogeneity and prior evidence suggesting increased risk in high-altitude regions, a study of N=883 families in the Peruvian Andes was performed. This study identified associations between preeclampsia and a fetal locus containing clotting factor genes *PROZ*, *F7*, and *F10*.<sup>60</sup>
- Genetic data have also been used to examine whether HDPs increase later-life CVD risk. Specifically, univariate mendelian randomization demonstrated that HDPs were positively associated with CAD (OR, 1.24 [95% CI, 1.08–1.43]) and

ischemic stroke (OR, 1.27 [95% CI, 1.12–1.44]).<sup>61</sup> Associations with CAD were partly attenuated in mediation analyses that accounted for SBP (direct effect OR, 1.10 [95% CI, 1.02–1.18]) and type 2 diabetes (direct effect OR, 1.16 [95% CI, 1.04–1.29]).

### **Prevention**

#### *Breastfeeding*

- Among 3598 participants from the Avon Longitudinal Study of Parents and Children cohort, after a mean follow-up of 18 years after delivery, breastfeeding for 6 to 9 months among females with HDP was associated with significant reductions in DBP ( $-4.87$  mmHg [95% CI,  $-7.86$  to  $-1.88$ ]), mean arterial pressure ( $-4.61$  mmHg [95% CI,  $-7.45$  to  $-1.77$ ]), and LDL-C ( $-0.40$  mmol/L [95% CI,  $-0.62$  to  $-0.17$  mmol/L]).<sup>62</sup>

#### *Lifestyle Modifications*

- PA is recommended for pregnant females without obstetrical or medical complications.<sup>63–65</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>66</sup>
- Aerobic exercise for  $\approx$ 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>67</sup>
- A meta-analysis of 20 studies up to 2019 showed the effectiveness of lifestyle intervention and bariatric surgery on reduced risk of HDP (OR, 0.45 [95% CI, 0.32–0.63]), gestational hypertension (OR, 0.61 [95% CI, 0.44–0.85]), and preeclampsia (OR, 0.67 [95% CI, 0.51–0.88]).<sup>68</sup>

#### *Aspirin*

- Low-dose aspirin started in early pregnancy reduces risk for some APOs among higher-risk females. A 2021 meta-analysis by the US Preventive Services Task Force reported a lower risk of preeclampsia (RR, 0.85 [95% CI, 0.75–0.95]), perinatal mortality (RR, 0.79 [95% CI, 0.66–0.96]), PTB <37 weeks (RR, 0.80 [95% CI, 0.67–0.95]), and fetal growth restriction (RR, 0.82 [95% CI, 0.68–0.99]) and no significant increase in bleeding-related harms.<sup>69</sup>
- Specific aspirin dose 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 pre-eclampsia (RR, 0.38 [95% CI, 0.20–0.72]).<sup>70</sup> Aspirin doses <150 mg produced no significant reductions. The number of pregnant females needed to treat with 150 mg aspirin to prevent 1 case of

preeclampsia was 39 (95% CI, 23–100). There was a maximum 30% reduction in risk of all gestational age preeclampsia at all aspirin doses.

### **Complications: Maternal CVD**

- 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>71</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 various 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]) over a median of 9.25 years (IQR, 5.53–13.78 years).<sup>72</sup>
- In a 1980 to 2004 national cohort study from Norway, in 508 422 females 16 to 49 years of age at first birth, preeclampsia was associated with a significantly higher risk for HF (HR, 2.00 [95% CI, 1.50–2.68]) compared with normotension over a median 11.8 years of follow-up.<sup>73</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>74</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**

- 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>75</sup>
- Among 2 437 718 individuals born in Denmark from 1978 to 2018 (102 095 of their mothers had HDP,

4.19%),<sup>76</sup> during a median follow-up of 41 years, maternal HDP was associated with a 26% (HR, 1.26 [95% CI, 1.18–1.34]) higher risk of all-cause mortality in offspring.<sup>77</sup> Offspring mortality given maternal preeclampsia, eclampsia, and hypertension was also elevated (OR, 1.29 [95% CI, 1.20–1.38], OR, 2.88 [95% CI, 1.79–4.63], and OR, 1.12 [95% CI, 0.98–1.28], respectively).

## **Gestational Diabetes**

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

- The pooled global standardized prevalence of gestational diabetes in 2021 was estimated at 14.0%.<sup>76</sup> This ranged from 7.1% in North America and the Caribbean to 27.6% in the Middle East and North Africa. The standardized prevalence of gestational diabetes in low-, middle- and high-income countries was 12.7%, 9.2%, and 14.2%, respectively.
- In a meta-analysis of 254 studies of 15 572 847 pregnant women between 2014 and 2019, weighted prevalence of gestational diabetes in the 24 European countries was estimated at 10.9% (95% CI, 10.0%–11.8%;  $P = 100\%$ ).<sup>78</sup>
- The US national prevalence of gestational diabetes was 8.3% in 2021, an increase of 38% from 2016 according to birth data from the NVSS.<sup>79</sup> Rates of gestational diabetes rose steadily with maternal age: In 2021, the rate for mothers ≥40 years of age was almost 6 times as high compared with mothers <20 years of age (15.6% versus 2.7%).
- The prevalence of gestational diabetes was highest in NH Asian females (14.9%), followed by NH American Indian or Alaska Native females (11.8%), Native Hawaiian or Other Pacific Islander females (10.6%), Hispanic females (8.5%), NH White females (7.0%), and NH Black females (6.5%).<sup>80</sup>
- The prevalence of gestational diabetes increases with each adiposity category ranges from 3.7% among females with underweight to 12.6% among females with obesity (Chart 11-5).
- 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>81</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 at 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>8</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>82</sup>
- In a cohort of 595 pregnant females in 4 US areas (Chicago, IL; Schuylkill County, Pennsylvania; Pittsburgh, PA; and San Antonio, TX), perceived discrimination (self-reported as based on sex, race, income level or social status, age, and physical appearance) was associated with the 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>83</sup>
- A systematic review of 17 studies demonstrated that individuals with gestational diabetes had statistically significant differences in the diversity of gut microbes.<sup>84</sup> Six prospective studies found that microbiota change during pregnancy is associated with risk of gestational diabetes. There was considerable heterogeneity in the type of microbiota change evaluated in these 6 studies.

- Among 8 574 264 females 15 to 44 years of age at first live singleton birth in the United States, 1 747 066 (20%) were born outside the United States.<sup>85</sup> In females born outside the United States, gestational diabetes rates were higher than in females born in the United States (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 studied, with the exception of females born in Japan (who had lower rates than those born in the United States).

### Genetics/Family History

- Although gestational diabetes is thought to be heritable, heritability estimates 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 (30.1% versus 13.2%;  $P<0.001$ ).<sup>86</sup> Gestational diabetes and type 2 diabetes also demonstrate high levels of genetic correlation ( $r_g=0.71$ ).
- Reflecting the hypothesis that gestational diabetes and diabetes have a shared genetic architecture, the majority of 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>87</sup>
- An early GWAS of gestational diabetes in the FinnGen cohort and UK Biobank participants of European ancestry identified 4 maternal loci: *GCKR*, *HLA*, *TCF7L2*, and *MTNR1B*. All of these maternal loci are known to affect type 2 diabetes as well.<sup>88</sup> Similarly, in a multiancestry GWAS of n=5485 females with gestational diabetes and n=347 856 females without gestational diabetes that also included UK Biobank participants, 5 gestational diabetes loci were identified: *MTNR1B*, *TCF7L2*, *CDKAL1*, *CDKN2A/2B*, and *HKDC1*. *HKDC1* was the only locus without evidence pointing to a shared pathophysiology between gestational diabetes and type 2 diabetes.<sup>89</sup>
- Recently, a large GWAS of gestational diabetes (N=12 332 cases) was published in FinnGen Finnish participants.<sup>90</sup> By identifying 13 loci, 9 of which were new, this GWAS approximately tripled the number of gestational diabetes loci. Findings suggests that the genetic architecture of gestational diabetes includes 2 distinct categories. The first category overlaps type 2 diabetes and

includes *GCKR* and *TCF7L2*. The second category includes *ESR1* and *MAP3K15*, which suggests the possibility of different actions or regulations during pregnancy.

- 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 US 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>91</sup> Similarly, among the US-based nuMoM2b cohort, compared with the general population, participants with a high diabetes GRS and low PA levels had higher odds of a gestational diabetes diagnosis (OR, 3.4 [95% CI, 2.3–5.3]). In contrast, compared with the general population, participants with a low diabetes GRS and high PA levels had a lower odds of a gestational diabetes diagnosis (OR, 0.5 [95% CI, 0.3–0.9]).<sup>92</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>93</sup>

## Prevention

- A meta-analysis of 35 randomized trials showed that exercise interventions during pregnancy decrease the incidence of developing gestational diabetes (pooled OR, 0.61 [95% CI, 0.51–0.74]), particularly when they are supervised, have a low to moderate intensity level, and are initiated during the first trimester of pregnancy.<sup>12</sup>
- A meta-analysis of 7 trials with 1647 participants showed that probiotics did not lower the risk of gestational diabetes compared with placebo (mean RR, 0.80 [95% CI, 0.54–1.20]).<sup>94</sup> Furthermore, in 4 of these studies, probiotics increased the risk of pre-eclampsia compared with placebo (RR, 1.85 [95% CI, 1.04–3.29]).

## Complications: Maternal Cardiovascular Risk Factors and CVD

- 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>95</sup>

## Complications: Offspring Morbidity and Mortality

- In a meta-analysis of 24 prospective and retrospective studies, offspring exposed to gestational diabetes in utero had higher SBP (mean difference, 1.75 mm Hg [95% CI, 0.57–2.94]), BMI z score (mean difference, 0.11 [95% CI, 0.02–0.20]), and glucose (SMD, 0.43 [95% CI, 0.08–0.77]) compared with those not exposed to gestational diabetes.<sup>96</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>97</sup> Findings were similar when a sibship design was used (ie, comparing gestational diabetes-exposed with unexposed siblings) and when controlling for maternal prepregnancy BMI and paternal diabetes status.

## Preterm Birth

### Incidence, Prevalence, and Secular Trends

- An analysis of all birth certificates for singleton births registered in the United States from 2014 to 2022 showed that PTB and early-term birth rates rose from 2014 to 2022 (by 12% and 20%, respectively), whereas full/late and postterm births declined (by 6% and 28%, respectively).<sup>98</sup> Similar trends were noted across maternal age and race and Hispanic-origin groups. The largest increase was observed for births at 37 weeks (42%).
- Among all singleton deliveries at a single US tertiary care center, compared with the overall PTB rate before the COVID-19 pandemic (11.1% among 17 687 deliveries from January 1, 2018–January 31, 2020), the rate was significantly lower during the pandemic (10.1% among 5396 deliveries from April 1, 2020–October 27, 2020;  $P=0.039$  for comparison); spontaneous PTB rates also decreased during the pandemic (from 5.7% to 5.0%;  $P=0.074$ ). However, decreases in spontaneous PTB occurred only among females from more advantaged neighborhoods (versus less advantaged neighborhoods; from 4.4% to 3.8% versus from 7.2% to 7.4%), White females (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>99</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 prevalence and odds of

PTB (10.8% versus 6.0%; OR, 3.0 [95% CI, 1.15–7.85]).<sup>100</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>101</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>102</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>103</sup>
- In an umbrella review of 85 eligible meta-analyses including 1480 primary studies providing data on 166 associations for the risk of PTB, the following 7 risk factors provided robust evidence for their association with PTB: amphetamine exposure (random-effects OR, 4.11 [95% CI, 1.8–9.37]), isolated single umbilical artery (OR, 2.12 [95% CI, 1.31–3.43]), maternal personality disorder (OR, 2.98 [95% CI, 1.38–6.44]), SDB (OR, 2.32 [95% CI, 1.87–2.89]), prior induced termination of pregnancy with vacuum aspiration (OR, 1.20 [95% CI, 1.13–1.27]), low gestational weight gain (OR, 1.64 [95% CI, 1.55–1.74]), and interpregnancy interval after miscarriage <6 months (OR, 0.79 [95% CI, 0.73–0.84]).<sup>104</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,<sup>105</sup> and risk was greater among NH Black females compared with NH White females. In a study of >14 000 mothers in California, the risk of PTB associated with increasing temperature was numerically but not statistically higher among Black mothers (24.6% [95% CI, 1.0%–55.3%]) and Hispanic mothers (17.4% [95% CI, 3.0%–35.0%]) compared with Asian mothers (7.3% [95% CI, –11.3% to 31.0%]) or White mothers (7.3% [95% CI, –6.8% to 22.1%];  $P=0.56$ , 0.64, and 1.0, respectively, with White mothers as reference group).<sup>106</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

for each 5.6°C increase in weekly mean temperature.<sup>105</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 increase in 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>107</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 the 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>108</sup>

### **Social Determinants of Health and Health Equity in PTB**

- In a meta-analysis of 13 studies of 9299 females, racial discrimination was associated with an increased odds of PTB (pooled OR, 1.40 [95% CI, 1.17–1.68]).<sup>109</sup>
- 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%) higher rate of PTB after covariate adjustment (crude rate, 15.28% versus 13.36%, respectively).<sup>110</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>111</sup>
- In a study from data from the California Office of Statewide Health Planning and Development, 2794 females with unstable housing were propensity score matched with 2318 control subjects.<sup>112</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];  $P<0.001$ ).
- A retrospective study of US Vital Statistics data in 2018 showed that a county-level Maternal Vulnerability Index (a composite measure of 43 area-level indicators categorized into 6 themes reflecting physical, social, and health care landscapes) was associated with PTB (OR, 1.07 [95% CI, 1.01–1.13]).<sup>113</sup> In adjusted analyses of PTB categories (extreme [gestational age ≤28 weeks], very [gestational age 29–31 weeks], moderate [gestational age 32–33 weeks], and late [gestational age 34–36 weeks]), Maternal Vulnerability Index had the greatest association with extreme PTB (aOR, 1.18 [95% CI, 1.07–1.29]).

**Genetics/Family History**

- There is evidence of intergenerational transmission of PTB risk.<sup>114</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>115</sup>
- A maternal GWAS (43 568 females of European ancestry) of gestational duration ( $n=68\,732$ ) and spontaneous PTB ( $n=98\,370$ ) identified 15 loci for gestational duration and 4 loci for spontaneous PTB.<sup>116</sup> Consistent with previous GWASs, the *EBF1* and *EEFSEC* loci were associated with gestational duration and spontaneous PTB,<sup>117</sup> whereas associations with *GC*, *RHAG*, *WNT3A*, and *GNAQ* were novel. Genes at identified loci have previously established roles in uterine development, maternal nutrition, and vascular control. Despite its large size, the relatively small number of identified loci, particularly for spontaneous PTB, highlights the challenges associated with characterizing the genetic architecture underlying parturition timing.
- A large maternal GWAS of gestational duration ( $n=195\,555$ ) and preterm delivery ( $n=18\,797$ ) in women of European ancestry identified 22 and 7 loci, respectively.<sup>118</sup> Effect sizes for gestational duration were very small, increasing gestation by 7 to 27 hours per coded allele. It is interesting that 15 of the 22 loci identified for gestational duration acted through the maternal genome, whereas 7 loci acted through the maternal and fetal genomes. Only 2 loci for gestational duration acted through the fetal genome. The genetic architecture governing gestational duration and preterm delivery also showed strong inverse correlation ( $r_g=-0.62$ ). Last, GRS for gestational duration explained 2.2% of trait variance. For preterm delivery, the GRS showed modest discrimination (AUC, 0.61).
- An international study that evaluated genetic scores known to be associated with adult height, BMI, BP, blood glucose, and type 2 diabetes in 10 734 female-infant duos of European ancestry found that taller genetic maternal height was associated with longer gestational duration (0.14 d/cm [95% CI, 0.10–0.18];  $P=2.2\times10^{-12}$ ), 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>119</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>120</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>121</sup>
- Black race–White race disparities in PTB are also present among females of high SES; among 21 706 86 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, multiracial NH White/Black, and NH Black were 5.5% versus 6.1% versus 9.9%, respectively, for PTB at <37 weeks' gestation and 0.2% versus 0.4% versus 1.2% for PTB at <28 weeks' gestation.<sup>122</sup>

**Complications: Maternal CVD and Mortality**

- Among 57 904 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]; median follow-up, 28 years), type 2 diabetes (HR, 1.17 [95% CI, 1.03–1.33]; median follow-up, 32 years), and hyperlipidemia (HR, 1.07 [95% CI, 1.03–1.11]; median follow-up, 26 years).<sup>123</sup>
- In a meta-analysis of 14 studies, females with a history of PTB (<37 weeks' gestation) had a 63% (95% CI, 1.39%–1.93%) higher risk of CVD compared with females with no history of PTB.<sup>124</sup>
- Among 2 189 477 females with a singleton delivery in 1973 to 2015, risk of all-cause mortality was higher among those mothers 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, 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>125</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 childhood and adulthood (pooled OR, 1.72 [95% CI, 1.12–2.65]).<sup>126</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 compared with those born term.
- In cosibling analyses, associations remained significant for type 1 and 2 diabetes but were largely attenuated for hypertension and lipid disorders (suggesting that shared familial genetic and lifestyle risk factors for PTB and hypertension or lipid disorders accounted for much of their associations).<sup>127–129</sup>
- Among participants in the WHI study, being born preterm was associated with incident hypertension (53.2% versus 51%; HR, 1.10 [95% CI, 1.03–1.19];  $P=0.008$ ) and early-onset hypertension (<50 years of age; 14.7% versus 11.7%; OR, 1.31 [95% CI, 1.15–1.48];  $P<0.0001$ ).<sup>130</sup>

### Offspring Cardiac Remodeling and HF

- In a 2020 meta-analysis of 32 studies, individuals born preterm had higher LV mass (increase compared with 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>131</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>132</sup>

### Offspring CVD and Mortality

- Among 2 141 709 live-born singletons in the Swedish Birth Registry from 1973 to 1994 followed up through 2015 (maximum, 43 years of age), gestational age at birth was inversely associated with risk for premature CHD (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>133</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>134</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 infants born LBW (<2500 grams or 5 lb 8 ounces) rose 3% in 2021 (8.52% versus 8.24% in 2020).<sup>135</sup> Prevalence of LBW by race is shown in Chart 11-6.

#### Risk Factors (Including Social Determinants)

- Among 1 482 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 mmHg or DBP of 80–85 mmHg; 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>102</sup>

- In an individual participant data meta-analysis of 265 270 births from 39 cohorts in Europe, North America, and Australia, prepregnancy underweight BMI ( $\text{BMI} < 18.5 \text{ kg/m}^2$ ; OR, 1.67 [95% CI, 1.58–1.76]) was associated with higher risks for SGA delivery.<sup>8</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 females with normal weight (1.81 [95% CI, 1.73–1.89]) and overweight (1.23 [95% CI, 1.14–1.33]) but not females with obesity.
- Among 8259 pregnant females in the nuMoM2b cohort, periconceptional dietary quality was associated with risks for SGA (birth weight  $< 10$ th percentile for gestational age) and LBW ( $< 2500 \text{ g}$ ). 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 (aRR, 1.24 [95% CI, 1.02–1.51] and 1.32 [95% CI, 1.02–1.71], respectively).<sup>40</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>136</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>137</sup> There were 19 367 SGA infants. Females with SGA infants had lower pregravid fasting glucose (4.69 mmol/L versus 4.73 mmol/L), random glucose (4.86 mmol/L versus 4.89 mmol/L), and triglyceride (0.99 mmol/L versus 1.02 mmol/L) levels than those without SGA infants. Therefore, prepregnancy cardiometabolic biomarkers were not associated with the development of SGA.
- In an individual participant data meta-analysis from the International Prediction of Pregnancy Complications Network of studies on pregnancy complications of 94 studies of 53 countries and 4539 640 pregnancies, being SGA was more likely among babies born to Black/African mothers compared with White mothers globally (OR, 1.39 [95% CI, 1.13–1.72]).<sup>138</sup>

## Environmental Exposures

- In a systematic review of studies examining associations of air pollution, significant associations were found with LBW for 25 of 29 studies (examining a total of  $> 18$  million births) in the United States.<sup>105</sup>
- The median risk was 10.8% higher (range, 2.0%–36.0%) for whole-pregnancy PM2.5 exposure per IQR greater exposure (eg, 6 studies considered a whole-pregnancy median of  $3.9 \mu\text{g}/\text{m}^3$  [IQR, 1.35–6.45  $\mu\text{g}/\text{m}^3$ ] of PM2.5 exposure), and in 1 study, risk was higher by 3% for each 5-km closer proximity to a solid waste plant.<sup>105</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  $5.6^\circ\text{C}$  higher weekly mean temperature, and in 1 study, whole-pregnancy ambient local temperature  $> 95$ th percentile was associated with an RR of 2.49 (95% CI, 2.20–2.83).<sup>105</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 the 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 infants (pooled standardized OR, 0.94 [95% CI, 0.92–0.97]).<sup>108</sup>

## Social Determinants of Health/Health Equity

- In a meta-analysis of 3 studies of 1588 participants from the United States and Australia, racial discrimination was associated with increased odds of SGA (OR 1.23 [95% CI, 0.76–1.99]).<sup>109</sup>
- 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 a 0.88% (95% CI, 0.23%–1.54%) higher rate of LBW ( $< 2500 \text{ g}$ ) after covariate adjustment (crude rate, 11.59% versus 10.24%, respectively).<sup>110</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>120</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>139</sup>

### **Genetics/Family History**

- Birth weight shows evidence of intergenerational transmission, which may extend across 3 generations.<sup>140</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>141</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>142</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>124</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>143</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>126</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>127</sup>
- A 2018 meta-analysis of 49 studies with 4 053 367 participants found a J-shaped association between birth weight and adult type 2 diabetes, with the lowest risk in the 3.5- to 4-kg category.<sup>144</sup> The pooled HRs were 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 a pooled analysis from 22 389 men from the HPFS and 162 231 women from the Nurses' Health and Nurses Health II Studies, participant-reported LBW was associated with a greater risk of cardiovascular and respiratory disease mortality among women, and high birth weight was associated with a greater cancer mortality risk in both men and women.<sup>145</sup> Compared with women with a birth weight of 3.16 to 3.82 kg, the pooled HRs for all-cause mortality were 1.13 (95% CI, 1.08–1.17), 0.99 (95% CI, 0.96–1.02), 1.04 (95% CI, 1.00–1.08), and 1.03 (95% CI, 0.96–1.10) for women with a birth weight of <2.5, 2.5 to 3.15, 3.83 to 4.5, and >4.5 kg, respectively. Women with a birth weight <2.5 kg had an elevated risk of mortality

resulting from CVDs (HR, 1.15 [95% CI, 1.05–1.25]) and respiratory diseases (HR, 1.35 [95% CI, 1.18–1.54]), whereas those with birth weight >4.5 kg had a higher risk of cancer mortality (HR, 1.15 [95% CI, 1.00–1.31]). Among men, birth weight was unrelated to all-cause mortality but was inversely associated with CVD mortality and positively associated with cancer mortality ( $P_{\text{linear trend}}=0.012$  and 0.0039, respectively).

## Pregnancy Loss

### Incidence, Prevalence, and Secular Trends

- In 2021, the stillbirth ( $\geq 28$  weeks' gestation) rate in the United States was 2.80 per 1000 live births and fetal deaths.<sup>146</sup>
- Black birthing people had a substantial decrease in infant mortality rates from 2020 to 2021, declining 4% from 10.34 to 9.89 per 1000. However, the infant mortality rate for Black birthing people in 2021 was still nearly double the national rate of 5.74 per 1000.

### Risk Factors (Including Social Determinants)

- Antiphospholipid syndrome was associated with higher risk for pregnancy loss (RR, 2.42 [95% CI, 1.46–4.01] for loss at <10 weeks; RR, 1.33 [95% CI, 1.00–1.76] for loss at  $\geq 10$  weeks) in a meta-analysis of 212 184 females (including 770 with antiphospholipid syndrome) from 8 studies.<sup>147</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>105</sup>
- In a systematic review of 2 US studies (>200 000 births) examining heat, the risk for stillbirth was 6% higher per  $1^{\circ}\text{C}$  higher ambient temperature the week before delivery during the warm season.<sup>105</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) for each  $1^{\circ}\text{C}$  rise in environmental temperature.<sup>107</sup>

### Genetics/Family History

- The heritability of any pregnancy loss has been reported at 29% (95% CI, 20%–38%) for any miscarriage.<sup>148</sup>
- Fetal genetic factors also play a role in recurrent pregnancy loss. Fetal aneuploidy is common in first-trimester spontaneous miscarriages but is also seen in recurrent pregnancy loss, increasing with maternal age (in 1 study accounting for 78%

of miscarriages in females  $\geq 35$  years of age with recurrent pregnancy loss versus 70% in females with nonrecurrent pregnancy loss).<sup>149</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>150</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>151</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 *FGF9*, *TLE1*, and *TLE4*.<sup>148</sup>

### Prevention

- In a meta-analysis of 23 relatively homogeneous studies of 608 243 pregnant females, having been vaccinated with the COVID-19 mRNA vaccine was associated with a lower risk of stillbirth by 15% (pooled OR, 0.85 [95% CI, 0.73–0.99]).<sup>152</sup> COVID-19 mRNA vaccination in pregnancy is shown to be safe; there was no evidence of a higher risk of adverse outcomes, including miscarriage, earlier gestation at birth, placental abruption, PE, postpartum hemorrhage, maternal death, ICU admission, lower birthweight z score, or neonatal ICU admission ( $P>0.05$  for all outcomes).

### 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>153</sup> The risk was greater for females with  $\geq 2$  pregnancy losses (HR, 1.34 [95% CI, 1.21–1.62]) compared with those with 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>154</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>155</sup>
  - A systematic review of 84 studies (28 993 438 patients) with a median follow-up of 7.5 years postpartum evaluated the associations between APOs and CVD.<sup>124</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 Abruption

### Incidence, Prevalence, and Secular Trends

- The majority of studies have reported an incidence of 0.5% to 1% for placental abruption.<sup>156</sup> In the nuMoM2b study, placental abruption was identified in 62 of 9450 nulliparous females (0.66%); 35 (56%) were antepartum and 27 (44%) were intrapartum.<sup>157</sup>

### Risk Factors (Including Social Determinants)

- In the nuMoM2b study, risk factors for placental abruption were studied in 9450 females.<sup>157</sup> For females with abruption, the mean gestational age at delivery was  $35.6 \pm 4.4$  weeks; it was  $38.8 \pm 2.2$  weeks for females without abruption. Several risk factors for placental abruption were identified in a case-crossover study (mothers with placental abruption in one pregnancy vs no placental abruption in another pregnancy) in Finland, Malta, and Aberdeen.<sup>158</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 to be 16% (95% CI, 8%–23%).<sup>159</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>159</sup> Independent loci suggestively associated with placental abruption included rs4148646 and rs2074311 in *ABCC8*; rs7249210, rs7250184, rs7249100, and rs10401828 in *ZNF28*; rs11133659 in *CTNND2*; 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>159</sup>
- Mendelian randomization causal inference studies of hypertensive indices suggest that SBP increases the odds of placental abruption (OR, 1.33 [95% CI, 1.05–1.68] per 10-mm Hg increment).<sup>160</sup>

### Maternal CVD

- A meta-analysis of 11 cohort studies of 6 325 152 pregnancies analyzed the association between placental abruption and CVD.<sup>161</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>162</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 2021, there were 451 945 hospital discharges for HDP, 170 975 for preexisting diabetes and gestational diabetes, 105 480 for PTB, and 15 855 for SGA/LBW.
- In 2021, there were 137 213 visits to the ED for HDP, 28 568 for preexisting diabetes and gestational diabetes, 46 517 for PTB, and 391 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>163</sup>

## Cost

- Pregnancy and postpartum care accounted for \$71.3 (\$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 (\$4.8–\$6.3) billion and \$28.2 (\$21.8–\$37.6) billion, respectively.<sup>164</sup>
- The cost of the 9 common maternal morbidity conditions for all US births in 2019 was \$32.3 billion from conception through the child's fifth birthday.<sup>165</sup> Two-thirds of these costs occurred within the first year postpartum, and the majority of the costs were due to child outcomes (compared with maternal outcomes; 74% versus 26%). The largest costs included maternal mental health conditions (\$18.1 billion), hypertensive disorders (\$7.5 billion), gestational diabetes (\$4.8 billion), and PTB (\$13.7 billion),

## Global Burden

### (See Tables 11-1 and 11-2 and Charts 11-7 and 11-8)

- In 2015, an estimated 20.5 million infants were born with LBW worldwide.<sup>166</sup>
- Analysis of WHO and UNICEF data estimates that 23.4 million liveborn babies (17.4%) were born SGA in 2020 worldwide. There was marked regional variation in SGA, with more than a third (40.9%) of all newborns in southern Asia being SGA compared with 10.7% in sub-Saharan Africa and <10% in other regions.<sup>167</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>168</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%;  $P=0.629$ ).<sup>168</sup> 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>169</sup>
- Based on 204 countries and territories in 2021, the incidence of maternal hypertensive disorders was highest for regions in sub-Saharan Africa and lowest for East Asia (Chart 11-7). In 2021, the incidence of maternal hypertensive disorders among females 15 to 49 years of age was 18.00 (95% UI, 15.30–21.47) million new cases with an average rate of 923.48 (95% UI, 785.15–1101.80) per 100 000 female population 15 to 49 years of age (Table 11-1).<sup>170</sup>
- Based on 204 countries and territories in 2021, the highest rates of neonatal PTB among regions were found for South Asia, followed by the Caribbean and Oceania. Rates were lowest for East Asia (Chart 11-8). The incidence of neonatal PTB was 21.55 (95% UI, 21.38–21.73) million new cases with an average rate of 16 658.81 (95% UI, 16 523.66–16 795.10) per 100 000 births (Table 11-2).<sup>170</sup>

**Table 11-1. Global Incidence of Maternal Hypertensive Disorders Among Females 15 to 49 Years of Age, 2021**

	Incidence, female (95% UI)
No. (millions), 15–49 y, 2021	18.00 (15.30 to 21.47)
Percent change (%) in number, 15–49 y, 1990–2021	15.29 (8.08 to 21.03)
Percent change (%) in number, 15–49 y, 2010–2021	3.17 (0.01 to 6.08)
Rate per 100 000, 15–49 y, 2021	923.48 (785.15 to 1101.80)
Percent change (%) in rate, 15–49 y, 1990–2021	−20.89 (−25.83 to −16.95)
Percent change (%) in rate, 15–49 y, 2010–2021	−4.08 (−7.02 to −1.37)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>170</sup>

**Table 11-2. Global Incidence of Neonatal PTB by Sex, 2021**

	Incidence		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
No. (millions), 2021	21.55 (21.38 to 21.73)	12.33 (12.19 to 12.46)	9.22 (9.11 to 9.33)
Percent change (%) in number, 1990–2021	−6.29 (−7.37 to −5.20)	−8.34 (−9.49 to −6.91)	−3.41 (−5.11 to −1.75)
Percent change (%) in number, 2010–2021	−8.12 (−9.17 to −7.08)	−9.07 (−10.53 to −7.67)	−6.81 (−8.34 to −5.33)
Rate per 100 000, at birth, 2021	16,658.81 (16,523.66 to 16,795.10)	18,418.41 (18,214.58 to 18,620.88)	14,772.58 (14,595.11 to 14,941.39)
Percent change (%) in rate, at birth, 1990–2021	−4.55 (−5.65 to −3.44)	−6.48 (−7.65 to −5.02)	−1.79 (−3.52 to −0.10)
Percent change (%) in rate, at birth, 2010–2021	−2.16 (−3.28 to −1.06)	−3.09 (−4.64 to −1.60)	−0.87 (−2.50 to 0.70)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; PTB, preterm birth; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>170</sup>

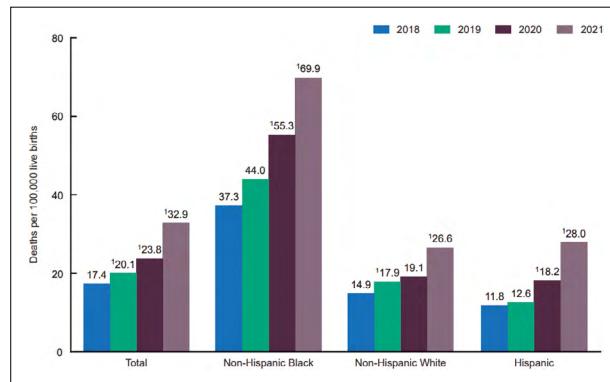
	Gestational Weight Gain Category		
	Pre-Pregnancy Body Mass Index Category	Low ( $\leq 1.1$ SD)	Medium (-1.0 to 0.9 SD)
Underweight	1.09 (0.94 – 1.26)	1.04 (0.96 – 1.12)	1.13 (0.98 – 1.30)
Normal weight	1.04 (1.01 – 1.08)	Referent	1.10 (1.06 – 1.14)
Overweight	1.23 (1.16 – 1.32)	1.38 (1.33 – 1.43)	1.63 (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. aORs 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).

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

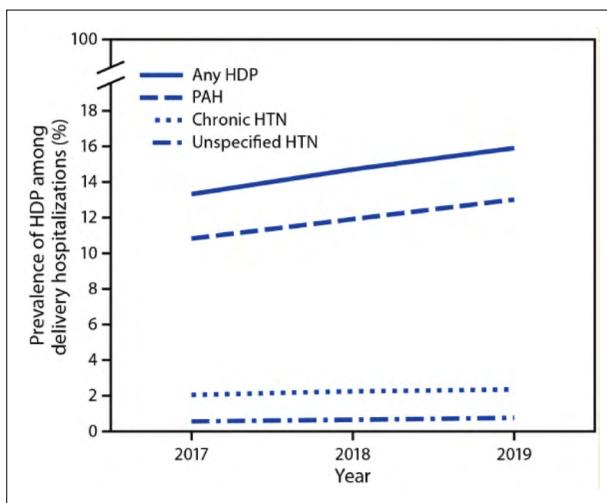
Source: Data derived from Santos et al.<sup>8</sup>

**Chart 11-2. Maternal mortality rates, by race and Hispanic origin: United States, 2018 to 2021.**

Race groups are single race.

<sup>1</sup>Statistically significant increase from previous year ( $P<0.05$ ).

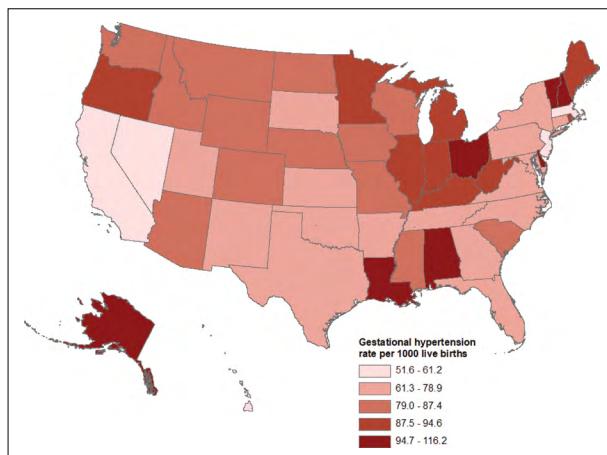
Source: Reprinted from Hoyert.<sup>13</sup>



**Chart 11-3. Prevalence of hypertensive disorders in pregnancy\* among delivery hospitalizations, by year, NIS, United States, 2017 to 2019.**

HDP indicates hypertensive disorder in pregnancy; HTN, hypertension; NIS, National Inpatient Sample; and PAH, pregnancy-associated hypertension.

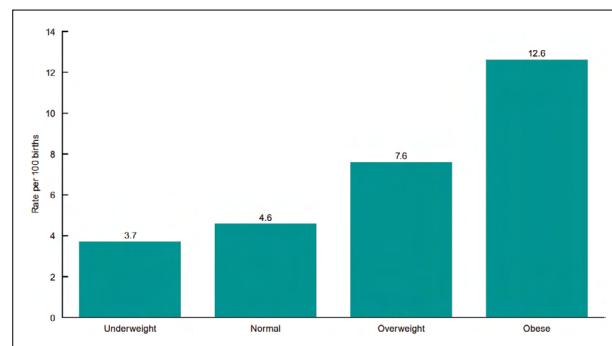
\*HDPs are defined as chronic hypertension, PAH (ie, gestational hypertension, preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia), and unspecified maternal hypertension.  
Source: Reprinted from Ford et al.<sup>171</sup>



**Chart 11-4. 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 3736144 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>172</sup>

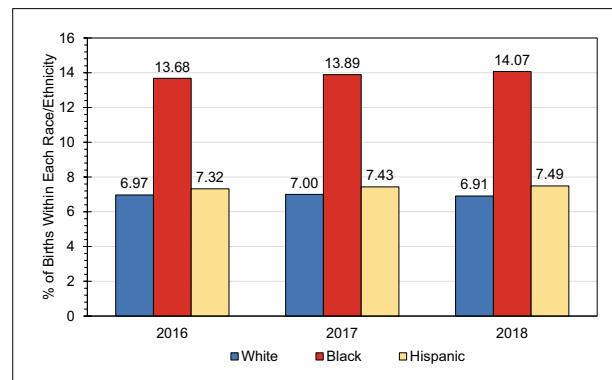


**Chart 11-5. Rate of gestational diabetes, by BMI: United States, 2020.**

Significant increasing trend ( $P<0.05$ ).

BMI indicates body mass index.

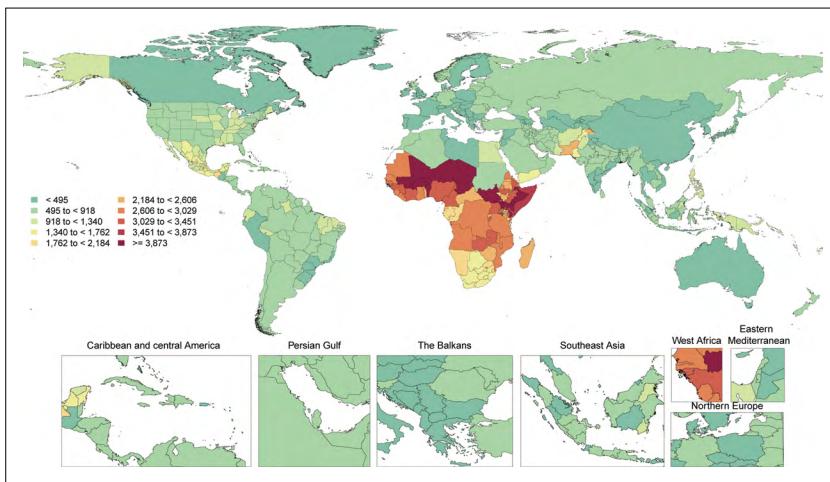
Source: Reprinted from Gregory and Ely.<sup>80</sup>



**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>173</sup>

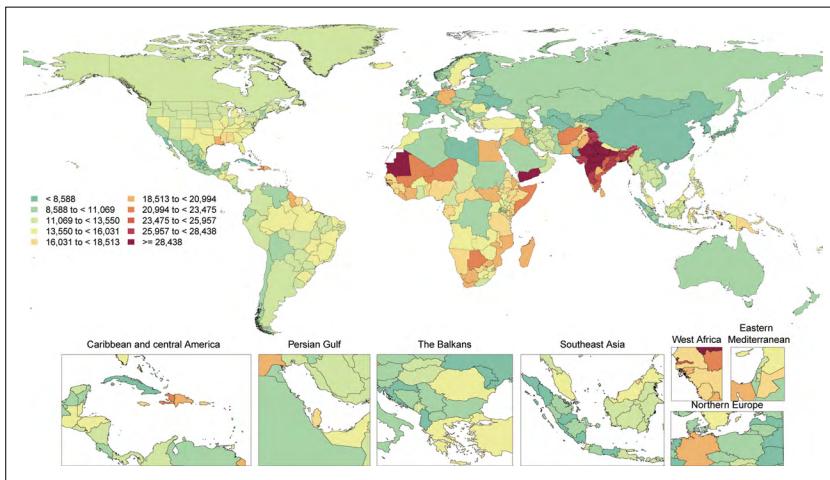


**Chart 11-7. Global incidence rates of maternal hypertensive disorders per 100 000 females, 15 to 49 years of age, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>170</sup>



**Chart 11-8. Global incidence rates of neonatal PTB per 100 000, both sexes, at birth, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and PTB, preterm birth.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>170</sup>

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## 12. KIDNEY DISEASE

**ICD-10 N18.0. See Table 12-1 and Charts 12-1 through 12-13**

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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 that do not incorporate race have been developed and validated. The eGFR equation with creatinine from 2021 was used for calculating CKD estimates in the 2023 USRDS report.<sup>6</sup> The 2024 Kidney Disease: Improving Global Outcomes CKD guidelines recommend using the combination of creatinine- and cystatin C-based eGFR equation for CKD staging when cystatin C is available.<sup>7</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).
- ESKD is defined as severe CKD requiring long-term kidney replacement therapy such as hemodialysis, peritoneal dialysis, or kidney transplantation.<sup>8</sup> Individuals with ESKD are an extremely high-risk population for CVD morbidity and mortality.

The 2025 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 2025. 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

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

- Using data from NHANES 2017 to 2020, the USRDS has estimated the prevalence of CKD by eGFR and albuminuria categories as shown in Chart 12-1. The overall prevalence of CKD (eGFR  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  or ACR  $\geq 30 \text{ mg/g}$ ; shown in yellow, orange, and red in Chart 12-1) in 2017 to 2020 was 14.0%.<sup>9</sup>
- The overall prevalence of CKD increases substantially with age, with 9% of adults  $<65$  years of age and 33.2% of adults  $\geq 65$  years of age having CKD in 2017 to 2020.<sup>9</sup>
- According to NHANES 2017 to 2020, the prevalence of ACR  $\geq 30 \text{ mg/g}$  was 13.5% for NH Black adults, 10.9% for Hispanic adults, and 9.2% for NH White adults. In contrast, the prevalence of eGFR  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , calculated with the newer eGFR equations without the race coefficient, was lowest among Hispanic adults (2.2%) followed by NH White adults (6.3%) and highest for NH Black adults (9.1%).<sup>9</sup>
- The overall prevalence of CKD (incorporating eGFR  $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  or ACR  $\geq 30 \text{ mg/g}$ ) was highest among NH Black adults (18.8%) followed by NH White adults (12.1%) and Hispanic adults (12.0%). The prevalence of CKD decreased compared with the previous NHANES cycle (2013–2016) for NH White adults and Hispanic adults but increased in NH Black adults.<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>10</sup>
- In 2021, the age-, race-, and sex-adjusted prevalence of ESKD in the United States was 2219 per million people, a decrease of 3.5% from its peak in 2019.<sup>1</sup> The overall prevalence count increased slightly, from 807 920 in 2020 to 808 536 in 2021.
- ESKD prevalence varied by race and ethnicity (Chart 12-2). In 2021, ESKD prevalence was highest in Black adults, followed by Native American adults, Hispanic adults, Asian adults, and White adults. ESKD prevalence also was higher among Hispanic people than among NH people.
- Among those with prevalent ESKD, in 2021 compared with 2020, the use of in-center hemodialysis remained the most common modality but continued to decrease from 59.8% to 58.3% (Chart 12-3). All other modalities increased: transplantation from 30.6% to 31.8%, peritoneal dialysis from 8.1% to 8.3%, and home hemodialysis from 1.5% to 1.6%.<sup>1</sup>

## Incidence

### (See Chart 12-4)

- According to 2022 data from the Veterans Affairs Health System, the CKD incidence rate (categories 3–5) increased with age. The incidence rates per 1000 patient-years were 7.0 (18–29 years of age), 12.6 (30–39 years of age), 27.5 (40–49 years of age), 51.4 (50–59 years of age), 81.9 (60–69 years of age), and 110.1 ( $\geq 70$  years of age).<sup>11</sup>
- The incidence of ESKD in 2021, adjusted for age, sex, and race and ethnicity, was 363 per million people, a small increase from the low of 360 per million people in 2020. The incidence count increased from 130 522 in 2020 to 135 972 in 2021.<sup>9</sup> The incidence of ESKD was higher in males than females (Chart 12-4).
- By modality, the initiation of in-center hemodialysis decreased from 83.9% to 83.8%, whereas peritoneal dialysis remained the same at 12.7%, and home hemodialysis also remained at 0.3%.<sup>1</sup>

## Secular Trends

### (See Charts 12-5 and 12-6)

- Among Medicare beneficiaries, the prevalence of CKD (based on coded diagnosis) increased from 9.2% in 2011 to 14.2% in 2021 (Chart 12-5).
- According to NHANES data, the overall prevalence of reduced eGFR and excess ACR across categories was generally similar from 2005 to 2020 (Chart 12-6).
- Between 2013 to 2016 and 2017 to 2020, the prevalence of CKD stage 3 decreased among individuals  $<65$  years of age, from 1.6% to 1.3%, but was unchanged among those  $\geq 65$  years of age.<sup>9</sup>
- By race and ethnicity, the prevalence of stage 3 and 4 CKD increased from 7.9% to 8.8% in NH Black individuals, was unchanged at 6.3% among NH White individuals, and decreased slightly from 2.6% to 2.0% in Hispanic individuals.<sup>9</sup> However, the prevalence of stage 5 CKD remained unchanged at 0.1% in NH White individuals, decreased from 0.5% to 0.3% among NH Black individuals, but increased slightly from 0.1% to 0.2% in Hispanic individuals.
- From 2001 to 2019, the prevalence count of ESKD had been increasing (409 226 in 2001 to 806 939 in 2019), attributable primarily to a combination of an aging and growing population and improved survival with ESKD.<sup>1</sup> This prevalence count has since slowed down or flattened in 2020 (805 629) and 2021 (808 536). The incidence rate itself has been declining since 2006 (sex- and age- adjusted incidence rate 425 per

million population in 2006 to 363 per million population in 2021). However, despite the change in incidence rate, the absolute incidence count had been steadily increasing over the years until 2020, when it dropped from 134 837 in 2019 to 130 719 in 2020. In the year 2020, the 6.2% decline in adjusted incidence rate was also accompanied by a 1.9% decline in the adjusted prevalence rate and the accompanying flattening or slight decline in prevalence count. This decline was explained mostly by the effects of COVID-19 in the ESKD population. In 2021, the incident count increased sharply to 135 972, a number that is below the pre-COVID-19 trajectory for 2021 but above the expected number if pre-2020 growth rates had been applied to the 2020 count.

- The adjusted ESKD incidence by age declined slightly in most age groups except those  $\geq 75$  years of age.<sup>1</sup> This group had demonstrated a large decrease in the incidence rate from 2019 (1586 per million population) to 2020 (1452 per million population), which increased again to 1581 per million population in 2021, making the largest contribution to the increase in incidence count.
- The adjusted ESKD incidence decreased in all race and ethnicity groups from 2001 until 2018 or 2019.<sup>1</sup> After 2019, ESKD incidence increased among Black individuals but not among members of other race and ethnicity groups. In 2021, the incidence of ESKD among Black individuals was 3.8 times the incidence of NH White individuals; the incidence among Native American individuals was 2.3 times as high, and it was twice as high among Hispanic individuals.

## Risk Factors

- 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>12</sup>
- In the ARIC study, incident hospitalization with any major CVD event (HF, AF, CHD, or stroke) was associated with an increased risk of ESKD (HR, 6.63 [95% CI, 4.88–9.00]). In analyses by CVD event type, the association with ESKD 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>13</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>14</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>15</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>16</sup>
- In a meta-analysis of 23 studies, preeclampsia was associated with increased risk of ESKD (RR, 4.90 [95% CI, 3.56–6.74]) and CKD (RR, 2.11 [95% CI, 1.72–2.59]).<sup>17</sup>
- In a meta-analysis of 31 studies, living kidney donation was associated with a greater decline in GFR in older donors (>60 years of age), female donors, and donors with obesity with a BMI >30 kg/m<sup>2</sup>.<sup>18,19</sup>
- In a meta-analysis of 20 studies, lithium treatment was associated with a prevalence rate of 25.5% for impaired kidney function (eGFR <60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>). In a comparison of 14 187 patients on lithium and 722 529 on nonlithium treatment, lithium treatment was associated with higher risk of subsequent CKD (eGFR <60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>) with a pooled OR of 2.09 (95% CI, 1.24–3.51).<sup>20</sup>
- An analysis using NHANES data examined the relationship between LBW compared with normal birth weight and subsequent development of reduced kidney function (defined as eGFR < 90 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> using the pediatric Schwartz equation).<sup>21</sup> The analysis included 6336 children (12–15 years of age) and reported the prevalence of reduced kidney function at 30.1% (95% CI, 25.2%–35.6%) for children born with LBW compared with 22.4% (95% CI, 20.5%–24.3%) in children with normal birth weight.
- A prospective study enrolled 3409 adults with autosomal dominant polycystic kidney disease and reported an association of each additional l/m of height-adjusted total kidney volume on MRI with lower eGFR (regression coefficient, 17.02 [95% CI, 15.94–18.11]) and worse patient-reported health-related quality of life (autosomal dominant polycystic kidney disease Impact Scale physical score regression coefficient, 1.02 [95% CI, 0.65–1.39]), decreased work productivity (work days missed, regression coefficient, 0.55 [95% CI, 0.18–0.92]), and increased health care resource use (hospitalizations, OR, 1.48 [95% CI, 1.33–1.64]) during follow-up.<sup>22</sup>
- In an analysis of adults with obesity but without baseline CKD or diabetes enrolled in MESA, linear mixed-effects and multistate models adjusted for demographics, time-varying covariates including BP, and comorbidities were used to examine associations of weight change and slow walking pace (<2 miles/h) with rate of annual eGFR decline and incident CKD (defined as eGFR with the combined creatinine–cystatin equation <60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>).<sup>23</sup> Among the 1208 included MESA participants, 15% developed CKD during follow-up. Slow walking pace was associated with eGFR decline (−0.27 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> [95% CI, −0.42 to −0.12]) and CKD (aHR, 1.48 [95% CI, 1.08–2.01]). Weight gain was associated with CKD risk (aHR, 1.34 [95% CI, 1.02–1.78] per 5-kg weight gain from baseline).

## Social Determinants of CKDs/Health Equity

- According to NHANES 2015 to 2018, the prevalence of CKD was 19.5% for adults with less than a high school education, 17.2% for those with a high school degree or equivalent, and 13.1% for those with some college or more.<sup>9</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>24</sup>
- The REGARDS study included 4198 Black participants and 7799 White participants at least 45 years of age recruited from 2003 through 2007 across the continental United States with baseline eGFR >60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> with a repeat kidney function assessment at 9 years of follow-up. Stroke Belt residence was independently associated with eGFR change (−0.10;  $P<0.001$ ) and incident CKD (RR, 1.14 [95% CI, 1.01–1.30]).<sup>25</sup> Albuminuria was more strongly associated with eGFR change ( $\beta$ , −0.26 versus −0.17;  $P_{\text{interaction}}=0.01$ ) in Black participants compared with White participants with similar results for incident CKD.

## 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>26,27</sup>
- GWASs in >1 million individuals revealed >260 candidate loci for CKD phenotypes, including eGFR and serum urate.<sup>28–31</sup> 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>32</sup> A multiancestry meta-analysis of GWASs including >1 500 000 individuals for creatinine-based eGFR led to the identification of 126 novel loci.<sup>33</sup> Heritability analysis showed that DNA methylation variations mediated about half of the heritability of kidney disease. Multiple lines of evidence established the causal role of *SLC47A1* in the development of kidney disease.

- Whole-genome sequencing–based GWASs, which provided a more granular understanding of the genetic architecture, in >23 000 multiancestry populations identified 3 novel loci associated with eGFR that are more commonly observed in individuals from non-European ancestry.<sup>34</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.
- Refinement in discovery and validation efforts combining multiomics data has identified 182 likely causal genes for kidney function.<sup>35</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>36</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>37</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>38</sup>
- Although certain variants of *APOL1* increase risk, this explains only a portion of the racial disparity in ESKD risk.<sup>37</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>39</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>40</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>41</sup> Individuals belonging to the highest 2% of the multiancestry

genome-wide CKD PRS distribution had an ≈3-fold higher risk of CKD across ancestries.<sup>42</sup>

- Using data from 29 315 individuals of European ancestry, a GWAS for urinary uromodulin levels identified 2 loci (*KRT40* and *UMOD-PDILT*).<sup>43</sup> A GWAS in the same population for urinary uromodulin levels indexed to urinary creatinine revealed 2 loci (*WDR72* and *UMOD-PDILT*).<sup>43</sup>
- A GWAS meta-analysis in 343 339 individuals for annual decrease in eGFR yielded 11 genomic loci.<sup>44</sup> The 11 loci associated with eGFR decline were also associated with cross-sectional eGFR.<sup>44</sup> Apart from identifying the *UMOD-PDILT* locus, gene prioritization analysis identified *SPATA7*, *GALNTL5*, *TPPP*, and *FGF5* as candidate genes for eGFR decline.<sup>44</sup>
- An analysis combining genetic, gene expression, splicing, and methylation data from up to 430 human kidneys to examine the renal mechanisms in BP regulation revealed connections of 1038 renal genes with 479 variants associated with BP.<sup>45</sup> Colocalization and mendelian randomization analyses established the causal role of 179 renal genes in the regulation of BP.<sup>45</sup>
- Post-GWAS analysis integrating Bayesian colocations, transcriptome-wide association studies, and mendelian randomization studies has prioritized *CASP9* as a risk locus for kidney disease.<sup>46</sup> Murine models showed that inhibition of *CASP9*, through either gene knockout or pharmacological inhibition, was associated with lower apoptosis, improved mitophagy, reduced inflammation, and protection from renal fibrosis.<sup>46</sup>

## Awareness, Treatment, and Control

- In a cohort study of 192 108 US patients with hypertension or diabetes, it was assessed that approximately two-thirds of patients with albuminuria were undetected because of lack of testing.<sup>47</sup>
- A clinical trial found that home-based screening of the general population for increased ACR with a urine collection device had a high participation rate (59.4% [95% CI, 58.3%–60.5%]) with high sensitivity (96.6% [95% CI, 91.5–99.1]) and specificity (97.3% [95% CI, 94.7–98.8]) to detect high ACR.<sup>48</sup>
- CKD awareness has increased over time but remains low. In a study of NHANES 1999 to 2018, CKD awareness increased from 11.2% in 1999 to 2002 to 19.8% in 2015 to 2018.<sup>49</sup> Awareness increased with higher CKD stage and was generally higher among Black individuals, younger age groups, and individuals with diabetes, hypertension, and higher BMI.<sup>49</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>9</sup>

- Among adults with CKD treated in the Veterans Health Administration, the proportion of adults with controlled BP declined from 78% to 71% from 2011 to 2015 with a slight increase to 72.9% by 2019.<sup>50</sup> Among adults with CKD with BP above goal, the age-adjusted proportion who did not receive antihypertensive treatment throughout the decade increased from 10.8% to 21.6%.<sup>50</sup>
- Among patients with CKD with hypertension, an intensive SBP treatment goal of <130 mmHg compared with a standard goal of <140 mmHg decreased the risk of all-cause mortality (HR, 0.79 [95% CI, 0.63–1.00]) in a pooled analysis of 4 randomized clinical trials.<sup>51</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>9</sup> In a study of patients with CKD with diabetes in a large health care system, HbA1c <6% and ≥9% was associated with high risk for all-cause death.<sup>52</sup>
- Children <7 years of age with CKD are more likely to have both undiagnosed and undertreated hypertensive BP.<sup>53</sup> At visits where participants <7 years of age had hypertensive BP readings, 46% had unrecognized and untreated hypertensive BP compared with 21% of visits for children ≥13 years of age. The youngest age group was associated with higher odds of unrecognized hypertensive BP (aOR, 2.11 [95% CI, 1.37–3.24]) and lower odds of antihypertensive medication use among those with unrecognized hypertensive BP (aOR, 0.51 [95% CI, 0.27–0.996]).

## Complications

- DALYs for CKD were 457.25 per 100 000 in 2002 versus 536.85 per 100 000 in 2019.<sup>54</sup>

## Cost

- In 2020, Medicare spent >\$85.4 billion caring for people with CKD and \$50.8 billion caring for people with ESKD.<sup>9</sup> ESKD care accounts for >7% of total Medicare expenditures for just 1% of the Medicare population.<sup>55</sup>
- In inflation-adjusted dollars, Medicare spending per person per year for beneficiaries with ESKD decreased from \$96 451 in 2010 to \$79 439 in 2020: \$116 383 to \$95 932 for beneficiaries receiving hemodialysis, \$89 962 to \$81 525 for beneficiaries receiving peritoneal dialysis, and \$42 917 to \$39 264 for beneficiaries with a kidney transplantation.<sup>9</sup> After adjustment for inflation, total spending among Medicare fee-for-service beneficiaries with CKD decreased for the first time in 2020 with expenditures \$2 billion lower than in 2019.<sup>9</sup>

- Total hospitalization expenditure in Medicare fee-for-service beneficiaries with ESKD was \$12.1 billion in 2020.<sup>9</sup>

## Global Burden of Kidney Disease

### (See Table 12-1 and Charts 12-7 and 12-8)

- Based on 204 countries and territories in 2021<sup>54</sup>:
  - The total prevalence of CKD was 673.72 (95% UI, 629.10–722.36) million cases, a 27.33% (95% UI, 26.32%–28.31%) increase since 2010. There were 1.53 (95% UI, 1.39–1.64) million total deaths attributable to CKD (Table 12-1). The age-standardized prevalence of CKD was highest for Central, Southeast, and South Asia. Prevalence was lowest for Western Europe (Chart 12-7).
  - Central sub-Saharan Africa, central Latin America, and eastern sub-Saharan Africa had the highest age-standardized mortality rates estimated for CKD among regions. Rates were the lowest for Eastern Europe (Chart 12-8).

## Kidney Disease and CVD

### CKD and CVD Outcomes

- There is a strong and consistent association of reduced eGFR and higher albuminuria with CVD risk.<sup>56</sup> In an analysis of 114 cohorts, lower eGFR based on creatinine alone, lower eGFR based on creatinine and cystatin C, and more severe urine ACR (compared with normal eGFR and urine ACR) were each associated with increased rates of adverse outcomes, including adverse kidney outcomes, CVDs, and hospitalizations. For example, eGFR based on creatinine and cystatin of 45 to 59 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> and urine ACR of 10 to 29 mg/g was associated higher risk of all-cause mortality (HR, 2.2 [95% CI, 2.1–2.3]), cardiovascular mortality (HR, 2.7 [95% CI, 2.4–3.0]), and kidney failure with replacement therapy (HR, 12.5 [95% CI, 5.4–29.1]).
- Even low-grade albuminuria is associated with poor outcomes. A study of NHANES 1999 to 2016 found that compared with the reference group (quartile 1, ACR <4.171 mg/g), low-grade albuminuria was associated with all-cause mortality (quartile 3, ACR ≥6.211–<10.010 mg/g; HR, 1.25 [95% CI, 1.11–1.41]; quartile 4, ACR ≥10.010 mg/g; HR, 1.57 [95% CI, 1.41–1.76]) in a multivariable model.<sup>47</sup>
- The association of reduced eGFR with CVD risk is generally similar across age, race, and sex subgroups,<sup>57</sup> although albuminuria tends to be a stronger risk factor for females than for males and for older (>65 years of age) than for younger people.<sup>58</sup>

- In Framingham Offspring Study participants without CVD, participants with 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>10</sup>
- The addition of eGFR and albuminuria improves CVD prediction beyond traditional risk factors.<sup>58–60</sup> The AHA's PREVENT CVD risk equations include eGFR and albuminuria.<sup>61</sup>
- In an analysis of >4 million adults from 35 cohorts, inclusion of eGFR and albuminuria significantly improved prediction for CVD mortality beyond SCORE and ASCVD beyond PCE in validation data-sets ( $\Delta$  C statistic, 0.027 [95% CI, 0.018–0.036] and 0.010 [95% CI, 0.007–0.013]) and categorical NRI (0.080 [95% CI, 0.032–0.127] and 0.056 [95% CI, 0.044–0.067], respectively).<sup>60</sup>
- In a mendelian randomization analysis of 4 population data sources (Emerging Risk Factors Collaboration, European Prospective Investigation Into Cancer and Nutrition–Cardiovascular Disease Study, Million Veteran Program, and UK Biobank), in those with eGFR 60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>, each 5-mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> lower eGFR was associated with a 14% (95% CI, 3%–27%) higher risk of CHD.<sup>62</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>63</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>64</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>65</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>66</sup>

### **Prevalence of CVD Among People With CKD (See Charts 12-9 through 12-12)**

- People with CKD, as well as those with ESKD, have an extremely high prevalence of comorbid CVDs, ranging from IHD and HF to arrhythmias and VTE (Charts 12-9 and 12-10).
- In 2020, CVD was present in 35.6% 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>
- Of the types of CVD, HF (24%) and CAD (34%) are the most prevalent according to data of Medicare beneficiaries in 2020.<sup>1</sup> Previous studies of community based cohorts have also demonstrated that the attributable risk of CKD to CVD is greatest for HF and CHD. After adjustment for demographics, cohort, hypertension, diabetes, hyperlipidemia, and tobacco use, risk differences comparing participants with and those without CKD (per 1000 PY) were 2.3 (95% CI, 1.2–3.3) for HF, 2.3 (95% CI, 1.2–3.4) for CHD, and 0.8 (95% CI, 0.09–1.5) for stroke.<sup>67</sup>
  - The prevalence of CVD in patients with ESKD differs by treatment modality. Approximately 77.3% of patients with ESKD 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>68</sup> Albuminuria was associated with higher prevalence of AF and percent time in AF and nonsustained VT.
  - Among patients with CKD, the presence of diabetes had less of an effect on hospitalization rate than did presence of CVD. For example, compared with beneficiaries with stage 3 CKD who had neither diabetes nor CVD, the adjusted hospitalization rate was  $\approx$ 30% higher among beneficiaries with diabetes (but not CVD) but was  $\approx$ 160% higher among beneficiaries with CVD (but not diabetes). The rate was 280% higher among individuals with both diabetes and CVD.<sup>1</sup>
  - Rates of hospitalizations for cardiovascular causes were stable from 2013 to 2019 and then decreased substantially in 2020 (Chart 12-11).
  - During 2018 to 2020, the 2-year adjusted survival probability after a first hospitalization for various cardiovascular conditions was lower among beneficiaries with CKD than for those without CKD and worse among those with more advanced CKD (Chart 12-12).

### **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 PY) for HF, 24.5 versus 8.4 for CHD, and 13.4 versus 4.8 for stroke.<sup>67</sup>

- Both eGFR and albuminuria appear to predict HF events (improvement in C statistic of 0.0258) more strongly than CHD or stroke events.<sup>58</sup>
- In a meta-analysis of patients with CKD, the prevalence of PH was 23% and was associated with increased risk of CVD (RR, 1.67 [95% CI, 1.07–2.60]) and mortality (RR, 1.44 [95% CI, 1.17–1.76]).<sup>69</sup>
- Among Medicare beneficiaries with CKD, presence of PH was associated with an increased risk of mortality after 1 year (HR, 2.87 [95% CI, 2.79–2.95]), 2 to 3 years (HR, 1.56 [95% CI, 1.51–1.61]), and 4 to 5 years (HR, 1.47 [95% CI, 1.40–1.53]) of follow-up and a higher risk of all-cause, cardiovascular, and noncardiovascular hospitalization during the same period.
- Despite having higher overall event rates than NH White people, NH Black people with CKD have similar (or possibly lower) rates of ASCVD events (HR, 1.08 [95% CI, 0.87–1.34]), HF events (HR, 1.05 [95% CI, 0.83–1.32]), or composite of HF or death (HR, 0.96 [95% CI, 0.80–1.14]) after adjustment for demographic factors, baseline kidney function, and cardiovascular risk factors.<sup>70</sup> However, the risk of HF associated with CKD might be greater for Black people (HR, 1.59 [95% CI, 1.29–1.95]) than for White people.<sup>67</sup>
- Clinically significant bradyarrhythmias (event rate, 3.90 [95% CI, 1.04–14.63] per patient-month) appear to be more common than ventricular arrhythmias (event rate, 0.00 [95% CI, 0.00–0.02] per patient-month) among patients on hemodialysis and are highest in the immediate hours before dialysis sessions.<sup>71</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>72</sup>

### **CKD-Specific Risk Factors for CVD**

- In a study of 906 participants with CKD and hypertension, patients with ambulatory BP above goal, the risk of cardiovascular events was greater in the absence (HR, 2.79 [95% CI, 1.64–4.75]) and presence (HR, 2.05 [95% CI, 1.10–3.84]) of nocturnal dipping.<sup>73</sup> Patients at the ambulatory BP goal but who did not experience nocturnal dipping had an increased risk of the cardiovascular end point (HR, 2.06 [95% CI, 1.15–3.68]).
- In a study of 57 health care centers, lower eGFR was very strongly associated with increased prevalence of anemia. The prevalence of severe anemia (hemoglobin <10 g/dL) in men was 1.3%, 3.1%,

7.5%, 17.4%, and 29.7% across eGFR categories of 60 to 74, 45 to 59, 30 to 44, 15 to 29, and <15 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>, respectively.<sup>74</sup> Although iron studies were checked infrequently in patients with anemia, low iron test results were highly prevalent in those tested: 60.4% and 81.3% of male and female, respectively. Erythropoietin-stimulating agent use was uncommon with a prevalence of use of <4%. Lower hemoglobin was independently associated with poor clinical outcomes. For example, hemoglobin <9 g/dL was associated with higher rates of CVD (HR, 2.09 [95% CI, 1.00–2.17] in men and HR, 1.93 [95% CI, 1.87–2.00] in women).

- 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>75</sup>
- A study found significant associations of fibroblast growth factor-23 with both HFpEF (HR, 1.41 [95% CI, 1.21–1.64] per 1-SD increase in the natural log of fibroblast growth factor-23) and HFrEF (HR, 1.27 [95% CI, 1.05–1.53] per 1-SD increase in the natural log of fibroblast growth factor-23) in patients with CKD.<sup>76</sup>
- A study showed a significant association between severity of CKD and coronary flow reserve (adjusted  $\beta=0.016$ ;  $P=0.045$ ). Both CKD (HR, 2.6 [95% CI, 1.5–4.5]) and depressed coronary flow reserve (HR, 3.2 [95% CI, 2.0–5.2]) showed an independent association with higher risk of cardiac death or hospitalization for HF.<sup>77</sup>
- In the German diabetes dialysis study (4D), 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>78</sup>
- In a secondary analysis of the STABILITY trial, elevated interleukin-6 level ( $\geq 2.0$  ng/L versus <2.0 ng/L) was associated with increased risk of major atherosclerotic cardiovascular events across kidney function strata: normal kidney function (HR, 1.35 [95% CI, 1.02–1.78]), mild CKD (HR, 1.57 [95% CI, 1.35–1.83]), and moderate to severe CKD (HR, 1.60 [95% CI, 1.28–1.99]).<sup>79</sup>
- A proteomic risk model, which consisted of 32 proteins, was superior to both the 2013 ACC/AHA PCE and a modified PCE that included eGFR (C statistics were 0.84 and 0.89 for the protein models compared with 0.70 and 0.73 for the clinical models).<sup>80</sup>
- Lipoprotein(a) was not associated with the risk for recurrent ASCVD events [HR, 1.04 (95% CI, 0.95–1.15) per 1-SD increase in lipoprotein(a)] in adults

with CKD, although it was associated with a risk for kidney failure [HR, 1.16 (95% CI, 1.04–1.28) per 1-SD increase in lipoprotein(a)].<sup>81</sup>

### CVD as a Risk Factor for CKD and ESKD

- In an analysis of >25 million individuals, prevalent and incident CVDs were associated with subsequent kidney failure with replacement therapy with aHRs of 3.1 (95% CI, 2.9–3.3), 2.0 (95% CI, 1.9–2.1), 4.5 (95% CI, 4.2–4.9), and 2.8 (95% CI, 2.7–3.1) after incident CHD, stroke, HF, and AF, respectively.<sup>82</sup>
- A study of participants from the CRIC with CKD also demonstrated a 2- to 3-fold higher risk of ESKD after HF hospitalizations.<sup>83</sup>

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

#### Medication Use

- According to NHANES data, the percentage of adults with CKD taking statins increased from 17.6% in 1999 to 2002 to 35.7% in 2011 to 2014. However, there was no difference in statin use for those with versus without CKD (RR, 1.01 [95% CI, 0.96–1.08]).<sup>84</sup>
- Among veterans with diabetes and CKD, the proportion receiving an ACE inhibitor/ARB was 66% (95% CI, 62%–69%) in 2013 to 2014.<sup>85,86</sup>
- In NHANES 1999 to 2014, 34.9% of adults with CKD used an ACE inhibitor/ARB. The use of ACE inhibitors/ARBs increased in the early 2000s among adults with CKD but plateaued subsequently.<sup>85</sup>
- Among Medicare beneficiaries with CKD, in 2019, 54.4% of patients with CKD were on β-blockers and 64.3% were on lipid-powering agents.<sup>9</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>87</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>88</sup>
- In a post hoc analysis of the TIPS-3 trial, which randomized people without previous CVD to aspirin (75 mg daily) or placebo, aspirin reduced risk of cardiovascular events in patients with moderate to advanced CKD (HR, 0.57 [95% CI, 0.34–0.94]).<sup>89</sup>
- A trial of 90 patients with CKD did not support the use of sodium bicarbonate for vascular dysfunction in participants with CKD and normal serum bicarbonate levels. After 1 month of treatment with sodium bicarbonate, flow-mediated dilation

increased significantly from baseline ( $3.99 \pm 4.8$  versus  $6.39 \pm 7.3$ ;  $P=0.003$ ).<sup>90</sup>

- In a target trial emulation of statin initiation in US veterans >65 years of age with CKD stages 3 to 4 and no prior ASCVD, statin initiation was significantly associated with a lower risk of all-cause mortality (HR, 0.91 [95% CI, 0.85–0.97]) but not MACEs (HR, 0.96 [95% CI, 0.91–1.02]).<sup>91</sup>
- In 115 000 adults with newly diagnosed AF, CKD severity was associated with lower receipt of rate control agents, anticoagulation, and AF procedures. For example, patients with eGFR 15 to 29 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> had lower adjusted use of rate control agents (aHR, 0.61 [95% CI, 0.56–0.67]), warfarin (aHR, 0.89 [95% CI, 0.84–0.94]), DOACs (aHR, 0.23 [95% CI, 0.19–0.27]), and AF-related procedures (aHR, 0.73 [95% CI, 0.61–0.88]) compared with patients with eGFR >60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>.<sup>92</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>93</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>94</sup> In the RENAL-AF trial of 154 patients undergoing hemodialysis, there was inadequate power to draw any conclusion about rates of major or clinically relevant nonmajor bleeding comparing apixaban and warfarin in patients with AF and ESKD on hemodialysis.<sup>95</sup> Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism among this population on anticoagulation, highlighting the need for future randomized studies evaluating the risks versus benefits of anticoagulation among patients with AF and ESKD on hemodialysis.
- In a randomized trial of 97 patients comparing apixaban and vitamin K antagonist in patients with AF on hemodialysis (median follow-up time, 462 days [253–702 days]), no differences were observed in safety or efficacy outcomes. Composite primary safety outcome events occurred in 22 patients (45.8%) on apixaban and in 25 patients (51.0%) on vitamin K antagonist (HR, 0.93 [95% CI, 0.53–1.65];  $P_{\text{noninferiority}}=0.157$ ). Composite primary efficacy outcome events occurred in 10 patients (20.8%) on apixaban and in 15 patients (30.6%) on vitamin K antagonist ( $P=0.51$ , log rank). There

were no significant differences in individual outcomes (all-cause mortality, 18.8% versus 24.5%; major bleeding, 10.4% versus 12.2%; and MI, 4.2% versus 6.1%, respectively).<sup>96</sup>

- SGLT-2 inhibitor (dapagliflozin) use reduced the risk of a composite of a sustained decline in eGFR of at least 50%, ESKD, or death attributable to renal and cardiovascular causes among those with diabetes and nondiabetic CKD.<sup>97</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 0.61 [95% CI, 0.47–0.79] in the secondary prevention group).
- A prespecified analysis showed that baseline kidney function did not modify the benefit of dapagliflozin in patients with HF and a mildly reduced or preserved EF. The effect of dapagliflozin on the primary outcome was not affected by baseline eGFR category (eGFR  $\geq$ 60 mL·min $^{-1}$ ·1.73 m $^{-2}$ : HR, 0.84 [95% CI, 0.70–1.00]; eGFR 45–<60 mL·min $^{-1}$ ·1.73 m $^{-2}$ : HR, 0.68 [95% CI, 0.54–0.87]; eGFR <45 mL·min $^{-1}$ ·1.73 m $^{-2}$ : HR, 0.93 [95% CI, 0.76–1.14];  $P_{\text{interaction}}=0.16$ ). Over a median follow-up of 2.3 years (IQR, 1.7–2.8 years), the overall incidence rate of the kidney composite outcome was low (1.1 events per 100 patient-years) and was not influenced by treatment with dapagliflozin (HR, 1.08 [95% CI, 0.79–1.49]). However, dapagliflozin attenuated the decline in eGFR from baseline (difference, 0.5 mL·min $^{-1}$ ·1.73 m $^{-2}$  per year [95% CI, 0.1–0.9];  $P=0.01$ ) and from month 1 to month 36 (difference, 1.4 mL·min $^{-1}$ ·1.73 m $^{-2}$  per year [95% CI, 1.0–1.8];  $P<0.001$ ).<sup>98</sup>
- Similarly, another trial examining another SGLT-2 inhibitor (empagliflozin) enrolled both individuals with CKD with diabetes and those with CKD without diabetes ( $n=6609$ ) and reported a 28% reduction (HR, 0.72 [95% CI, 0.64–0.82]) in the progression of kidney disease or death resulting from cardiovascular causes compared with placebo.<sup>99</sup>
- In an individual patient-level meta-analysis of 6 trials including 49 875 participants that studied 4 different SGLT-2 inhibitors, there was a 16% reduced risk of serious hyperkalemia (HR, 0.84 [95% CI, 0.76–0.93]).<sup>100</sup>
- In an RCT of 7437 individuals with stage 3 to 4 CKD and type 2 diabetes, a novel mineralocorticoid receptor antagonist (finerenone) 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>101</sup>
- In a secondary analysis of the FIDELIO-DKD trial enrolling patients with CKD and type 2 diabetes, finerenone use was associated with lower incidence of new-onset AF (HR, 0.71 [95% CI, 0.53–0.94]).<sup>102</sup>

- In a systematic review of clinical trials of interventions to attenuate vascular calcification in people with CKD, magnesium and sodium thiosulfate consistently showed attenuation of vascular calcification. Studies examining intestinal phosphate binders, alterations in dialysate calcium concentration, vitamin K therapy, calcimimetics, and antiresorptive agents had conflicting or inconclusive outcomes. On the other hand, trials involving vitamin D therapy and HMG-CoA reductase inhibitors did not demonstrate attenuation of vascular calcification.<sup>103</sup>

#### *Cardiovascular Procedures and Devices in CKD*

- In a study of 17 910 patients undergoing angiography for stable IHD in Alberta, Canada, those with ESKD (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>104</sup>
- Among patients who underwent TAVR in the PARTNER trial, CKD stage either improved or was unchanged after the procedure.<sup>105</sup>
- In intermediate-risk patients with aortic stenosis and CKD, SAPIEN 3 TAVR and SAVR were associated with a similar risk of reaching the composite primary outcome of death, stroke, rehospitalization, and new hemodialysis after a 5-year follow-up.<sup>106</sup>
- Among patients who underwent lower-extremity bypass surgery in the USRDS 2006 to 2011, females with ESKD were less likely than males with ESKD to receive an autogenous vein graft (55% versus 61%;  $P<0.001$ ). Among those who received a prosthetic graft, acute graft failure was higher for females (HR, 1.23 [95% CI, 1.03–1.46]).<sup>107</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>108</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 $^{-1}$ ·1.73 m $^{-2}$  or receiving dialysis) and moderate or severe myocardial ischemia reported similar rates of death or nonfatal MI (estimated 3-year event rate, 36.4% versus 36.7%; aHR, 1.01 [95% CI, 0.79–1.29]).<sup>109</sup>
- A study of the NIS from 2009 to 2018 found that a consistent downward trend in the percentage of ICD implantation across all 3 subgroups by

CKD status was also observed: no CKD (4.4% in 2009 versus 1.2% in 2018), CKD (2.6% in 2009 versus 1.0% in 2018), and ESKD (2.1% in 2009 versus 0.6% in 2018). From 2009 to 2018, there was a significant increase in the trend of adjusted in-hospital mortality in overall patients undergoing ICD implantation (0.83% in 2009, 1.21% in 2018;  $P=0.02$ ). However, no significant trend was seen in adjusted in-hospital mortality in individual subgroups of no CKD ( $P=0.35$ ), CKD ( $P=0.21$ ), and ESKD ( $P=0.16$ ) over the course of the study period.<sup>110</sup>

### Lifestyle Interventions

- 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>111</sup>
- A randomized clinical trial enrolling 160 patients with stage 3 or 4 CKD noted that both  $V_{O_2}$ peak and METs increased significantly in the lifestyle intervention group by 9.7% and 30%, respectively, without change in the usual care group during a 3-year lifestyle intervention program.<sup>112</sup>
- A study of CKD participants found that greater ultraprocessed food intake was associated with higher risk of CKD progression (tertile 3 versus tertile 1: HR, 1.22 [95% CI, 1.04–1.42];  $P_{\text{trend}}=0.01$ ).<sup>113</sup>

### Cardiovascular Hospitalization and Mortality Attributable to CVD Among People With CKD (See Chart 12-13)

- 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 Services 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>114</sup>
- Data from the prospective CRIC study demonstrated that the crude rate of HF admissions was 5.8 per 100 PY among those with CKD. The rates of both HF hospitalizations and rehospitalization were even higher across categories of lower eGFR and higher urine ACR (Chart 12-13).<sup>83</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 (HR, 1.21 [95% CI, 1.08–1.36]), HF (HR, 1.43 [95% CI, 1.22–1.67]), all-cause mortality (HR, 1.23 [95% CI, 1.13–1.34]), and cardiovascular death (HR, 1.55 [95% CI, 1.29–1.87]) in the FHS after accounting for clinical cardiovascular risk factors.<sup>115</sup>
  - The stronger associations observed with outcomes (relative to creatinine or creatinine-based eGFR) might be explained in part by non-glomerular filtration rate determinants of cystatin C such as chronic inflammation.<sup>116</sup>

### Footnote

A portion of the data reported here have been supplied by the USRDS.<sup>9</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.

**Table 12-1. Global Mortality and Prevalence of CKD, by Sex, 2021**

	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), 2021	1.53 (1.39 to 1.64)	673.72 (629.10 to 722.36)	0.79 (0.72 to 0.86)	314.95 (293.39 to 338.12)	0.73 (0.65 to 0.80)	358.78 (335.68 to 383.64)
Percent change (%) in total number, 1990–2021	176.41 (144.32 to 197.02)	91.96 (89.58 to 94.71)	172.41 (126.11 to 205.89)	93.48 (90.97 to 96.23)	180.88 (147.91 to 209.62)	90.65 (88.23 to 93.53)
Percent change (%) in total number, 2010–2021	44.29 (35.20 to 51.41)	27.33 (26.32 to 28.31)	43.20 (30.21 to 53.32)	27.12 (26.01 to 28.11)	45.49 (35.48 to 54.61)	27.51 (26.54 to 28.58)
Rate per 100 000, age standardized, 2021	18.50 (16.72 to 19.85)	8006.00 (7482.12 to 8575.62)	21.91 (19.66 to 23.60)	7808.96 (7288.71 to 8366.60)	15.90 (14.22 to 17.27)	8182.65 (7653.14 to 8764.76)
Percent change (%) in rate, age standardized, 1990–2021	24.53 (10.18 to 33.52)	-0.83 (-1.89 to 0.07)	20.88 (-0.37 to 34.22)	-0.05 (-1.03 to 0.86)	25.76 (11.86 to 38.20)	-1.33 (-2.47 to -0.37)
Percent change (%) in rate, age standardized, 2010–2021	5.39 (-1.15 to 10.43)	1.49 (0.98 to 2.02)	4.10 (-5.08 to 10.86)	1.43 (0.90 to 1.97)	6.07 (-0.96 to 12.62)	1.59 (1.07 to 2.20)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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; GBD, Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>54</sup>

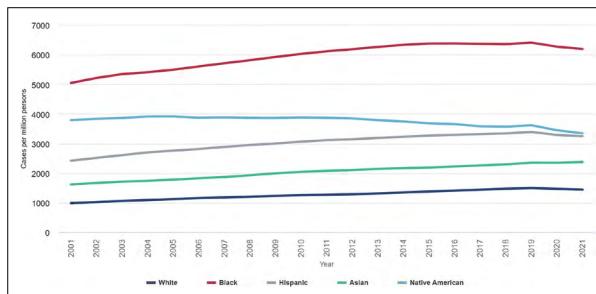
eGFR Categories	A1: Normal to mildly increased (ACR <30 mg/g)	A2: Moderately increased (ACR 30–299 mg/g)	A3: Severely increased (ACR ≥300 mg/g)	Total
G1: Normal or high (eGFR ≥90 ml/min/1.73m <sup>2</sup> )	59.8	5.0	0.68	65.5
G2: Mildly decreased (eGFR 60–89 ml/min/1.73m <sup>2</sup> )	26.2	2.4	0.35	28.9
G3a: Mildly to moderately decreased (eGFR 45–59 ml/min/1.73m <sup>2</sup> )	3.1	0.79	0.12	4.0
G3b: Moderately to severely decreased (eGFR 30–44 ml/min/1.73m <sup>2</sup> )	0.61	0.32	0.18	1.1
G4: Severely decreased (eGFR 15–29 ml/min/1.73m <sup>2</sup> )	0.07	0.08	0.18	0.34
G5: Kidney failure (eGFR <15 ml/min/1.73m <sup>2</sup> )	0.00	0.02	0.13	0.15
Total	89.8	8.6	1.6	100

**Chart 12-1. Percentage of NHANES participants within the KDIGO CKD risk categories defined by eGFR and ACR, United States, 2017 to 2020.**

Green indicates low risk; yellow, moderately high risk; orange, high risk; and 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.

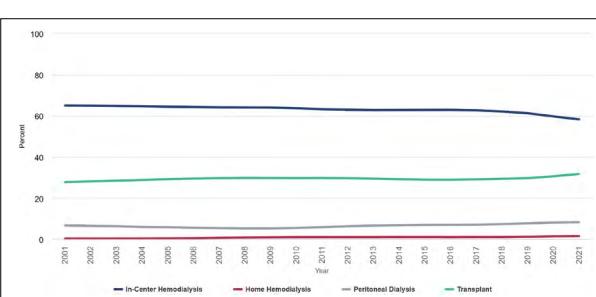
Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 1, Table 1.1,<sup>1</sup> using NHANES.<sup>117</sup>

**Chart 12-2. ESKD prevalence, by racial group, United States, 2000 to 2021.**

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

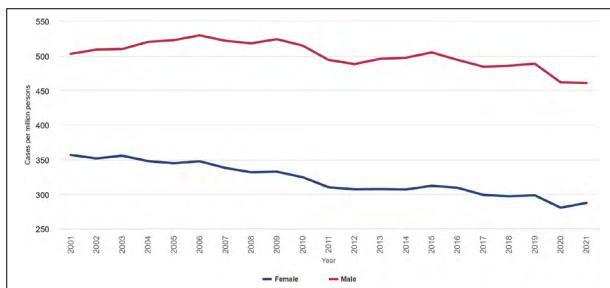
ESKD indicates end-stage renal disease.

Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 2, Figure 1.8.<sup>1</sup>

**Chart 12-3. Prevalent ESKD, by modality, United States, 2000 to 2021.**

ESKD indicates end-stage renal disease.

Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 2, Figure 1.6.<sup>1</sup>

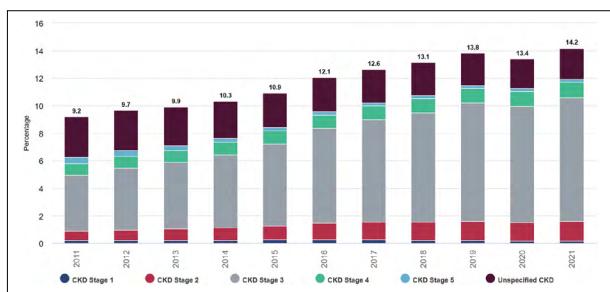


**Chart 12-4. ESKD incidence, by sex, United States, 2000 to 2021.**

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

ESKD indicates end-stage renal disease.

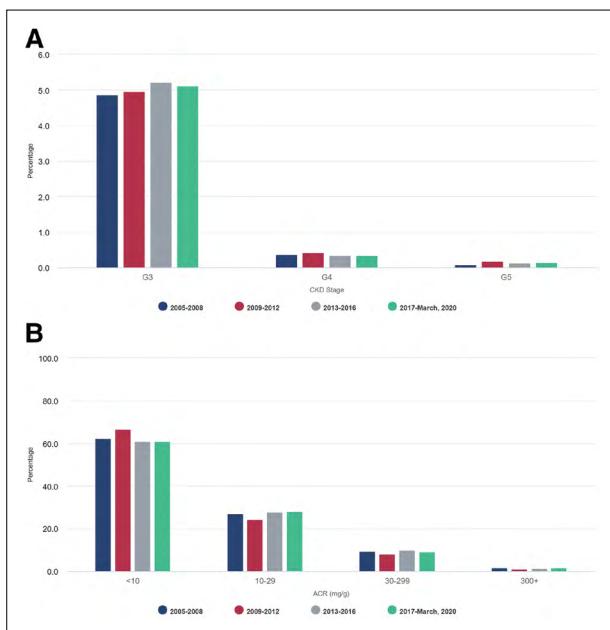
Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 2, Figure 1.4.<sup>1</sup>



**Chart 12-5. Prevalence of CKD, overall and by CKD category, among Medicare beneficiaries ≥66 years of age, United States, 2011 to 2021.**

CKD indicates chronic kidney disease.

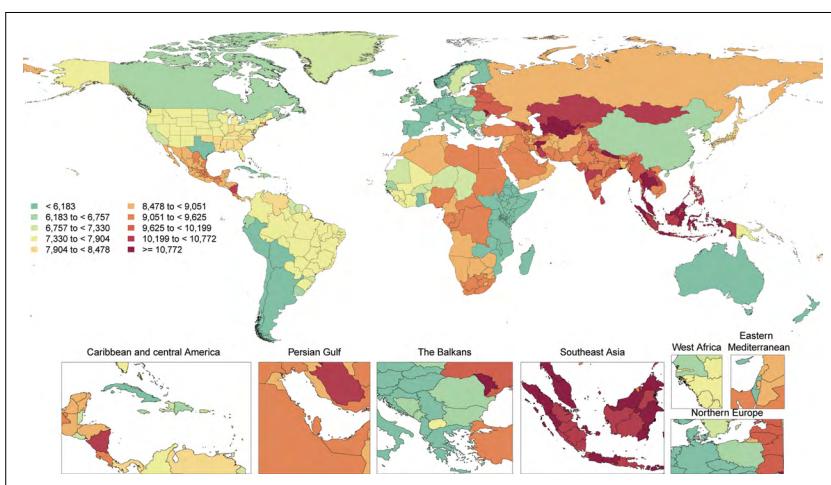
Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 1, Figure 2.1.<sup>1</sup>



**Chart 12-6. Prevalence of reduced eGFR by stage, United States, 2005 to 2020.**

**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; CKD, chronic kidney disease; and eGFR, glomerular filtration rate.

Source: Reprinted from 2023 United States Renal Data System Annual Data Report, volume 1, Figures 1.3 and 1.4,<sup>1</sup> using National Health and Nutrition Examination Survey.<sup>117</sup>

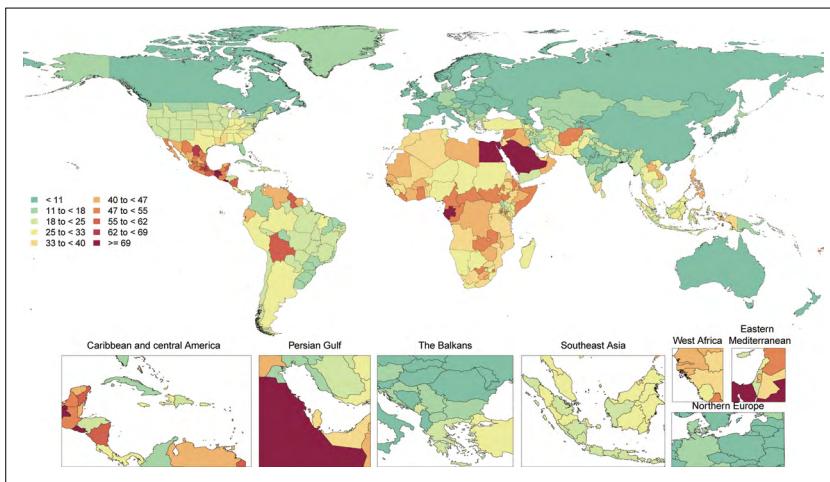


**Chart 12-7. Age-standardized global prevalence rates for CKD per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

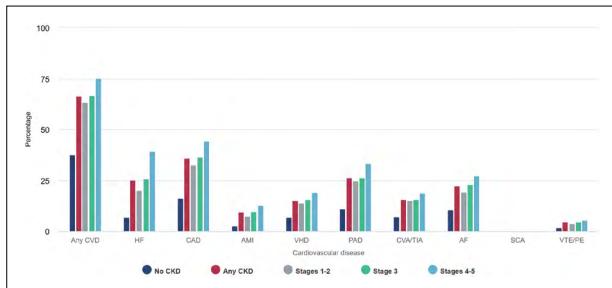
Source: Data courtesy of the GBD Study, Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>54</sup>

**Chart 12-8. Age-standardized global mortality rates for CKD per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

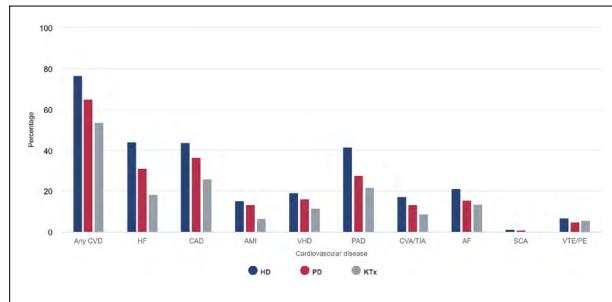
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>54</sup>

**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.

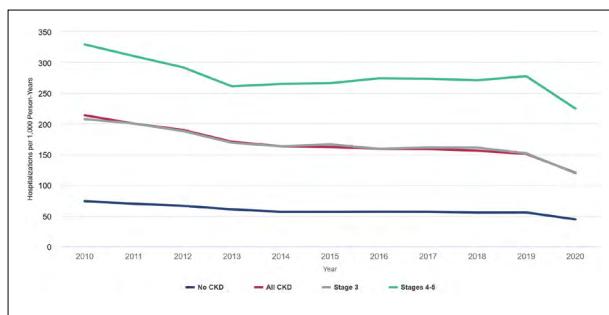
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; HF, heart failure; PAD, peripheral artery disease; PE, pulmonary embolism; SCA, sudden cardiac arrest; TIA, transient 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>118</sup>

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

AF indicates atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; CVA, cerebrovascular accident; CVD, cardiovascular disease; ESKD, 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.

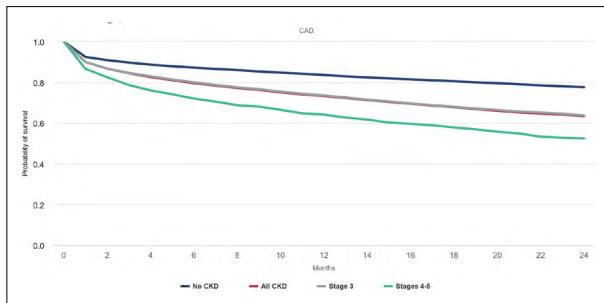
Source: Reprinted from 2020 United States Renal Data System Annual Data Report, volume 2, Figure 8.1.<sup>118</sup>



**Chart 12-11. Rate of hospitalization for CVD in older US adults, 2010 to 2020.**

CKD indicates chronic kidney disease; and CVD, cardiovascular disease.

Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 1, Figure 3.9.<sup>9</sup>



**Chart 12-12. Survival probability in older US adults after hospital admission for a CVD, by CKD status and stage, 2018 to 2020.**

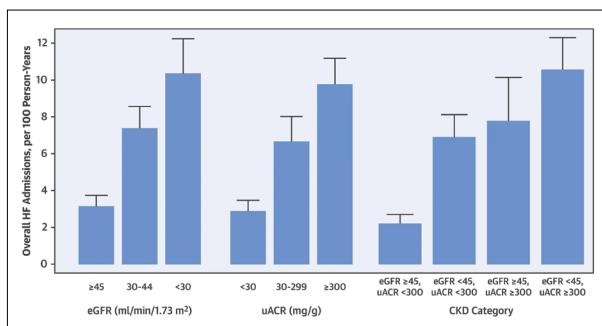
Older adults: ≥66 years of age.

CAD indicates coronary artery disease; CKD, chronic kidney disease; and CVD, cardiovascular disease.

Source: Reprinted from 2022 United States Renal Data System Annual Data Report, volume 1, Figure 3.10.<sup>9</sup>

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**Chart 12-13. 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>83</sup> Copyright © 2019, with permission from the American College of Cardiology Foundation.

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## 13. SLEEP

**See Charts 13-1 through 13-4**

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In 2022, the AHA added sleep duration as an eighth metric of cardiometabolic health, elevating AHA's Life's Simple 7 to Life's Essential 8.<sup>1</sup> Sleep duration is 1 component of sleep health, a construct that goes beyond the absence of a sleep disorder (eg, insomnia or OSA). Sleep health refers to regularity, satisfaction, alertness, timing, efficiency, and duration of sleep<sup>2</sup> that have been identified by the AASM to be essential to overall health.<sup>3</sup> Sleep quality is frequently assessed with the Pittsburgh Sleep Quality Index, for which a score  $>5$  is considered poor quality.<sup>4</sup> The composite score of sleep health is assessed with a 7-day sleep diary and questionnaire and defined by 6 components: (1) regularity (midpoint of sleep deviating by  $\leq 1$  hour), (2) satisfaction (rating fair or very good to the question related to satisfaction with sleep), (3) alertness (score  $\leq 7.5$  on a sleepiness scale), (4) timing (average midpoint of sleep between 2 and 4 AM), (5) efficiency (average  $\geq 85\%$ ), and (6) duration (average total sleep duration within recommendations for age group).<sup>5</sup>

The AASM and the Sleep Research Society recommend that adults obtain  $\geq 7$  hours of sleep per night to promote optimal health.<sup>6</sup> Sleeping  $>9$  hours may be appropriate for some individuals (eg, younger individuals or ill adults), but for others, it is unclear whether this much sleep is associated with health benefits or health risks. The AASM also published guidelines for pediatric populations on a 24-hour scale: 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>7</sup> Unless otherwise noted, throughout this chapter, short sleep refers to  $<7$  hours of sleep per night for adults and less than the minimum recommended daily hours of sleep for age for children; long sleep refers to  $>9$  h/night for adults and more than the upper range of recommended duration for children.

The 2025 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 2025. 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.

SDB represents upper airway dysfunction and is characterized by snoring or increased resistance to airflow with or without partial or total occlusion of the airways. SDB encompasses loud snoring, OSA, and central apneas. OSA is the most common type of SDB and is categorized by the frequency of complete and incomplete occlusion of airways during sleep (apneas and hypopneas, respectively) that results in reduced oxygen saturation and arousals or awakenings at night. The 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) and diagnosed with overnight polysomnography or home sleep test.

Insomnia is characterized by 3 symptoms assessed by questionnaire: difficulty initiating sleep, difficulty maintaining sleep, and early morning awakening. Adults with insomnia report dissatisfaction with their sleep, feeling unrefreshed on awakening, and experiencing sleep difficulties despite having adequate opportunity for sleep. Acute insomnia may occur over a short period of time and resolve on its own, whereas chronic insomnia is characterized by the persistence of symptoms occurring at least 3 times/wk for  $\geq 3$  months. It is important to note that insomnia may or may not be accompanied by short sleep duration, and these phenotypes may confer different degrees of cardiovascular risk.

### Prevalence

#### Adults

**(See Charts 13-1 through 13-3)**

- Data from NHANES 2017 to 2020, completed before the COVID-19 pandemic, showed that adults  $\geq 20$  years of age had shorter sleep duration on workdays (7.6 hours [95% CI, 7.5–7.6]) compared with free days (8.2 hours [95% CI, 8.2–8.3]).<sup>8</sup> Overall, 23.1% (95% CI, 21.3%–24.9%) of adults had short sleep on workdays compared with 12.9% (95% CI, 11.6%–14.1%) on free days, and 19.7% (95% CI, 18.5%–21.0%) of adults had long sleep on workdays compared with 38.5% (95% CI, 36.7%–40.3%) on free days. Females reported 7.7 hours of sleep (95% CI, 7.7–7.8) on workdays and 8.4 hours (95% CI, 8.3–8.5) on free days compared with 7.4 hours (95% CI, 7.4–7.5) and 8.1 hours (95% CI, 8.0–8.2) of sleep for males on workdays and free days, respectively. Sleep debt, the difference between sleep duration on workdays and free days, was 0.73 hours (95% CI, 0.68–0.77). On average, 30.5% of adults had  $\geq 1$ -hour sleep debt (95% CI, 26.8%–33.3%) and 9.75% had  $\geq 2$  hours sleep debt (high sleep debt; 95% CI, 8.65%–10.8%). Prevalence of high sleep debt was greater in younger adults, NH Black adults, full-time workers, and regular shift workers.

- Analysis of BRFSS 2022 data indicates that the proportion of adults reporting short sleep (<7 hours) was lowest among older adults (>65 years of age) with 29.5% of females and 26.5% of males in this older age group reporting <7 hours of sleep per night (Chart 13-1).<sup>9</sup>
- The prevalence of short sleep differs by disability status such as difficulty in hearing, vision, cognition, or mobility or any difficulty in self-care and independent living. According to BRFSS 2016 data, 43.8% of adults with at least 1 disability reported insufficient sleep compared with 31.6% of adults with no disability.<sup>10</sup> Compared with having no disability, having an increasing number of disabilities was associated with a higher likelihood of reporting short sleep 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.
- In adulthood, insomnia symptoms were least frequent in adults 26 to 40 years of age and most frequent in adults >65 years of age.<sup>11</sup> 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. 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.
- The NHIS 2022 asked respondents, "During the past 30 days, how often did you wake up feeling well rested?" Results indicated that females reported never or some of the days more frequently than males for all age groups (unpublished tabulation using NHIS<sup>12</sup>; Chart 13-2).
- The NHIS 2022 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?" Females more often reported having any sleep problem on most or all days than males for all age groups (unpublished tabulation using NHIS<sup>12</sup>; Chart 13-3).
- Data from NHANES 2017 to 2020 showed that trouble sleeping was more prevalent in older adults, females, NH White adults, and unemployed individuals.<sup>8</sup> Daytime sleepiness was more prevalent among younger adults, females, NH White adults, people who were unemployed, and people with lower income.

### **Children/Adolescents**

- According to parental report in the 2020 to 2021 National Survey of Children's Health, 34.4% of children 4 months to 17 years of age slept less than

recommended for their age. Prevalence of short sleep duration was 36.8% (95% CI, 35.5%–38.1%) in infants and children 4 months to 5 years of age, 35.2% (95% CI, 33.9%–36.5%) for children 6 to 11 years of age, and 31.6% (95% CI, 30.4%–32.8%) for adolescents 12 to 17 years of age.<sup>13</sup>

- In the Penn State Child Cohort, children were followed up from childhood to adolescence to young adulthood.<sup>14</sup> Insomnia symptoms were present in 23.9% of NH White children, 22.4% of Black children, and 24.3% of Hispanic children. Black children compared with NH White children had higher risk of childhood-onset persistent insomnia through young adulthood (OR, 2.58 [95% CI, 1.29–5.14]).

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

- Older adults, but not middle-aged adults, are less likely to report short sleep than younger adults. The RR of reporting short sleep in adults ≥65 years of age relative to those 20 to 44 years of age in NHANES 2005 to 2016 was 0.81 (95% CI, 0.75–0.87).<sup>15</sup> In middle-aged adults 45 to 64 years of age, the RR was 1.02 (95% CI, 0.97–1.08). Middle-aged adults had lower risk of reporting long sleep (RR, 0.80 [95% CI, 0.71–0.90]), whereas older adults had greater risk of reporting long sleep (RR, 1.41 [95% CI, 1.25–1.59]).

### **Risk Factors**

- A meta-analysis evaluated the association of socio-economic indicators and sleep, measured with actigraphy, from studies performed in the United States, Europe, Asia, and Canada.<sup>16</sup> Higher income and educational levels were associated with longer sleep duration ( $r=0.18$  [95% CI, 0.13–0.24] and  $r=0.12$  [95% CI, 0.04–0.21], respectively) and better sleep efficiency ( $r=0.15$  [95% CI, 0.05–0.24] and  $r=0.15$  [95% CI, 0.07–0.23], respectively).
- According to NHANES 2017 to 2020 data, the odds of reporting trouble sleeping were higher in adults 40 to 59 years of age (OR, 1.62 [95% CI, 1.37–1.92]) and 60 to 74 years of age (OR, 1.44 [95% CI, 1.21–1.71]) compared with adults 20 to 39 years of age.<sup>8</sup> Males had lower odds than females (OR, 0.80 [95% CI, 0.68–0.93]). Hispanic adults and NH Black adults had lower odds than NH White adults (Hispanic adults: OR, 0.64 [95% CI, 0.50–0.81]; NH Black adults: OR, 0.64 [95% CI, 0.53–0.76]).
- Data from the MESA showed that greater AHI score was associated with obesity (+19 events/h per 11 kg/m<sup>2</sup>), male sex (+13 events/h versus female sex), older age (+7 events/h per 20 years of age), and Chinese ancestry (+5 events/h versus White ancestry, adjusted for obesity).<sup>17</sup>

- Data from the Ardakan cohort study on aging (N=5197) in Iran showed that 76.4% of community-dwelling adults ≥50 years of age had poor sleep quality measured with the Pittsburgh Sleep Quality Index.<sup>18</sup> Male sex (aOR, 0.55 [95% CI, 0.46–0.66]), being married (OR, 0.41 [95% CI, 0.30–0.54]), having a college education (aOR, 0.73 [95% CI, 0.59–0.92]), working (aOR, 0.67 [95% CI, 0.57–0.80]), living with others (OR, 0.40 [95% CI, 0.28–0.58]), and having good (aOR, 0.60 [95% CI, 0.51–0.70]) or extremely good (aOR, 0.39 [95% CI, 0.28–0.53]) self-rated health were associated with lower odds of poor sleep quality. Having a financial level categorized as low (aOR, 1.24 [95% CI, 1.03–1.48]) or lowest (aOR, 1.27 [95% CI, 1.03–1.58]), respiratory diseases (OR, 1.64 [95% CI, 1.22–2.21]), CVD (aOR, 1.17 [95% CI, 1.01–1.35]), musculoskeletal disease (aOR, 1.47 [95% CI, 1.23–1.75]), and borderline anxiety (aOR, 3.36 [95% CI, 2.42–4.59]) was associated with higher odds of poor sleep quality.
- NHANES 2005 to 2014 data in 22 471 adults showed that the prevalence of sleep disorders increased from 7.5% in 2005 to 2006 to 10.4% in 2013 to 2014. Having a higher HEI score, indicative of a higher diet quality, was associated with reduced risk of reporting a sleep disorder (optimal versus inadequate HEI score: aOR, 0.913 [95% CI, 0.912–0.915]). Higher intakes of greens and beans, total vegetables, and total protein foods and lower intakes of added sugars and saturated fats were the top 5 most important components, accounting for 85% of the weights for sleep disorders.<sup>19</sup>
- A study combining data from the Nurses' Health Study, Nurses' Health Study II, and HPFS evaluated the risk of developing OSA based on baseline dietary patterns.<sup>20</sup> Over up to 18 years of follow-up, 8856 individuals developed OSA. Risk of OSA was lower in those in the highest quintile of AHEI scores compared with those in the lowest quintile (HR, 0.76 [95% CI, 0.71–0.82]). This was no longer significant after adjustment for BMI, waist circumference, and history of diabetes and hypertension. Risk of OSA was higher in those in the highest quintile of Empirical Dietary Inflammatory Pattern scores compared with those in the lowest quintile (HR, 1.94 [95% CI, 1.81–2.08]). This remained significant after adjustment for BMI, waist circumference, and history of diabetes and hypertension (HR, 1.31 [95% CI, 1.22–1.41]).
- In a community cohort of females, higher Mediterranean diet score was associated with better sleep quality ( $\beta=-0.31$  [SE, 0.08]), better sleep efficiency ( $\beta=-0.31$  [SE, 0.08]), and fewer sleep disturbances ( $\beta=-0.31$  [SE, 0.08]) on the Pittsburgh Sleep Quality Index after 1 year.<sup>21</sup>

## Social Determinants/Health Equity

### Race and Ethnicity and Sleep (See Chart 13-4)

- According to parental report in the 2020 to 2021 National Survey of Children's Health, among children 4 months to 17 years of age, 38.1% (95% CI, 36.2%–40.1%) of Hispanic children and 51.2% (95% CI, 49.1%–53.4%) of NH Black children slept less than recommended for their age compared with 28.4% (95% CI, 27.6%–29.1%) of NH White children.<sup>13</sup>
- 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>22</sup>
- In BRFSS 2022, NH Black adults had the highest percentage of respondents reporting sleeping <7 h/night for males and females (47.6% and 45.4%, respectively), whereas NH Asian adults (33.3% and 36.0%) and NH White adults (34.4% and 32.4%) had the lowest percentage of respondents reporting sleeping <7 hours (Chart 13-4).
- In 890 patients newly diagnosed with OSA, Black males had the most severe OSA (AHI score  $52.4\pm39.4$  events/h) compared with White males ( $39.0\pm28.9$  events/h), Black females ( $33.4\pm32.3$  events/h), and White females ( $26.2\pm23.8$  events/h).<sup>23</sup>
- In a sample of Black adults from the JHS, participants who expressed increasing everyday discrimination between examinations 1 and 3 (spanning 2000–2004 and 2008–2013) had worsening sleep quality ( $\beta=-0.13$  [SE, 0.06]) compared with those with stable low discrimination.<sup>24</sup> There was no association with self-reported sleep duration.

### Other Social Determinants of Sleep

- 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.<sup>25</sup> 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.

- 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 (young,  $r=-0.135$ ; middle-aged,  $r=-0.126$ ; older,  $r=-0.135$ ), daily minutes of television watching (young,  $r=-0.132$ ; middle-aged,  $r=-0.171$ ; older,  $r=-0.129$ ), social media use (young,  $r=-0.131$ ; middle-aged,  $r=-0.196$ ; older,  $r=-0.163$ ), and internet use (young,  $r=-0.152$ ; middle-aged,  $r=-0.233$ ; older,  $r=-0.093$ ) and lower regularity of lifestyle behaviors (young,  $r=-0.320$ ; middle-aged,  $r=-0.340$ ; older,  $r=-0.283$ ) were correlated with lower sleep health.<sup>26</sup> In young adults 18 to 34 years of age, number of pets ( $r=-0.063$ ) and daily reading minutes ( $r=-0.066$ ) were also inversely related to sleep health, whereas in middle-aged adults 35 to 54 years of age, higher daily minutes of reading ( $r=-0.111$ ) and lower moderate to vigorous PA ( $r=0.075$ ) were associated with poorer sleep health. In older adults  $\geq 55$  years of age, less time in moderate to vigorous PA ( $r=0.090$ ) and higher percent of sedentary time ( $r=-0.102$ ) were associated with poorer sleep health.

## Family History and Genetics

- Heritability estimates for sleep disorders, including OSA, are  $\approx 40\%$ .<sup>27</sup>
- A UK Biobank study ( $N=85670$ ) using accelerometer-derived measures of sleep and rest-activity patterns identified 47 loci across 8 sleep traits encompassing sleep duration, quality, and timing.<sup>28</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>29</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 (*HCRTR1*, *HCRTR2*). 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>30</sup>
- A GWAS of rapid eye movement sleep behavioral disorder, a more severe sleep subtype, identified 5 loci at or near *SNCA*, *GBA*, *TMEM175*, *INPP5F*, and *SCARB2* in 2 case-control GWASs ( $n$  cases=2843,  $n$  controls=139 636).<sup>31</sup> Colocalization analyses to examine whether lead variants at these 5 loci also are associated with brain or whole-blood gene expression found strong evidence of colocalization in the *SNCA* locus with *SNCA* antisense-1 expression in the brain.
- 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>32</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>33</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>34</sup>

- The genetic architecture of sleep shares commonalities with several psychiatric disorders and plasma proteins. In the UK Biobank, significant genetic correlations were noted between a sleep health score composed of measures of sleep duration, snoring, insomnia, chronotype, and daytime dozing with 4 psychiatric disorders (major depressive disorder, attention deficit/hyperactivity disorder, schizophrenia, and autism spectrum disorder) and 9 plasma proteins, including cytochrome c oxidase.<sup>35</sup> Elevated cytochrome c oxidase levels were associated with long-term sleep deprivation in rats.<sup>36</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/h), with OSA but no treatment (AHI>1 event/h), and with OSA with CPAP treatment.<sup>37</sup> 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 mmHg [25th–75th percentile, −19 to 0 mmHg]), whereas SBP increased in the untreated OSA group (median change, 4 mmHg [25th–75th percentile, 0–10 mmHg]). DBP did not differ between groups at baseline, nor did the 6-month change in DBP differ between groups.
- A meta-analysis of 8 RCTs examining patients with OSA (AHI≥5 events/h) randomized to either CPAP therapy or control (sham CPAP, pills, or no CPAP) for follow-up of 6 to 84 months did not reveal any reduction in the risk of major cerebrovascular and cardiovascular events (RR, 0.87 [95% CI, 0.70–1.10]),<sup>38</sup> MI (RR, 1.04 [95% CI, 0.79–1.37]), stroke (RR, 0.94 [95% CI, 0.71–1.26]), hospital admission for heart failure (RR, 0.92 [95% CI, 0.68–1.23]), new-onset AF (RR, 0.94 [95% CI, 0.54–1.64]), and cardiovascular mortality (RR, 0.94 [95% CI, 0.62–1.43]) were not influenced by CPAP treatment.

## Mortality

- A community-based prospective cohort study examined associations between sleep duration trajectories between 2006 and 2010 and mortality through 2017 in adults free of CVD and cancer.<sup>39</sup> Compared with those with normal stable sleep (defined as sleep duration 7–8 h/night for 4 years), risk of all-cause mortality was increased in those with normal-decreasing (HR, 1.34 [95% CI, 1.15–1.57]) and those with low-stable (HR, 1.50 [95% CI, 1.07–2.10]) sleep patterns.

- Data from the Southern Community Cohort Study revealed racial differences in associations between sleep duration and mortality in a predominantly low-income US population.<sup>40</sup> Sleeping <5 h/night versus 8 h/night was associated with increased all-cause mortality in NH White individuals (weekday: HR, 1.23 [95% CI, 1.04–1.46]; weekend: HR, 1.26 [95% CI, 1.06–1.51]) but not Black individuals (weekday: HR, 1.08 [95% CI, 0.97–1.20]; weekend: HR, 1.11 [95% CI, 1.00–1.24]). Similar findings were observed for long sleep. For NH White individuals but not Black individuals, sleeping ≥10 h/night versus 8 h/night was associated with higher risk of all-cause mortality (White individuals, weekday: HR, 1.23 [95% CI, 1.02–1.48]; weekend: HR, 1.25 [95% CI, 1.08–1.46]; Black individuals, weekday: HR, 1.14 [95% CI, 1.04–1.25]; weekend: HR, 1.08 [95% CI, 1.00–1.16]).

- A meta-analysis of 5 prospective studies of 116969 employed adults from 5 countries (England, The Netherlands, Scotland, United States, and South Korea) found that short sleep duration (cutoff varied by study, ranging between <6 and <7 h/night) was associated with increased all-cause mortality risk (RR, 1.16 [95% CI, 1.11–1.22]).<sup>41</sup> Long sleep duration (cutoff varied by study, ranging between ≥8 and >8 h/night) was also associated with increased risk of all-cause mortality (RR, 1.18 [95% CI, 1.12–1.23]) but with significant heterogeneity.
- The Japan Multi-Institutional Collaborative Cohort assessed sleep regularity using a single question, "Are your bedtimes and wake times regular?"<sup>42</sup> In adults 35 to 69 years of age, having irregular sleep increased the risk of all-cause mortality compared with having regular sleep (HR, 1.30 [95% CI, 1.18–1.44]). Data were significant in adults <60 years of age (HR, 1.36 [95% CI, 1.14–1.55]) and ≥60 years of age (HR, 1.15 [95% CI, 1.00–1.31]) and in males (HR, 1.31 [95% CI, 1.16–1.48]) but not females (HR, 1.06 [95% CI, 0.89–1.27]).
- Data from the MESA Sleep Ancillary study (N=2032) showed that participants with more irregular (sleep duration SD >120 minutes) compared with more regular (sleep duration SD ≤60 minutes) sleep duration were more likely to have high CAC burden (>300; PR, 1.33 [95% CI, 1.03–1.71]) and low ABI (<0.9; PR, 1.75 [95% CI, 1.03–2.95]) in fully adjusted models.<sup>43</sup>
- In the Sleep Heart Health Study, middle-aged to older adults were followed up for 11.8 years (IQR, 10.4–15.9 years).<sup>44</sup> Insomnia was not associated with all-cause mortality (crude model: HR, 1.06 [95% CI, 0.75–1.50]; fully adjusted model: HR, 1.11 [95% CI, 0.77–1.62]). Presence of OSA, defined as AHI ≥15 events/h, was associated with increased risk of all-cause mortality in crude (HR,

1.47 [95% CI, 1.30–1.65]) but not fully adjusted (HR, 1.01 [95% CI, 0.89–1.15]) models. Presence of co-occurring insomnia and OSA was associated with risk of all-cause mortality in crude (HR, 1.77 [95% CI, 1.29–2.42]) and fully adjusted (HR, 1.47 [95% CI, 1.06–2.04]) models. Similar findings for co-occurring insomnia and OSA were observed in the Wisconsin Sleep Cohort.<sup>45</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>46</sup>
- In the PURE study, which included participants 35 to 70 years of age from 21 countries, risk of mortality was increased in those sleeping ≤6 h/d (HR, 1.09 [95% CI, 0.99–1.20]), 8 to 9 h/d (HR, 1.05 [95% CI, 0.99–1.12]), 9 to 10 h/d (HR, 1.17 [95% CI, 1.09–1.25]), and ≥10 h/d (HR, 1.41 [95% CI, 1.30–1.53]) compared with those sleeping 6 to 8 h/d in fully adjusted models.<sup>47</sup>
- Data from the 2020 Canadian Community Health Survey revealed that adults who met recommended sleep duration had 1.24 years (95% CI, 0.87–1.61) longer life expectancy at 20 years of age than those with short sleep and 2.56 years (95% CI, 1.97–3.12) longer life expectancy than those with long sleep.<sup>48</sup>

## Complications

### Sleep Duration

- A meta-analysis examined sleep duration and total CVD (26 articles), CHD (22 articles), and stroke (16 articles).<sup>49</sup> 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]).
- 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>50</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 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 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.<sup>51</sup> 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.
- Analysis of the UK Biobank study (N=468941) found that participants who reported short sleep or long sleep had an increased risk of incident HF compared with adequate sleepers.<sup>52</sup> In males, the aHR was 1.24 (95% CI, 1.08–1.42) for short sleep and 2.48 (95% CI, 1.91–3.23) for long sleep. In females, the aHR was 1.39 (95% CI, 1.17–1.65) for short sleep and 1.99 (95% CI, 1.34–2.95) for long sleep.
- A prospective, population-based cohort study in China enrolled 52599 Chinese adults 18 to 98 years of age and examined self-reported sleep duration trajectories over 4 years.<sup>53</sup> 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>53</sup>

- The association between daytime napping and CHD was evaluated in a meta-analysis of 5 prospective and 3 cross-sectional studies.<sup>53</sup> After adjustment for nighttime sleep duration and other confounders, the pooled RR of CHD was 1.30 (95% CI, 1.06–1.60). Each 15-minute increase in daytime napping was associated with 5% higher risk of CHD (RR, 1.05 [95% CI, 1.02–1.08]) with high heterogeneity.
- In the Rush Memory and Aging Project, daytime napping in older adults ( $81.4 \pm 7.5$  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>54</sup>
- In MESA, adding short sleep duration to Life's Simple 7 score improved the prediction of incident CVD. Those in the highest versus lowest tertile of Life's Simple 7 had 38% lower risk of developing CVD (HR, 0.62 [95% CI, 0.37–1.04]).<sup>55</sup> When adequate sleep duration was added to the score, those in the highest tertile had 43% lower risk of incident CVD (HR, 0.57 [95% CI, 0.33–0.97]).
- Data from NHANES 2005 to 2014 showed that having high CVH, assessed with the AHA's Life's Essential 8, which includes sleep duration, was associated with lower all-cause (HR, 0.60 [95% CI, 0.48–0.90]) and cardiovascular (HR, 0.46 [95% CI, 0.31–0.68]) mortality.<sup>56</sup> Meeting ideal sleep health metrics was associated with reduced all-cause (HR, 0.97 [95% CI, 0.95–0.99]) but not cardiovascular (HR, 0.97 [95% CI, 0.93–1.00]) mortality.

### **Restful Sleep and Sleepiness**

- Medical records from patients in Japan (N=1980476) were examined to determine whether restful sleep was associated with incident CVD over an average of 1122 days ( $\approx 3$  years).<sup>57</sup> 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").
- 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>58</sup>
- A meta-analysis combined data from 17 prospective cohort studies with a total of 153909 participants to examine the association between 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 cardiovascular 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 cardiovascular mortality (RR, 1.47 [95% CI, 1.09–1.98]) compared with no excessive daytime sleepiness.<sup>59</sup>

- Data from the MIDUS study examined the association of a composite sleep health measure (regularity, satisfaction, alertness, timing, efficiency, 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>60</sup>

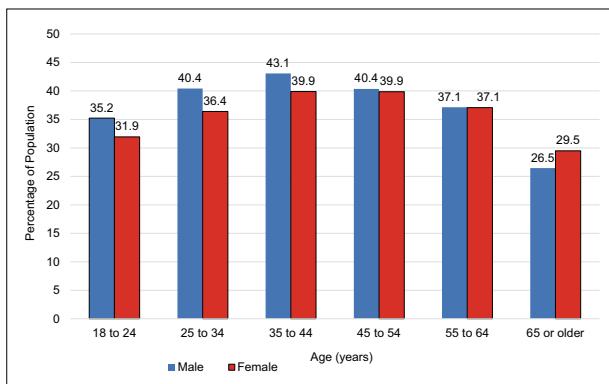
### **Obstructive Sleep Apnea**

- In the JHS 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>61</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  $\leq 60$  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>62</sup>
- A meta-analysis of 32 observational studies indicated higher odds of having WMHs in those with mild (OR, 1.70 [95% CI, 0.9–3.6]), moderate to severe (OR, 3.9 [95% CI, 2.7–5.5]), and severe (OR, 4.3 [95% CI, 1.9–9.6]) OSA.<sup>63</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>64</sup>

### Insomnia

- In 14 cohort studies with a mean follow-up of 10.8 years, risk of hypertension was increased in adults with insomnia (RR, 1.21 [95% CI, 1.10–1.33]) with high heterogeneity.<sup>65</sup>
- Trajectories of sleep quality were evaluated over a median 19.15 years of follow-up in SWAN participants (n=2964) 42 to 52 years of age at baseline.<sup>66</sup> Females with trajectories characterized by persistently high insomnia symptoms had higher risk of CVD (HR, 1.71 [95% CI, 1.19–2.46]) compared with females with persistently low insomnia symptoms trajectories. Compared with females with low insomnia symptoms and moderate or moderate to long sleep duration, females with high insomnia symptoms and short sleep duration (HR, 1.70 [95% CI, 1.06–2.72]) or high insomnia symptoms and moderate or moderate to long sleep duration (OR, 1.75 [95% CI, 1.03–2.98]) had higher risk of CVD.
- 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



**Chart 13-1. Prevalence of reporting sleep duration <7 h/night in US adults, by sex and age, 2022.**

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>9</sup>

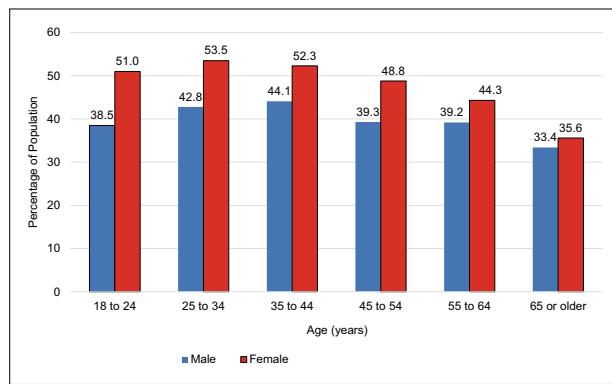
symptoms and CVD. Patients with nonrestful sleep, difficulty initiating sleep, and difficulty maintaining sleep had 16% (HR, 1.16 [95% CI, 1.07–1.24]), 22% (HR, 1.22 [95% CI, 1.06–1.40]), and 14% (HR, 1.14 [95% CI, 1.02–1.27]) higher risk of CVD, respectively, compared with those without. Having any insomnia complaint was associated with 13% higher risk (HR, 1.13 [95% CI, 1.08–1.19]).<sup>67</sup>

### Cost

- Analysis of data from the 2018 MEPS among a nationally representative US sample estimated that the direct health care costs of sleep disorders is approximately \$94.9 billion per year.<sup>68</sup> Individuals with sleep disorders have almost twice the number of office visits, 1.4 times the number of emergency visits, and 1.8 times the number of prescription fills as those without sleep disorders.

### Global Burden

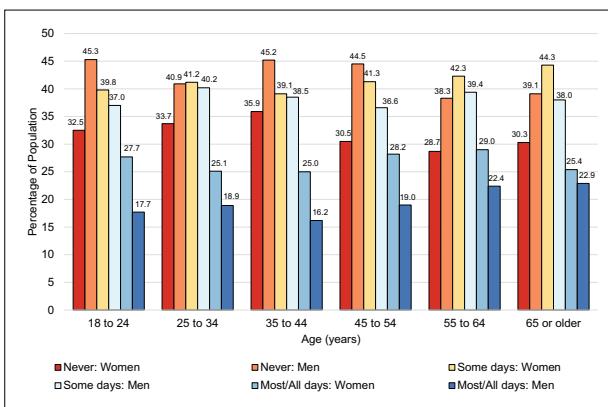
- An analysis of the global prevalence and burden of OSA estimated that 936 (95% CI, 903–970) million males and females 30 to 69 years of age have mild to severe OSA and 425 (95% CI, 399–450) million have moderate to severe OSA globally.<sup>69</sup>



**Chart 13-2. Prevalence of reporting being well rested never or some days, by sex and age, 2022.**

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?"

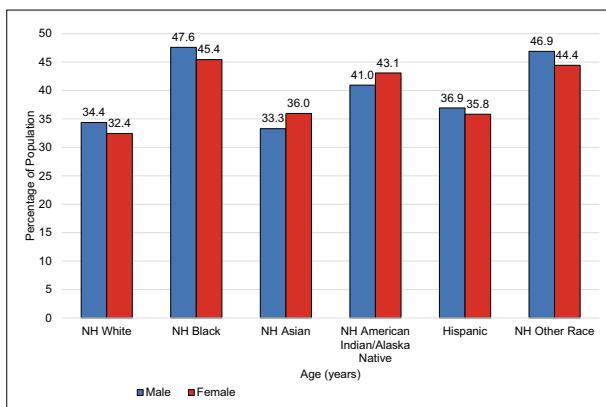
Source: Unpublished tabulation using National Health Interview Survey.<sup>12</sup>



**Chart 13-3. Prevalence of reporting difficulty falling asleep or maintaining sleep never, some, or most/all days in US adults, by sex and age, 2022.**

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>12</sup>



**Chart 13-4. Prevalence of reporting sleep duration <7 h/night in US adults, by sex and race, 2022.**

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>9</sup>

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## 14. TOTAL CARDIOVASCULAR DISEASES

**ICD-9 390 to 459; ICD-10 I00 to I99. See Tables 14-1 through 14-4 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  $\geq 20$  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 individuals, 10.0% among NH Black individuals, 8.2% among Hispanic individuals, 7.7% among Asian individuals, 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,

The 2025 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 2025. 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.

30.5%; and stroke, 4.7%. 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 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  $\geq 40$  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 PY.<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

- In a 20-year follow-up of the ATTICA study (2002–2022) with 1988 participants (50% male,  $45 \pm 14$  years of age), 718 experienced a fatal or nonfatal CVD event (crude incidence, 36.1%; males, 40.2%, females, 32.1%;  $P < 0.001$ ).<sup>5</sup> Lifetime risk is the estimation of the cumulative risk of developing a certain disease during an individual's remaining life span. Lifetime CVD risk was similar for males and females ( $P = 0.245$ ), with a progressive decline from 68% and 63% at 40 years of age to 56% and 50% at age 50 years of age and 55% for both at 60 years of age, respectively. In an external validation study of the QRiskLifetime incident CVD risk prediction tool using Clinical Practice Research Datalink data ( $n = 1\,260\,329$  females and  $n = 1\,223\,265$  males), discrimination was excellent (Harrell C statistic, 0.844 in females, 0.808 in males) but moderate to poor when stratified by age group (Harrell C statistic in people 30 to 44 years of age, 0.714 for both; 75 to 84 years of age, 0.578 in females, 0.556 in males).<sup>6</sup> QRiskLifetime underpredicted 10-year CVD risk in all age groups except females 45 to 64 years of age with worse underprediction in older age groups. Adults with the highest lifetime risk were

younger (mean, 50.5 years of age for females and 46.3 years of age for males) compared with those with the highest 10-year risk (mean, 71.3 years of age for females and 63.8 years of age for males). The Cardiovascular Lifetime Risk Pooling Project estimated the long-term risks of CVD among 30 447 participants with a mean of 55.0 years of age (SD, 13.9 years) from 7 US cohort studies.<sup>7</sup> After 538 477 PY 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 ≥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 ≥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.

- The remaining lifetime risk for ASCVD among predominantly White participants from the FHS in 3 epochs (epoch 1, 1960–1979; epoch 2, 1980–1999; epoch 3, 2000–2018) was examined.<sup>8</sup> Life expectancy increased by 10.1 years among males and 11.9 years among females across the 3 epochs. Furthermore, the remaining lifetime risk of ASCVD from 45 years of age reduced from 43.7% in epoch 1 to 28.1% in epoch 3 ( $P<0.0001$ ) in both sexes and across BMI, BP, diabetes, cholesterol, smoking, and FRS strata ( $P<0.001$  for all).

## Secular Trends

- 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 PY 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>9</sup> However, incidence rates of hypertension per 1000 PY increased significantly.

## Risk Factors

- During up to 30 years of follow-up in a prospective study of 210 240 participants in the Nurses' Health Study, those with a higher Portfolio Diet Score (plant protein, nuts, viscous fiber, phytosterols, and plant monounsaturated fats) had a lower risk of total CVD (pooled HR, quintile 5 versus 1, 0.86 [95% CI, 0.81–0.92]) after multivariable adjustment.<sup>10</sup> A 25% higher Portfolio Diet Score was associated with a lower risk of total CVD (pooled HR, 0.92 [95% CI, 0.89–0.95]).
- In a cross-sectional study of 13 965 US adults without CVD from NHANES 2005–2018, 26.6% were current marijuana users.<sup>11</sup> After adjustment for sociodemographic and lifestyle factors using inverse probability of treatment weighting, there were no significant differences between current and never users in the burden of mean 10-year ASCVD risk scores (2.8% versus 3.0%;  $P=0.49$ ), 30-year FRSs (22.7% versus 24.2%;  $P=0.25$ ), and various cardiometabolic biomarkers.
- A prospective study assessed the association between ultraprocessed food consumption and CVD risk in 26 369 participants from the Swedish Malmö Diet and Cancer Study.<sup>12</sup>
  - Over a median follow-up of 24.6 years, 6236 participants developed CVD. The aHR in the fourth versus first quartile of ultraprocessed food intake was 1.18 (95% CI, 1.08–1.29) for CVD, 1.20 (95% CI, 1.07–1.35) for CHD, and 1.17 (95% CI, 1.03–1.32) for ischemic stroke.
- In a prospective cohort study of 156 787 postmenopausal females ≥40 years of age from the UK Biobank followed up for a median of 12.5 years, the cumulative incidence of cardiovascular morbidity and mortality was 1.2% (0.97 cases per 1000 women-years).<sup>13</sup> Not having taken oral contraception (aHR, 1.24 [95% CI, 1.10–1.40]), not having children (aHR, 1.22 [95% CI, 1.04–1.44]), and early menarche (11–12 years: aHR, 1.24 [95% CI, 1.05–1.47]; ≤10 years: aHR, 1.33 [95% CI, 1.02–1.74]) were independently associated with cardiovascular morbidity and mortality.
- In a prospective cohort study of 16 031 females ≥62 years of age from the WHS, higher levels of accelerometer-measured total PA and moderate to vigorous PA were associated with a lower risk of CVD and ischemic stroke over a mean follow-up of 7.1 years.<sup>14</sup> Females in the highest quartile of total volume of PA (total average daily vector magnitude) and moderate to vigorous PA (>120 minutes) had a 43% (95% CI, 24%–58%) and 38% (95% CI, 18%–54%) lower hazard of total CVD, respectively, compared with those in the lowest quartile. Females who spent <7.4 hours sedentary per day had a 33%

(95% CI, 11%–49%) lower hazard of total CVD compared with those who spent ≥9.5 hours sedentary. Replacing 10 minutes of sedentary behavior with moderate to vigorous PA was associated with a 4% lower incidence of total CVD (HR, 0.96 [95% CI, 0.93–0.99]).

- In a meta-analysis of 13 cohort studies (844 175 participants; 115 392 CVD, 30 377 IHD, and 14 419 stroke events), vegetarians had a lower risk of CVD (RR, 0.85 [95% CI, 0.79–0.92];  $P=68\%$ ) and IHD (RR, 0.79 [95% CI, 0.71–0.88];  $P=67\%$ ) compared with nonvegetarians. Vegans had a marginally lower risk of IHD (RR, 0.82 [95% CI, 0.68–1.00];  $P=0\%$ ) compared with nonvegetarians.
- Among 1252 participants from the Dallas Heart Study, CAC scores and hepatic steatosis prevalence were higher in those with type 2 diabetes.<sup>15</sup> CAC was associated with ASCVD events regardless of type 2 diabetes status ( $P_{\text{interaction}}=0.02$ ). Hepatic triglyceride content was inversely associated with ASCVD risk in participants with type 2 diabetes (HR, 0.91 [95% CI, 0.83–0.99] per 1% increase in hepatic triglyceride content;  $P=0.02$ ,  $P_{\text{interaction}}=0.02$ ).
- Among 42 711 adults from the NHANES, including 5015 adults with CVD, magnesium depletion scores were calculated from diuretic use, proton pump inhibitor use, eGFR, and heavy drinking.<sup>16</sup> Individuals with magnesium depletion scores of ≥3 had higher odds of total CVD compared with those with magnesium depletion scores of 0 (aHR, 2.27 [95% CI, 1.38–3.72]).<sup>16</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 PY.<sup>17</sup> Females hospitalized for bulimia nervosa had a higher incidence of CVD (10.34 [95% CI, 7.77–13.76] per 1000 PY) than females hospitalized for pregnancy-related events (1.02 [95% CI, 0.99–1.06] per 1000 PY). 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 PY 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 PY]) than females with migraine without aura or no migraine (2.11 [95% CI, 1.98–2.24]).<sup>18</sup>
- Air pollution, as defined by increased ambient exposure to particulate matter (particles with median

aerodynamic diameter <2.5  $\mu\text{m}$ ), 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. According to data from HeartScore, a community-based cohort of adults residing in western Pennsylvania with exposure to ambient fine particulate (PM2.5) and black carbon, mean PM2.5 exposure among Black individuals was  $16.1 \pm 0.75 \mu\text{g}/\text{m}^3$  versus  $15.7 \pm 0.73 \mu\text{g}/\text{m}^3$  in White individuals ( $P=0.0001$ ). Black carbon exposure among Black individuals was  $1.19 \pm 0.11 \mu\text{g}/\text{m}^3$ , and mean black carbon exposure among White individuals was  $1.16 \pm 0.13 \mu\text{g}/\text{m}^3$  ( $P=0.0001$ ). Mediation analysis demonstrated that 24% of the association between race and the composite outcome of CVD deaths and nonfatal CVD events was mediated by exposure to PM2.5 and that the association between race and composite clinical outcome was no longer significant after adjustment for income and education.<sup>19</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 (PM1 [particles with aerodynamic diameter <1  $\mu\text{m}$ ], PM2.5, PM10 [particles with aerodynamic diameter <10  $\mu\text{m}$ ], 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 PM1, 9.1% (OR, 1.09 [95% CI, 1.08–1.10]) higher 10-year ASCVD risk for PM2.5, 4.6% (OR, 1.05 [95% CI, 1.04–1.05]) higher 10-year ASCVD risk for PM10, and 6.4% (OR, 1.06 [95% CI, 1.06–1.07]) higher 10-year ASCVD risk for NO<sub>2</sub> (all  $P<0.001$ ). However, PA attenuated the association between air pollution and 10-year ASCVD risk.<sup>20</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>21</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>22</sup> However, an increase in potassium intake may be beneficial in lowering BP levels, but excessive potassium supplementation should be avoided.<sup>23</sup>
- A prospective analysis of dietary patterns among adults in the Nurses' Health Study (1984–2016), Nurses' Health Study II (1991–2017), and HPFS (1986–2012) with 5 257 190 PY 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>24</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 (0.57 kg/m<sup>2</sup> [95% CI, 0.51–0.63]) and higher WC (0.57 cm [95% CI, 0.47–0.67]) compared with a low intake of unhealthy foods.<sup>25</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 youths who followed a healthier eating pattern (milk, yogurt, fruit, and vegetables with less sugar, beef/lamb/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>26</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>27</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>28</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 a 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>29</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>30</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>31</sup>
- Among 15 103 individuals with type 2 diabetes without CVD and with serum 25-hydroxyvitamin D measurements in the UK Biobank, there were 3534 incident CVD events over a median of 11.2 years of follow-up.<sup>32</sup> Participants with higher serum 25-hydroxyvitamin D concentrations had lower CVD risk. The multivariable-adjusted HRs across categories of serum 25-hydroxyvitamin D of <25.0, 25.0 to 49.9, 50.0 to 74.9, and ≥75.0 nmol/L were 1.00 (reference), 0.87 (95% CI, 0.80–0.96), 0.80 (95% CI, 0.72–0.88), and 0.75 (95% CI, 0.64–0.88) for total CVD events ( $P_{\text{trend}} < 0.001$ ).
- In a retrospective cohort study of medical records of females who had ≥1 singleton live births (N=2 359 386) from the National Health Service hospitals in England between 1997 and 2015, females who had prior gestational hypertension or prior preeclampsia had 1.45 (95% CI, 1.33–1.59) and 1.62 (95% CI, 1.48–1.78) higher adjusted hazards of total CVD, respectively, than those who were normotensive.<sup>33</sup>
- Among 103 388 adults in the web-based NutriNet-Santé cohort (mean, 42.2±14.4 years of age; 79.8% female; 904 206 PY), consuming artificial sweeteners from all dietary sources, including beverages, tabletop sweeteners, and dairy products, among others, was associated with 1.09 (95% CI, 1.01–1.18) higher CVD risk.<sup>34</sup> Similarly, among 109 043 females in the WHS, during an average of 17.4 years of follow-up, 11 597 CVD events occurred.<sup>35</sup> Higher intake of added sugar (≥15.0% energy intake daily) was positively associated with total CVD (HR, 1.08 [95% CI, 1.01–1.15]). Consuming ≥1 servings of SSBs or ASBs daily was associated with 1.29 ([95% CI, 1.17–1.42]) and (1.14 [95% CI, 1.03–1.26]) higher risk of total CVD, respectively. A prospective analysis of participants

in the International Cardiovascular Cohort evaluated whether 5 childhood cardiovascular risk factors (BMI, SBP, TC level, triglyceride level, and youth smoking) were associated with fatal or nonfatal CVD events in adulthood after an average follow-up of 35 years.<sup>36</sup> Each 1-unit increase in combined-risk z score (unweighted mean of the 5 risk scores) was associated with a 2.71 (95% CI, 2.23–3.29) and 2.75 (95% CI, 2.48–3.06) higher risk of a fatal or nonfatal CVD event, respectively. The HR for fatal CVD in adulthood ranged from 1.30 (95% CI, 1.14–1.47) per 1-unit increase in the z score for TC level to 1.61 (95% CI, 1.21–2.13) for youth smoking (yes versus no).

## Social Determinants of Health/Health Equity

- Data from 6 prospective cohort studies (1985–2015) with 40998 participants were analyzed to assess the association between education and lifetime CVD risk.<sup>37</sup> Compared with college graduates, those with less than high school or high school completion had higher lifetime CVD risks. For middle-aged men, the HRs for a CVD event were 1.58 (95% CI, 1.38–1.80), 1.30 (95% CI, 1.10–1.46), and 1.16 (95% CI, 1.00–1.34) for those with less than high school, high school, and some college, respectively. For females, the HRs were 1.70 (95% CI, 1.49–1.95), 1.19 (95% CI, 1.05–1.35), and 0.98 (95% CI, 0.83–1.15).
- In a cross-sectional analysis of 6424 adults with diabetes from the 2019 and 2020 NHIS, 13.3% were identified as food insecure.<sup>38</sup> Adults with food insecurity were more likely to have ASCVD than food-secure adults (28.9% versus 23.7%;  $P=0.008$ ). After adjustment for traditional CVD risk factors, all levels of food insecurity were associated with ASCVD compared with food security (marginal security: OR, 1.60 [95% CI, 1.18–2.18]; low security: OR, 2.09 [95% CI, 1.58–2.74]; very low security: OR, 1.69 [95% CI, 1.22–2.34];  $P=0.001$ ).
- According to data from a nationally representative sample of Canadian adults ( $N=289\,800$ ), lower socioeconomic position was associated with 2.5 times increased odds of CVD morbidity and mortality (OR, 2.52 [95% CI, 2.28–2.76]).<sup>39</sup> Modifiable risk factors, including smoking, physical inactivity, obesity, diabetes, and hypertension, mediated 74% of associations between socioeconomic position and CVD morbidity and mortality.
- 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>40</sup> A 30-percentile point reduction in neighborhood deprivation was associated with 11% and 19% reductions in total mortality among males and females, 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>41</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>42</sup>
- Among Black adults and White adults in the ARIC study, residence in the lowest quartile of neighborhood socioeconomic status during young, middle, and older adulthood was associated with 18% (HR, 1.18 [95% CI, 1.02–1.36]), 21% (HR, 1.21 [95% CI, 1.04–1.39]), and 12% (HR, 1.12 [95% CI, 0.99–1.26]) higher risk of total CVD, respectively, compared with residence in the highest quartile.<sup>43</sup>
- In a cross-sectional analysis of data on 387 044 adults in the 2016 to 2019 BRFSS, 9% had self-reported ASCVD (CHD or stroke).<sup>44</sup> Female sex, household income below \$75 000, unemployment, and challenges with health care access were significantly associated with a higher burden of comorbidities (hypertension, hyperlipidemia, diabetes, current cigarette smoking, and CKD) among those with ASCVD. An analysis using the CDC WONDER database to examine sex- and race-based differences in cardiovascular mortality from 1999 to 2019 determined that the age-adjusted mortality in Black females and White females declined over the observation years (from 602.1 and 447.0 per 100 000 population in 2009, respectively, to 351.8 and 267.5 per 100 000 population in 2019, respectively).<sup>45</sup> Cardiovascular mortality rates decreased for Black males from 824.1 in 1999 to 526.3 per 100 000 population in 2019 and in White males from 637.5 in 1999 to 396.0 per 100 000 population in 2019. The rate ratio for cardiovascular mortality in 2019 was 1.32 (95% CI, 1.30–1.33) for Black females and 1.33 (95% CI, 1.32–1.34) for Black males relative to their White counterparts.

## Psychological Health

- In a study of 853 participants from the ATTICA study (2002–2012), those with high irrational beliefs and anxiety symptoms had a 2.38 (95% CI, 1.75–3.23) higher risk of developing CVD during the 10-year follow-up compared with those without irrational beliefs and anxiety.<sup>46</sup> CRP, interleukin-6, and total antioxidant capacity were mediators in the association.
- A prospective analysis of females 65 to 99 years of age from the WHI Extension Study II who were free of MI, stroke, or CHD at baseline found that after adjustment for sociodemographic factors, health behaviors, and health status, social isolation and loneliness were associated with 1.08 (95% CI, 1.03–1.12) and 1.05 (95% CI, 1.01–1.09) higher risk of CVD, respectively.<sup>47</sup> Having high social isolation and high loneliness scores was associated with 1.13 (95% CI, 1.06–1.20) higher risk of CVD.
- In a cross-sectional analysis of data from the 2005 to 2018 NHANES among adults 20 to 39 years of age ( $n=10588$ ) and adults 40 to 79 years of age ( $n=16848$ ), depression, measured by the Patient Health Questionnaire-9, was significantly associated with 10-year ASCVD risk, measured by the PCE.<sup>48</sup> The 10-year ASCVD risk was higher among those with mild depression (6.9%) and major depression (7.6%) compared with those with no depression (6.0%) among females 40 to 79 years of age ( $P<0.001$ ). Similarly, among males 40 to 79 years of age, the 10-year ASCVD risk was higher among those with mild depression (11.1%) and major depression (11.3%) compared with those with no depression (9.9%;  $P<0.001$ ). Lifetime CVD risk was higher among males and females 20 to 39 years of age with mild depression or major depression compared with those with no depression ( $P<0.001$ ).
- In a cross-sectional analysis of electronic health record data of 591 257 adults who received primary care in Minnesota and Wisconsin between 2016 and 2018, those with a history of serious mental illness (bipolar disorder, schizophrenia, or schizoaffective disorder) had a higher 10-year FRS (mean, 9.44% [95% CI, 9.29%–9.60%]) than those without serious mental illness (mean, 7.99% [95% CI, 7.97%–8.02%]).<sup>49</sup> Likewise, 30-year CVD rate was significantly higher in those with serious mental illness (25% in the highest-risk group) compared with those without (11% in the highest-risk group;  $P<0.001$ ). In a follow-up study using the same dataset, patients with current depression had higher 10-year CVD risk ( $b=0.59$  [95% CI, 0.44–0.74]) and 30-year CVD risk (OR, 1.32 [95% CI, 1.26–1.39]) than those with controlled depression.<sup>50</sup> Those with

current depression also had higher 10-year CVD risk ( $b=0.55$  [95% CI, 0.37–0.73]) and 30-year CVD risk (OR, 1.56 [95% CI, 1.48–1.65]) than those without depression.

## Risk Prediction

- Among 6434 participants from the MESA, a social disadvantage score was created that was based on household income, educational attainment, single-living status, and experience of lifetime discrimination.<sup>51</sup> Over a median follow-up of 17.0 years, there were 775 incident ASCVD events and 1573 deaths. Increasing social disadvantage score was significantly associated with incident ASCVD (HR per 1-unit increase, 1.15 [95% CI, 1.07–1.24]) and all-cause mortality (HR per 1-unit increase, 1.13 [95% CI, 1.08–1.19]) after adjustment for traditional risk factors. However, adding the social disadvantage score to the PCE did not significantly improve discrimination ( $P=0.208$ ) or reclassification ( $P=0.112$ ) of 10-year ASCVD risk.
- In a cross-sectional study of 11 937 adults from NHANES 2003 to 2018, total TyG index, TyG-WC, TyG-waist-to-height ratio, and TyG-BMI were significantly and positively associated with CVD and CVD mortality.<sup>52</sup> TyG-waist-to-height ratio was the strongest predictor of CVD mortality (HR, 1.66 [95% CI, 1.21–2.29]). TyG index correlated most strongly with CHD risk (OR, 2.52 [95% CI, 1.66–3.83]), whereas TyG-WC correlated most strongly with total CVD (OR, 2.37 [95% CI, 1.77–3.17]), congestive HF (OR, 2.14 [95% CI, 1.31–3.51]), and AP (OR, 2.38 [95% CI, 1.43–3.97]). TyG-waist-to-height ratio correlated most strongly with MI (OR, 2.24 [95% CI, 1.45–3.44]).
- The DIAL2 was updated using data from 467 856 people with type 2 diabetes without a history of CVD from the Swedish National Diabetes Register.<sup>53</sup> The updated DIAL2 model was recalibrated for Europe's low- and moderate-risk regions and externally validated in 218 267 individuals with type 2 diabetes from the Scottish Care Information—Diabetes and Clinical Practice Research Datalink. The DIAL2 model demonstrated good discrimination, with C indices of 0.732 (95% CI, 0.726–0.739) in Clinical Practice Research Datalink and 0.700 (95% CI, 0.691–0.709) in Scottish Care Information—Diabetes, providing a useful tool for predicting CVD-free life expectancy and lifetime CVD risk for people with type 2 diabetes without previous CVD in the European low- and moderate-risk regions.
- The PREVENT equations are risk prediction tools that estimate the 10- and 30-year risk of total CVD, which includes both ASCVD and HF, in adults 30 to 79 years of age.<sup>54</sup> The base equation

includes age, sex, non-HDL-C, statin treatment, SBP, antihypertensive medication use, smoking status, diabetes, and eGFR and adjusts for the competing risk of non-CVD death. The PREVENT add-on equations offer additional models that include urine ACR and HbA1c, when clinically indicated for measurement, or social determinants of health, such as the Social Deprivation Index, when available. The PREVENT (base and add-on) model performance demonstrated excellent accuracy and precision in external validation for the composite of CVD (median C statistics ranging from 0.757–0.813; median calibration slopes ranging from 0.94–1.05).

- A validation study of the PREVENT equations among 6612004 US adults 30 to 79 years of age without known CVD observed that median C statistics for CVD were 0.794 (interquartile range, 0.763–0.809) in females and 0.757 (interquartile range, 0.727–0.778) in males.<sup>55</sup> The calibration slopes were 1.03 (interquartile range, 0.81–1.16) and 0.94 (interquartile range, 0.81–1.13) among females and males, respectively. Adding urine ACR, HbA1c, and Social Deprivation Index together to the base model slightly improved discrimination ( $\Delta$  C statistic, 0.004 [interquartile range, 0.004–0.005] and 0.005 [interquartile range, 0.004–0.007] among females and males, respectively). Calibration improved significantly when the urine ACR was added to the base model for those with marked albuminuria (>300 mg/g; 1.05 [interquartile range, 0.84–1.20] versus 1.39 [interquartile range, 1.14–1.65] in the base model without urine ACR;  $P=0.01$ ).
- 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 to 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>56</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=406834).<sup>57</sup>
- In an analysis of electronic health record data from 56 130 Asian individuals (Asian Indian, Chinese, Filipino, Vietnamese, Japanese, and other Asian) and 19 760 Hispanic individuals (Mexican, Puerto Rican, and other Hispanic) who received care in

Northern California between 2006 and 2015, the PCE overestimated ASCVD risk by 20% to 60%.<sup>58</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>59</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>60</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,  $LDL_{Martin}$  and  $LDL_{Sampson}$ , did not underestimate or overestimate ASCVD risk compared with the traditional  $LDL_{Friedewald}$  equation in primary prevention using AHA/ACC guidelines.<sup>61</sup> However, the  $LDL_{Friedewald}$  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>62</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, 147 645 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>63</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.
- Including a history of APO (placenta previa, preterm delivery, placenta abruption, stillbirth, abortion, pregnancy-induced hypertension/preeclampsia, gestational diabetes, and ectopic pregnancy) in the FRS enhanced the prediction of CVD among 4013 females in the Tehran Lipid and Glucose

Study compared with the original FRS that included traditional CVD risk factors (C statistic difference, 0.0053).<sup>64</sup> Females who had a history of multiple APOs had a higher CVD risk compared with those with 1 or no adverse pregnancy outcomes (1 APO: aHR, 1.22 [95% CI, 1.01–1.47]; 2 APOs: aHR, 1.94 [95% CI, 1.54–2.51]; ≥3 APOs: aHR, 2.48 [95% CI, 1.51–4.07]). Among 95 465 ever-gravid females who participated in the Nurses' Health Study, a history of pregnancy loss was associated with a higher risk for CVD (aHR, 1.21 [95% CI, 1.10–1.33]) over a mean follow-up of 23.10 years.<sup>65</sup>

## Borderline Risk Factors/Subclinical/Unrecognized Disease

- Among 2119 participants in the Framingham Offspring Cohort study, the aHR for CVD events among those with concurrent high central pulse pressure and high carotid-femoral PWV compared with those with concurrent low central pulse pressure and low carotid-femoral PWV was 1.52 (95% CI, 1.10–2.11).<sup>66</sup>
- Among 1005 patients with known CAD who had 2 CCTA 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>67</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>68</sup>
- Among individuals  $\geq 45$  years of age participating in the CORE-Thailand registry, having a low ABI <0.9 was associated with a 49% increased (OR, 1.49 [95% CI, 1.08–2.08]) risk of a decline in glomerular filtration rate >40%, eGFR <15 mL·min $^{-1}$ ·1.73 m $^{-2}$ , doubling of serum creatinine, or initiation of dialysis.<sup>69</sup>

## Genetics and Family History

- Genetic contributors to the end points that make up 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], and 25 [Peripheral Artery Disease and Aortic Diseases]).

- The performance of an ASCVD GRS for the prediction of ASCVD incidence has been evaluated.<sup>70</sup> In ancestrally diverse populations from the ARIC, MESA, and UK Biobank studies, improved prediction of ASCVD for White populations, African populations, and South Asian populations was demonstrated over the PCE when an ASCVD GRS was incorporated. NRI 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.

## Prevention

**(See Chapter 2 [Cardiovascular Health] for more detailed statistics on healthy lifestyle and low risk factor levels.)**

- Good adherence to CPAP use among adults with OSA is associated with an HR of 0.69 (95% CI, 0.52 with 0.92) compared to nonuse and poor adherence among adults with OSA for whom CPAP was recommended.<sup>71</sup>
- High adherence to a healthy reference diet, which emphasizes the intake of healthy foods, was associated with 14% and 12% lower risks of CVD ( $HR_{Q4\text{vs}Q1}$ , 0.86 [95% CI, 0.78–0.94]) and CHD ( $HR_{Q4\text{vs}Q1}$ , 0.88 [95% CI, 0.78–1.00]).<sup>72</sup>
- According to data from NHANES, REGARDS, and RCTs on BP-lowering treatments, it is estimated that achieving the 2017 ACC/AHA BP goals could prevent 3.0 (uncertainty range, 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 (uncertainty range, 2.2–4.4) million.<sup>73</sup>
- Comparison of 3 healthy eating patterns over a total 52-week period in youths 9 to 18 years of age with BMI  $>95$ th percentile, including the AHA, Mediterranean, and plant-based diets, identified significant differences in compliance and CVD risk factors.<sup>74</sup> The plant-based diet was associated with best compliance (81% for plant-based compared with 62% for AHA and 56% for Mediterranean;  $P<0.001$ ). 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.

- A meta-analysis of the CVD benefits of yoga therapy has demonstrated improvements in SBP and DBP (WMD,  $-4.56 \text{ mmHg}$  [95% CI,  $-6.37$  to  $-2.75$ ] and WMD,  $-3.39 \text{ mmHg}$  [95% CI,  $-5.01$  to  $-1.76$ ], respectively), BMI (WMD,  $-0.57 \text{ kg/m}^2$  [95% CI,  $-1.05$  to  $-0.10$ ]), HbA1c mmol/L (WMD,  $-0.14$  [95% CI,  $-0.24$  to  $-0.03$ ]), and LDL-C (WMD,  $-7.59 \text{ mg/dL}$  [95% CI,  $-12.23$  to  $-2.95$ ]).<sup>75</sup>

## Awareness, Treatment, and Control

- According to a systematic review and meta-analysis of the effects of  $\alpha$ -linolenic acid supplementation (flaxseed, walnuts, perilla) on CVD risk, among 1183 individuals, compared with placebo, dietary  $\alpha$ -linolenic acid supplementation significantly reduced CRP concentration (SMD,  $-0.38 \text{ mg/L}$  [95% CI,  $-0.72$  to  $-0.04$ ]), tumor necrosis factor- $\alpha$  concentration (SMD,  $-0.45 \text{ pg/mL}$  [95% CI,  $-0.73$  to  $-0.17$ ]), triglyceride in serum (SMD,  $-4.41 \text{ mg/dL}$  [95% CI,  $-5.99$  to  $-2.82$ ]), and SBP (SMD,  $-0.37 \text{ mmHg}$  [95% CI,  $-0.66$  to  $-0.08$ ]) but led to a significant increase in LDL-C concentrations (SMD,  $1.32 \text{ mg/dL}$  [95% CI,  $0.05$ – $2.59$ ]).<sup>76</sup>  $\alpha$ -Linolenic acid supplementation had no significant effect on interleukin-6, DBP, TC, or HDL-C (all  $P \geq 0.05$ ). Subgroup analysis revealed that  $\alpha$ -linolenic acid supplementation at a dose of  $\geq 3 \text{ g/d}$  from flaxseed and flaxseed oil had a more prominent effect on improving CVD risk profiles.
- Intensive lifestyle intervention may reduce long-term variability of fasting blood glucose, TC, and LDL-C according to a post hoc secondary analysis from the Look AHEAD study.<sup>77</sup> Intensive lifestyle intervention, 175 min/wk of supervised individual or group PA sessions among individuals 53 to 66 years of age, was associated with reduced variability of fasting blood glucose ( $\beta = -1.49$  [95% CI,  $-2.39$  to  $-0.59$ ]), TC ( $\beta = -1.12$  [95% CI,  $-1.75$  to  $-0.48$ ]), and LDL-C ( $\beta = -1.04$  [95% CI,  $-1.59$  to  $-0.49$ ]), as well as increased variability of SBP ( $\beta = 0.27$  [95% CI,  $0.00$ – $0.54$ ]). No significant effect of intensive lifestyle intervention was found on the variability of DBP ( $\beta = -0.08$  [95% CI,  $-0.22$  to  $0.05$ ]).
- 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>78</sup>

- Among 202072 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 compared with males varied by agent. The OR for treatment in females compared with males was 0.65 (95% CI, 0.69–0.72) for antiplatelet drugs, 0.93 (95% CI, 0.83–1.04) for  $\beta$ -blockers, 0.86 (95% CI, 0.77–0.96) for ACE inhibitors or ARBs, 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>79</sup>
- Among 284954 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 females and Black individuals, Hispanic individuals, and Asian individuals, statins were less likely to be prescribed or adhered to.<sup>80</sup>

## Mortality

(See Tables 14-1 through 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, declined into the 2010s, but increased again in the later 2010s to 2022.
- CHD (39.5%) was the leading cause of CVD death in the United States in 2022, followed by stroke (17.6%), other minor CVD causes combined (17.0%), HBP (14.0%), HF (9.3%), and diseases of the arteries (2.6%; Chart 14-4).
- In 2022, 941 652 US deaths were attributable to CVD (Table 14-1). The age-adjusted death rate

attributable to CVD did not change from 224.3 per 100 000 people in 2012 to 224.3 per 100 000 in 2022 (unpublished NHLBI tabulation using CDC WONDER<sup>81</sup>). The AAMRs for 2022 by sex, ethnicity, and race are available in Table 14-1.

- On the basis of 2022 mortality data (unpublished NHLBI tabulation using the NVSS<sup>82</sup>):
  - HD and stroke currently claim more lives each year than cancer and chronic lower respiratory disease combined. In 2022, 206.8 of 100 000 people died of HD and stroke.
  - In 2022, 3 279 857 resident deaths were registered in the United States, which is 184 374 fewer deaths than in 2021. Of all registered deaths, the 10 leading causes accounted for 72.3%. The 10 leading causes of death in 2022 were the same as those in 2021. From 2021 to 2022, 9 of the 10 leading causes of death had an decrease in age-adjusted death rates. The age-adjusted rate decreased 3.8% for HD, 2.9% for cancer, 1.1% for unintentional injuries, 57.3% for COVID-19, 3.9% for stroke, 1.2% for chronic lower respiratory diseases, 6.8% for AD, 5.1% for diabetes, and 4.8% for chronic liver disease and cirrhosis. The age-adjusted death rates increased 1.5% for kidney disease.<sup>83</sup>
- CHD accounted for 371 506 (39.5%) of the total 941 652 CVD deaths in 2022 (unpublished NHLBI tabulation using NVSS<sup>82</sup>).
- The number of CVD deaths for both sexes and by age categories 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 783 475 in 2011 to 941 652 in 2022 (Chart 14-9). Although the number of CVD deaths per year was greatest among females between 1984 and 2013, beginning in 2013, CVD deaths in males exceeded the number of CVD-related deaths in females.
- 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>84</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>85</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>86</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>87</sup>

## Health Care Use: Hospital Discharges/ Ambulatory Care Visits

### (See Chart 14-14)

- From 2011 to 2021, the number of inpatient discharges from short-stay hospitals with CVD as the principal diagnosis decreased from ≈5.2 million to 4.7 million. 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>88</sup>).
- From 1993 to 2021, the number of hospital discharges for CVD in the United States increased in the first decade and then began to generally decline in the second decade (Chart 14-14).
- In 2019, there were 106 381 000 physician office visits with a primary diagnosis of CVD (unpublished NHLBI tabulation using NAMCS<sup>89</sup>). In 2021, there were 6 867 805 ED visits and 4 741 970 hospital inpatient discharges with a primary diagnosis of CVD (unpublished NHLBI tabulation using HCUP<sup>88</sup>).

- Between 2008 and 2018, there has been a declining trend in hospitalization rates from 5.6 million to 5 million per year.<sup>90</sup> The recent decline in CVD hospitalization rates has been driven by a decline in CVD hospitalization rates among NH Black residents and Hispanic US residents.

## Cost

**(See Chapter 28 [Economic Cost of Cardiovascular Disease] for detailed information.)**

- The estimated direct and indirect cost of CVD for 2020 to 2021 was \$417.9 billion (MEPS,<sup>91</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>92</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 \$38985 with follow-up (12 months) costs of \$35260 per patient for patients with type 2 diabetes experiencing a CVD-related event (MI, TIA, stroke).
- According to microsimulations based on Markov modeling, underestimation of SBP is associated with higher health care costs of \$241300 per 1000 patients and 11.8 CVD events per 1000 individuals that might have been prevented if SBP had been measured appropriately.<sup>93</sup>

## Global Burden

**Table 14-1; Charts 14-10 through 14-13, 14-15, and 14-16; and Supplemental Material**

- According to an updated analysis of the GBD Study 1990 to 2019, the age-standardized rates of DALYs and death attributed to metabolic disease decreased by 28% (95% UI, 23.8%–32.5%) and 30.4% (95% UI, 26.6%–34.5%), respectively, from 1990 to 2019.<sup>94</sup> The age-standardized rate of DALYs for metabolic-attributed CVD was 3573.4 (95% UI, 3240.3–3870.5) per 100 000 population in 1990 and was 176.1 (95% UI, 156.2–192) per 100 000 population in 2019, a 30.4% (95% UI, 26.6%–34.5%) decline. In 2019, the Central Asia region showed the highest age-standardized rates of DALYs and deaths (8507.1 [95% UI, 7677.8–9386.5] and

454.0 [95% UI, 402.5–501.5]). In contrast, the high-income Asia Pacific region had the lowest age-standardized rate of DALYs and deaths (431.0 [95% UI, 384.8–7373.8] and 24.3 [95% UI, 20.0–171.5]), respectively. The country with the highest age-standardized rate of deaths was Uzbekistan (577.2 [95% UI, 485.7–662.8]) followed by Azerbaijan and Tajikistan, and the country with the lowest rate was Japan (24.0 [95% UI, 19.9–27.3]), with a difference of ≈24 times between the highest and lowest countries.

- A systematic review and meta-analysis estimated the global age-standardized rate of premature CVD mortality.<sup>95</sup> The pooled age-standardized rate of premature CVD mortality from total CVD was 96.04 per 100 000 people (95% CI, 67.18–137.31). Subgroup analyses revealed higher age-standardized mortality rates for IHD (15.57 [95% CI, 11.27–21.5]) compared with stroke (12.36 [95% CI, 8.09–18.91]), males (37.50 [95% CI, 23.69–59.37]) compared with females (15.75 [95% CI, 9.61–25.81]), and middle-income countries (90.58 [95% CI, 56.40–145.48]) compared with high-income countries (21.42 [95% CI, 15.63–29.37]).
- Death rates for CVD, CHD, stroke, and all CVD in selected countries in 2020 are presented in Charts 14-10 through 14-13.
- CVD mortality and prevalence vary widely among world regions. In 2021, based on 204 countries and territories<sup>96</sup>:

–19.41 (95% UI, 17.78–20.67) million total deaths were estimated for CVD globally, which amounted to an increase of 18.51% (95% UI, 12.42%–24.19%) from 2010. The age-standardized death rate per 100 000 population was 235.18 (95% UI, 214.64–250.52), which represents a decrease of –14.55% (95% UI, –18.73% to –10.55%) from 2010. There were 612.06 (95% UI, 570.32–649.81) million prevalent cases of CVD in 2021, an increase of 33.46% (95% UI, 30.72%–36.68%) compared with 2010. The age-standardized prevalence rate was 7178.73 (95% UI, 6696.15–7620.67) per 100,000, an increase of 1.38% (95% UI, –0.58% to 3.55%) from 2010. (Table 14-4).

- The highest mortality rates estimated for CVD among regions were for Central Asia and Eastern Europe, with high levels also seen for Oceania, North Africa and the Middle East, and central sub-Saharan Africa. Rates were lowest for high-income Asia Pacific and Australasia (Chart 14-15).
- CVD prevalence among regions was estimated as highest for North Africa and the Middle East followed by Eastern Europe and Central Asia.

Prevalence was lowest for high-income Asia Pacific and Southeast Asia (Chart 14-16).

- CVD represents 37% of deaths in individuals <70 years of age that are attributable to noncommunicable diseases.<sup>97</sup>

- In 2019, 27% of the world's deaths were caused by CVD, making it the predominant cause of death globally.<sup>97</sup>
- See the Supplemental 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, 2022: all ages‡	Age-adjusted mortality rates per 100 000 (95% CI),‡ 2022
Both sexes	127 900 000 (48.6%)	28 600 000 (9.9%)	941 652	224.3 (223.8–224.8)
Males	65 400 000 (52.4%)	14 800 000 (10.9%)	494 740 (52.5%)§	273.9 (273.1–274.7)
Females	62 500 000 (44.8%)	13 800 000 (9.2%)	446 912 (47.5%)§	183.1 (182.6–183.7)
NH White males	51.2%	11.3%	371 064	277.8 (276.9–278.7)
NH White females	44.6%	9.2%	338 610	186.2 (185.5–186.8)
NH Black males	58.9%	11.3%	64 606	379.7 (376.5–382.8)
NH Black females	59.0%	11.1%	58 860	246.9 (244.8–248.9)
Hispanic males	51.9%	8.7%	37 257	202.4 (200.2–204.6)
Hispanic females	37.3%	8.4%	30 676	133.0 (131.4–134.5)
NH Asian males	51.5%	6.9%	14 106	154.7 (152.1–157.3)
NH Asian females	38.5%	4.9%	13 150	104.9 (103.1–106.7)
NH American Indian/Alaska Native	...	...	4 874	193.3 (187.8–198.9)
NH Native Hawaiian or Pacific Islander			1 421	245.8 (232.7–258.9)

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>98</sup>

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

\*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 people, American Indian or Alaska Native people, 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 decedents, Asian and Pacific Islander decedents, 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 people, Filipino people, Japanese people, and other Asian 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 2020 US population estimates. Mortality (for underlying cause of CVD): Unpublished NHLBI tabulation using CDC Wonder<sup>81</sup> and National Vital Statistics System.<sup>82</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).

**Table 14-2. CVD and Other Major Causes of Death: All Ages, <85 Years of Age, and ≥85 Years of Age, by Sex, 2022**

Cause	ICD-10 code	Total deaths	Deaths, <85 y of age	Deaths, ≥85 y of age
CVD	I00–I99	941 652	600 457	341 164
Males		494 740	361 069	133 646
Females		446 912	239 388	207 518
HD	I00–I09, I11, I13, I20–I51	702 880	454 071	248 782
Males		386 766	283 868	102 877
Females		316 114	170 203	145 905
Cancer	C00–C97	608 371	506 309	102 057
Males		319 336	269 772	49 560
Females		289 035	236 537	52 497
COVID-19	U07.1	186 552	133 481	53 070
Males		102 660	77 174	25 485
Females		83 892	56 307	27 585
Accidents	V01–X59, Y85–Y86	227 039	199 946	27 074
Males		151 629	140 159	11 453
Females		75 410	59 787	15 621
Stroke	I60–I69	165 393	97 683	67 708
Males		71 819	49 764	22 053
Females		93 574	47 919	45 655
CLRD	J40–J47	147 382	110 035	37 345
Males		69 004	54 086	14 916
Females		78 378	55 949	22 429
AD	G30	120 122	46 735	73 387
Males		37 475	17 480	19 995
Females		82 647	29 255	53 392
All other CVD	Residual, I10, I12, I15, I70–I99	73 379	48 703	24 674
Males		36 155	27 437	8 716
Females		37 224	21 266	15 958

Deaths with age not stated are not included in the totals.

AD indicates Alzheimer disease; CLRD, chronic lower respiratory disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; HD, heart disease; 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>82</sup>

**Table 14-3. Age-Adjusted Death Rates per 100 000 People for CVD, CHD, and Stroke, by US State, 2022**

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change, 2012–2022	Rank	Death rate	% Change, 2012–2022	Rank	Death rate	% Change, 2012–2022
Alabama	49	307.1	4.3	15	76.6	−22.4	49	51.1	3.4
Alaska	7	195.5	2.7	10	71.2	−5.9	19	35.1	−17.5
Arizona	13	201.6	3.5	23	83.2	−17.8	17	34.5	15.4
Arkansas	48	290.0	2.0	51	126.3	−6.5	43	46.0	−6.4
California	15	203.2	−2.3	20	80.7	−21.1	29	39.8	12.5
Colorado	3	178.3	1.6	3	63.0	−13.7	15	33.8	3.6
Connecticut	5	183.1	−6.3	6	67.2	−22.3	9	30.1	11.5
Delaware	32	229.4	5.0	27	86.6	−21.8	51	56.9	48.9
District of Columbia	37	243.6	−8.7	46	109.8	−20.6	34	42.1	24.6
Florida	14	202.0	1.7	24	85.2	−16.4	41	45.1	46.9

(Continued)

**Table 14-3. Continued**

State	CVD			CHD			Stroke		
	Rank	Death rate	% Change, 2012–2022	Rank	Death rate	% Change, 2012–2022	Rank	Death rate	% Change, 2012–2022
Georgia	39	246.8	2.6	8	68.1	-16.3	39	44.0	5.3
Hawaii	4	182.8	1.0	9	68.6	-0.6	28	39.5	12.1
Idaho	17	204.4	0.2	14	75.5	-11.3	16	34.4	-7.4
Illinois	30	225.5	0.0	13	75.4	-26.9	32	41.4	9.9
Indiana	38	244.9	-1.5	31	91.5	-18.9	33	41.9	-1.9
Iowa	31	228.2	2.8	37	99.6	-16.5	12	32.0	-6.0
Kansas	35	232.8	4.6	32	94.5	5.2	22	35.8	-9.1
Kentucky	44	270.7	0.2	43	105.2	-12.4	36	42.9	-3.1
Louisiana	47	288.1	5.2	42	103.2	-7.4	48	50.2	14.4
Maine	23	212.3	9.4	25	85.8	2.8	6	29.4	-14.1
Maryland	26	216.2	-4.2	22	81.6	-25.8	38	43.8	19.8
Massachusetts	1	171.8	-5.7	1	60.6	-25.2	2	25.6	-9.6
Michigan	43	269.4	6.3	47	113.2	-13.5	40	44.2	18.4
Minnesota	2	175.3	4.3	2	61.3	-7.8	11	31.8	-3.5
Mississippi	51	327.7	7.3	48	120.1	0.6	50	54.2	12.2
Missouri	40	254.3	1.1	44	105.7	-15.1	26	39.1	-7.5
Montana	19	207.0	3.8	35	96.8	14.2	3	26.5	-20.1
Nebraska	25	214.4	6.3	7	68.1	-11.6	20	35.1	0.8
Nevada	41	255.9	4.6	39	102.0	4.1	30	40.0	16.5
New Hampshire	6	191.4	1.9	11	74.3	-20.0	10	30.3	3.6
New Jersey	8	197.2	-10.7	12	75.0	-30.8	8	30.0	-8.4
New Mexico	22	209.3	8.5	41	103.0	6.3	25	38.1	25.9
New York	11	200.4	-12.6	40	102.6	-23.3	1	24.5	-7.8
North Carolina	34	231.5	2.5	26	86.1	-14.7	47	47.7	11.5
North Dakota	12	201.5	-3.3	16	78.3	-20.8	13	32.8	-12.0
Ohio	42	259.4	4.7	36	99.4	-14.5	45	46.5	12.8
Oklahoma	50	312.9	10.2	45	107.0	-27.6	27	39.5	-13.7
Oregon	24	212.4	14.2	4	65.1	-7.5	46	47.1	25.6
Pennsylvania	29	224.6	-2.4	28	87.0	-19.9	23	36.6	-2.3
Rhode Island	16	204.0	-1.2	33	94.7	-20.3	5	29.2	-4.5
South Carolina	36	241.6	-0.5	19	80.4	-19.2	42	45.6	-0.6
South Dakota	21	208.7	-0.7	38	101.7	-8.3	14	33.1	-11.4
Tennessee	46	284.8	6.6	50	124.7	-11.0	44	46.4	3.5
Texas	33	230.0	0.9	30	89.9	-12.0	35	42.3	1.3
Utah	20	207.7	6.8	5	65.1	-5.3	18	34.6	-8.3
Vermont	18	206.6	2.8	34	96.2	-2.0	4	27.1	-24.4
Virginia	27	216.4	0.8	18	80.3	-9.4	31	41.2	1.3
Washington	9	197.3	4.2	21	81.1	-7.2	24	36.7	6.9
West Virginia	45	273.5	-1.5	49	121.8	-6.6	37	43.4	-9.5
Wisconsin	28	218.8	3.1	29	88.9	-7.2	21	35.3	-2.1
Wyoming	10	200.3	-7.5	17	78.4	-21.3	7	29.8	-14.6
Total United States		224.3	0.0		87.6	-16.9		39.5	7.2

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>82</sup>

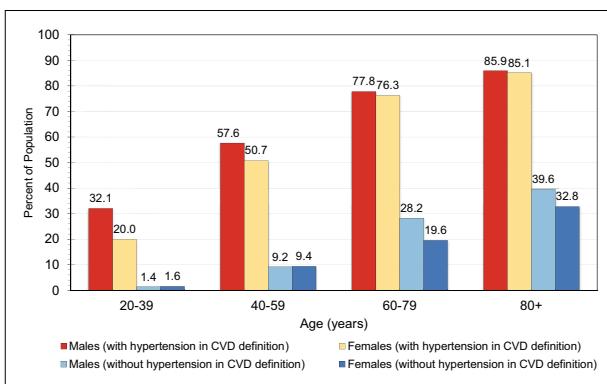
**Table 14-4. Global Mortality and Prevalence of CVD by Sex, 2021**

	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), 2021	19.41 (17.78 to 20.67)	612.06 (570.32 to 649.81)	10.24 (9.52 to 10.97)	307.99 (286.99 to 328.53)	9.18 (8.16 to 9.95)	304.07 (283.99 to 322.69)
Percent change (%) in total number, 1990–2021	57.46 (48.32 to 67.12)	111.38 (107.59 to 115.51)	68.27 (54.53 to 81.65)	114.40 (110.50 to 118.99)	46.93 (36.70 to 57.84)	108.41 (104.83 to 112.25)
Percent change (%) in total number, 2010–2021	18.51 (12.42 to 24.19)	33.46 (30.72 to 36.68)	19.76 (11.27 to 28.62)	32.88 (29.79 to 36.31)	17.14 (10.31 to 24.35)	34.05 (31.59 to 36.91)
Rate per 100 000, age standardized, 2021	235.18 (214.64 to 250.52)	7,178.73 (6,696.15 to 7,620.67)	281.11 (259.77 to 301.13)	7,666.88 (7,159.91 to 8,166.57)	196.69 (175.27 to 213.19)	6,750.55 (6,298.73 to 7,163.16)
Percent change (%) in rate, age standardized, 1990–2021	−34.33 (−37.79 to −30.75)	0.88 (−0.64 to 2.69)	−30.05 (−35.23 to −24.88)	0.44 (−1.13 to 2.30)	−38.67 (−42.68 to −34.36)	1.03 (−0.54 to 2.82)
Percent change (%) in rate, age standardized, 2010–2021	−14.55 (−18.73 to −10.55)	1.38 (−0.58 to 3.55)	−13.45 (−19.37 to −7.29)	0.51 (−1.56 to 2.86)	−15.75 (−20.50 to −10.69)	2.24 (0.42 to 4.29)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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; GBD, Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

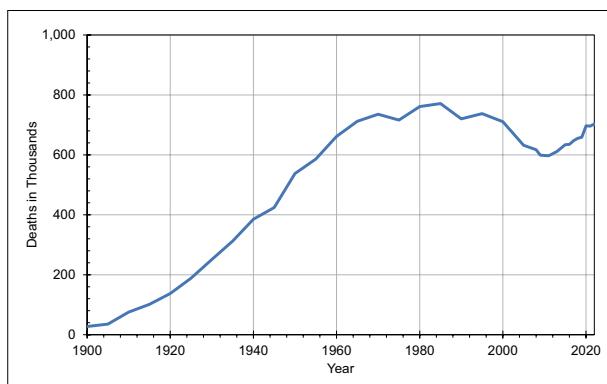
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>96</sup>

**Chart 14-1. Prevalence of CVD in US adults ≥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.

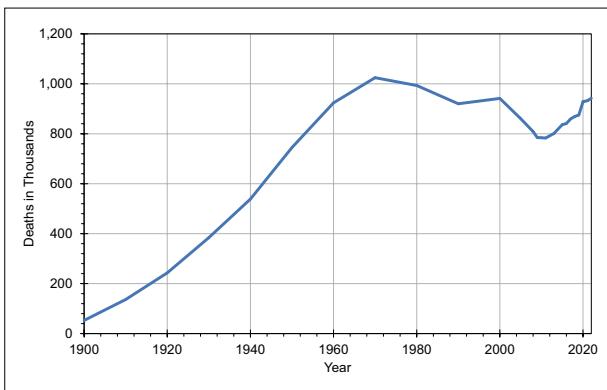
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>1</sup>

**Chart 14-2. Deaths attributable to diseases of the heart, United States, 1900 to 2022.**

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>82</sup>

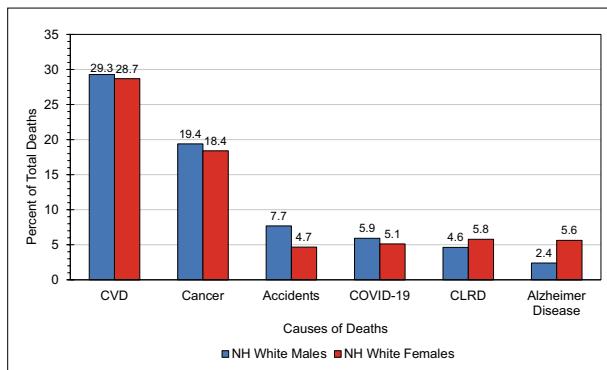


**Chart 14-3. Deaths attributable to CVD, United States, 1900 to 2022.**

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>82</sup>

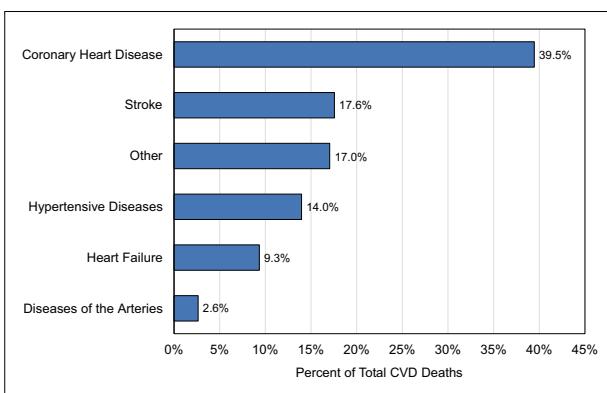


**Chart 14-5. CVD and other major causes of death for NH White males and females, United States, 2022.**

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>82</sup>

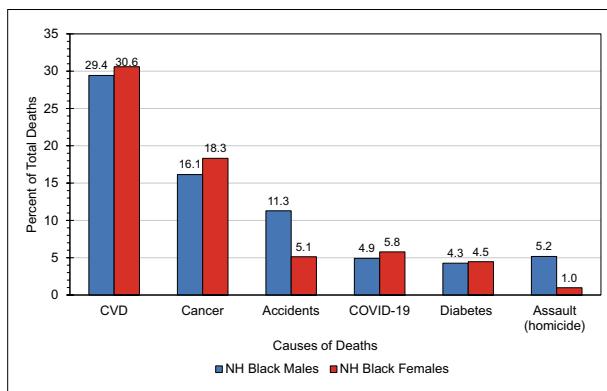


**Chart 14-4. Percentage breakdown of deaths attributable to CVD, United States, 2022.**

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*.

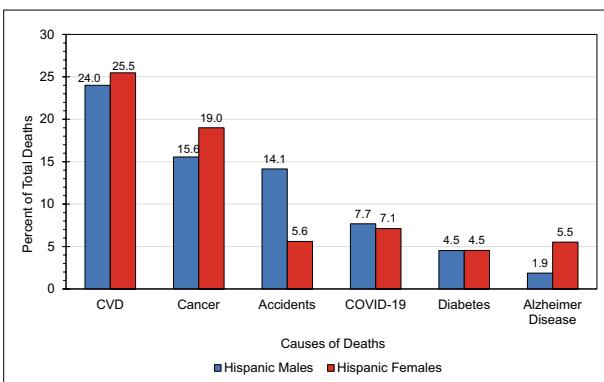
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>82</sup>



**Chart 14-6. CVD and other major causes of death for NH Black males and females, United States, 2022.**

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.

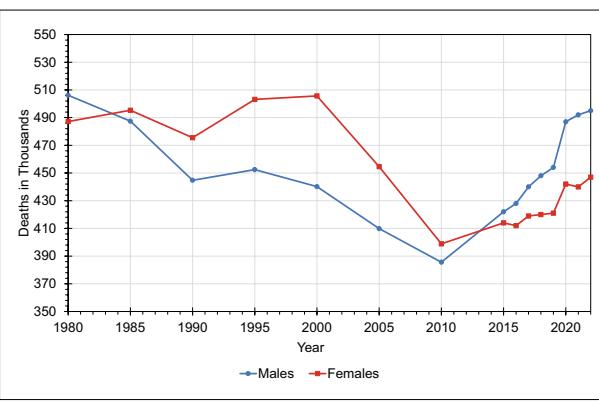
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>82</sup>



**Chart 14-7. CVD and other major causes of death for Hispanic or Latino males and females, United States, 2022.**

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*; and NH, non-Hispanic.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System.<sup>82</sup>

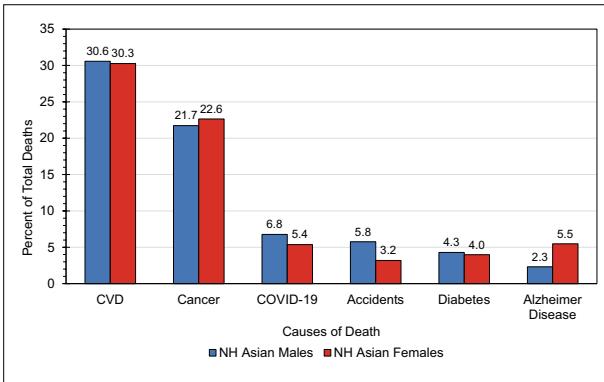


**Chart 14-9. CVD mortality trends for US males and females, 1980 to 2022.**

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>82</sup>

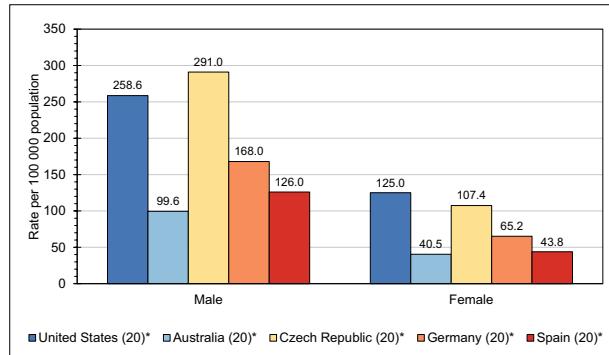


**Chart 14-8. CVD and other major causes of death for NH Asian or Pacific Islander males and females, United States, 2022.**

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>82</sup>



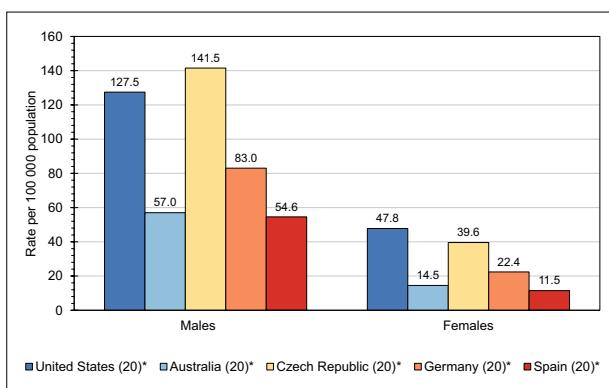
**Chart 14-10. Death rates per 100,000 population for CVD in selected countries for adults 35 to 74 years of age, 2020.**

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>99</sup>



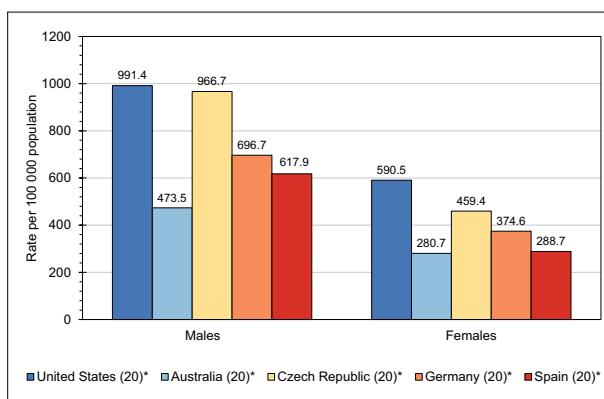
**Chart 14-11. Death rates per 100 000 population for CHD in selected countries for adults 35 to 74 years of age, 2020.**

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>99</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.**

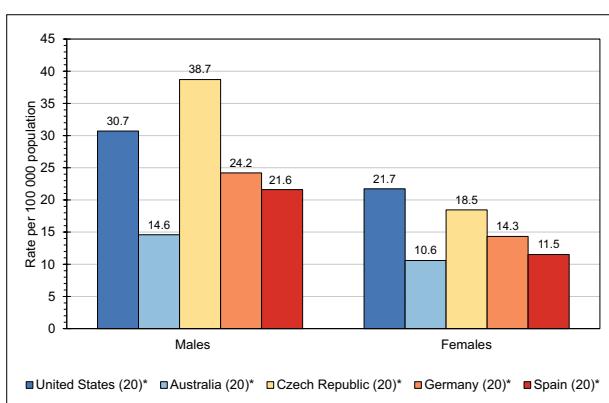
Rates are adjusted to the European Standard Population.

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>99</sup>



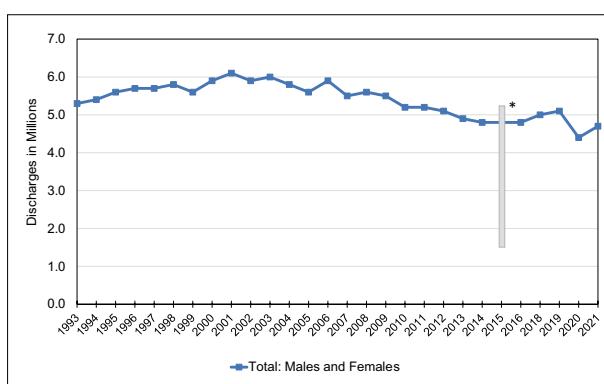
**Chart 14-12. Death rates per 100 000 population for stroke in selected countries for adults 35 to 74 years of age, 2020.**

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>99</sup>



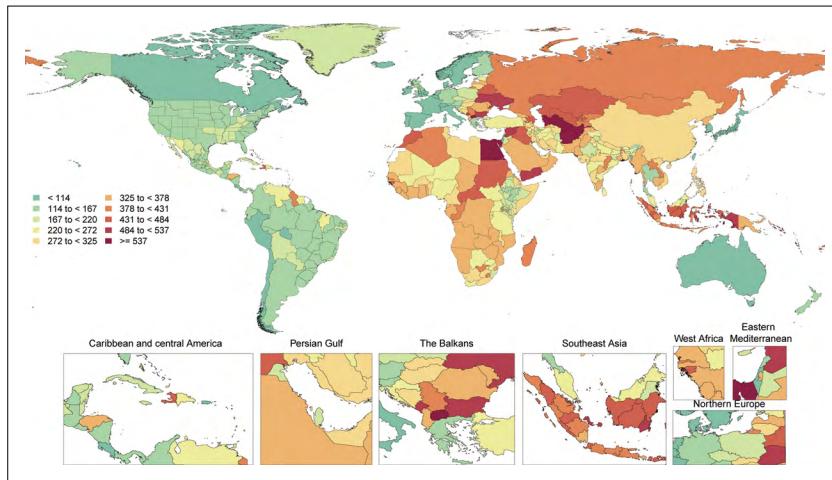
**Chart 14-14. Hospital discharges for CVD, US adults, 1993 to 2021.**

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.

\*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from *International Classification of Diseases, 9th Revision* to *International Classification of Diseases, 10th Revision*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>88</sup>

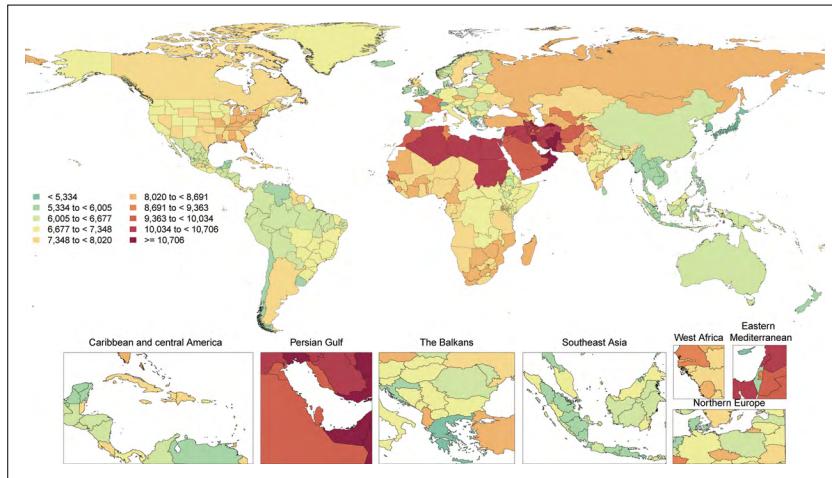


**Chart 14-15. Age-standardized global mortality rates of CVDs per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>96</sup>



**Chart 14-16. Age-standardized global prevalence rates of CVDs per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>96</sup>

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## 15. STROKE (Cerebrovascular Diseases)

**ICD-9 430 to 438; ICD-10 I60 to I69. See Tables 15-1 through 15-7 and Charts 15-1 through 15-15**

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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 BRFSS<sup>1</sup> 2022 data (unpublished NHLBI tabulation), stroke prevalence in adults was 3.4% (median) in the United States with the lowest prevalence in Puerto Rico (1.8%) and South Dakota (2.1%) and the highest prevalence in Arkansas (4.8%).
- 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>2</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 610000 of these are first attacks and 185000 are recurrent attacks (GCNKSS, NINDS, and NHLBI; GCNKSS

The 2025 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 2025. 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 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 [95% CI, 6.57–8.96] million), ICH accounted for 27.9% (3.41 [95% CI, 2.97–3.91] million), and SAH accounted for 9.7% (1.18 [95% CI, 1.01–1.39] million).<sup>3</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>3</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.
- A population-based cohort study from Ontario, Canada, assessed the influence of age on the association between sex and the incidence of stroke or TIA from January 1, 2003, to March 31, 2018.<sup>4</sup> The study followed up 9.2 million adults for a median of 15 years and observed 280197 incident stroke or TIA events. Females had an overall lower adjusted hazard of stroke or TIA than males (HR, 0.82 [95% CI, 0.82–0.83]), which held true for all stroke types except SAH (HR, 1.29 [95% CI, 1.24–1.33]). A U-shaped association between age and sex differences in the incidence of stroke or TIA was seen with the hazard of stroke being higher in females among those  $\leq 30$  years of age (HR, 1.26 [95% CI, 1.10–1.45]), lower among those between 40 and 80 years of age (40–49 years of age: HR, 0.84 [95% CI, 0.82–0.87]; 50–59 years of age: HR, 0.69 [95% CI, 0.68–0.70]; 60–69 years of age: HR, 0.69 [95% CI, 0.68–0.70]; and 70–79 years of age: HR, 0.80 [95% CI, 0.79–0.81]), and similar among those  $\geq 80$  years of age (HR, 0.99 [95% CI, 0.98–1.01]).
- A population-based incidence study conducted in Oxfordshire, England, from April 2002 to March 2018 found that between 2002 to 2010 and 2010 to 2018, stroke incidence increased significantly among subjects  $<55$  years of age (IRR, 1.67 [95% CI, 1.31–2.14]) but fell significantly among those  $\geq 55$  years of age (IRR, 0.85 [95% CI, 0.78–0.92];  $P < 0.001$  for difference).<sup>5</sup>
- A systematic review found among 50 studies in 20 countries that temporal trends in stroke incidence are diverging by age in high-income countries, with

less favorable trends at younger versus older ages (pooled relative temporal rate ratio, 1.57 [95% CI, 1.42–1.74]).<sup>6</sup> The overall relative temporal rate ratio was consistent by sex (males, 1.46 [95% CI, 1.34–1.60]; females, 1.41 [95% CI, 1.28–1.55]) and by stroke subtype (ischemic, 1.62 [95% CI, 1.44–1.83]; ICH, 1.32 [95% CI, 0.91–1.92]; SAH, 1.54 [95% CI, 1.00–2.35]) but was greater in studies reporting trends solely after 2000 (1.51 [95% CI, 1.30–1.70]) versus solely before 2000 (1.18 [95% CI, 1.12–1.24]) and was highest in population-based studies in which the most recent reported period of ascertainment started after 2010 (1.87 [95% CI, 1.55–2.27]).

- In the multicenter ARIC study of Black adults 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>7</sup> Data from the Danish Stroke Registry and the Danish National Patient Registry showed that the incidence rate per 100 000 PY 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 (−1.5 [95% CI, −1.9 to −1.1] and −1.2 [95% CI, −1.9 to −0.6], respectively), especially in those  $\geq 70$  years of age.<sup>8</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%/y–3.2%/y) among Asian American females and 2.4%/y (95% CI, 1.3%/y–3.6%/y) among Asian American males.<sup>9</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%/y–4.2%/y] among females and decline of 3.2%/y [95% CI, 1.9%/y–4.5%/y] among males).
- A meta-analysis assessing temporal trends in stroke incidence between January 1997 and December 2021 by age and sex in Latin America and the Caribbean region found unfavorable changes in stroke incidence in younger people (<55 years of age) with a higher incidence rate after 2010 compared with before 2010 (IRR, 1.37 [95% CI, 1.23–1.50]).<sup>10</sup> The overall relative temporal trend ratio was 1.65 (95% CI, 1.50–1.80) in the younger compared with older age group with a greater increase

in young females (pooled relative temporal trend ratio, 3.08 [95% CI, 1.18–4.97];  $P_{\text{heterogeneity}} < 0.001$ ).

- A study assessing stroke registry data in Iran among hospitalized patients with first or recurrent stroke found that stroke rates had increased over time, ranging from 6.59 to 8.91 per 10 000 cases from April 2001 to March 2022 to 11.17 to 13.82 per 10 000 cases from April 2014 to March 2015.<sup>11</sup> The average annual increase in stroke incidence based on *ICD-10* in different reference populations ranged from 1.56% (95% CI, 0.14%–2.97%) to 2.67% (95% CI, 1.25%–4.09%). A similar trend for the whole reference population was seen for stroke incidence rate based on WHO-MONICA with an average annual change of 2.5% (95% CI, 1.28%–3.72%) to 3.64% (95% CI, 2.47%–4.82%).

## 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>
- The FINGER trial in 1259 adults 60 to 77 years of age found that a 2-year multidomain intervention with diet, PA, cognitive activity, and vascular monitoring compared with general health advice resulted in a reduced incidence of stroke (HR, 0.71 [95% CI, 0.51–0.99]).<sup>14</sup>

### High BP

(See Chapter 8 [High Blood Pressure] for more information.)

(See Tables 15-2 and 15-3 and Charts 15-2 and 15-3)

#### Observational Studies

- High BP is associated with stroke mortality. Among 430 977 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 PY in BP groups were 39 in the normal BP, 71 in the prehypertension-low, 83 in the prehypertension-high, 283 in the isolated systolic hypertension, 82 in the isolated diastolic hypertension, and 375 in the systolic-diastolic hypertension groups. Compared with normal BP, multiadjusted HRs for stroke mortality were 1.20 (95% CI, 1.06–1.36) in the prehypertension-low, 1.53 (95% CI, 1.37–1.70) in the prehypertension-high, 2.52 (95% CI, 2.28–2.78)

in the isolated systolic hypertension, 2.51 (95% CI, 1.94–3.21) in the isolated diastolic hypertension, and 5.60 (95% CI, 5.06–6.21) in the systolic-diastolic hypertension groups. For all BP categories relative to normal BP, HRs for hemorrhagic stroke mortality were larger than those for ischemic stroke mortality.<sup>15</sup>

- Higher SBP and DBP are associated with incident stroke. Among 36352 adults  $\geq 35$  years of age recruited from rural areas of Fuxin County, Liaoning Province, China, the overall rate of stroke over a median of 12.5 years was 7.0%. 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) after adjustment for demographic, clinical, and behavioral characteristics.<sup>16</sup> Ideal BP for lower stroke risk varied by BMI: At  $BMI < 24 \text{ kg/m}^2$ , stroke risk was elevated (HR  $> 1$ ) in those with  $BP > 130/80 \text{ mmHg}$ , whereas at  $BMI \geq 24 \text{ kg/m}^2$ , stroke risk was elevated (HR  $> 1$ ) in those with  $BP > 120/80 \text{ mmHg}$ .
- Higher pulse pressure is associated with incident stroke. In a longitudinal cohort study of 11848 adult participants in 12 countries in Europe, Asia, and South America undergoing 24-hour ambulatory BP assessment with a median follow-up of 13.7 years and 846 stroke events, the rate of stroke was 5.2 per 1000 PY. A 1-SD increment in mean pulse pressure (10.0 mmHg) was independently associated with stroke risk.<sup>17</sup> For participants  $\leq 40$  years of age, a 1-SD increment in mean ambulatory pulse pressure was associated with a 3-fold higher risk of stroke (aHR per SD, 3.06 [95% CI, 1.03–9.09]). The aHRs per SD were 1.40 (95% CI, 0.76–2.58) for 40 to 50 years of age, 1.51 (95% CI, 1.14–1.99) for 50 to 60 years of age, 1.44 (95% CI, 1.24–1.67) for 60 to 70 years of age, and 1.18 (95% CI, 1.09–1.28) for  $> 70$  years of age.
- However, SBP/DBP combinations are associated with stroke risk in nonlinear patterns that do not simply reflect pulse pressure. 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  $< 110/\leq 60 \text{ mmHg}$  (HRs  $< 0.90$  relative to BP of 120/80 mmHg) and stroke risk was highest in the SBP/DBP range of 170 to 190/85 to 100 mmHg (HRs  $> 2.00$  relative to BP of 120/80 mmHg; Chart 15–2).<sup>18</sup>
- Genetically predicted higher BP measures are associated with incident ischemic stroke. In a mendelian randomization study of 86060 adults 40 to 79 years of age in China, a 10-mmHg increment in genetically predicted SBP was associated with higher risk

of ischemic stroke (HR, 1.37 [95% CI, 1.30–1.45]) and ICH (HR, 1.71 [95% CI, 1.58–1.87]).<sup>19</sup> In a mendelian randomization study of adults  $\geq 55$  years of age in the multiancestry MEGASTROKE consortium, a 1-SD increment in genetically predicted pulse pressure was associated with higher risk of ischemic stroke (aOR, 1.23 [95% CI, 1.13–1.34]) independently of genetically predicted mean arterial pressure, and this result was replicated in the UK Biobank.<sup>20</sup>

- High SBP and DBP are associated with incident ICH and SAH. Among 947378 adults 20 to 64 years of age in the Korean National Health Insurance Service Database who had stable BP levels during 10 years of observation, with 355 ICH and 566 SAH cases, ICH and SAH incidence rates increased across BP categories among both males and females (Table 15–2).<sup>21</sup> Among 500598 adults 40 to 69 years of age in the UK Biobank, with 539 cases of SAH over a mean of 4.5 years of follow-up, SBP and DBP analyzed as continuous variables were positively associated with SAH risk (HR per 10 mmHg of SBP, 1.10 [95% CI, 1.05–1.15]; HR per 10 mmHg of DBP, 1.17 [95% CI, 1.07–1.27]; Chart 15–3).<sup>22</sup> The authors also meta-analyzed the UK Biobank results for SBP categories with 4 additional studies for a total of 809983 participants and 1465 SAH cases, showing increasing SAH incidence rates across BP categories among both males and females (Table 15–3).

### Interventional Studies

- In a meta-analysis of 66 trials of SBP-lowering interventions including 324812 participants and 11437 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>23</sup>
- In a meta-analysis of 14 randomized trials comparing more and less intensive BP targets that included 60870 participants and 1323 strokes over an average follow-up of 3.95 years, more intensive BP control was associated with a lower risk of stroke (OR, 0.79 [95% CI, 0.67–0.93]).<sup>24</sup> The trials differed in the specific BP targets, and the average achieved SBP reduction in the more intensive treatment was 7.69 mmHg (95% CI, 7.64–7.71 mmHg).

### High BP and Stroke Prognosis

- In a meta-analysis of 26 studies including 56513 patients undergoing intravenous thrombolysis for

AIS, 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>25</sup> Higher pretreatment (aOR, 0.91 [95% CI, 0.84–0.98]) and posttreatment (aOR, 0.70 [95% CI, 0.57–0.87]) SBP values were associated with lower likelihood of 3-month functional independence.

### **Diabetes**

(See Chapter 9 [Diabetes] for more information.)

#### *Observational Studies*

- In a meta-analysis of 64 cohort studies involving 775 385 individuals and 12 539 incident strokes, diabetes was associated with stroke risk in females (aRR, 2.28 [95% CI, 1.93–2.69]) and in males (aRR, 1.83 [95% CI, 1.60–2.08]).<sup>26</sup> The magnitude of the RR was greater in females (ratio of female aRR/male aRR, 1.27 [95% CI, 1.10–1.46]), suggesting that diabetes is a more potent risk factor for stroke among females.
- 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>27</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]).

#### *Interventional Studies*

- 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 19 RCTs with 155 027 participants with type 2 diabetes demonstrated that GLP1-RA treatment was associated with reduced stroke risk (RR, 0.84 [95% CI, 0.77–0.93]).<sup>30</sup>
- Glucagon-like peptide 1 agonists reduce blood glucose through multiple mechanisms, including stimulating insulin secretion, blocking glucagon secretion, slowing digestion, and increasing satiety. In a meta-analysis of 7 RCTs that included 56 004 patients with type 2 diabetes, treatment with glucagon-like peptide 1 agonists reduced the risk of nonfatal stroke by 15% (HR, 0.85 [95% CI, 0.76–0.94]),

fatal stroke by 19% (HR, 0.81 [95% CI, 0.62–1.08]), and total stroke by 16% (HR, 0.84 [95% CI, 0.76–0.93]).<sup>31</sup>

- SGLT-2 inhibitors reduce blood glucose through reducing renal glucose reabsorption. In a meta-analysis of 5 RCTs that included 46 969 patients with type 2 diabetes, treatment with SGLT-2 inhibitors did not reduce stroke risk (HR, 0.96 [95% CI, 0.87–1.07]).<sup>32</sup>

### **Diabetes and Stroke Prognosis**

- 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>33</sup>
- In the GWTG-Stroke registry involving 409 060 participants ≥65 years of age from 1690 sites in the United States, diabetes was associated with a higher risk of adverse outcomes 3 years after ischemic stroke, including all-cause mortality (46.0% versus 44.2%, a difference of 1.8 per 100; aHR, 1.24 [95% CI, 1.23–1.25]), all-cause hospital readmission (71.3% versus 63.7%, a difference of 7.6%; aHR, 1.22 [95% CI, 1.21–1.23]), a composite of mortality and cardiovascular readmission (69.5% versus 64.3%, a difference of 5.2%; aHR, 1.19 [95% CI, 1.18–1.20]), and ischemic stroke/TIA readmission (15.9% versus 13.3%, a difference of 2.6%; aHR, 1.18 [95% CI, 1.16–1.20]).<sup>34</sup>
- In a meta-analysis of 5 studies involving 2565 patients with AIS, hyperglycemia (random blood glucose >140 mg/dL) at stroke admission was associated with higher risk of symptomatic ICH (9.3% versus 5.5%; aOR, 1.80 [95% CI, 1.30–2.50]), higher odds of poor clinical outcome at 90 days (61.0% versus 47.2%; aOR, 1.82 [95% CI, 1.52–2.19]), and higher odds of all-cause mortality at 90 days (25.7% versus 13.1%; aOR, 2.51 [95% CI, 1.65–3.82]) after adjustment for age, sex, and other confounding factors that varied by study.<sup>35</sup>

### **Disorders of Heart Rhythm**

(See Chapter 18 [Disorders of Heart Rhythm] for more information.)

#### *Atrial Fibrillation*

- In an international multicenter prospective cohort of patients with cryptogenic stroke or TIA who had a continuous cardiac monitor placed (N=250), 43% had a probable cardiac cause identified at 12 months of follow-up. The most common causes identified were AF and atrial flutter (29%).<sup>36</sup>
- 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 with continuous cardiac monitoring versus 1.8% with usual care;

median time to detection was 99 and 181 days, respectively.<sup>37</sup> In a prespecified secondary analysis, predictors of poststroke detection of AF in the continuous monitoring arm (N=242) included congestive HF (HR, 5.06 [95% CI, 1.45–17.64]) and LA enlargement (HR, 3.32 [95% CI, 1.34–8.19]).<sup>38</sup>

- Biomarkers such as high levels of troponin, BNP, NT-proBNP, 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 (hypertension, diabetes, HF, CAD).<sup>39,40</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>41</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>42</sup>
- In a meta-analysis of 28 studies (N=2 612 816 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>43</sup> For the choice of anticoagulant postoperatively, a study from the STS database of 26 522 patients with AF after cardiac surgery (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>44</sup>
- In a meta-analysis of 21 national cohort studies including 9.7 million global participants eligible for oral anticoagulants, the prevalence of DOAC use increased from 0.00 (95% CI, 0.00–0.00) in 2010 to 0.45 (95% CI, 0.45–0.46) in 2018.<sup>45</sup> On the other hand, the prevalence of vitamin K antagonist use decreased from 0.42 (95% CI, 0.22–0.65) in 2010 to 0.32 (95% CI, 0.32–0.32) in 2018. Nine percent of participants in 2018 were treated with antiplatelet agents only.
- 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>46</sup>
- In an analysis using individual participant data from 5 randomized trials of oral antithrombotic therapy in AF, among 1163 patients with AF and a stroke after

randomization, the cumulative incidence of recurrent stroke at 1 year was 7% (95% CI, 5.2%–8.7%), and the cumulative incidence of mortality at 3 months was 12.4% (95% CI, 10.5%–14.4%).<sup>47</sup> The risk of recurrent stroke in this population of patients with AF and ischemic stroke remained similar even when accounting for the competing risk of death.

- In STROKESTOP, an RCT in participants 75 to 76 years of age, an invitation to AF screening (defined as twice-daily handheld electrocardiographic recordings over 2 weeks) was found to be cost-effective with 65 QALYs gained per 1000 individuals invited for screening and \$1.92 million saved per 1000 individuals.<sup>48</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 (aHR, 0.69 [95% CI, 0.60–0.79];  $P<0.05$ ).<sup>49</sup>
- 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>50</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>51</sup>

#### *High Blood Cholesterol and Other Lipids*

*(See Chapter 7 [High Blood Cholesterol and Other Lipids] for more information.)*

#### *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.
  - A meta-analysis of LDL-C-lowering drug treatment trials has demonstrated that every 1-mmol/L (≈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>52</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>53</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>54</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) and those receiving less intensive treatment (OR, 1.05 [95% CI, 0.85–1.31]).<sup>55</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>52</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>56</sup> Genetic predisposition to higher HDL-C has been associated with lower risk of small-vessel ischemic stroke in mendelian randomization analyses.<sup>57,58</sup>

#### HDL/LDL Ratio

- Among 384 093 participants in the UK Biobank, compared with an HDL-C/LDL-C ratio of 0.4 to 0.6, an HDL-C/LDL-C ratio <0.4 was associated with a higher risk of ischemic stroke (HR, 1.12 [95% CI, 1.02–1.22]) after full multivariable adjustment.<sup>59</sup> An HDL-C/LDL-C ratio >0.6 was associated with higher risk of hemorrhagic stroke after full multivariable adjustment (HR, 1.25 [95% CI, 1.03–1.52]).

#### 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 (comparing Q4 vs Q1: HR, 2.53 [95% CI, 2.34–2.73]).<sup>60</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>61</sup>
- In an RCT of 8179 participants in 11 countries with established CVD or diabetes, 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>62</sup>

#### Remnant Cholesterol

- Remnant cholesterol is defined as the cholesterol content of triglyceride-rich lipoproteins, including chylomicron remnants, very low-density lipoproteins, and intermediate-density lipoproteins. Remnant cholesterol can be measured in the laboratory or calculated (TC-[HDL-C+LDL-C]). Remnant cholesterol is associated with inflammation, oxidative stress, and accelerated atherosclerosis. In a meta-analysis (N=7 studies), compared with low concentrations of remnant cholesterol, elevated concentrations were associated with an increased risk of total stroke (RR, 1.43 [95% CI, 1.24–1.66]).<sup>63</sup> The associations held for lipid levels collected in both fasting and nonfasting states.
- Among 10 067 middle-aged and elderly Chinese individuals, remnant cholesterol was associated with stroke risk after adjustment for multiple stroke risk factors and lipid therapy but not other lipid levels (compared with those in the lowest quartile, adjusted HR for those in highest quartile, 1.26 [95% CI, 1.06–1.50]).<sup>64</sup> The association was nonlinear with a point of inflection for remnant cholesterol <1.78 mmol/L: Remnant cholesterol concentrations were associated with increased risk of stroke when remnant cholesterol was <1.78 mmol/L (HR, 1.25 [95% CI, 1.09–1.44]) but not when remnant cholesterol was ≥1.78 mmol/L (HR, 0.89 [95% CI, 0.74–1.08]).
- In a mendelian randomization study among 958 434 participants drawn from several large-scale genome-wide association databases designed to strengthen causal inference, genetic variants associated with remnant cholesterol levels were associated with increased risk of total stroke (OR, 1.23 [95% CI, 1.12–1.35];  $P=3.72\times10^{-6}$ ).<sup>65</sup> Effects on stroke were not independent of effects of LDL-C, although they were for CAD end points.

#### 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>66</sup>
- A meta-analysis of 141 cohort studies showed that low cigarette consumption ( $\approx$ 1 cigarette/d) carries an RR of developing stroke of 1.52 (95% CI, 1.10–2.10) compared with the RR associated with high cigarette consumption ( $\approx$ 20 cigarettes/d) of 2.90 (95% CI, 1.54–2.35).<sup>67</sup> The risk associated with low cigarette consumption is much higher than what would be predicted from a linear or log-linear dose-response relationship between smoking and risk of stroke.<sup>67</sup>
- A comprehensive search included 6 studies with 10 244 01 participants in observational studies that

assessed the association of current or former use of electronic nicotine delivery systems with risk of stroke compared with nonsmokers.<sup>68</sup> Electronic nicotine delivery systems use was associated with a significant increased risk of stroke (OR, 1.52 [95% CI, 1.17–1.97]) compared with nonuse, but no association was found between former electronic nicotine delivery systems use and risk of stroke (OR, 1.03 [95% CI, 0.87–1.21]).

- A post hoc analysis of the SPS3 trial addressed the rate of persistent smoking after ischemic stroke and its association with a MACE composite of stroke (ischemic and hemorrhagic), MI, and mortality.<sup>69</sup> Among 2874 patients included in the study, 570 (20%) were smokers at enrollment, 408 (71.5%) continued to smoke, and 162 (28.4%) quit smoking by 3 months. Rates of MACEs were higher in the persistent smokers compared with never smokers (18.4% versus 14.2%), as was death (7.7% versus 6.3%, respectively). In an adjusted analysis, the risk of MACEs and death was higher in the persistent smokers compared with never smokers (HR for MACE, 1.56 [95% CI, 1.16–2.09]; HR for death, 2.0 [95% CI, 2.18–3.12]). The risk of stroke and MI did not differ according to smoking status.
- Exposure to secondhand smoke, also called passive smoking or secondhand tobacco smoke, is a risk factor for stroke.
  - A systematic review of 24 articles on the association between secondhand smoke and multiple outcomes found that the RR for both sexes combined was 1.35 (95% CI, 1.22–1.50) for stroke with higher risk in females (1.43 [95% CI, 1.28–1.61]) than in males (1.40 [95% CI, 1.09–1.81]).<sup>70</sup>
  - A study using NHANES data sampled from 1988 to 1994 and 1999 to 2012 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 (AAMR,  $96.4 \pm 20.8$  per 100 PY versus  $56.7 \pm 4.8$  per 100 PY;  $P=0.026$ ).<sup>71</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>72</sup> A meta-analysis of 75 studies from 32 countries found that for every 1% decrease in population smoking prevalence (mean, 19.3%, range, 0.3%–72.9%), SAH incidence declined by 2.4% (95% CI, 1.6%–3.3%).<sup>73</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 and 15% to 46% with pharmacological therapy without behavioral interventions.<sup>74</sup>

- In a meta-analysis of 18 studies and 17 982 adult participants with CHD who were smoking at the time of diagnosis, smoking cessation was associated with a lower risk of cardiovascular death (HR, 0.61 [95% CI, 0.49–0.75]).<sup>75</sup> A secondary analysis including 9 studies and 11 352 participants showed that smoking cessation was associated with a lower risk of nonfatal stroke (HR, 0.70 [95% CI, 0.53–0.90]).
- In a cross-sectional study from 2016 to 2018 of the US CDC BRFSS survey of stroke survivors ( $N=6867\,786$  stroke survivors), the estimated prevalence of cigarette use was 23.6% (95% CI, 22.7%–24.5%) and prevalence of e-cigarette use was 13.5% (95% CI, 11.8%–15.3%).<sup>76</sup> In a meta-analysis 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>77</sup>
- A cross-sectional study of BRFSS between 2016 and 2020 assessed the association between cannabis use (the number of days in the past 30 days marijuana or hashish was used) and cardiovascular outcomes. The association between daily cannabis use and the composite outcome of CHD, MI, and stroke was an aOR of 1.16 (95% CI, 0.98–1.38) and stroke was an aOR of 1.28 (95% CI, 1.13–1.44).<sup>78</sup> Among nontobacco smokers, daily cannabis use was associated with the composite outcome (aOR, 1.77 [95% CI, 1.31–2.40]) and stroke (aOR, 2.16 [95% CI, 1.43–3.25]).

### PA/Inactivity

(See Chapter 4 [Physical Activity and Sedentary Behavior] for more information.)

- The GBD Study 2019 estimated that low PA 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>3</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>79</sup>
- In the REGARDS study, sedentary time was independently associated with higher stroke risk (HR per 1-h/d increase in sedentary time, 1.14 [95% CI, 1.02–1.28]) independently of PA levels.<sup>80</sup> Light-intensity PA associated with reduced risk of incident

- stroke (HR per 1-h/d increase, 0.86 [95% CI, 0.77–0.97]).
- 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>81</sup>

#### *PA and Stroke Severity/Prognosis*

- 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>82</sup>
- In a longitudinal cohort study of 3472 stroke survivors, prestroke physical inactivity was associated with higher odds of dependency for activities of daily living 3 months after stroke (OR, 2.30 [95% CI, 1.89–2.80]).<sup>83</sup>
- In an observational analysis of 1367 stroke survivors (median, 72 years of age, 62% male) in EFFECTS, poststroke increasing PA sustained for 6 months was associated with higher odds of good functional outcome (mRS score 0–2) at 6 months (aOR, 2.54 [95% CI, 1.72–3.75]) compared with poststroke decreasing PA becoming inactive over 6 months.<sup>84</sup> The association was consistently observed across many demographic and comorbidity subgroups.

#### *Cardiorespiratory Fitness*

- In the UK Biobank cohort study (N=66 438; 40–69 years of age), higher cardiorespiratory fitness measured by a treadmill test was associated with lower ischemic stroke (highest tertile versus lowest: HR, 0.71 [95% CI, 0.57–0.89]) but not with hemorrhagic stroke (HR, 0.96 [95% CI, 0.68–1.37]).<sup>85</sup> Similarly, in the REGARDS study (N=24 162; ≥45 years of age), an association of non-exercise-estimated cardiorespiratory fitness with incident ischemic stroke was observed among White participants (highest tertile versus lowest: HR, 0.54 [95% CI, 0.43–0.69]) but not in Black participants (HR, 1.00 [95% CI, 0.74–1.37]), and there was no association with hemorrhagic stroke in either race group.<sup>86</sup> Similar results were observed among Chinese individuals in the China Health and Retirement Longitudinal Study (N=10 507; median age, 56 years), in which higher estimated cardiorespiratory fitness at baseline was associated with lower stroke risk (highest quartile, 4.65 strokes per 1000 PY versus lowest quartile, 16.92 strokes per 1000 PY; HR, 0.45 [95% CI, 0.32–0.63]).<sup>87</sup> The association was observed in males (highest quartile, 6.23 strokes per 1000 PY versus lowest quartile, 17.79 strokes per 1000 PY; HR, 0.61 [95% CI, 0.40–0.95]) and in females (highest quartile, 3.19 strokes per 1000 PY versus lowest quartile,

16.13 strokes per 1000 PY; HR, 0.28 [95% CI, 0.15–0.50]).

- Improved cardiorespiratory fitness over time is associated with lower stroke risk. In the Oslo Ischemia Cohort Study (N=1403 males; 40–59 years of age), individuals with an improvement in cardiorespiratory fitness assessed by a bicycle electrocardiographic test between baseline and >7 years later from unfit (below median) to fit (above the median) had 66% lower risk (95% CI, 33%–83%) of incident stroke over 23.6 years compared with those who declined from fit to unfit. Those who declined to unfit had 2.35 times (95% CI, 1.49–3.63) greater risk of incident stroke compared with those who were continuously fit.<sup>88</sup> Similarly, in the Henry Ford FIT Project (N=9496 male and female individuals; mean age, 55 years), improved cardiorespiratory fitness measured by exercise test between baseline and >12 months later was associated with lower ischemic stroke risk (for each 1-MET increase in fitness: aHR, 0.91 [95% CI, 0.88–0.94]).<sup>89</sup>

#### *Nutrition*

(See Chapter 5 [Nutrition].)

#### *Kidney and Liver Disease*

(See Chapter 12 [Kidney Disease] for more information.)

- 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>90</sup> The association did not substantially attenuate with further adjustment for hypertension.
- COMBINE-AF evaluated the safety and efficacy of DOACs versus warfarin across continuous CrCl.<sup>91</sup> Among 71 683 patients, the mean CrCl was  $75.5 \pm 30.5$  mL/min. The incidence of stroke and systemic embolism, major bleeding, ICH, and death increased significantly with worsening kidney function. Major bleeding did not differ between patients randomized to standard-dose DOACs and those randomized to warfarin across continuous CrCl values down to 25 mL/min ( $P_{\text{interaction}} = 0.61$ ). Compared with warfarin, standard-dose DOAC use resulted in a significantly lower hazard of ICH (−6.2% in HR per 10-mL/min decrease in CrCl;  $P_{\text{interaction}} = 0.08$ ). Compared with warfarin, standard-dose DOAC resulted in significantly lower hazard of stroke and systemic embolism (−4.8% in HR per 10-mL/min decrease in CrCl;  $P_{\text{interaction}} = 0.01$ ).
- In a study from the multicenter Japan Stroke Data Bank including 10 392 adult participants with an acute stroke occurring between October 2016 and December 2019, lower eGFR was associated with

high risk of cardioembolic stroke (aOR per 1-SD decrease in eGFR, 1.20 [95% CI, 1.13–1.28]) and lower risk of small-vessel occlusion stroke (aOR per 1-SD decrease in eGFR, 0.89 [95% CI, 0.84–0.94]).<sup>92</sup> In addition, eGFR <45 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> and proteinuria were associated with increased risk of an unfavorable functional outcome, defined as an mRS score of 3 to 6 at discharge, after cardioembolic stroke (OR, 1.30 [95% CI, 1.01–1.69] and 3.18 [95% CI, 2.03–4.98], respectively) and small-vessel occlusion (OR, 1.44 [95% CI, 1.01–2.07] and 2.08 [95% CI, 1.08–3.98], respectively).

- The AXADIA-AFNET 8 trial randomized patients with AF on chronic hemodialysis to either apixaban (2.5 mg twice daily) or a vitamin K antagonist.<sup>93</sup> The primary efficacy outcome was a composite of ischemic stroke, all-cause death, MI, and DVT or PE. There were no differences in safety or efficacy outcomes. Patients with AF on hemodialysis who were on oral anticoagulation remained at high risk of cardiovascular events.
- Among 232 236 patients in the GWTG-Stroke registry, admission eGFR was inversely associated with mortality and poor functional outcomes. After adjustment for potential confounders, lower eGFR was associated with increased mortality, with the highest mortality among those with eGFR <15 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> without dialysis (aOR, 2.52 [95% CI, 2.07–3.07]) compared with those 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>94</sup>
- In a retrospective observational cohort study (N=85 116 patients with incident nonvalvular AF), stroke rates increased from 1.04 events per 100 PY in stage 1 CKD to 3.72 in stage 4 to 5 CKD.<sup>95</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>96</sup> Notably, the mean±SD eGFR was 43.9±17.4 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> in females (22% had an eGFR <30 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>) and 45.7±16.4 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> in males (18% had an eGFR <30 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>).
- In the ARIC study cohort (N=12 588 participants; median follow-up time, 24.2 years), those in the top quartile of concentration of the liver enzyme γ-glutamyl transpeptidase compared with those in the lowest 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>97</sup> There was a dose-response association ( $P_{\text{trend}} < 0.001$ ).
- A systematic review of 33 studies (N=10 592 851) examined whether MASLD was associated with cardiovascular events.<sup>98</sup> The pooled OR found that

MASLD was associated with stroke (1.6 [95% CI, 1.2–2.1]), MI (1.6 [95% CI, 1.5–1.7]), AF (1.7 [95% CI, 1.2–2.3]), and major adverse cardiovascular and cerebrovascular events (2.3 [95% CI, 1.3–4.2]).

### Stroke After Procedures and Surgeries

- In a meta-analysis of 13 studies among patients undergoing TAVR, including 8 randomized trials and 5 observational studies (N=128 471 patients), embolic protection device use was associated with a reduction in risk of stroke (OR, 0.84 [95% CI, 0.74–0.95]) and disabling stroke (OR, 0.37 [95% CI, 0.21–0.67]) but not nondisabling stroke (OR, 0.94 [95% CI, 0.65–1.37]).<sup>99</sup>
- 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>100</sup> Axillary cannulation (OR, 0.60 [95% CI, 0.49–0.73]) and retrograde cerebral perfusion (OR, 0.75 [95% CI, 0.61–0.93]) were associated with lower risk of postoperative stroke.
- In a meta-analysis of 11 controlled studies (N=3667 patients) of patients undergoing Stanford type B thoracic aortic dissection repair, the endovascular approach was associated with lower risk of stroke than open surgery (3.7% versus 5.0%; RR, 0.71 [95% CI, 0.51–0.98]).<sup>101</sup>
- In a retrospective observational registry analysis using the Nationwide Readmissions Database, among 42 114 admissions for LAAO, early stroke (during index admission or within 90 days) occurred in 0.63% of patients; 67% of readmissions with strokes occurred <45 days after implantation.<sup>102</sup> Rates of early stroke after LAAO declined from 2016 to 2019 (0.64% versus 0.46%;  $P_{\text{trend}} < 0.001$ ).
- In a meta-analysis of 14 published real-world cohorts of patients undergoing cardiac catheterizations (N=2 188 047 catheterizations), the pooled incidence of perioperative stroke was 193 (95% CI, 105–355) per 100 000.<sup>103</sup> Transradial access was associated with a lower risk of perioperative stroke than transfemoral access in adjusted analyses (OR, 0.66 [95% CI, 0.49–0.89]) and in the subgroup limited to prospective cohorts (OR, 0.67 [95% CI, 0.48–0.94]). No independent predictors of perioperative stroke risk were identified.
- 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>104</sup>
- In a meta-analysis among 22 studies of patients undergoing LVAD implantation (N=53 227 patients; 24.2% female), females had a higher risk of total

stroke (OR, 1.32 [95% CI, 1.06–1.66]), ischemic stroke (OR, 1.80 [95% CI, 1.22–2.64]), and hemorrhagic stroke (OR, 1.72 [95% CI, 1.09–2.70]).<sup>105</sup>

- In a nationwide prospective cohort study from Denmark (N=78 096 patients ≥65 years of age undergoing hip fracture surgery), patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score >5 had a higher risk of ischemic stroke at 1 year compared with those with a score of 1 among those both with and without AF (for those with AF: 1.9% versus 8.6%; aHR 5.53 [95% CI, 1.37–22.24]; for those without AF: 1.6% versus 7.6%; aHR, 4.91 [95% CI, 3.40–7.10]).<sup>106</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>107</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]; ≥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>108</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>109</sup>
- In a systematic review and meta-analysis of 16 cohort studies and 2 case-control studies including 7.8 million participants, females who had a miscarriage or stillbirth had a higher risk of stroke (HR, 1.07 [95% CI, 1.00–1.14] and 1.38 [95% CI, 1.11–1.71], respectively). This increased with each additional miscarriage and stillbirth.<sup>110</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>111</sup>

- 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 ≥5 kg) but not in males.<sup>112</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>113</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>114</sup> The aHR for nonsteroidal anti-inflammatory drug use ≥24 d/mo was 2.29 (95% CI, 1.36–3.84).
- 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 PY versus 3.61 per 1000 PY; aHR, 1.23 [95% CI, 1.05–1.44]).<sup>115</sup>
- Among people living with HIV, females had a higher incidence of stroke or TIA than males, especially at younger ages.<sup>116</sup> Compared with females without HIV, females living with HIV had a 2-fold higher incidence of ischemic stroke.<sup>117</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 delivery (RR, 2.83 [95% CI, 2.20–3.63]).<sup>118</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.)

- Among 6214 participants without history of stroke in the ELSA dataset, over 8 years of follow-up, compared with those with good sleep quality, poor baseline sleep quality was associated with long-term stroke risk (HR, 2.37 [95% CI, 1.44–3.91]).<sup>119</sup> Worsened sleep quality was associated with stroke risk among those with baseline good (HR, 2.08

[95% CI, 1.02–4.26]) and intermediate (HR, 2.15 [95% CI, 1.16–3.98]) sleep quality; improved sleep quality was associated with decreased stroke risk among those with baseline poor sleep quality (HR, 0.31 [95% CI, 0.15–0.61]).

- Among 4785 Chinese adults >65 years of age in the 2011 CHARLS, short and long sleep durations were not associated with stroke risk in those who reported good general health status.<sup>120</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>121</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>122</sup>

## Psychosocial Factors

### Psychological Distress

- 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>123</sup>
- In a prospective cohort study in Australia (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>124</sup>
- Among 20 688 adults with hypertension in the China Stroke Primary Prevention Trial, those who reported high levels of psychological stress had 1.40 times the risk of first stroke (95% CI, 1.01–1.94) and 1.45 times the risk of first ischemic stroke (95% CI, 1.01–2.09) compared with those who reported low levels of psychological stress.<sup>125</sup>
- In a meta-analysis of 8 cohort studies involving 3.7 million participants, having posttraumatic stress disorder was associated with higher risk for stroke (HR, 1.59 [95% CI, 1.36–1.86]).<sup>126</sup>

### Depression and Depressive Symptoms

- In a meta-analysis of 17 prospective cohort studies involving 57 761 participants, depressive disorder or depressive symptoms were associated with higher stroke risk (HR, 1.39 [95% CI, 1.22–1.58]).<sup>127</sup>
- In INTERSTROKE there was an increased odds of acute stroke in people with depressive symptoms compared with those without depressive symptoms (OR, 1.46 [95% CI, 1.34–1.58]), and the odds of stroke increased as the number of depressive symptoms increased.<sup>128</sup>
- In REGARDS (N=16 368; ≥45 years of age), persistently elevated depressive symptoms were associated with higher risk of incident stroke in Black participants without diabetes (HR, 2.64 [95% CI, 1.48–4.72]) but not in White participants without diabetes (HR, 1.06 [95% CI, 0.50–2.25]).<sup>129</sup>
- In REGARDS, depressive symptom score assessed by the 4-item Center for Epidemiological Studies Depression scale was associated with incident stroke.<sup>130</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.
- Among 1 068 117 older adults in the Information System for Research in Primary Care of Catalonia, antidepressant medication use was associated with increased risk for stroke (current users: HR, 1.04 [95% CI, 1.02–1.06]; recent users: HR, 3.34 [95% CI, 3.27–3.41]; and past users: HR, 2.06 [95% CI, 2.02–2.10]) compared with antidepressant nonusers.<sup>131</sup>
- Among 7108 CHARLS participants followed up for 8 years, those with depressive symptoms but no chronic diseases had 1.66 times the risk of incident stroke (95% CI, 0.95–2.90), those with depressive symptoms and 1 chronic disease had 1.94 times the risk of incident stroke (95% CI, 1.17–3.24), and those with depressive symptoms and at least 2 chronic diseases had 3.00 times the risk of incident stroke (95% CI, 1.85–4.88) compared with those with no depressive symptoms and no chronic diseases.<sup>132</sup>

### Social Isolation and Loneliness

- 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>133</sup>

### Social Determinants of Health/Health Equity

- A meta-analysis of cohort and case-control studies between January 2000 and May 2022 examined the association between SES and health-related quality of life after stroke and found that across all SES indicators, people with stroke who have lower SES have poorer overall health-related quality of life than those with higher SES. In the “global” meta-analysis combining different SES indicators in 17 studies, health-related quality of life among survivors of stroke was lower in the low-SES group than in the high-SES group (SMD, −0.36 [95% CI, −0.52 to −0.20];  $P<0.0001$ ). Similar results were found when education and income indicators were used separately (low- versus high-education SMD, −0.38 [95% CI, −0.57 to −0.18];  $P<0.0001$ ; low-versus high-income SMD, −0.39 [95% CI, −0.59 to −0.19];  $P<0.0001$ ).<sup>134</sup>
- A cohort study of 3024 Black adult participants in the JHS without prevalent CVD at visit 1 (2000–2004) assessed the association of economic food insecurity and risk of incident CHD, HF, and stroke. In an analysis adjusted for cardiovascular risk and socioeconomic factors, economic food insecurity (defined as receiving food stamps or self-reported not enough money for groceries) was associated with higher risk of incident CHD (HR, 1.76 [95% CI, 1.06–2.91]) and incident HFrEF (HR, 2.07 [95% CI, 1.16–3.70]) but not stroke.<sup>135</sup>
- In a multi-institutional, retrospective cohort study of consecutively hospitalized patients with radiographically confirmed stroke and SARS-CoV-2 presenting from March through November 2020, 159 patients across 5 Comprehensive Stroke Centers in metropolitan Chicago, IL, were assessed to determine whether household income was associated with functional outcomes after stroke and COVID-19. Ischemic stroke occurred in 115 patients (72.3%; median NIHSS score, 7; interquartile range, 0.5–18.5) and hemorrhagic stroke in 37 (23.7%). When age, sex, severe COVID-19, and NIHSS score were controlled for, patients with ischemic stroke and household income above the Chicago median were more likely to have a good functional outcome at discharge (OR, 7.53 [95% CI, 1.61–45.73];  $P=0.016$ ).<sup>136</sup>
- In the United States in 2019, males had a lower relative burden of stroke mortality, which ranked fifth and accounted for 4.4% of deaths, compared with females, for whom it ranked third and accounted for 6.2% of deaths.<sup>137</sup>

- Females have a higher lifetime risk of stroke than males. In the Framingham original cohort, 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>138</sup>
- In the GCNKS, 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>139</sup>
- A cohort study of cardiovascular events in transgender individuals enrolled 2842 transfeminine and 2118 transmasculine participants with a mean follow-up of 4.0 and 3.6 years, respectively.<sup>140</sup> Incident strokes occurred in 54 transfeminine participants or 4.8 events (95% CI, 3.7–6.3) per 1000 PY and 16 transmasculine participants or 2.1 events per 1000 PY. The adjusted cumulative incidence rate of ischemic stroke among transfeminine women who initiated estrogen therapy compared with cisgender women was increased by 37.2% (95% CI, 2.1%–62.8%) and increased by 27.2% compared with cisgender men (95% CI, −2.7% to 50.7%). A systematic review examined the risk of CVD in transgender people.<sup>141</sup> The meta-analysis of 10 studies showed that transwomen had 1.3 times higher risk of stroke (95% CI, 1.0–1.8) compared to cisgender men and transmen had 1.3 times higher risk of stroke (95% CI, 1.0–1.6) compared with cisgender women.
- A systematic review conducted between January 2008 and July 2021 looked at sex differences in ischemic strokes among young adults (18–45 years of age).<sup>142</sup> Overall, in young adults  $\leq 35$  years of age, the estimated effect size favored more ischemic strokes in females (IRR, 1.44 [95% CI, 1.18–1.76];  $P=82\%$ ) and a nonsignificant sex difference in young adults 35 to 45 years of age (IRR, 1.08 [95% CI, 0.85–1.38];  $P=95\%$ ).
- A systematic review and meta-analysis through 2020 in Latin America and the Caribbean focused on individuals  $\geq 18$  years of age and found a higher stroke incidence among males than females.<sup>143</sup> The overall pooled stroke incidence was 255 (95% CI, 217–293) per 100 000 PY, with higher incidence rates in males (261 [95% CI, 221–301]) compared with females (217 [95% CI, 184–250]) per 100 000 PY.
- In NOMAS, among 3298 stroke-free participants recruited between 1993 and 2001, the greatest incidence rate was observed in Black individuals (13/1000 PY) followed by Hispanic individuals (10/1000 PY), and lowest rate was seen in White

individuals (9/1000 PY).<sup>144</sup> However, by 85 years of age, the greatest incidence rate was in Hispanic individuals. The increased rate among Hispanic individuals was largely explained by education and insurance status but remained significant for females  $\geq 70$  years of age (aHR, 1.48 [95% CI, 1.13–1.93]).

- A cohort study compared Black participants and White participants in the SPRINT trial with the same groups in the observational ARIC study to assess whether clinical trial participation mitigated disparities in stroke risk.<sup>145</sup> The risk of stroke between self-reported White participants in SPRINT and ARIC was not significantly different (inverse propensity-weighted HR 0.78 [0.52–1.19]). Black ARIC participants were twice as likely to have a stroke as White ARIC participants (inverse propensity-weighted HR, 1.96 [95% CI, 1.41–2.71]), but Black SPRINT participants did not have higher stroke risk compared with self-reported White SPRINT or White ARIC participants (inverse propensity-weighted HR, 0.99 [95% CI, 0.68–1.77] and 0.95 [95% CI, 0.57–1.59], respectively). Black SPRINT participants in the intensive BP control group had a lower risk of stroke compared with Black ARIC participants (inverse propensity-weighted HR, 0.39 [95% CI, 0.20–0.75]). The authors concluded that the absence of the racial disparity in stroke incidence in SPRINT indicated that aspects of the disparity are modifiable.
- A retrospective cohort of Black participants and White participants in the ARIC, MESA, and REGARDS studies (1983–2019) compared the performance of stroke-specific algorithms with PCE developed for ASCVD for the prediction of new-onset stroke.<sup>146</sup> The study looked at 62 482 participants who were at least 45 years of age and free of stroke or TIA. Significant differences in discrimination were observed by race: C indexes were 0.76 for all 3 models in White females versus 0.69 in Black females (all  $P < 0.001$ ) and between 0.71 and 0.72 in White males and between 0.64 and 0.66 in Black males (all  $P > 0.001$ ). All algorithms exhibited worse discrimination in Black individuals than in White individuals, suggesting a need to expand the pool of risk factors and improve modeling techniques to address observed racial disparities and improve model performance.
- A retrospective observational study of patients presenting to the Yale New Haven Hospital with AIS from 2010 to 2020 classified patients as presenting early (within 4.5 hours from last known well) or late (beyond 4.5 hours).<sup>147</sup> A total of 2643 patients with AIS were included (36.6% presented early and 63.4% presented late). Patients presenting late were more likely to be Black or African American, Asian,

Pacific Islander, American Indian or Alaska Native, or undetermined race than White race (37.1% versus 26.9%;  $P < 0.0001$ ); to arrive by means other than EMS (32.7% versus 16.1%;  $P < 0.0001$ ); to have an NIHSS score  $< 6$  (68.7% versus 55.2%;  $P < 0.0001$ ); and to present from a neighborhood with a higher Area Deprivation Index category ( $P = 0.0001$ ) that was nearer to the hospital (median, 5.8 miles versus 7.7 miles;  $P = 0.0032$ ). Being of Black or African American race, Asian, Pacific Islander, American Indian or Alaska Native, or undetermined race (OR, 1.083 [95% CI, 1.039–1.127]); Area Deprivation Index by units of 10 (OR, 1.022 [95% CI, 1.020–1.024]); arrival by means other than EMS (OR, 1.193 [95% CI, 1.145–1.124]); and an NIHSS score  $< 6$  (OR, 1.085 [95% CI, 1.041–1.129]) were associated with late presentation.

- In a study of NH White females and Black females from the WHI (N=126018, 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>148</sup> Adjustment for socioeconomic factors and stroke risk factors attenuated this association, although the higher risk for Black females remained statistically significant in those 50 to  $< 60$  years of age (HR, 1.76 [95% CI, 1.09–2.83]).
- In an analysis of pooled SHS and ARIC data, there were 2842 stroke events (7.6%) among 3182 American Indian participants without prior stroke followed up from 1988 to 2008; there were 613 stroke events (5.9%) 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>149</sup>
- A retrospective study of 34 596 patients admitted to 43 hospitals from January 2016 to September 2020 assessed racial disparities in mechanical thrombectomy in 26 640 NH White individuals (77.0%) and 7956 Black individuals (23.0%) and found that Black individuals with stroke underwent mechanical thrombectomy less frequently than White individuals (aOR, 0.65 [95% CI, 0.54–0.76]), in part because of longer times from last known well to hospital arrival and a lower rate of documented acute large-vessel occlusion (see Organization of Stroke Care section).<sup>150</sup>

## TIA: Incidence and Prognosis

- Among 14 059 participants in the FHS (1948–2017), the incidence of TIA was 1.19 per 1000 PY.<sup>151</sup> In those with a TIA (median follow-up, 8.9 years), 29.5% had a stroke with a median time to

stroke of 1.64 years (interquartile range, 0.07–6.6 years). Compared with age- and sex-matched control subjects without TIA, participants who experienced a TIA were at a higher risk of stroke (aHR, 4.37 [95% CI, 3.30–5.71]). The 90-day stroke risk after TIA was 16.7% in the period of 1948 to 1985, 11.1% between 1986 and 1999, and 5.9% from 2000 to 2017 (HR for 90-day risk of stroke for the epoch 2000–2017 compared with 1948–1985, 0.32 [95% CI, 0.14–0.75]).

- TIA confers a substantial short-term risk of stroke, hospitalization for CVD events, and death. 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>152</sup> When studies were categorized according to date of publication (before 1999, 1999–2007, after 2007), the risk of subsequent ischemic stroke slightly declined over time.
- In the Oxford Vascular Study, acute lesions on MRI were identified in 13% of participants with TIA.<sup>153</sup> In age- and sex-adjusted analyses, participants with acute MRI lesions 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 substudy of the SpecTRA multicenter cohort of participants with transient neurological symptoms, MRI diffusion-weighted imaging performed within 7 days of an event identified a lesion in 35.1% of participants.<sup>154</sup> Among participants with focal symptoms, increased duration of symptoms (up to 24 hours) was directionally proportional to the probability of identifying a lesion (ranging from 30% at <1 hour duration to 72% at 24 hours). This relationship was not present among those with mixed or nonfocal symptoms, in whom the predicted probability of a lesion was 35%.
- Among patients with TIA enrolled in the POINT trial, 188 of 1964 patients (9.6%) enrolled with TIA had an mRS score <1 (some disability) at 90 days.<sup>155</sup> In multivariable analysis, age, subsequent ischemic stroke, serious adverse events, and major bleeding were significantly associated with disability in TIA.
- TIA also may be associated with cognitive decline. In an individual participant meta-analysis of 6 RCTs testing various interventions among patients with or at risk of vascular disease (N=64 106 patients) in which cognitive performance was measured before and after outcome events, cognitive aging was estimated from normalized neuropsychological test scores.<sup>156</sup> Compared with those with no event, patients with stroke experienced 18 years

(95% CI, 10–28;  $P<0.0001$ ) of cognitive aging and those with TIA experienced 3 years (95% CI, 0–6;  $P=0.021$ ) of cognitive aging, whereas MI ( $P=0.60$ ) and other hospitalizations ( $P=0.26$ ) were not associated with cognitive aging.

## Recurrent Stroke: Incidence, Race and Ethnicity, and Risk Factors

- 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>157</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>158</sup>
- Among 1701 community-living participants in the Rotterdam Study who had a first stroke between 1990 and 2020, the overall 10-year recurrence risk was 18.0% (95% CI, 16.2%–19.8%), 19.3% (95% CI, 16.3%–22.3%) in males, and 17.1% (95% CI, 14.8%–19.4%) in females.<sup>159</sup> Recurrent stroke risk declined substantially over time, with a 10-year risk of 21.4% (95% CI, 17.9%–24.9%) between 1990 and 2000 and 11.0% (95% CI, 8.3%–13.8%) between 2010 and 2020.
- Among 396 patients 18 to 55 years of age with ischemic stroke or TIA from 3 European centers in 2007 to 2010, the cumulative 10-year incidence rate per 1000 PY was 14.9 (95% CI, 11.3–19.3) for any recurrent cerebrovascular event.<sup>160</sup>
- A meta-analysis of 13 cohorts with 59 919 participants found that MetS was associated with higher risk of recurrent stroke (RR, 1.46 [95% CI, 1.07–1.97]).<sup>161</sup>
- The IPSS compared outcomes after posterior circulation arterial ischemic stroke and anterior circulation arterial ischemic stroke in neonates and children with AIS up to 18 years of age.<sup>162</sup> Recurrent ischemic events were more frequent in posterior circulation arterial ischemic stroke than anterior circulation arterial ischemic stroke (30% versus 22%;  $P=0.02$ ) despite similar rates of secondary preventive antithrombotic treatment. Multivariable logistic regression analysis found that posterior circulation arterial ischemic stroke (OR, 1.69 [95% CI, 1.08–2.65];  $P=0.02$ ) and cervicocephalic artery dissections (OR, 2.39 [95% CI, 1.36–4.22];  $P=0.003$ ) were risk factors for recurrent ischemic events in children.
- Clinical features associated with recurrent stroke among participants enrolled in the RE-SPECT ESUS trial were assessed.<sup>163</sup> A total of 384 of

5390 participants had recurrent stroke (annual rate, 4.5%) over a median follow-up of 19 months. Multivariable models revealed that stroke or TIA before the index event (HR, 2.27 [95% CI, 1.83–2.82]), creatinine clearance <50 mL/min (HR, 1.69 [95% CI, 1.23–2.32]), male sex (HR, 1.60 [95% CI, 1.27–2.02]), and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of 4 (HR, 1.55 [95% CI, 1.15–2.08]) and ≥5 (HR, 1.66 [95% CI, 1.21–2.26]) versus CHA<sub>2</sub>DS<sub>2</sub>-VASc scores of 2 to 3 were independent predictors for recurrent stroke.

- A post hoc cohort study was conducted using data from the CNSR from 2007 to 2018 and included patients with ischemic stroke who were enrolled in CNSR in phases I or III within 7 days of symptom onset.<sup>164</sup> Over 10 years, the adjusted cumulative incidence of recurrent stroke within 12 months decreased from 15.5% (95% CI, 14.8%–16.2%) to 12.5% (95% CI, 11.9%–13.1%;  $P<0.001$ ). Although the stroke recurrence rate in China decreased significantly, ≈12.5% of patients still experienced stroke recurrence within 12 months.
- Among 128 789 Medicare beneficiaries from 1999 to 2013, the incidence of recurrent stroke per 1000 PY 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 1-year risk of recurrent stroke (aHR, 1.36 [95% CI, 1.29–1.44]).<sup>165</sup>
- 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>166</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>167</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>168</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 low or no adherence.<sup>169</sup>
- Data from 2015 to 2019 in 1458 hospitals in China found that an increase of 10 µg/m<sup>3</sup> in PM1 (particles with aerodynamic diameter <1 µm) was associated with a 1.64% increment in stroke recurrence.<sup>170</sup>
- In a multicenter Japanese registry (N=12 576 patients with ischemic stroke), both eGFR<45 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> (aHR compared with eGFR ≥60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>, 1.22 [95% CI, 1.09–1.37]) and severe proteinuria (aHR, 1.25 [95% CI, 1.07–1.46]) were independently associated with increased risk of recurrent stroke (overall rate of recurrent stroke was 48.0 per 1000 patient-years).<sup>171</sup>
- In a meta-analysis of 52 studies (N=21 473 patients with stroke), of which 19 studies were adjusted for potential confounding variables, high D-dimer concentrations within 24 hours of stroke (compared with normal for each study) were associated with stroke recurrence (OR, 1.23 [95% CI, 1.11–1.36]) and early neurological deterioration (OR, 1.79 [95% CI, 1.12–2.87]).<sup>172</sup> High fibrinogen concentrations were associated with stroke recurrence (OR, 1.23 [95% CI, 1.17–1.42]) and early neurological deterioration (OR, 2.38 [95% CI, 1.16–4.9]).
- In an individual participant meta-analysis (10 prospective studies, N=8420 patients with ischemic stroke/TIA), interleukin-6 (RR, 1.09 [95% CI, 1.00–1.19]) and high-sensitivity CRP (RR, 1.05 [95% CI, 1.00–1.11]) were marginally associated with recurrent stroke after adjustment for risk factors and treatment.<sup>173</sup>
- In a meta-analysis of 4 studies (N=2452 patients with ischemic stroke), uric acid concentrations were independently associated with risk of recurrent stroke (pooled OR, 1.80 [95% CI, 1.47–2.20]).<sup>174</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>175</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 Jisei 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 an mRS score of 0 to 2 at 3 months (OR, 2.89 [95% CI, 1.38–6.05];  $P=0.005$ ).<sup>176</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 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>177</sup>

## Genetics and Family History

- Ischemic stroke is heritable, although heritability estimates vary by ischemic stroke subtype.<sup>178</sup> A study of  $n=3752$  patients with ischemic strokes and  $n=5972$  control subjects 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%).
- 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>179</sup>
- The largest multiancestry GWAS of stroke conducted to date reported 32 genetic loci for any stroke or stroke subtypes.<sup>180</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.
- Because previous multiancestry stroke GWASs were conducted primarily in European ancestral populations, GWASs in populations with proportionately greater representation of non-European participants also have been conducted.<sup>181</sup> One study in 5 ancestries (33% non-European) with  $n=110\,182$  cases and  $n=1\,503\,898$  controls identified 61 novel independent loci for stroke and stroke subtypes. Putative causal genes included *SH3PXD2A*, *FURIN*, *GRK5*, and *NOS3*, and lead variant effect sizes were highly correlated across ancestral populations. Cross-ancestry and ancestry-specific GRSs predicted ischemic stroke in African populations, East Asian populations, and European populations independently of risk factors.

- Recognizing stroke disparities in African populations, GWASs in African populations are emerging. The first (and only) GWAS of ischemic stroke in indigenous African populations ( $N=1683$  cases) identified 2 risk-reducing loci at or near *AADACL2* and *MIR5186*.<sup>182</sup> It is interesting that neither locus was observed in stroke GWASs conducted in African American or European ancestry populations. Potential reasons for poor transferability include heterogeneity by ancestral background or small-vessel disease stroke subtype.
- Some stroke genetic loci may be subtype specific.<sup>180</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* shared influence 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>183</sup> Other genes strongly implicated in ICH are *PMF1* and *SLC25A44*, which have been linked to ICH with small-vessel disease.<sup>184,185</sup>
- A multiancestry 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>186</sup>
- An initial GWAS of small-vessel stroke from the International Stroke Consortium ( $n=4203$  cases and  $n=50\,728$  controls) identified a novel association with a region on chromosome 16q24.2.<sup>187</sup> A follow-up study that included  $n=7338$  cases and  $n=254\,798$  controls identified 5 loci in European or transethnic meta-analysis (*ICA1L-WDR12-CARF-NBEAL1*, *ULK4*, *SPI1-SLC39A13-PSMC3-RAPSN*, *ZCHC14*, and *ZBTB14-EPB41L3*).<sup>188</sup> By extending analyses to simultaneously consider cerebral WMHs 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.
- GWASs also have examined early-onset ischemic stroke. One study of participants 18 to 59 years of age ( $n=16\,730$  cases and  $n=599\,237$  controls from 48 studies) identified 2 independent variants at *ABO*, a known stroke locus.<sup>189</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>190</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. Low-frequency coding variants also may affect ischemic stroke risk, including variants at *ABO*, *TPTE*, *MEP1A*, and *DDX31*.<sup>191</sup> However, the rarity of these variants has made replication challenging.

- Stroke GWASs are now being extended to evaluate genetic correlates of recovery.<sup>192,193</sup> For example, in the VISP study (N=488), suggestive ( $P<5\times 10^{-6}$ ) evidence of association with motor improvement was identified for 115 new loci. These suggestive loci included variants with putative roles in neuronal repair and did not overlap with loci previously identified for stroke.
- 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>194</sup>
- Genetic determinants of coagulation factors, including factor XI and factor VII, have been implicated in the pathogenesis of ischemic stroke.<sup>195,196</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>197</sup>

## Awareness

- Awareness of stroke symptoms and signs among US adults 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>198</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>199</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 control subjects.<sup>200</sup>

- A retrospective ecological study assessed whether Face, Arm, Speech, Time (abbreviated F.A.S.T. for public health messaging) public awareness campaigns in the general population increased activations of EMS for potential stroke in Quebec, Canada, from 2015 to 2019.<sup>201</sup> After 5 campaigns of median duration 9 weeks each, mean daily EMS calls increased by 28% ( $P<0.001$ ) for any suspected stroke and by 61% ( $P<0.001$ ) for stroke with symptom onset  $<5$  hours compared with 10.1% for headache (negative control;  $P=0.012$ ). Three of the 5 individual campaigns led to increases in daily EMS calls for stroke (highest OR, 1.26 [95% CI, 1.11–1.43]). There were no significant changes in calls after individual campaigns for suspected stroke with symptom onset  $<5$  hours.

## Stroke Mortality

### (See Table 15-1 and Charts 15-4 through 15-6)

- In 2022 (unpublished NHLBI tabulations using CDC WONDER<sup>202</sup> and the NVSS<sup>203</sup>):
  - On average, someone died of a stroke every 3 minutes 11 seconds.
  - Stroke accounted for  $\approx 1$  of every 20 deaths in the United States.
  - When considered separately from other CVDs, stroke ranks fifth among all causes of death, behind diseases of the heart, cancer, unintentional injuries/accidents, and COVID-19.
  - The number of deaths with stroke as an underlying cause was 165 393 (Table 15-1); the age-adjusted death rate for stroke as an underlying cause of death was 39.5 per 100 000, whereas the age-adjusted rate for any mention of stroke as a cause of death was 71.6 per 100 000.
  - Approximately 65% 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 56.6% of US stroke deaths in 2022.
- Conclusions about changes in stroke death rates from 2012 to 2022 are as follows<sup>202</sup>:
  - The age-adjusted stroke death rate increased 7.0% (from 36.9 per 100 000 to 39.5 per 100 000), whereas the actual number of stroke deaths increased 28.7% (from 128 546 to 165 393 deaths).

- Age-adjusted stroke death rates increased 9.2% for males and 5.8% for females.
- Crude stroke death rates remained the same among people 25 to 34 years of age (0.0%; from 1.3 to 1.3 per 100 000) and increased among people 35 to 44 years of age (14.0%; from 4.3 to 4.9 per 100 000), 45 to 54 years of age (7.8%; from 12.8 to 13.8 per 100 000), 55 to 64 years of age (17.4%; from 28.7 to 33.7 per 100 000), 65 to 74 years of age (11.0%; from 75.7 to 84.0 per 100 000), and >85 years of age (12.1%; from 931.2 to 1043.9 per 100 000). In comparison, the crude stroke death rates declined among those 75 to 84 years of age (−2.6%; 272.2 to 265.0 per 100 000). There has been a recent flattening of or increase in death rates among most age groups (Charts 15-4 and 15-5).
- There are substantial geographic disparities in stroke mortality, with higher rates in the southeastern United States known as the Stroke Belt (2018–2020; Chart 15-6). 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>204</sup>

### Racial and Ethnic Disparities

#### (See Chart 15-7)

- In 2022, NH Black males and females had higher age-adjusted death rates for stroke than NH White males and females, NH Asian males and females, NH Native Hawaiian or Other Pacific Islander males and females, NH American Indian or Alaska Native males and females, and Hispanic males and females in the United States (except NH Native Hawaiian or Other Pacific Islander females, who had the highest age-adjusted death rate among females; Chart 15-7).
- Age-adjusted stroke death rates increased among all racial and ethnic groups; however, in 2022, rates remained higher among NH Black people (57.2 per 100 000; change since 2018, 7.9%) than among NH White people (38.3 per 100 000; change since 2018, 6.4%), NH Asian people (30.3 per 100 000; change since 2018, 3.8%), NH Native Hawaiian or Other Pacific Islander (52.7 per 100 000; change since 2018, 13.1%), NH American Indian or Alaska Native people (30.3 per 100 000; change since 2018, −1.3%), and Hispanic people (35.3 per 100 000; change since 2018, 10.3%).<sup>202</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>7</sup>

### Complications and Recovery

#### 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>205</sup>
- In the Swedish Stroke Registry (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; mRS score ≥3) at 12 months<sup>206</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 a meta-analysis of 22 studies including 5125 participants, the prevalence of lateropulsion (pusher syndrome) after stroke was 55.1% (95% CI, 35.9%–74.2%).<sup>207</sup> This decreased from 52.8% (95% CI, 40.7%–65%) in the acute phase to 37% (95% CI, 26.3%–47.7%) in the early subacute phase and 22.8% (95% CI, 0%–46.3%) in the late subacute phase.
- In a meta-analysis of 55 studies, 56.7% (95% CI, 48.3%–65.1%) of people returned to work after stroke at 1 year and 66.7% (95% CI, 60.2%–73.2%) returned at 2 years in population-based studies.<sup>208</sup>

#### Comorbid 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>209</sup>

- 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>210</sup>
- In a meta-analysis of 26 366 participants from 42 studies, the prevalence of poststroke dysphagia was 42%.<sup>211</sup> Poststroke dysphagia was associated with high risk of pneumonia (OR, 4.08 [95% CI, 2.13–7.79]) and mortality (OR, 4.07 [95% CI, 2.17–7.63]). Factors associated with increased risk of poststroke dysphagia include hemorrhagic stroke type (OR, 1.52 [95% CI, 1.13–2.07]), prior stroke (OR, 1.40 [95% CI, 1.18–1.67]), severe stroke (OR, 1.38 [95% CI, 1.17–1.61]), female sex (OR, 1.25 [95% CI, 1.09–1.43]), and diabetes (OR, 1.24 [95% CI, 1.02–1.51]).
- 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>212</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 a sensitivity of 82.6% and specificity of 59.8%. The addition of the panel to clinical predictors significantly improved the AUCs of receiver-operating characteristic curves for both outcomes.
- 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/h was 71% (95% CI, 66.6%–74.8%) and with AHI >30 episodes/h was 30% (95% CI, 24.4%–35.5%).<sup>213</sup> Severity and prevalence of SDB were similar at all time periods after stroke.
- In the BASIC project, Mexican American people had a higher prevalence of poststroke SDB, defined as an AHI ≥10, than NH White people (68.5% versus 49.5%) after adjustment for confounders (PR, 1.21 [95% CI, 1.01–1.46]).<sup>214</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>215</sup>

## Depression

- 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>216</sup>
- In a secondary analysis of a randomized, multi-center, 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>217</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>218</sup>
- In a secondary analysis of the AFFINITY trial including 1221 participants recruited within 2 weeks of stroke and randomized to fluoxetine or placebo, 36.6% of participants developed depression in the year after their stroke (17.9% had early, 7.4% had late, and 11.4% had persistent depression).<sup>219</sup> Increased stroke severity, defined as doubling of the measured NIHSS score, was associated with increased risk of early (RR, 2.08 [95% CI, 1.65–2.62]), late (RR, 1.53 [95% CI, 1.14–2.06]), and persistent (RR, 2.50 [95% CI, 1.89–3.32]) depression. In addition, history of depression and having a partner were associated with increased risk of persistent depression (RR, 6.28 [95% CI, 2.88–13.71] and 3.94 [95% CI, 2.42–6.41], respectively).

## Functional Impairment

Functional and cognitive impairment and dementia are common after stroke, with the incidence increasing with duration of follow-up.

- In secondary analysis of the AFFINITY RCT evaluating the use of fluoxetine after stroke, improvement in the mRS score was observed in 95% of participants at 12 months.<sup>220</sup> Functional recovery was associated with younger age (<70 years of age at time of stroke); absence of prestroke history of diabetes, CHD, or ischemic stroke; prestroke history of depression, relationship with a partner, living with

others, independence, or paid employment; absence of fluoxetine intervention; ischemic stroke (versus hemorrhagic stroke); and lower baseline NIHSS and Patient Health Questionnaire-9 scores.

- In the EFFECTS cohort of 1367 participants with stroke, there were 2 distinct PA trajectories observed within the first 6 months after a stroke: those who increased their PA and sustained it, and those who decreased their PA and eventually became inactive.<sup>84</sup> In this cohort, increased PA within the first 6 months after a stroke was associated with functional recovery at 6 months (aOR, 2.54 [95% CI, 1.72–3.75]).
- In a substudy of the prehospital FAST-MAG RCT, ultraearly rapid neurological improvement, defined as an improvement of  $\geq 2$  on the Los Angeles Motor Scale between prehospital and early after the ED, in ischemic stroke or TIA occurred in 31% of patients (N=1245).<sup>221</sup> In addition, compared with those without, any ultraearly rapid neurological improvement was associated with an overall improved recovery (mRS score, 0–1 in 65% versus 35.4%;  $P<0.001$ ), increased probability of being discharged home (56.8% versus 30.2%;  $P<0.0001$ ), and reduced 90-day mortality (3.7% versus 16.4%;  $P<0.0001$ ).

#### Cognitive Impairment and Dementia

- In a study among 4 centers in Shanghai (N=383 patients with AIS), the prevalence of cognitive impairment (MoCA score <22) was 49.6% at 2 weeks and 34.2% at 6 months.<sup>222</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 AUC of 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>223</sup>
- In a multicenter cohort study of 912 patients with lacunar strokes and 425 control subjects, vascular cognitive impairment was identified in 38.8% of patients with lacunar strokes versus 13.4% of control subjects.<sup>224</sup> Factors associated with vascular cognitive impairment included diabetes (aOR, 1.98 [95% CI, 1.40–2.80]) and higher BMI (aOR, 1.03 [95% CI, 1.00–1.05]). On the other hand, years of full-time education was found to be associated with lower risk of vascular cognitive impairment (aOR, 0.92 [95% CI, 0.86–0.99]).

#### Stroke in Infants and Children

- Strokes occurring in childhood and the perinatal period ( $\leq 28$  days of age) are considered distinct entities because of differences in their treatment, diagnostic workup, risk factors, and secondary prevention measures.<sup>225</sup>

#### Perinatal Stroke Incidence

- In neonates ( $\leq 28$  days of age), the annual incidence of arterial ischemic stroke is 18.51 per 100 000 live births (95% CI, 12.70–26.97) according to a meta-analysis of 11 neonatal stroke studies.<sup>226</sup> The reported incidence of arterial ischemic stroke in neonates was  $\approx 6$  times higher than in older children in a large population-based Canadian study (neonates, 10.2/100 000 live births; childhood, 1.72/100 000 PY).<sup>227</sup> In a cohort of Northern California Kaiser members, the prevalence of perinatal hemorrhagic stroke was 6.2 in 100 000 live births (95% CI, 3.8–9.6), presenting with encephalopathy (100%) and seizures (65%).<sup>228</sup>

#### Childhood Stroke Incidence

- In children the annual incidence of arterial ischemic stroke is 1.28 per 100 000 (95% CI, 0.79–2.19) according to a meta-analysis of 11 childhood stroke studies.<sup>226</sup> The combined incidence rates for ischemic stroke compared across studies published before and after 2011 remained stable over time. Ischemic strokes are more common in Black children (2.62 per 100 000) than White children (1.01 per 100 000), according to a California-wide hospital discharge database (RR, 2.59 [95% CI, 2.17–3.09])<sup>229</sup> and a population-based cohort in southern England (RR, 2.28 [95% CI, 1.00–4.60]),<sup>230</sup> and are also more common in Asian children (2.92 [95% CI, 1.60–4.90] per 100 000) than White children (1.36 [95% CI, 1.06–1.74] per 100 000; RR, 2.14 [95% CI, 1.11–3.85]).<sup>230</sup> Most of the increased risk of ischemic stroke in Black children is explained by sickle cell disease, which increased stroke risk  $>200$  times (238 per 100 000 [95% CI, 78–556]) compared with those without (0.83 per 100 000) according to 18 childhood stroke cases captured in the Baltimore–Washington, DC, area.<sup>231</sup> Almost half of childhood strokes are hemorrhagic (49%), which includes ICH (33%) and SAH (16%), with a total estimated annual incidence of 1.1 hemorrhagic strokes per 100 000 children 0 to 19 years of age.<sup>229</sup>
- Reported incidence was higher in newborns than in older children (1/3500 live births/y versus 1–2/100 000 live births/y) with a ratio of  $\approx 6$  times higher.<sup>232</sup> A multicenter prospective study in Beijing included all live births from 17 representative maternal delivery hospitals from March 1, 2019,

to February 29, 2020.<sup>233</sup> A total of 27 cases were identified, and the incidence of perinatal stroke in Beijing was 1 in 2660 live births, including 1 in 5985 for ischemic stroke and 1 in 4788 for hemorrhagic stroke.

### Risk Factors

#### Perinatal

- Both maternal and neonatal factors are associated with perinatal strokes. A case-control study of 40 perinatal strokes and 120 controls nested in a cohort of 199 176 births in Kaiser Northern California found that history of infertility (OR, 7.5 [95% CI, 1.3–45.0]), oligohydramnios (OR, 5.4 [95% CI, 0.9–31.3]), preeclampsia (OR, 5.3 [95% CI, 1.3–22.0]), prolonged rupture of membranes (OR, 3.8 [95% CI, 1.1–12.8]), cord abnormality (OR, 3.6 [95% CI, 1.0–12.7]), chorioamnionitis (OR, 3.4 [95% CI, 1.1–10.5]), and primiparity (OR, 2.5 [95% CI, 1.0–6.4]) were significantly associated with perinatal strokes.<sup>234</sup> The risk of perinatal strokes increases with multiple risk factors ( $\geq 1$  risk factor: OR, 4.2 [95% CI, 1.4–14.8];  $\geq 2$  risk factors: OR, 6.5 [95% CI, 2.6–16.5];  $\geq 3$  risk factors: OR, 25.3 [95% CI, 7.9–87.1]).
- An Australian study compared 66 perinatal stroke cases with Australian general population data and found that 87% (52/60) of perinatal strokes had multiple risk factors.<sup>235</sup> The following risk factors were more common among perinatal strokes than the general population: cesarean delivery (50% versus 32%;  $P=0.04$ ), 5-minute Apgar score  $<7$  (16.7% versus 2.0%;  $P<0.01$ ), neonatal resuscitation (45.5% versus 19%;  $P<0.01$ ), and primiparity (64.8% versus 43%;  $P<0.01$ ).
- In a multicenter prospective study in Beijing that included 27 cases of perinatal stroke and 108 controls drawn from among 17 817 live births from 17 representative maternal delivery hospitals in 2019 to 2020, risk factors include primiparity (56% versus 33%;  $P=0.045$ ), placental or uterine abruption/acute chorioamnionitis (7% versus 1%;  $P=0.025$ ), intrauterine distress (59% versus 27%;  $P=0.002$ ), asphyxia/resuscitation (44% versus 8%;  $P<0.001$ ), and severe infection (15% versus 2%;  $P=0.015$ ).<sup>233</sup>

#### Childhood

- The causes of childhood stroke can be categorized into 3 broad groups: (1) structural genetic predisposition (congenital HD, genetic arteriopathies, collagen defect), (2) hematologic genetic predisposition (hereditary thrombophilia, sickle cell disease), and (3) acquired exposures (infection, trauma, radiation, drugs).<sup>236</sup>
- One study reviewed vascular imaging of 355 pediatric ischemic stroke cases and found 36%

with definite and 9.6% with possible arteriopathy, an acquired vascular pathology from infection.<sup>237</sup> The VIPS international case-control study of 326 pediatric AIS cases and 115 controls found that an active herpes infection, even if asymptomatic, defined by active immunoglobulin M antibody titers was associated with increased risk of stroke (OR, 2.2 [95% CI, 1.2–4.0]).<sup>238</sup> An international study including 61 centers in 21 countries found that 6.9% (23/335) of pediatric patients with ischemic stroke tested positive for SARS-CoV-2, which was the main cause in 6 cases, contributory in 13, and incidental in 3.<sup>239</sup>

- In an analysis of data from the IPSS from 2003 to 2014 (N=3253 children with ischemic stroke), 903 (28%) had cardiac disease as the primary cause of stroke, including 231 (7%) with isolated patent foramen ovale. Of the n=672 patients with cardiac disease not attributable to patent foramen ovale, 177 (26%) were periprocedural with index stroke occurring within 72 hours of cardiac surgery (n=92) or cardiac catheterization (n=63) or supported with mechanical device (n=24).<sup>240</sup> In a separate analysis of the IPSS, among 2768 cases of ischemic strokes, cardioembolism was less frequent in posterior circulation strokes (19% versus 32%;  $P<0.001$ ).<sup>162</sup>
- Without intervention, 10% of children with sickle cell disease will develop an ischemic stroke by adulthood.<sup>241</sup> In recent decades, the use of transcranial Doppler ultrasound for screening and the implementation of regular blood transfusion therapy for children exhibiting abnormal transcranial Doppler velocities have led to a 10-fold reduction in stroke prevalence among children with HbSS and HbS $\beta$  thalassemia in high-income countries.<sup>242</sup> An open-label phase 2 trial (SPHERE) in Tanzania showed that even initial therapy with hydroxyurea among children with sickle cell disease and elevated transcranial Doppler velocities reduced primary stroke risk (treatment with hydroxyurea decreased transcranial Doppler velocities to  $149\pm27$  cm/s compared with baseline of  $182\pm12$  cm/s;  $P<0.0001$ ).<sup>243</sup> A double-blinded RCT (SPIN) in Nigeria showed that for children with sickle cell who had a stroke in low-income countries, low-dose hydroxyurea is non-inferior to moderate-dose hydroxyurea for secondary stroke prevention (IRR of stroke or death in low versus moderate dose, 0.98 [95% CI, 0.30–4.88];  $P=0.74$ ).<sup>244</sup>

#### Complications

- A cohort study of 100 term newborns with arterial ischemic strokes with 7 years of follow-up found that 91% of children attended a regular school, 32% developed cerebral palsy, 20% experienced

seizures, and 28% experienced learning difficulties at school.<sup>245</sup> In a meta-analysis of school-aged children with intraventricular hemorrhage, there was 61% increased risk of hemiplegia (95% CI, 39.2%–82.9%), and 24.2-point lower IQ (95% CI, 17.7–30.7 points lower).<sup>246</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>247</sup> The sole predictor of recurrence was the presence of an arteriopathy, which increased the risk of recurrence 5-fold compared with previously healthy children with no risk identified after an appropriate stroke assessment (HR, 5.0 [95% CI, 1.8–14]).
- A retrospective study of 83 children first diagnosed with ischemic and hemorrhagic stroke at the Pediatric Department, Chiang Mai University Hospital between January 1, 2009, and December 31, 2018 followed up 51 patients with ischemic (56%) and 32 with hemorrhagic (35.2%) stroke, with a median age at onset of 6.9 years for ischemic and 5.3 years for hemorrhagic stroke.<sup>248</sup> The mortality rate was higher in hemorrhagic compared with ischemic stroke (16.6 [95% CI, 8.9–30.8] versus 1.1 [95% CI, 0.3–4.6] per 100 PY). Thirty children (36.1%) developed epilepsy during the follow-up (median duration, 26 months). Recurrent stroke occurred in 1 child with ischemic and 1 child with hemorrhagic stroke. Neurological deficits were seen in 70% of childhood ischemic strokes during the follow-up.

### Cost

- In a study of 111 pediatric stroke cases admitted to a single American 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>249</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>250</sup>

### Stroke in Young Adults and in Midlife

- Approximately 10% to 20% of strokes occur in adults <55 years of age, generally referred to as young adult and midlife. The GCNKSS, a retrospective population-based epidemiology study, found

that the proportion of all strokes in adults <55 years of age increased from 12.9% in 1993 to 1994 to 18.6% in 2005 ( $P<0.0001$ ), which was true in both Black Americans and White Americans.<sup>251</sup> In the 20 to 54 years of age group, among Black individuals, incidence of stroke increased from 83 per 100 000 PY (95% CI, 64–101) in 1993 to 1994 to 128 per 100 000 PY (95% CI, 106–149) in 2005; and among White individuals, incidence increased from 26 per 100 000 PY (95% CI, 22–31) in 1993 to 1994 to 48 per 100 000 PY (95% CI, 42–53) in 2005. A systematic review of studies reporting stroke incidence in high-income countries comparing younger (usually <45, <55, or <60 years of age) with older age during at least 2 time periods found that among 50 studies in 20 countries, temporal trends in stroke incidence are diverging by age, with less favorable trends at younger versus older ages (pooled relative temporal rate ratio, 1.57 [95% CI, 1.42–1.74]; see the Secular Trends section).<sup>6</sup>

- In the GCNKSS, among young adults 20 to 44 years of age, stroke incidence per 10 000 PY was 17 in 1993 to 1994 and rose to 28 in 2015 ( $P<0.05$ ).<sup>139</sup> In midlife, among adults 45 to 64 years of age, stroke incidence was 165 in 1993 to 1994 and 171 in 2015 with no significant change over time. From 1985 to 2017, 4451 first-time ischemic strokes were captured in the population-based Dijon Stroke Registry; of these, 469 (10.5%) were in adults 18 to 55 years of age.<sup>252</sup> In young adults 18 to 45 years of age, incidence per 100 000 PY was 5.4 (95% CI, 4.3–6.9) before 2003 and rose to 12.8 (95% CI, 10.7–15.1) after 2003. In midlife adults 45 to 55 years of age, incidence per 100 000 PY was 47 (95% CI, 37–61) before 2003 and rose to 82 (95% CI, 67–100) after 2003.
- Stroke incidence may differ by sex among younger adults. In 1 retrospective cohort of young adults with first-time strokes in a US nationwide claims database, there were more young females than males with strokes in the 25 to 34 (male/female IRR, 0.70 [95% CI, 0.57–0.86]) and 35 to 44 years of age groups (IRR, 0.87 [95% CI, 0.78–0.98]) from 2001 until 2014.<sup>253</sup> Similarly, a population-based study of residents in Ontario, Canada, found more females than males with first-time strokes or TIAs among those 18 to 29 years of age (female HR, 1.26 [95% CI, 1.10–1.45]), with no sex difference among those 30 to 39 years of age (female HR, 1.00 [95% CI, 0.94–1.06]) and fewer females than males among those 40 to 49 years of age (female HR, 0.84 [95% CI, 0.82–0.87]).<sup>4</sup>

### Risk Factors

- A pooled analysis of consecutive patients with ischemic stroke 18 to 50 years of age looked at

differences in prevalence of risk factors and causes of ischemic stroke between different ethnic and racial groups, geographic regions, and countries with different income levels.<sup>254</sup> A total of 17 663 patients from 32 cohorts in 29 countries were included. Hypertension and diabetes were most prevalent in Black individuals (hypertension, 52.1%; diabetes, 20.7%) and Asian individuals (hypertension 46.1%, diabetes, 20.9%). Patients in low- and middle-income countries were younger, had fewer vascular risk factors, and more often died within 3 months compared with those from high-income countries (OR, 2.49 [95% CI, 1.42–4.36]).

- The distribution of risk factors according to the IPSS classification in patients with cryptogenic and noncryptogenic stroke according to the TOAST and ASCOD classification was assessed among 1322 patients 18 to 49 years of age with first-ever, imaging-confirmed ischemic stroke between 2013 and 2021 (median age, 44.2 years; 52.7% males).<sup>255</sup> Of these, 333 (25.2%) had a cryptogenic stroke according to the TOAST classification. Additional classification with the ASCOD criteria reduced the number patients with cryptogenic stroke to 260 (19.7%). When risk factors according to the IPSS were considered, the number of patients with no potential cause or risk factor for stroke reduced to 10 (0.8%).
- A prospective multicenter study of strokes in Korea, the CRCS-K-NIH, analyzed 7095 patients with AIS 18 to 50 years of age from 2008 to 2019.<sup>256</sup> Over 12 years, smoking decreased from 68.2% to 54.7% in males ( $P<0.001$ ) and remained similar from 10.7% to 13.2% in females ( $P=0.32$ ); obesity (BMI  $\geq30$  kg/m $^2$ ) more than doubled from 5.2% to 13.1% in males ( $P<0.001$ ) and increased from 5.4% to 9.2% in females ( $P=0.053$ ). However, there was no change over time in hypertension, diabetes, and hyperlipidemia. Although secondary preventions improved over time, including dual antiplatelets for minor strokes (26.7% to 47.0%;  $P<0.001$ ), DOACs for AF (0% to 56.2%;  $P<0.001$ ), and statins for large-vessel atherosclerosis (76.1% to 95.3%;  $P<0.001$ ), the 1-year stroke recurrence rate increased (4.1% to 5.5%;  $P=0.04$ ).

### Long-Term Outcomes

- In a Dutch population-based study of 15 527 patients 18 to 49 years of age with stroke, the 15-year mortality in 30-day ischemic stroke survivors was 5.1 times (95% CI, 4.7–5.4) that of the general population.<sup>257</sup> The standardized mortality rate for 30-day survivors of ICH was 8.4 times (95% CI, 7.4–9.3) that of the general population.
- A hospital-based study followed up 694 patients 18 to 50 years of age with first-ever TIA, ischemic

stroke, or ICH.<sup>258</sup> Those investigators found that after a mean follow-up duration of 8.1 years (SD, 7.7 years), young patients with stroke had higher risk of being unemployed (females OR, 2.3 [95% CI, 1.8–2.9]; males OR, 3.2 [95% CI, 2.5–4.0]). Functional outcomes assessed by the mRS and instrumental activities of daily living found that the greatest predictors of poor functional outcome (mRS score  $>2$ , instrumental activities of daily living  $>8$ ) 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]).<sup>259</sup>

- In the Young ESUS longitudinal cohort study conducted in 41 stroke research centers in 13 countries, a total of 535 consecutive patients  $\leq$ 50 years of age (mean  $\pm$  SD age, 40.4  $\pm$  7.3 years; 297 [56%] male) with a diagnosis of embolic stroke of undetermined source were enrolled.<sup>260</sup> The recurrent ischemic stroke and death rate was 2.19 per 100 patient-years, and the ischemic stroke recurrence rate was 1.9 per 100 patient-years.

### Organization of Stroke Care

- The RACECAT trial assessed 1401 patients with suspected acute large-vessel occlusion stroke in Catalonia, Spain, between March 2017 and June 2020.<sup>261</sup> The investigators compared transportation to an EVT-capable center (n=688) with transportation to the closest local stroke center (n=713) and assessed disability at 90 days. Patients directly transported to EVT-capable centers had lower odds of thrombolysis (229/482 [47.5%] versus 282/467 [60.4%]; OR, 0.59 [95% CI, 0.45–0.76]) and higher odds of EVT (235/482 [48.8%] versus 184/467 [39.4%]; OR, 1.46 [95% CI, 1.13–1.89]). There was no significant difference in 90-day neurological outcomes. Among patients with ICH (n=302), direct transfer to an EVT-capable center resulted in worse functional outcome at 90 days (OR, 0.63 [95% CI, 0.41–0.96]).<sup>262</sup>
- MSUs are ambulances equipped with a CT scanner and personnel able to treat acute stroke in the prehospital setting.<sup>264</sup> An observational, prospective multicenter trial in the US (BEST-MSU) assessed outcomes from MSU or standard of care within 4.5 hours after onset of acute stroke symptoms.<sup>265</sup> Using on a 1-week-on/1-week-off study design, the trial found that n=617 received care by MSU and n=430 by EMS. Utility-weighted mRS scores at 90 days were better in those treated with the MSU (0.73) compared with EMS (0.67; OR, 2.12 [95% CI, 1.54–2.93]). A prospective nonrandomized study in Germany enrolled patients with suspected stroke (B\_PROUD).<sup>266</sup> Simultaneous dispatch of MSU with conventional ambulance (n=749) compared with conventional ambulance alone (n=794) showed that

- patients with MSU dispatched had lower median mRS score at 3 months (1; interquartile range, 0–3) compared with those with conventional ambulance dispatched (2; interquartile range, 0–3; OR for worse mRS score, 0.71 [95% CI, 0.58–0.86]).
- A retrospective study of US patients ≥65 years of age in the GWTG-Stroke linked to a Medicare database looked at the effect of earlier thrombolysis treatment in patient receiving thrombolysis and thrombolysis combined with EVT.<sup>267</sup> Among n=38913 treated with thrombolysis and n=3946 treated with both thrombolysis and EVT, each 15-minute delay in door-to-needle time for thrombolysis was associated with higher odds of never discharged home (aOR, 1.12 [95% CI, 1.06–1.19]), less time spent at home (aOR, 0.93 [95% CI, 0.89–0.98]), and higher all-cause mortality (aHR, 1.07 [95% CI, 1.02–1.11]). In the secondary analysis, thrombolysis and EVT were compared with EVT only. Shorter door-to-needle time for thrombolysis (≤60, 45, and 30 minutes) achieved better functional outcome (mRS score 0–2) at discharge (22.3%, 23.4%, and 25.0%, respectively) compared with EVT only (16.4%  $P<0.001$  for each).
  - An observational study in the United Kingdom characterized factors leading to longer ambulance on-scene times for suspected patients with stroke. Among N=2307 patients, 3 potentially modifiable factors were identified as contributors to extended on-scene times: performing additional advanced neurological assessment added 10% (34 minutes versus 31 minutes;  $P<0.001$ ), intravenous cannulation added 13% (35 minutes versus 31 minutes;  $P<0.001$ ), and ECGs added 22% (35 minutes versus 28 minutes;  $P<0.001$ ). In a multinational survey of neurointerventionalists to quantify time savings that could be achieved in optimizing workflows for EVT, prenotification of the neurointerventional team ( $\approx$ 19 minutes), optimizing the spatial setup ( $\approx$ 18 minutes), streamlining workflow in the ED ( $\approx$ 17 minutes), all-time available anesthesiologist ( $\approx$ 18 minutes), and prepared thrombectomy equipment and kits ( $\approx$ 13 minutes) were identified as time-saving steps.<sup>268</sup>
  - A wide array of artificial intelligence clinical decision support systems have been developed for the diagnosis and recognition of early ischemic stroke. A systematic review and meta-analysis of artificial intelligence–driven ASPECTS software for the detection of early stroke changes in noncontrast CT, including 11 studies with N=1976 patients, found good reliability of automatic predictions compared with reference standard (intraclass correlation coefficient, 0.72 [95% CI, 0.61–0.80]).
  - Adequate transition of care behaviors was assessed in 550 participants with ischemic stroke

(2018–2021) in the Transition of Care Stroke Disparities Study who were discharged home or to rehabilitation and had an mRS score of 0 to 3.<sup>269</sup> Using a summary metric of adequate transition of care behavior, investigators found that 1 in 3 patients did not attain 30-day adequate transition of care behaviors. COMPASS, a large cluster randomized pragmatic trial, addressed transitional care in patients with stroke enrolled 40 North Carolina hospitals (N>6000).<sup>270</sup> The intervention included telephone visit within 2 days and a clinical visit between 7 and 14 days of discharge, which incorporated education and caregiver support. Hospitals had difficulty maintaining staffing; only 35% of patients completed in-person clinic visits, and 59% had outcomes data, which did not show significant benefit (functional status based on Stroke Impact Scale-16 at 90 days; 80.6±21.1 in treatment group versus 79.9±21.4 in usual care;  $P=0.61$ ).

## Hospital Discharges and Ambulatory Care Visits

- In 2021, there were 889 399 inpatient discharges from short-stay hospitals with stroke as the principal diagnosis (HCUP, unpublished NHLBI tabulation).
- In 2021, there were 806 960 ED visits with stroke as the principal diagnosis (HCUP,<sup>271</sup> unpublished NHLBI tabulation). In 2019, physician office visits for a first-listed diagnosis of stroke totaled 2 782 000 (NAMCS,<sup>272</sup> unpublished NHLBI tabulation).
- 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  $\geq$ 4 days than White people.<sup>273</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>274</sup> Length of stay declined from 6.8 to 5.7 days in the endovascular era, but total charges were higher (\$56 691 versus \$53 878).
- A systemic review comparing complications of intravenous tenecteplase with alteplase for the treatment of AIS examined results from 26 studies.<sup>275</sup> The RR of symptomatic ICH in tenecteplase- versus alteplase-treated patients was 0.89 (95% CI, 0.65–1.23).

- AURORA, a pooled patient-level study of 5 randomized clinical trials, included patients with large-vessel occlusions of the anterior circulation with  $>6$  and up to 24 hours from last known well.<sup>276</sup> Among N=505 patients, including 266 receiving EVT and 239 controls, EVT resulted in less disability at 90 days (aOR, 2.54 [95% CI, 1.83–3.54]). No significant difference between patients receiving EVT and controls was found in mortality at 90 days (16.5% versus 19.3%) or symptomatic ICH (5.3% versus 3.3%).
- A systematic review examined the effect of EVT in patients with occlusions of the basilar artery by 4 randomized clinical trials (BEST, BASICS, BAOCHE, and ATTENTION).<sup>277</sup> A total of 988 patients were enrolled (556 in EVT and 432 in medical therapy). Patients undergoing EVT were more likely to achieve favorable outcomes (mRS score 0–3: RR, 1.54 [95% CI, 1.16–2.04]) and functional independence (mRS score 0–2: RR, 1.83 [95% CI, 1.08–3.08]) at 90 days. However, patients undergoing EVT had higher risk of symptomatic ICH (RR, 7.48 [95% CI, 2.27–24.61]). A systematic review examined the effects of EVT in anterior circulation strokes with large core infarcts (ASPECTS 3–5) by 3 randomized clinical trials (RESCUE Japan-LIMIT, ANGEL-ASPECT, and SELECT-2).<sup>278</sup> A total of 1101 patients were included (510 in EVT, and 501 in medical management). The RR for the primary outcome of mRS score of 0 to 2 favored EVT (RR, 2.53 [95% CI, 1.84–3.47]). Symptomatic ICH occurred more frequently in the EVT arm but did not reach significance (RR, 1.84 [95% CI, 0.94–3.60]).
- In an individual patient-level meta-analysis of 7 cohort studies, a 10-point increase in mean SBP levels during the first 24 hours after EVT was associated with a lower functional improvement (aOR, 0.88 [95% CI, 0.84–0.93]), mRS score  $\leq 2$  (aOR, 0.87 [95% CI, 0.82–0.93]), and higher all-cause mortality (aOR, 1.15 [95% CI, 1.06–1.23]) at 3 months.<sup>279</sup> However, a recent RCT of 821 patients in China who underwent successful EVT comparing intensive BP control (target  $<120$  mm Hg) with less intensive BP control (target, 140–180 mmHg) was stopped prematurely because of safety concerns. Patients in the more intensive BP control arm had a higher incidence of poor functional outcome and early neurological deterioration.<sup>280</sup>
- A systematic review examined the efficacy of general anesthesia versus nongeneral anesthesia techniques such as conscious sedation or local anesthesia alone among patients undergoing EVT for large-vessel occlusion strokes.<sup>281</sup> Seven RCTs were included that enrolled a total of 980 patients

(487 in general anesthesia, 493 in nongeneral anesthesia). General anesthesia improved recanalization during EVT from 75.6% to 84.6% (OR, 1.75 [95% CI, 1.26–2.42]) and the proportion of patients achieving functional recovery at 3 months (36.2% versus 44.6%; OR, 1.43 [95% CI, 1.04–1.98]).

## Cost

- In 2020 to 2021 (average annual; MEPS,<sup>282</sup> unpublished NHLBI tabulation):
  - The estimated direct medical cost of ischemic stroke/TIA was \$25.0 billion. This includes hospital outpatient or office-based health care professional visits, hospital inpatient stays, ED visits, prescribed medicines, and home health care. Separate estimates of the direct medical cost of hemorrhagic and unspecified stroke are not available. The indirect cost of stroke (all types) mortality was \$24.0 billion.
- 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 \$7034 for ischemic stroke/TIA (unpublished NHLBI tabulation using MEPS).<sup>282</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 minor stroke (NIHSS score  $\leq 5$ ) or high-risk TIA (n=62518 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>283</sup>
- In an analysis of trends in physician reimbursement from 2000 to 2019, after adjustment for inflation, the average reimbursement for stroke (ICD-10 I60–I63) procedures decreased by an average of 0.43%/y (11.2% from 2000–2019).<sup>284</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  $\geq 80$  years of age.<sup>285</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>285</sup>

## Global Burden of Stroke

### Prevalence

(See Tables 15-4 through 15-7 and Charts 15-8 through 15-11)

Based on 204 countries and territories in 2021<sup>286</sup>:

- Globally, there were 93.82 (95% UI, 89.03–99.34) million prevalent cases of all stroke subtypes. The age-standardized prevalence rate decreased by 1.34% (95% UI, –3.77% to 1.03%) from 2010 to 2021 (Table 15-4).
- Among regions, age-standardized stroke prevalence rates were highest for sub-Saharan Africa and East, Southeast, and Central Asia. Rates were the lowest for Australasia (Chart 15-8).
- The global prevalence of ischemic stroke was 69.94 (95% UI, 64.79–75.01) million cases. There was an increase of 1.07% (95% UI, –1.96% to 4.11%) in the age-standardized prevalence rate from 2010 to 2021 (Table 15-5).
- Among regions, age-standardized prevalence of ischemic stroke was highest for southern sub-Saharan Africa, followed by western sub-Saharan Africa and East and Central Asia (Chart 15-9).
- The global prevalence of ICH was 16.60 (95% UI, 15.16–18.18) million cases. There was a decrease of 9.39% (95% UI, –11.79% to –7.23%) in the age-standardized prevalence rate from 2010 to 2021 (Table 15-6).
- The prevalence of ICH among regions was highest for western sub-Saharan Africa, Southeast Asia, Oceania, and high-income Asia Pacific (Chart 15-10).
- The global prevalence of SAH was 7.85 (95% UI, 7.16–8.58) million cases. There was a decrease of 4.08% (95% UI, –5.91% to –1.95%) in the age-standardized prevalence rate from 2010 to 2021 (Table 15-7).
- Age-standardized prevalence of SAH among regions was highest for high-income Asia Pacific and Andean Latin America (Chart 15-11).

### Mortality

(See Tables 15-4 through 15-7 and Charts 15-12 through 15-15)

Based on 204 countries and territories in 2021<sup>286</sup>:

- The number of total deaths attributable to stroke was 7.25 (95% UI, 6.57–7.81) million, and the age-standardized mortality rate decreased by 17.45% (95% UI, –22.96% to –12.12%) since 2010 (Table 15-4).
- Age-standardized mortality attributable to stroke among regions was highest for Oceania and Southeast Asia. Rates were lowest for Australasia and Western Europe (Chart 15-12).

- Globally, the number of total deaths attributable to ischemic stroke was 3.59 (95% UI, 3.21–3.89) million. The age-standardized mortality rate decreased by 15.76% (95% UI, –20.47% to –11.09%) from 2010 (Table 15-5).
- Age-standardized mortality attributable to ischemic stroke among regions was highest for Eastern Europe, followed by North Africa and the Middle East and Central Asia. Mortality was lowest for Australasia (Chart 15-13).
- Globally, the number of total deaths attributable to ICH was 3.31 (95% UI, 3.02–3.59) million. The age-standardized mortality rate decreased by 19.35% (95% UI, –25.63% to –12.77%) from 2010 (Table 15-6).
- Among regions, ICH mortality was highest for Oceania, followed by Southeast and East Asia and central and eastern sub-Saharan Africa. (Chart 15-14).
- Globally, the number of total deaths attributable to SAH was 0.35 (95% UI, 0.31–0.40) million. The age-standardized mortality rate decreased 16.83% (95% UI, –23.82% to –8.26%) from 2010 (Table 15-7).
- Among regions, mortality estimated for SAH was highest for Oceania followed by Southeast Asia and Andean Latin America (Chart 15-15).

## COVID-19 and Stroke

- A systematic review assessed the risk of ischemic stroke in COVID-19 survivors after SARS-CoV-2 infection.<sup>287</sup> The analysis included 8 studies with 23 559 428 patients (mean age 56; 54.3% males), 15 959 84 of whom had COVID-19. Over the follow-up period, incident ischemic stroke occurred in 4.40 (95% CI, 4.36–4.43) of 1000 patients with a previous COVID-19 infection compared with 3.25 (95% CI, 3.21–3.29) of 1000 noninfected patients. Patients who were recovered from COVID-19 presented a higher risk of ischemic stroke (HR, 2.06 [95% CI, 1.75–2.41];  $P<0.0001$ ;  $P=63.7\%$ ) compared with people who did not have COVID-19. Patients with COVID-19 hospitalized at the time of the infection had a subsequent higher risk of stroke during the follow-up compared with those not hospitalized.
- A systematic review was conducted to identify the influence of the COVID-19 pandemic on the presentation and treatment of stroke globally in populations  $\geq 65$  years of age.<sup>288</sup> In 38 articles included, 84% of studies reported decreased admissions rates during the COVID-19 pandemic and higher severity of stroke on average among those admitted. Implementation of COVID-19 protocols resulted in

increased treatment times in 60% of studies and increased in-hospital mortality in 82% of studies. The prevalence of stroke subtype (ischemic or hemorrhagic) and primary treatment methods (thrombectomy or thrombolysis) did not vary attributable to the COVID-19 pandemic.

- A retrospective multicenter cohort study evaluated the safety and outcomes of revascularization treatments in consecutive patients with AIS who were tested for COVID-19.<sup>289</sup> Of the 15 128 patients, 853 (5.6%) were diagnosed with COVID-19; 5848 (38.7%) received intravenous thrombolysis only, and 9280 (61.3%) endovascular treatment (with or without intravenous thrombolysis). Patients with COVID-19 had a higher rate of symptomatic ICH (aOR, 1.53 [95% CI, 1.16–2.01]), symptomatic SAH (OR, 1.80 [95% CI, 1.20–2.69]), and symptomatic ICH and symptomatic SAH combined (OR, 1.56 [95% CI, 1.23–1.99]) and had an unfavorable shift in the distribution of mRS score at 3 months (OR, 1.42 [95% CI, 1.26–1.60]).
- An international multicenter retrospective cohort study of consecutive patients with AIS tested for SARS-CoV-2 receiving intravenous thrombolysis and endovascular treatment between 2020 and 2021 evaluated the safety and outcomes of revascularization treatments in patients with AIS with asymptomatic or symptomatic COVID-19 compared with COVID-19-negative controls.<sup>290</sup> Among 15 124 patients from 105 centers, 849 (5.6%) had COVID-19, of whom 395 (46%) were asymptomatic and 454 (54%) were symptomatic. Compared with controls, patients with asymptomatic COVID-19 and symptomatic COVID-19 had higher symptomatic ICH rates (COVID-19 controls, 5%; asymptomatic COVID-19, 7.6%; symptomatic COVID-19, 9.4%), with an aOR of 1.43 (95% CI, 1.03–1.99) and 1.63 (95% CI, 1.14–2.32), respectively.
- The Neuro-COVID Italy study, a multicenter, observational cohort study recruited consecutive hospitalized patients presenting new neurological disorders associated with COVID-19 (neuro-COVID-19).<sup>291</sup> Among 52 759 hospitalized patients with COVID-19, 1865 presented with 2881 neuro-COVID-19 cases. The incidence of neuro-COVID-19 declined over time in a comparison of the first 3 pandemic waves (8.4%, 5.0%, 3.3%, respectively;  $P=0.027$ ). The most frequent neurological disorders were acute encephalopathy (25.2%), hyposmia-hypogeusia (20.2%), AIS (18.4%), and cognitive impairment (13.7%). During a median of 6.7 months of follow-up, a good functional outcome was achieved by 64.6% of patients with neuro-COVID-19, and disabling symptoms were common only in stroke survivors (47.6%). Incidence of COVID-associated

neurological disorders decreased during the pre-vaccination phase of the pandemic.

- In an interim analysis of safety surveillance data from the Vaccine Safety Datalink, 10 162 227 vaccine-eligible members were monitored for selected outcomes from December 14, 2020, through June 26, 2021.<sup>292</sup> A total of 11 845 128 doses of mRNA vaccines (57% BNT162b2; 6 175 813 first doses and 5 669 315 second doses) were administered to 6.2 million individuals (mean age, 49 years; 54% females). The incidence of selected serious outcomes was not significantly higher 1 to 21 days after vaccination compared with 22 to 42 days after vaccination, including incidence of ischemic stroke (1612 versus 1781; RR, 0.97 [95% CI, 0.87–1.08]).
- A recent review looked at stroke and cerebrovascular disease as a complication of the SARS-CoV-2 infection and outlined the main clinical and radiological characteristics of cerebrovascular complications of vaccinations, with a focus on vaccine-induced immune thrombotic thrombocytopenia.<sup>293</sup> The review found that the risk of stroke and other outcomes of interest (thrombocytopenia, VTE, arterial thrombosis, cerebral venous sinus thrombosis, and MI) after a SARS-CoV-2 infection was significantly higher than after vaccination with either the Oxford-AstraZeneca or the Pfizer vaccine.
- A retrospective review of patients with a discharge diagnosis of AIS from the GWTG database from 2 Comprehensive Stroke Centers 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. Stroke volumes were found to be significantly lower during the peak COVID-19 period in 2020 compared with 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>294</sup>
- A cohort study using the French national database of hospital admissions extracted data on all hospitalizations in France with at least 1 stroke diagnosis between January 1, 2019, and June 30, 2020.<sup>295</sup> Stroke hospitalizations dropped from March 10, 2020 (slope gradient, -11.70) and began to rise again from March 22 (slope gradient, 2.090) to May 7, representing a total decrease of 18.42%. The

percentage change was  $-15.63\%$ ,  $-25.19\%$ , and  $-18.62\%$  for ischemic strokes, TIAs, and hemorrhagic strokes, respectively. Overall stroke hospitalizations in France experienced a decline during the first lockdown period, which could not be explained by a sudden change in stroke incidence and thus is likely to be a direct or indirect result of the COVID-19 pandemic.

- 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 neurological 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 neurological 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>296</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 (interquartile range, 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>297</sup>

**Table 15-1. Stroke in the United States**

Population group	Prevalence, 2017–2020, $\geq 20$ y of age	New and recurrent attacks, 1999, all ages	Mortality, 2022, all ages*	Age-adjusted mortality rates per 100 000 (95% CI)*, 2022
Both sexes	9 400 000 (3.3% [95% CI, 2.8%–3.8%])	795 000	165 393	39.5 (39.3–39.7)
Males	4 000 000 (2.9%)	370 000 (46.5%)†	71 819 (43.4%)†	40.5 (40.2–40.8)
Females	5 400 000 (3.6%)	425 000 (53.5%)†	93 574 (56.6%)†	38.2 (38.0–38.5)
NH White males	2.7%	325 000‡	51 042	38.6 (38.2–38.9)
NH White females	3.6%	365 000‡	68 887	37.5 (37.2–37.8)
NH Black males	4.8%	45 000‡	10 293	63.5 (62.2–64.8)
NH Black females	5.4%	60 000‡	12 363	52.2 (51.3–53.2)
Hispanic males	2.5%	...	6 673	37.6 (36.7–38.6)
Hispanic females	2.5%	...	7 551	33.0 (32.2–33.7)
NH Asian males	1.8%	...	2 852§	31.6 (30.4–32.7)§
NH Asian females	1.5%	...	3 630§	29.0 (28.1–30.0)§
NH American Indian or Alaska Native	...	...	747	30.3 (28.1–32.5)
NH Native Hawaiian or Other Pacific Islander	...	...	298	52.7 (46.6–58.9)

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>298</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 people, American Indian or Alaska Native people, 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 decedents, Asian and Pacific Islander decedents, 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 versus females.

‡Estimates include Hispanic and NH people. Estimates for White people include other non-Black races.

§Includes Chinese, Filipino, Japanese, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.<sup>299</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. 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>300</sup> Data include children. Mortality (for underlying cause of stroke): Unpublished NHLBI tabulation using National Vital Statistics System<sup>203</sup> and CDC WONDER.<sup>202</sup> These data represent underlying cause of death only.

**Table 15-2. Hemorrhagic Stroke in Relation to BP Categories in Korea Among 947 378 Adults 20 to 64 Years of Age Who Had Stable BP Levels During 10 Years of Observation, 2009 to 2018 (335 Cases of ICH and 566 Cases of SAH)**

Korean National Health Insurance Database	SBP/DBP categories, mm Hg				
	<110/<80	110–119/<80	120–129/<80	130–139/80–89	≥140/≥90
ICH					
Males					
Incidence rate per 100 000 PY	4.9	2.9	3.8	4.1	9.1
HR (95% CI)	1.00 (reference)	0.68 (0.43–1.08)	0.95 (0.52–1.74)	1.00 (0.65–1.56)	2.00 (1.20–3.33)
Females					
Incidence rate per 100 000 PY	2.7	2.4	3.4	5.4	7.5
HR (95% CI)	1.00 (reference)	0.91 (0.59–1.40)	1.24 (0.56–2.76)	2.02 (1.25–3.27)	2.76 (1.27–5.98)
SAH					
Males					
Incidence rate per 100 000 PY	4.4	3.8	6.1	6.8	16.8
HR (95% CI)	1.00 (reference)	0.89 (0.56–1.40)	1.48 (0.86–2.54)	1.64 (1.07–2.51)	4.22 (2.65–6.72)
Females					
Incidence rate per 100 000 PY	2.9	4.8	5.8	12.8	17.5
HR (95% CI)	1.00 (reference)	1.50 (0.96–2.26)	1.78 (0.94–3.34)	3.90 (2.69–5.67)	5.17 (3.00–8.90)

BP indicates blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; ICH, intracerebral hemorrhage; PY, person-years; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

Source: Shim et al.<sup>21</sup> Copyright © 2023 The Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

**Table 15-3. SAH in Relation to BP Categories in the United Kingdom Among 500 598 Adults 40 to 69 Years of Age Over a Mean of 4.5 Years of Follow-Up, 2006 to 2017 (539 Cases of SAH)**

	SBP categories, mm Hg					
UK Biobank	<120	120–129	130–139	140–159	160–179	>180
HR (95% CI)	1.00 (reference)	1.41 (1.02–1.95)	1.74 (1.28–2.38)	1.60 (1.18–2.16)	1.99 (1.39–2.84)	1.81 (1.02–3.21)
DBP categories, mm Hg						
	<80	80–84	85–89	90–99	100–109	>100
HR (95% CI)	1.00 (reference)	1.26 (1.00–1.58)	1.07 (0.83–1.39)	1.31 (1.03–1.66)	1.61 (1.09–2.40)	3.23 (1.66–6.31)
SBP categories, mm Hg						
Meta-analysis with 4 other studies	<120	120–130	130–140	140–160	160–180	>180
Males						
HR (95% CI)	1.00 (reference)	1.37 (1.00–1.90)	1.64 (1.00–2.69)	1.64 (0.93–2.91)	1.91 (1.01–3.59)	2.41 (0.63–9.12)
Females						
HR (95% CI)	1.00 (reference)	1.42 (1.09–1.84)	1.93 (1.49–2.50)	2.16 (1.40–3.32)	3.35 (1.77–6.34)	7.47 (1.53–36.52)

BP indicates blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

Source: Ewbank et al.<sup>22</sup> Copyright ©2023 The Authors. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License (CC-BY-NC 4.0 International), which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

**Table 15-4. Global Mortality and Prevalence of Total Stroke by Sex, 2021**

	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), 2021	7.25 (6.57 to 7.81)	93.82 (89.03 to 99.34)	3.78 (3.43 to 4.15)	47.81 (45.34 to 50.57)	3.48 (3.07 to 3.81)	46.01 (43.54 to 48.77)
Percent change (%) in total number, 1990–2021	44.09 (32.29 to 56.03)	86.09 (83.00 to 89.35)	57.69 (40.28 to 76.50)	93.20 (90.01 to 96.68)	31.75 (20.05 to 45.24)	79.23 (75.92 to 82.59)
Percent change (%) in total number, 2010–2021	14.30 (6.47 to 21.79)	28.39 (25.08 to 31.49)	15.88 (5.03 to 27.70)	27.56 (24.17 to 30.77)	12.62 (4.39 to 21.84)	29.26 (25.96 to 32.50)
Rate per 100 000, age standardized, 2021	87.45 (78.92 to 94.14)	1099.31 (1044.17 to 1162.11)	103.07 (93.06 to 112.85)	1184.35 (1124.19 to 1252.12)	74.54 (65.81 to 81.55)	1027.71 (974.35 to 1088.08)
Percent change (%) in rate, age standardized, 1990–2021	−39.40 (−43.96 to −34.65)	−8.48 (−9.67 to −7.33)	−34.32 (−41.22 to −27.04)	−6.69 (−8.08 to −5.37)	−44.16 (−48.91 to −38.75)	−10.82 (−12.10 to −9.49)
Percent change (%) in rate, age standardized, 2010–2021	−17.45 (−22.96 to −12.12)	−1.34 (−3.77 to 1.03)	−16.47 (−24.10 to −8.33)	−2.54 (−5.02 to −0.15)	−18.62 (−24.49 to −12.00)	−0.33 (−2.76 to 2.03)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

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**Table 15-5. Global Mortality and Prevalence of Ischemic Stroke by Sex, 2021**

	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), 2021	3.59 (3.21 to 3.89)	69.94 (64.79 to 75.01)	1.78 (1.61 to 1.96)	35.24 (32.61 to 37.81)	1.81 (1.57 to 2.00)	34.70 (32.10 to 37.27)
Percent change (%) in total number, 1990–2021	55.00 (43.20 to 66.76)	101.76 (97.30 to 105.84)	76.56 (56.08 to 99.55)	109.68 (104.98 to 114.08)	38.41 (27.12 to 50.27)	94.30 (90.22 to 98.95)
Percent change (%) in total number, 2010–2021	19.02 (12.15 to 25.83)	33.38 (29.23 to 37.48)	22.87 (12.41 to 34.82)	32.42 (28.25 to 36.59)	15.47 (8.48 to 22.87)	34.36 (30.09 to 38.57)
Rate per 100 000, age standardized, 2021	44.18 (39.29 to 47.81)	819.47 (760.26 to 878.71)	51.16 (46.21 to 56.22)	881.94 (818.60 to 944.54)	38.54 (33.46 to 42.53)	769.40 (712.98 to 825.99)
Percent change (%) in rate, age standardized, 1990–2021	−39.60 (−43.79 to −35.32)	−3.53 (−5.12 to −2.06)	−33.13 (−40.35 to −25.01)	−2.55 (−4.35 to −0.75)	−44.85 (−48.86 to −40.36)	−5.28 (−6.91 to −3.53)
Percent change (%) in rate, age standardized, 2010–2021	−15.76 (−20.47 to −11.09)	1.07 (−1.96 to 4.11)	−13.71 (−20.71 to −5.76)	−0.62 (−3.68 to 2.54)	−17.82 (−22.68 to −12.52)	2.46 (−0.82 to 5.48)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

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**Table 15-6. Global Mortality and Prevalence of ICH, by Sex, 2021**

	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), 2021	3.31 (3.02 to 3.59)	16.60 (15.16 to 18.18)	1.82 (1.63 to 2.05)	9.35 (8.49 to 10.24)	1.49 (1.31 to 1.67)	7.25 (6.66 to 7.92)
Percent change (%) in total number, 1990–2021	41.29 (27.35 to 56.22)	48.59 (43.95 to 52.76)	51.19 (31.05 to 75.70)	57.95 (52.65 to 62.71)	30.79 (14.97 to 50.11)	38.04 (33.41 to 42.20)
Percent change (%) in total number, 2010–2021	9.93 (1.28 to 19.05)	13.85 (10.57 to 16.89)	10.46 (−1.76 to 23.96)	14.15 (10.55 to 17.61)	9.27 (−0.51 to 20.73)	13.46 (10.31 to 16.30)
Rate per 100 000, age standardized, 2021	39.09 (35.65 to 42.45)	194.51 (177.99 to 212.53)	47.43 (42.33 to 53.18)	225.08 (204.86 to 245.59)	32.09 (28.31 to 35.99)	166.10 (152.20 to 181.16)
Percent change (%) in rate, age standardized, 1990–2021	−36.58 (−42.54 to −29.83)	−22.27 (−23.92 to −20.71)	−32.65 (−41.50 to −21.74)	−17.97 (−19.91 to −16.20)	−41.08 (−47.98 to −32.36)	−27.40 (−29.02 to −25.95)
Percent change (%) in rate, age standardized, 2010–2021	−19.35 (−25.63 to −12.77)	−9.39 (−11.79 to −7.23)	−19.13 (−27.98 to −9.54)	−9.35 (−11.87 to −6.92)	−19.89 (−26.98 to −11.60)	−9.45 (−11.70 to −7.46)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; ICH; intracerebral hemorrhage; and UI, uncertainty interval.

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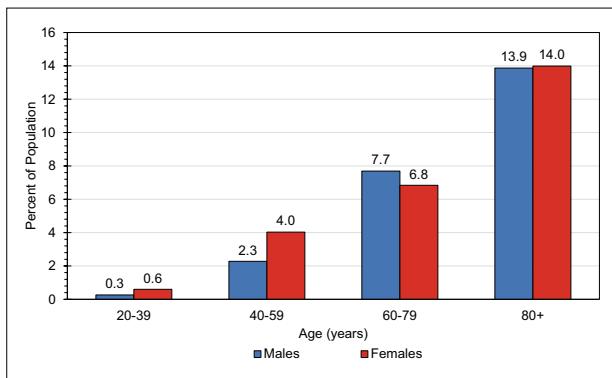
**Table 15-7. Global Mortality and Prevalence of SAH, by Sex, 2021**

	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), 2021	0.35 (0.31 to 0.40)	7.85 (7.16 to 8.58)	0.17 (0.14 to 0.22)	3.54 (3.22 to 3.89)	0.18 (0.16 to 0.21)	4.31 (3.95 to 4.69)
Percent change (%) in total number, 1990–2021	−5.89 (−22.78 to 25.51)	60.21 (56.86 to 63.39)	−3.98 (−25.98 to 57.27)	61.68 (57.93 to 65.11)	−7.67 (−25.96 to 26.54)	59.01 (55.62 to 62.07)
Percent change (%) in total number, 2010–2021	10.84 (1.56 to 22.37)	20.68 (18.39 to 23.46)	8.57 (−2.94 to 23.87)	20.77 (18.27 to 23.67)	13.13 (1.57 to 27.47)	20.61 (18.35 to 23.38)
Rate per 100 000, age standardized, 2021	4.18 (3.66 to 4.76)	92.17 (84.08 to 100.60)	4.48 (3.64 to 5.56)	85.52 (77.67 to 93.74)	3.91 (3.41 to 4.55)	97.88 (89.66 to 106.58)
Percent change (%) in rate, age standardized, 1990–2021	−56.12 (−64.27 to −40.74)	−16.13 (−17.70 to −14.76)	−55.15 (−65.76 to −23.58)	−14.16 (−15.73 to −12.76)	−57.16 (−65.47 to −41.07)	−17.64 (−19.20 to −16.20)
Percent change (%) in rate, age standardized, 2010–2021	−16.83 (−23.82 to −8.26)	−4.08 (−5.91 to −1.95)	−17.90 (−26.66 to −6.46)	−3.16 (−5.11 to −0.96)	−15.76 (−24.53 to −5.13)	−4.80 (−6.63 to −2.78)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

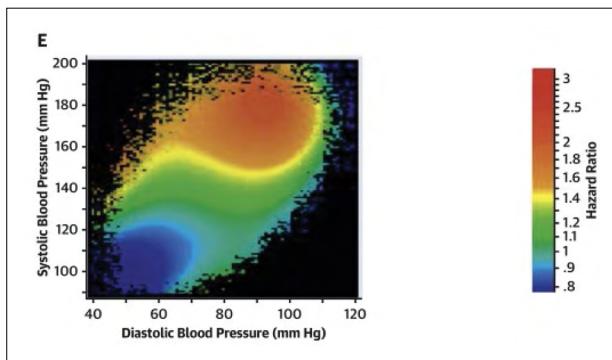
GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; SAH, subarachnoid hemorrhage; and UI, uncertainty interval.

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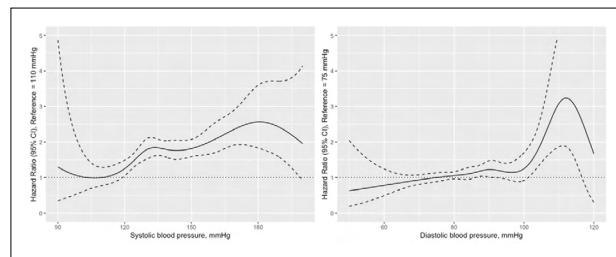
**Chart 15-1. Prevalence of stroke, by age and sex, United States (NHANES, 2017–2020).**

NHANES indicates National Health and Nutrition Examination Survey. Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>299</sup>

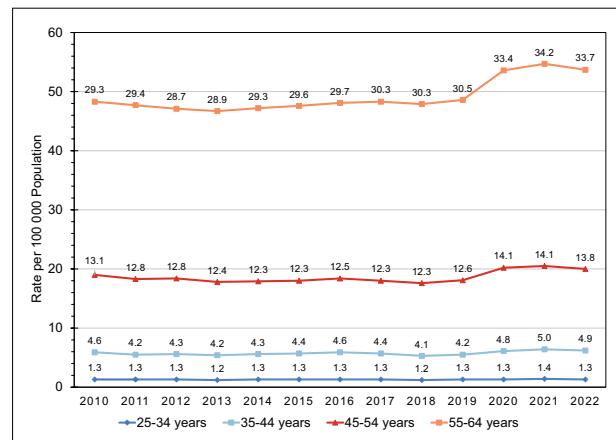


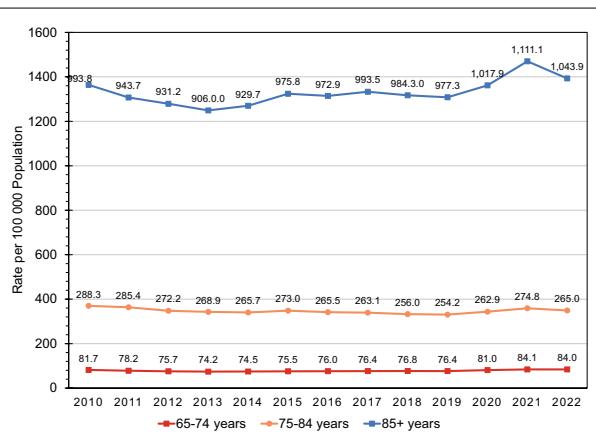
ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Source: Reprinted from Itoga et al.<sup>18</sup> Copyright © 2021, with permission from the American College of Cardiology Foundation.



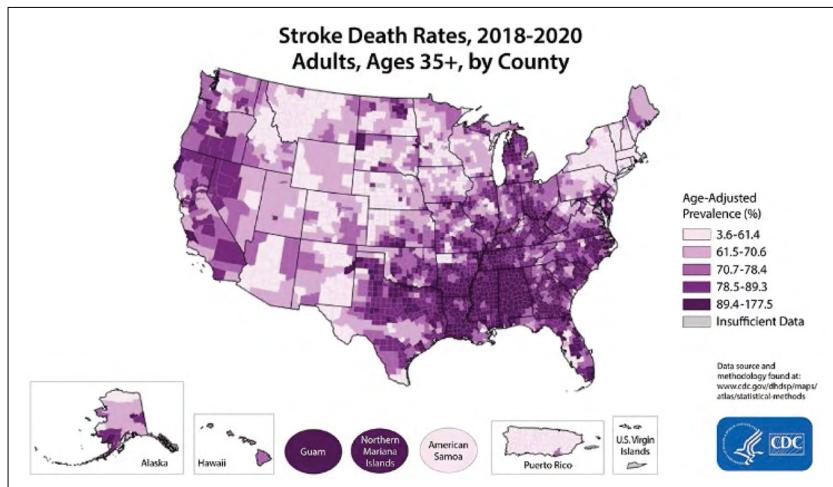
Nonlinear models including natural cubic splines at ESC/ESH guideline thresholds. **Left**, HR as a function of SBP. **Right**, HR as a function of DBP. Solid line represents the HR; dotted line represents the 95% CI. Reference for SBP was 110 mmHg and for DBP was 75 mmHg. DBP indicates diastolic blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HR, hazard ratio; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure. Source: Reprinted from Ewbank et al.<sup>22</sup> Copyright © 2023 The Authors. *European Journal of Neurology* published by John Wiley & Sons Ltd on behalf of European Academy of Neurology. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.





**Chart 15-5. Crude stroke mortality rates among older US adults ( $\geq 65$  years of age), 2010 to 2022.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>202</sup>

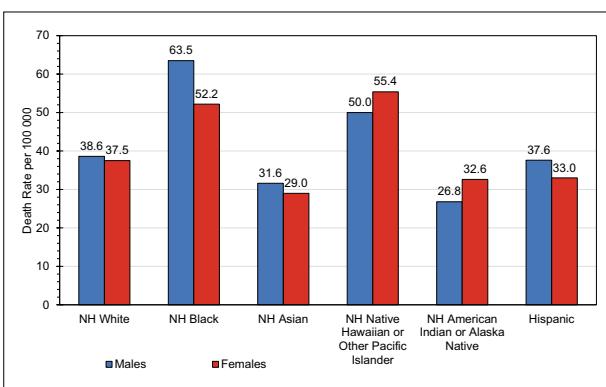


**Chart 15-6. Stroke death rates, 2018 through 2020, among adults  $\geq 35$  years of age, by US county.**

Rates are spatially smoothed to enhance the stability of rates in counties with small populations. ICD-10 codes for stroke: I60 through I69.

CDC indicates Centers for Disease Control and Prevention; and ICD-10, International Classification of Diseases, 10th Revision.

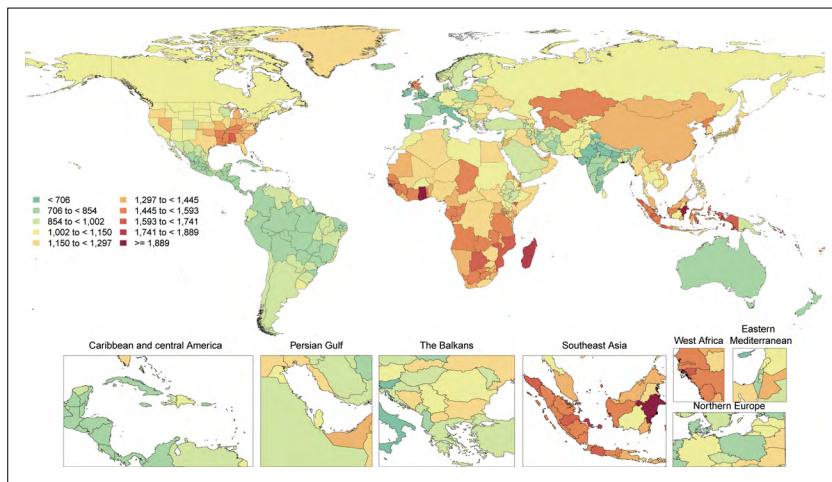
Source: Reprinted from the CDC.<sup>301</sup>



**Chart 15-7. Age-adjusted death rates for stroke, by sex and race and ethnicity, United States, 2022.**

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). 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>202</sup>

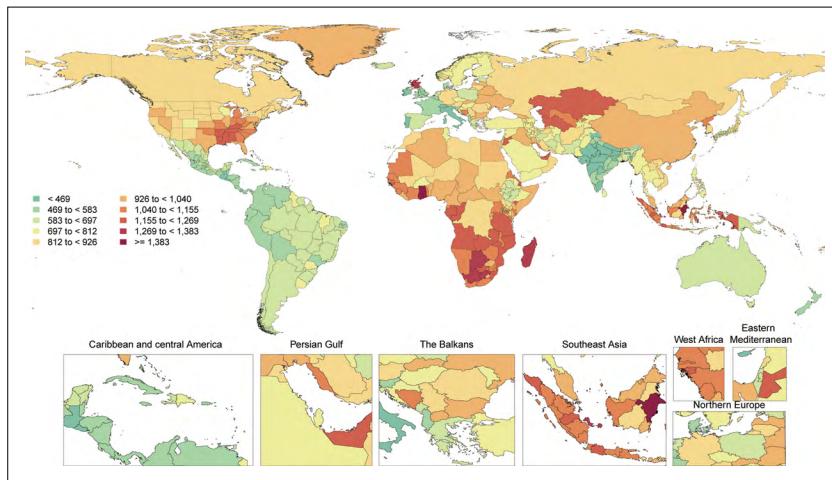


**Chart 15-8. Age-standardized global prevalence rates of total stroke (all subtypes) per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>286</sup>

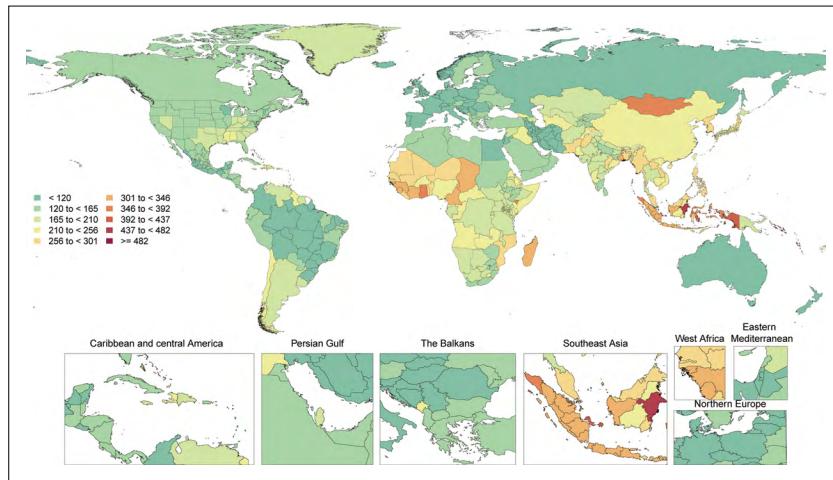


**Chart 15-9. Age-standardized global prevalence rates of ischemic stroke per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

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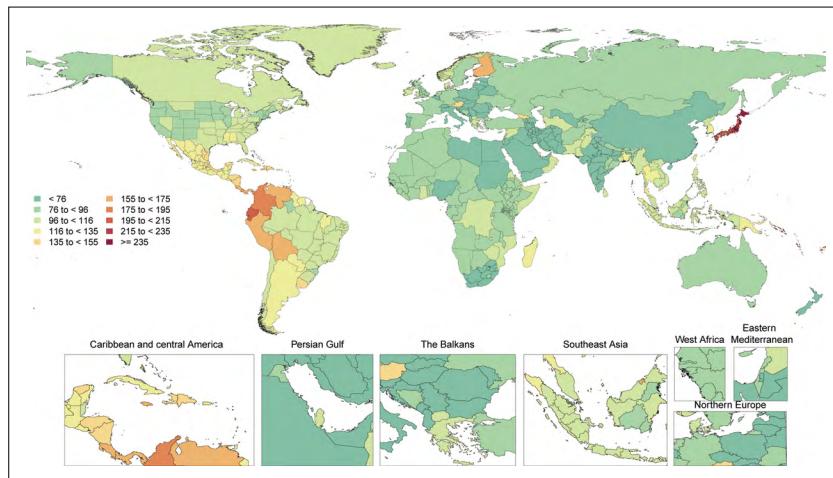


**Chart 15-10. Age-standardized global prevalence rates of ICH per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and ICH, intracerebral hemorrhage.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>286</sup>

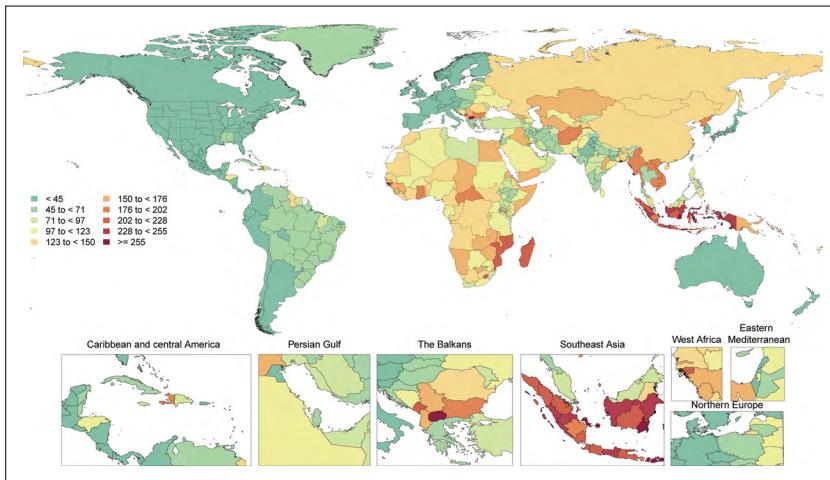


**Chart 15-11. Age-standardized global prevalence rates of SAH per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and SAH, subarachnoid hemorrhage.

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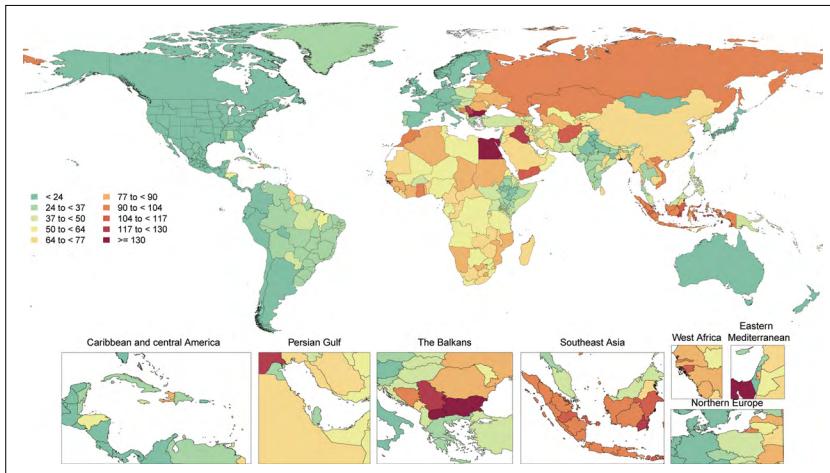


**Chart 15-12. Age-standardized global mortality rates of total stroke (all subtypes) per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

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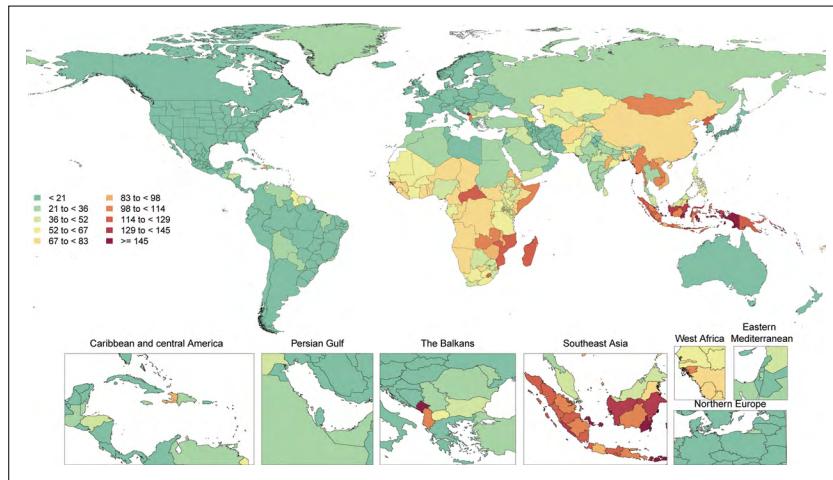


**Chart 15-13. Age-standardized global mortality rates of ischemic stroke per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

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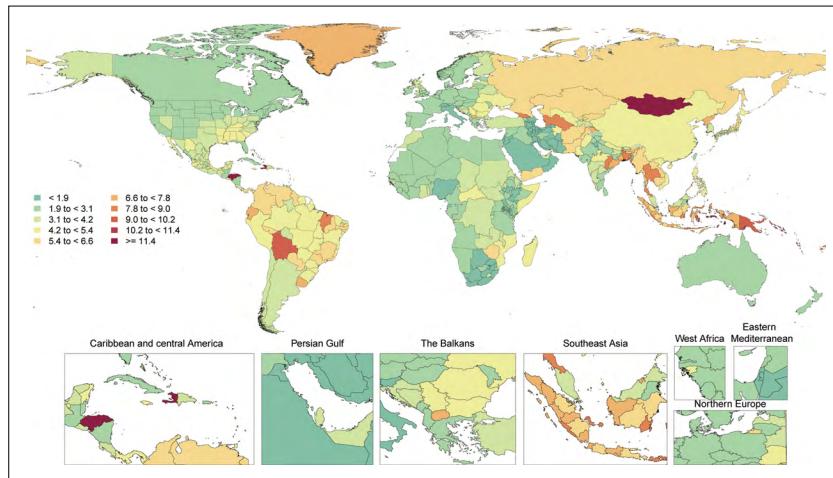


**Chart 15-14. Age-standardized global mortality rates of ICH per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and ICH, intracerebral hemorrhage.

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**Chart 15-15. Age-standardized global mortality rates of SAH per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and SAH, subarachnoid hemorrhage.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>286</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 through 16-3**

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### Definition

Brain health has traditionally been defined in terms of the absence of disease or the presence of a healthy state,<sup>1</sup> but it is an evolving concept with calls to include mental health and social well-being.<sup>2</sup> Brain health has been defined as “the state of brain functioning...allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders.”<sup>3</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 clinical cerebrovascular disease more broadly are important precursors and risk factors for cognitive decline and dementia; their presence indicates an absence of brain health. Conversely, evidence of systemic and cerebral vascular health has been associated with healthy aging and retained cognitive function.

Although this chapter provides prevalence and incidence estimates for dementia overall (unspecified) and separately for AD and vascular dementia, most dementia pathology is mixed, with contributions of both AD and vascular dementia. Postmortem neuropathology studies suggest that ≈1 in 4 people who receive a clinical diagnosis of AD have non-AD pathology as a primary explanation for their dementia.<sup>4</sup> Notably, neither cognitive performance nor demographic variables appear to have any bearing on which patients diagnosed with MCI will develop postmortem pathology consistent with AD. In addition, vascular dementia prevalence and incidence are likely underestimated because (1) most dementia cases have multiple pathologies at autopsy, including signs of ischemia, and (2) vascular disease is common.<sup>5,6</sup>

The 2025 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 2025. 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.

Last, there is also no evidence that the prevalence of pathological AD diagnosis or mean levels of global AD pathology have been decreasing, emphasizing the importance of understanding both trends and contributors to brain health. 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>7</sup> AD/ADR D refers to AD and AD-related dementias, including vascular contributions to cognitive impairment and dementia, frontotemporal degeneration, Lewy body dementia, and dementias of multiple causes.<sup>8</sup>

### Prevalence

#### Dementia

- A systematic analysis of data from the GBD Study showed that AD/ADR D was the fourth most prevalent neurological disorder in the United States in 2017, affecting 2.9 (95% UI, 2.6–3.2) million people.<sup>9</sup> Among 3496 participants in the HRS ≥65 years of age, 393 (10% [95% CI, 9%–11%]) had dementia, and 804 (22% [95% CI, 20%–24%]) were classified as having MCI in 2016.<sup>10</sup> Among neurological disorders, AD/ADR D was the leading cause of mortality in the United States (38 deaths per 100 000 population per year [95% UI, 38–39]), greater than that for stroke.<sup>9</sup>
- According to administrative claims data of US Medicare fee-for-service beneficiaries ≥65 years of age in 2014, AD/ADR D prevalence was 11.5% with a higher prevalence in females (12.2%) compared with males (8.6%); prevalence was higher in females among all reported races and ethnicities, but these numbers were not age adjusted.<sup>11</sup> In terms of age, AD/ADR D 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/ADR D 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.
- Of the 46.8 million people estimated to be living with dementia globally in 2015, 58% of them were living in low- or middle-income countries.<sup>12</sup> However, the predicted annual total cost of dementia per patient in 2015 was highest in higher-income countries: \$10 467 for upper-middle-income countries compared with \$3865 for low-middle-income countries and \$939 for low-income countries.<sup>13</sup> However, a systematic review estimated that low-income countries had the highest total cost as a percentage of their GDP (0.46%) followed by upper-middle-income countries (0.43%) and then low-middle-income countries (0.35%), dedicated to dementia care.<sup>14</sup>

- Young-onset dementia, defined as symptoms before 65 years of age, was estimated in a meta-analysis to have prevalence globally of 1.1 per 100 000 at 30 to 34 years of age, 1.0 per 100 000 at 35 to 39 years of age, 3.8 per 100 000 at 40 to 44 years of age, 6.3 per 100 000 at 45 to 49 years of age, 10.0 per 100 000 at 50 to 54 years of age, 19.2 per 100 000 at 55 to 59 years of age, and 77.4 per 100 000 at 60 to 64 years of age, although data for some age groups were limited in lower-middle-income countries.<sup>15</sup>
- The age-adjusted prevalence of subjective cognitive decline among adults  $\geq 45$  years of age in the United States, as assessed by BRFSS data between 2015 and 2020, was higher among Hispanic adults (11.4%) and American Indian or Alaska Native adults (16.7%) compared with NH White adults (9.3%) but similar in NH Black adults (10.1%) and lower among NH Asian or Pacific Islander adults (5.0%).<sup>16</sup>

### **Alzheimer Disease**

- In 2024,  $\approx 6.9$  million adults  $\geq 65$  years of age in the United States were living with AD. In other words, 10.9% of the US population, or  $\approx 1$  in 9 people, was living with AD.<sup>17</sup> Prevalence estimates for AD are estimated to be lower if the definition necessitates both clinical symptoms and AD biomarkers ( $\approx 4.8$  million adults  $\geq 65$  years of age).
- Prevalence estimates vary with age. According to data from CHAP, the 2020 US census-adjusted prevalence per 100 people is 5.3% (95% CI, 4.9%–5.7%) for 65 to 74 years of age, 13.8% (95% CI, 13.1%–14.5%) for 75 to 84 years of age, and 34.6% (95% CI, 33.3%–35.8%) for those  $> 85$  years of age.<sup>18</sup>

### **Vascular Dementia**

- Vascular dementia accounts for  $\approx 5\%$  to 10% of patients with dementia when both clinical and neuropathological criteria are used.<sup>17</sup> The prevalence is estimated to be between 15% and 20% in Europe and North America and as high as 30% in some Asian countries.<sup>19</sup>
- In a meta-analysis of studies from across the world (South America, Asia, Africa, Europe, and North America), the prevalence of vascular dementia was reported as higher in males than females (56 cases versus 32 cases per 10 000 people).<sup>20</sup>

### **Incidence**

#### **Dementia**

- In 2017, AD/ADRD had the fifth leading incidence rate of neurological disorders in the United States, after tension-type headache, migraine, traumatic brain injury, and stroke, 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 retrospective analysis of the HRS (N=3435), for up to 3 years after dementia onset, using the TICS to define dementia onset, Black individuals were less likely to receive a diagnosis of ADRD (unadjusted HR 0.73 [95% CI, 0.61–0.88]) compared with White respondents, with the effect estimate attenuated but remaining significant when adjusted for demographics, income, and level of education (HR, 0.79 [95% CI, 0.66–0.96]).<sup>21</sup>
- In a nationally representative cohort study of US veterans (N=1 869 090;  $\geq 55$  years of age receiving care in the Veterans Healthcare System between 1999 and 2019), there were significant differences in the incidence of dementia by race and ethnicity.<sup>22</sup> The age-adjusted incidence of dementia was higher among underrepresented racial and ethnic groups compared with White racial and ethnic groups (14.2 per 1000 PY [95% CI, 13.3–15.1] in American Indian or Alaska Native participants, 12.4 [95% CI, 11.7–13.1] in Asian participants, 19.4 [95% CI, 19.2–19.6] in Black participants, and 20.7 [95% CI, 20.1–21.3] in Hispanic participants compared with 11.5 [95% CI, 11.4–11.6] in White participants).
- Among those  $\geq 90$  years or age in the United States, the age-adjusted incidence rate of dementia was 100.5 cases per 1000 PY (95% CI, 92.8–108.3) with the highest rates among Black individuals (121.5 dementia cases per 1000 PY) and the lowest rates among Asian individuals (89.9 dementia cases per 1000 PY).<sup>23</sup>

### **Alzheimer Disease**

- Among 2794 individuals from CHAP, the annual incidence of clinically diagnosed AD was 3.6% (95% CI, 3.3%–3.9%).<sup>24</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 both Black individuals and White individuals.
- In 2011 in the United States, the average incidence of AD per year was 0.4% in individuals 65 to 74 years of age, 3.2% in individuals 75 to 84 years of age, and 7.6% in individuals  $\geq 85$  years of age.<sup>24</sup>

### **Vascular Dementia**

- In a US cohort of  $> 240 000$  females diagnosed with breast cancer at  $\geq 65$  years of age with 26 years of follow-up, the incidence rate of vascular dementia compared with White females (7.2 cases per 1000 PY) was higher in Black females (11.3 cases per 1000 PY; aHR versus White females, 1.51 [95% CI, 1.39–1.64]) and lower in Asian/Pacific Islander

females (5.58 cases per 1000 PY; aHR versus White females, 0.67 [95% CI, 0.57–0.79]).<sup>25</sup>

- Data from the nationally representative MHAS in Mexico, 2012 and 2015 waves, showed that the age- and sex-standardized incidence of vascular dementia among individuals  $\geq 50$  years of age in Mexico was 2.0 (95% CI, 1.3–2.7) per 1000 PY.<sup>26</sup>

## Lifetime Risk and Cumulative Incidence

### Dementia

- In a population-based Japanese cohort of individuals  $\geq 60$  years of age, the lifetime risk of dementia was 54.8% (95% CI, 49.4%–60.1%); elderly females had a greater lifetime risk (64.8% [95% CI, 57.4%–72.1%]) than elderly males (40.8% [95% CI, 33.0%–48.5%]).<sup>27</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>28</sup>
- According to nationwide individually linked cause-of-death and health register data in the Netherlands, the lifetime risk of dementia (estimated by the proportion of deaths in the presence of dementia) was  $\approx 24.0\%$ , higher for females (29.4%) than males (18.3%).<sup>29</sup>

### Alzheimer Disease

- In a population-based Japanese cohort of individuals  $\geq 60$  years of age, the lifetime risk of AD was  $\approx 2$ -fold higher for females (42.4% [95% CI, 35.1%–49.7%]) than for males (20.4% [95% CI, 6.6%–34.2%]).<sup>27</sup>
- The 2023 AD lifetime risk estimates according to the FHS (reported in 2014) at 45 years of age were 1 in 5 females and 1 in 10 males (competing mortality-adjusted cumulative incidence in females, 19.5% [95% CI, 17.8%–21.2%] and in males, 10.3% [95% CI, 8.9%–11.8%]).<sup>30,31</sup>

### Vascular Dementia

- In a population-based Japanese cohort of individuals  $\geq 60$  years of age, the estimated lifetime risk of vascular dementia was similar among females (16.3% [95% CI, 11.5%–21.1%]) and males (17.8% [95% CI, 12.9%–22.7%]).<sup>27</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%]); however, 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 globally 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>32</sup> The global all-age mortality rate from dementia increased 100.1% (95% CI, 89.1%–117.5%).
- A forecasting analysis based on the GBD Study 2019 projected stable global age-standardized prevalence (percentage change, 0.1% [–7.5% to 10.8%]) but an increase in the number of people living with dementia from 2019 to 2050, attributed largely to population growth and aging (57.4 [95% UI, 50.4–65.1] million cases in 2019 to 152.8 [95% UI, 130.8–175.9] million cases in 2050).<sup>33</sup> More females were estimated to be living with dementia in 2019 (RR, 1.69 [95% CI, 1.64–1.73]) and 2050 (RR, 1.67 [95% CI, 1.52–1.85]) 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 12.2% (95% CI, 11.7%–12.7%) in 2000 to 8.5% (95% CI, 7.9%–9.1%) in 2016.<sup>34</sup>
- An analysis of Medicare data estimates that the AD/ADRD prevalence in the US population will increase to 3.3% and that AD/ADRD will affect 13.9 million Americans by 2060.<sup>11</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>35</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 Danish older adults  $\geq 65$  years of age, from 2005 to 2018, the incidence of dementia declined by 22.5% in males and 34.2% in females.<sup>36</sup> After accounting for changes in age, the overall incidence of dementia decreased by 18.1% in males and 23.5% in females. Individuals with high educational attainment (10% males, 14.7% females), high household wealth (12.1% males, 21.4% females),

no history of stroke (7.0% males, 15.6% females), and low medication use (21% males, 19.7% females) had a lower incidence of dementia than the general population but with a similar pattern of decline over time.

- 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% (95% CI, 7%–19%) per calendar decade from 1998 through 2015 with a more pronounced reduction in males (24% [95% CI, 14%–32%]) than in females (8% [95% CI, 0%–15%]).<sup>37</sup>
- A meta-analysis of 53 cohorts from around the world demonstrated a decrease in dementia incidence across 3 older age groups (65–74, 75–84, and  $\geq 85$  years of age).<sup>38</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 to 74 years of age; OR, 0.20 [95% CI, 0.19–0.21] for those 75 to 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>39</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 difference over time ( $P$  ranging from 0.55–0.98 for tests of trend over time).
- In contrast to declining trends of dementia typically reported in high-income countries, Africa represents an understudied continent with a paucity of data available. Over a 9-year interval from 2009 to 2010 to 2018 to 2019, there was an increase in dementia prevalence from 6.4% to 8.9% among those  $>70$  years of age in Tanzania.<sup>40</sup> It is estimated that 212 million individuals  $\geq 60$  years of age will be living in Africa by the year 2050, suggesting a rapidly aging population.<sup>41</sup>
- Among 1554 participants from 1997 to 2022 (Religious Orders Study and the Rush Memory and Aging Project) with autopsy data, there were no differences in the age-standardized prevalence of pathological AD diagnosis ( $P=0.76$  across year of birth groups).<sup>42</sup> However, there was a decrease in the prevalence of neurodegenerative pathologies related to atherosclerosis/arteriosclerosis (eg, moderate to severe atherosclerosis was 54%

among those born from 1905–1914, 37% for 1915–1919, 30% for 1920–1924, and 22% for 1925–1930;  $P<0.001$  across birth year categories,  $\chi^2$  test).

### Alzheimer Disease

- 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% (95% CI, 8%–24%) per calendar decade from 1998 through 2015.<sup>37</sup>
- A meta-analysis of 35 cohorts from around the world demonstrated no significant decrease in the AD incidence rates across 3 older age groups (65–74 years,  $P=0.26$ ; 75–84 years,  $P=0.90$ ; and  $\geq 85$  years of age,  $P=0.54$ ).<sup>38</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 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>43</sup> In contrast, age-adjusted stroke mortality decreased by 21.6% during the same time period (from 358.5 per 1 000 000 in 2007 to 281.2 per 1 000 000 in 2016).

### Vascular Dementia

- For FHS participants  $\geq 60$  years of age, the 5-year age- and sex-adjusted incidence 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 ( $P_{\text{trend}}=0.004$ ).<sup>44</sup>
- According to 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>43</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, 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>45</sup>
- Among 3201 middle-aged adults (40–64 years of age) in the FHS (55% female) followed up over a median of 17 years, every 1-SD increase in cumulative SBP was associated with a higher odds of developing late-life ( $\geq 65$  years of age) all-cause dementia (OR, 1.50 [95% CI, 1.32–1.72]) and developing AD (OR, 1.45 [95% CI, 1.24–1.69]).<sup>46</sup>
  - In the CHARLS cohort (N=4824; 62% females), hypertension at middle age (<55 years of age) was associated with a faster decline in memory ( $\beta=-1.12$  [95% CI, −1.41 to −0.83]), orientation ( $\beta=-1.27$  [95% CI, −1.35 to −1.20]), and global cognition ( $\beta=-1.61$  [95% CI, −1.74 to −1.48]) compared with no hypertension over 8 years of follow-up.<sup>47</sup> Longer duration of hypertension was associated with poorer memory ( $\beta=-0.07$  [95% CI, −0.11 to −0.03]).
  - Among 2718 adults in CARDIA, longer duration of hypertension from early to middle adulthood was associated with significantly lower midlife scores on a measure of verbal memory (Rey Auditory Verbal Learning Test; 0.18 points lower [95% CI, 0.07–0.29 point lower];  $P=0.002$  per 5 additional years' duration) and with lower midlife scores, but not reaching statistical significance, on a measure of processing speed (digit symbol substitution test; 0.43 point lower [95% CI, 0.10 point higher–0.95 point lower];  $P=0.112$  per 5 additional years' duration) but not with a measure of executive function (Stroop test; 0.01 point lower [95% CI, 0.37 point higher–0.39 point lower];  $P=0.975$  per 5 additional years' duration).<sup>48</sup> Lower scores on verbal memory with longer hypertension duration were observed whether hypertension was controlled or uncontrolled.
  - 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>49</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 (4.44 points greater decline [95% CI, 0.99–7.88 points decline] on digit symbol substitution test over 10 years), even after adjustment for SBP exposure at midlife and late life.
  - In a meta-analysis of 3 studies including >2.3 million females, HDP was not significantly associated with higher risk for dementia (fixed-effects pooled HR, 1.08 [95% CI, 0.93–1.25]).<sup>50</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 (SMD, 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>51</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>49,52,53</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>54</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.
  - Among 2688 males of Japanese ancestry in the Kuakini HHP (mean age, 77 years) followed up for a mean of 8.63 years with 104 incident vascular dementia and 513 incident AD cases, late-life hypertension was associated with incident vascular dementia (HR, 1.78 [95% CI, 1.05–2.99] for  $BP \geq 140/90$  mmHg or self-reported antihypertensive use).<sup>55</sup> Late-life hypertension reduced the risk of AD among males with the *FOXO3* longevity genotype (HR, 0.73 [95% CI, 0.53–1.00]) but not among males without this genotype (HR, 1.09 [95% CI, 0.81–1.46]).
  - 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>56</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>57</sup> Among 12 298 adults in HRS and ELSA who were free of dementia 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 was associated with 0.022–SD/y faster (95% CI, 0.017–0.027) global cognitive decline.<sup>58</sup> Among 19 114 participants in the ASPREE trial, males in the highest SBP variability tertile compared with 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, 0.72–1.42]).<sup>59</sup> Among 820 older adults in the ACT study (mean age, 77 years), BP variability among those 90 years of age was associated with higher lifetime dementia risk (for each 1-SD increase in coefficient of variation: HR, 1.35 [95% CI, 1.02–1.79]).<sup>60</sup> BP variability was not associated with lifetime dementia risk at 60, 70, or 80 years of age.

- 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>61</sup>
- In ARIC (N=4761; 21% Black participants; 59% females), hypertension (both midlife 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>62</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]).
- An individual patient meta-analysis of 19 378 participants from 5 cohort studies found that differences between Black individuals 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>63</sup>
- An individual participant data meta-analysis of 34 519 older adults (mean age, 73 years) including 14 studies from COSMIC found a higher risk of dementia among participants with untreated hypertension compared with participants without hypertension (HR, 1.42 [95% CI, 1.15–1.76]) and compared with participants with treated hypertension (HR, 1.26 [95% CI, 1.03–1.54]).<sup>64</sup>

- The proportion of time spent in target SBP range may be associated with dementia risk. Among 8298 participants in the SPRINT MIND trial (mean age, 68 years; 35% female), greater time spent in the target SBP range (110–130 mmHg for the intensive treatment group or 120–140 mmHg for the standard treatment group) was associated with a lower risk of probable dementia (HR, 0.86 [95% CI, 0.76–0.98] for every 1-SD increase in time spent in the target SBP range).<sup>65</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>66</sup> The effect did not vary significantly by HFpEF versus HFpEF.
- In a meta-analysis of 4 longitudinal studies, the pooled RR for dementia associated with HF was 1.80 (95% CI, 1.41–2.31).<sup>67</sup>
- Among 6336 patients, the 1-year and 3-year cumulative incidences of ADRD after incident HF diagnosis were 7.6% (95% CI, 6.9%–8.3%) and 17.1% (95% CI, 16.2%–18.0%), respectively.<sup>68</sup> Patients with ADRD diagnosed after HF had a 3.7 times increased risk of death (95% CI, 3.34–4.10) compared with those who did not develop ADRD, even after adjustment for vascular risk factors, marital status, and education.
- Among 3052 patients with HF in the FHS, the 1-year and 3-year cumulative incidences of AD/ADRD were 3.3% (95% CI, 2.6%–3.9%) and 13.8% (95% CI, 12.5%–15.1%).<sup>69</sup>
- In the ASPREE trial, 19 114 adults without CVD or dementia at baseline were followed up for 9 years to determine trajectories of cognitive change after incident CVD (fatal CHD, nonfatal MI, stroke, hospitalization for HF).<sup>70</sup> After the CVD event, there was an acute decrement in processing speed (acute drop in cognitive score, -1.97 [95% CI, -2.53 to -1.41]) followed by declines in global cognitive function (annual change in cognitive score, -0.56 [95% CI, -0.76 to -0.36]), delayed recall (annual change in cognitive score, -0.10 [95% CI, -0.16 to -0.04]), and verbal fluency (annual change in cognitive score, -0.19 [95% CI, -0.30 to -0.01]). Similarly, in the 171 adults with a hospitalization for HF, there was an acute decrement in processing speed (acute drop in cognitive score, -2.85 [95% CI, -4.07 to -1.63]) followed by declines in global cognitive function (annual change in cognitive

score,  $-0.51$  [95% CI,  $-0.99$  to  $-0.04$ ]), delayed recall (annual change in cognitive score,  $-0.18$  [95% CI,  $-0.36$  to  $-0.01$ ]), and verbal fluency (annual change in cognitive score,  $-0.36$  [95% CI,  $-0.63$  to  $-0.09$ ]).

### 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>71</sup> Among 25980 adults in REGARDS, those with AF at baseline declined in mean word list learning score over 10 years of follow-up (decline in mean $\pm$ SD score from  $16.3\pm0.15$  to  $16.0\pm0.23$ ), whereas those without AF at baseline increased in mean word list learning score (increase in mean $\pm$ SD score from  $16.3\pm0.05$  to  $16.9\pm0.06$ ;  $P=0.03$  for AF versus no AF); however, there were no significant differences in trajectories of semantic fluency, word list delayed recall, or MoCA score.<sup>72</sup> Among 98484 patients with AF in the Kaiser system and 98484 matched controls without incident AF (2010–2017; median follow-up time, 3.3 years), incidence rates for dementia were higher for those with AF ( $2.79$  [95% CI,  $2.72$ – $2.85$ ] per 100 PY) versus without ( $2.04$  [95% CI,  $1.99$ – $2.08$ ] per 100 PY).<sup>73</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>74</sup>
- In the UK Biobank, of the 433 746 participants without baseline dementia or AF, having a younger age at AF onset during the median 12.6 years of follow-up was associated with a higher risk of all-cause dementia (aHR per 10-year decrease,  $1.23$  [95% CI,  $1.16$ – $1.32$ ]), AD (aHR per 10-year decrease,  $1.27$  [95% CI,  $1.13$ – $1.42$ ]), and vascular dementia (aHR per 10-year decrease,  $1.35$  [95% CI,  $1.20$ – $1.51$ ]) compared with participants with older age at AF onset.<sup>75</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>76,77</sup> In SNAC-K, AF was associated with increased risk of all-cause and vascular and mixed dementia (HR,  $1.40$  [95% CI,  $1.11$ – $1.77$ ] and  $1.88$  [95% CI,  $1.09$ – $3.23$ ], respectively); however, anticoagulant users with AF were less likely to develop dementia (HR,  $0.40$  [95% CI,  $0.18$ – $0.92$ ]) compared with nonusers with AF.<sup>76</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>78</sup> However, 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>77</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>79</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 of dementia (95% CI, 10%–31% lower) than treatment with warfarin.<sup>80</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>81</sup> In the Belgian nationwide cohort study (2013–2019), DOAC use was associated with a lower risk of dementia (HR  $0.91$  [95% CI,  $0.85$ – $0.98$ ]) compared with vitamin K antagonist use among 237 012 participants with AF.<sup>82</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 compared with warfarin was not associated with dementia risk (HR,  $0.99$  [95% CI,  $0.93$ – $1.06$ ]).<sup>83</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>84</sup>
- In a systematic review of 10 studies with 15 886 patients treated with catheter ablation and 42 684 patients treated with medical therapy (rate or rhythm control), 4 studies reported risk of dementia with the pooled-effect estimate suggesting a decreased risk of incident dementia among those who underwent ablation (HR,  $0.60$  [95% CI,  $0.42$ – $0.88$ ]).<sup>85</sup> These results, however, were limited by an inability to assess for publication bias because of the small number of

studies included. Another systematic review of 5 studies with 30 192 in the catheter ablation group and 95 457 in the non–catheter ablation group reported a significant reduction in risk of dementia (HR, 0.63 [95% CI, 0.52–0.77]) and AD (HR, 0.78 [95% CI, 0.66–0.92]) with ablation but not vascular dementia (HR, 0.63 [95% CI, 0.38–1.06]).<sup>86</sup> There were more patients with HF in the non–catheter ablation group (82.14% versus 17.86%).

### **Coronary Disease**

- In terms of coronary revascularization procedures, the evidence for an association between either CABG or PCI and later-life dementia is contradictory, although most studies do not suggest an association. One RCT did not suggest a difference in cognitive decline between PCI or CABG after 7.5 years of follow-up.<sup>87</sup> Among 1680 participants (mean age, 75 years at the time of procedure) in the HRS, there was also no significant difference in the rate of memory decline between those undergoing PCI and those undergoing CABG.<sup>88</sup> In CHS, there was an association between CABG and all-cause dementia (HR, 1.93 [95% CI, 1.36–2.74]) compared with those without a history of CABG.<sup>89</sup> Fewer studies have investigated PCI versus medical therapy and the risk of dementia, with 1 cohort study suggesting a lower risk of dementia in the PCI group (HR, 0.65 [95% CI, 0.46–0.84]) compared with the medically managed group.<sup>90</sup>
- Among a prospective cohort of 3146 participants in the CARDIA study (mean age, 55; 57% females, 48% Black participants), premature CVD ( $\leq 60$  years of age) was associated with worse midlife global cognition ( $-0.22$  [95% CI,  $-0.37$  to  $-0.08$ ]), verbal memory ( $-0.28$  [95% CI,  $-0.44$  to  $-0.12$ ]), processing speed ( $-0.46$  [95% CI,  $-0.62$  to  $-0.31$ ]), and executive function ( $-0.38$  [95% CI,  $-0.55$  to  $-0.22$ ] ).<sup>91</sup> Early CVD was also associated with greater brain MRI WMH and lower white matter integrity, as well as accelerated cognitive decline over 5 years (aOR, 3.07 [95% CI, 1.56–5.71]).
- 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>92</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 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.

- Among 30 465 participants in 6 different longitudinal cohort studies, acute MI (n=1033) was associated with faster declines in global cognition ( $-0.15$  points per year [95% CI,  $-0.21$  to  $-0.10$ ]), memory ( $-0.13$  points per year [95% CI,  $-0.22$  to  $-0.04$ ]), and executive function ( $-0.14$  points per year [95% CI,  $-0.20$  to  $-0.08$ ]) over the years after MI compared with pre-MI slopes.<sup>93</sup> It was not, however, associated with an acute decrease in any cognitive domain around the time of the event (eg, global cognition,  $-0.18$  points [95% CI,  $-0.52$  to  $0.17$ ]).

### **Subclinical Cardiac Disease**

- Subclinical measures of cardiac dysfunction are also associated with brain health outcomes. For example, asymptomatic LV hypertrophy, measured by LV mass index, has been associated with increased risk of cognitive decline and dementia and worse white matter burden in late life.<sup>94,95</sup> In MESA (N=4999; mean age, 61 years; 47% males; 26% Black participants, 22% Hispanic participants, and 13% Chinese participants; median follow-up, 12 years), both LV mass index and ratio of LV mass to volume were associated with increased risk of dementia (HR, 1.01 [95% CI, 1.00–1.02] and 2.37 [95% CI, 1.25–4.43], respectively).<sup>95</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>96</sup>
- In ARIC (N=5078), a state of atrial cardiopathy was associated with an increased risk of dementia (HR, 1.35 [95% CI, 1.16–1.58]), and only a small portion of the effect was mediated by either AF (4%;  $P=0.005$ ) or ischemic stroke (9%;  $P=0.048$ ).<sup>97</sup>
- In CARDIA, among 2653 participants with echocardiogram evaluation 25 years apart, a greater increase ( $\geq 1$  SD above the mean slope) in LV mass index and LA volume index and a greater decrease ( $\geq 1$  SD below the mean slope) in LVEF were found.<sup>98</sup> After adjustment for demographics and vascular risk factors, a greater increase in LV mass index over 25 years was associated with lower cognition on some but not all cognitive tests (eg, MoCA  $\geq 1$ -SD change mean  $-0.24$  [95% CI,  $-0.35$  to  $-0.12$ ] ) with no differences in cognitive performance for either a larger LA volume index or lower LVEF.

**Poststroke**

(See Chapter 15 [Stroke (Cerebrovascular Diseases)].)

**Diabetes**

- Diabetes is associated with worse cognitive functioning and faster cognitive decline. In cross-sectional analysis of UK Biobank participants, 914 participants with diabetes scored significantly lower than matched healthy participants on measures of executive function, processing speed, abstract reasoning, and numeric memory; they scored similarly on a measure of reaction time (Chart 16-1B).<sup>99</sup> In meta-analyses of 34 studies conducted by the same authors, 4735 participants with diabetes scored significantly lower than 17 496 healthy participants on 10 of 11 cognitive domains assessed (Chart 16-1C).<sup>99</sup> In a longitudinal analysis of ELSA participants with a median follow-up of 13 years, 576 participants experiencing incident diabetes declined faster on measures of global cognition (0.035 SD/y faster [95% CI, 0.015–0.054]), orientation (0.031 SD/y faster [95% CI, 0.002–0.060]), memory (0.016 SD/y faster [95% CI, 0.003–0.029]), and executive function (0.027 SD/y faster [95% CI, 0.013–0.042]) after diabetes onset than participants without diabetes.<sup>100</sup>
- Among 63 117 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, baseline diabetes was associated with 22% higher hazard (95% CI, 13%–31% higher) of AD. Incidence of AD was 8.5 cases per 1000 PY (95% CI, 8.0–9.0) for females who had diabetes versus 7.1 cases per 1000 PY (95% CI, 6.9–7.2) for females without diabetes.<sup>101</sup>
- In a mendelian randomization study of 115 875 adults, the RR 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>102</sup>
- Studies also have demonstrated an association between elevated glucose levels in early adulthood to midlife and worse midlife cognitive outcomes among participants without diabetes.<sup>103,104</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), the highest quartile of HbA1c variability compared with the lowest quartile was associated with greater decline in memory ( $\beta=-0.094$  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>105</sup> In a meta-analysis

of 5 longitudinal studies including >500 000 participants with diabetes with a mean follow-up of 6 years, risk of dementia was 6% higher (95% CI, 0.3%–12% higher) per increment in visit-to-visit HbA1c coefficient of variation across studies and 19% higher (95% CI, 6%–32% higher) per increment in visit-to-visit HbA1c SD across studies.<sup>106</sup>

- A history of hypoglycemia is also associated with worse brain health outcomes. 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>107</sup> In another meta-analysis of 10 studies including >1.4 million participants with diabetes, hypoglycemic episodes were associated with 44% higher risk (95% CI, 26%–65% higher) of dementia.<sup>108</sup> In a meta-analysis of 7 studies including 981 812 participants with diabetes, increasing number of hypoglycemic episodes was associated with higher risk of incident dementia (RR, 1.29 [95% CI, 1.15–1.44] for 1 hypoglycemic episode; 1.68 [95% CI, 1.38–2.04] for 2 hypoglycemic episodes; 1.99 [95% CI, 1.48–2.68] for ≥3 hypoglycemic episodes).<sup>109</sup>
- 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>110</sup>
- Late-life diabetes, poor glycemic control among those with diabetes, and diabetes duration (≥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>111</sup>
- Among 11 656 adults in ARIC (mean age, 57 years; 55% female), earlier age at diagnosis of incident diabetes was associated with higher risk of incident dementia (HR, 2.92 [95% CI, 2.06–4.14] for diabetes diagnosis at <60 years of age; HR, 1.73 [95% CI, 1.47–2.04] for diabetes diagnosis at 60–69 years of age; HR, 1.23 [95% CI, 1.08–1.40] for diabetes diagnosis at 70–79 years of age).<sup>112</sup>
- Among 356 052 participants <60 years of age in the UK Biobank (mean age, 55 years; 55% female) with 485 cases of young-onset incident dementia (<65 years of age) over a median follow-up of 9.18 years, having diabetes was associated with 65% higher risk of young-onset dementia (HR, 1.65 [95% CI, 1.15–2.36]).<sup>113</sup>

**Obesity**

- Midlife overweight and obesity are associated with increased risk of cognitive impairment and dementia. In a meta-analysis of 11 longitudinal studies including >64 000 participants, those who were overweight in midlife compared with those who were normal weight did not have a higher risk of the combined end point of cognitive impairment or all-cause dementia (RR, 1.14 [95% CI, 0.98–1.32]) but did have 1.64 times the risk of AD (95% CI, 1.23–2.18) and 1.49 times the risk of vascular dementia (95% CI, 1.06–2.10). Midlife obesity compared with normal weight was associated with 1.31 times the risk of cognitive impairment and all-cause dementia (95% CI, 1.02–1.68), 2.23 times the risk of AD (95% CI, 1.58–3.14), and 3.18 times the risk of vascular dementia (95% CI, 1.81–5.57).<sup>114</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>115</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>116</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>117</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>118</sup>
- The evidence for obesity and BMI in late life is less clear,<sup>119</sup> with some studies suggesting that obesity is protective or that weight loss may be a prodrome of late-life dementia.<sup>120,121</sup>
- In the Whitehall II Study (N=17 175), participant age modified the association between obesity and risk of dementia. Compared with healthy adults with normal weight, obesity at <60 years of age and 60 to 70 years of age was associated with increased risk of dementia (HR 1.69 [95% CI, 1.16–2.45] and 1.46 [95% CI, 1.02–2.08] for participants with obesity <60 years of age without and with other poorly controlled risk factors, respectively; HR, 1.47 [95% CI, 1.05–2.04] for participants with obesity 60

to 70 years old with other poorly controlled risk factors).<sup>122</sup> There was no association between obesity and risk of dementia in participants 60 to 70 years of age without other poorly controlled risk factors or in participants ≥70 years of age compared with healthy adults with normal weight.

- 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 age-, sex-, and ethnicity-adjusted 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>123</sup>
- One study showed that obesity may be associated with poorer cognition at baseline but slower cognitive decline over time.<sup>124</sup> In a meta-analysis of individual participant data consisting of 6 pooled cohorts with 28 867 participants free of dementia at baseline (mean age, 61 years; 55% female; 29% obese), participants with obesity had 0.36 point lower global cognition scores (95% CI, 0.17–0.56 point lower) and 0.56 point lower executive function scores (95% CI, 0.37–0.76 point lower) than participants with normal weight at baseline. Over a median follow-up of 6.5 years, participants with obesity had 0.03 point/y (95% CI, 0.01–0.05) slower decline in global cognition and 0.02 point/y (95% CI, 0.006–0.03) slower decline in executive function compared with participants with normal weight after adjustment for SBP and FPG. On the basis of those estimated trajectories, it would take adults with obesity 0.74 year longer (for global cognition) and 1.05 years longer (for executive function) than adults with normal weight to reach ≥0.5-SD decline from the baseline cognition score.

**Smoking**

- Smoking is a risk factor for dementia and poor cognitive outcomes, and studies suggest that quitting smoking is beneficial for brain health.<sup>125–127</sup>
- In an analysis from the NACC UDS, current smoking was associated with incident dementia (HR, 1.88 [95% CI, 1.08–3.27]) compared with non-smoking. Participants who quit within the past 10 years compared with nonsmokers were not more likely to develop dementia.<sup>126</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>125</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, 2.00–4.09]) and 3.13 times the risk of AD (HR, 3.13 [95% CI, 1.80–5.42]) compared with those with no exposure to secondhand smoke.<sup>128</sup>
- Among 353756 nonsmokers in the UK Biobank with 4113 developing incident dementia over a median 11.8 years of follow-up, secondhand smoke exposure was associated with increased risk of all-cause dementia compared with no exposure to second-hand smoke (HR, 1.11 [95% CI, 1.02–1.20] and 1.31 [95% CI, 1.13–1.52] for ≤4 and >4 h/wk of secondhand smoke exposure, respectively).<sup>129</sup>

### **Cardiovascular Risk Factor Burden**

(See Table 16-1)

- The AHA's ideal CVH metrics are associated with reduced cognitive decline. In a meta-analysis of 14 studies including >300 000 participants, of whom 8006 experienced incident dementia, a 1-point increment in Life's Simple 7 CVH score was associated with 6% lower rate of dementia (95% CI, 4%–8% lower).<sup>130</sup> The inverse relationship of higher CVH score with dementia risk was more pronounced for midlife CVH than for late-life CVH. 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>131</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>132</sup> Those with poor CVH (scores 0–6) had 3.2 cases of dementia per 1000 PY (95% CI, 2.5–4.0); those with intermediate CVH (scores 7–11) had 1.5 fewer cases per 1000 PY (95% CI, 0.7–2.3 fewer); and those with optimal CVH (scores 12–14) had 1.9 fewer cases per 1000 PY (95% CI, 1.1–2.8 fewer), with an HR for dementia of 0.89 per 1-point increment in CVH score (95% CI, 0.85–0.95).
- 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>133</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>134</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]).
- Among 259 718 participants in the UK Biobank with 4958 cases of incident dementia over a median 10.6 years of follow-up, lower AHA's Life's Essential 8 score was associated with higher risk of vascular dementia (HR, 1.86 [95% CI, 1.44–2.42]) for participants in the lowest versus highest quartile of AHA's Life's Essential 8 score.<sup>135</sup> There was no association between AHA's Life's Essential 8 score and risk of AD (HR, 0.98 [95% CI, 0.84–1.16]) for participants in the lowest versus highest quartile of AHA's Life's Essential 8 score.
- Among 316 669 participants in the UK biobank with 4238 incident cases of all-cause dementia (mean age, 56 years) over a median 12.6 years of follow-up, an optimal AHA's Life's Essential 8 score (score of 80–100 on a 100-point scale) was associated with a 14% lower risk of incident all-cause dementia (HR, 0.86 [95% CI, 0.83–0.89]) and 30% lower risk of vascular dementia (HR, 0.70 [95% CI, 0.65–0.75]) compared with a poor AHA's Life's Essential 8 score (score of 0–49).<sup>136</sup> The association between AHA's Life's Essential 8 score and risk of dementia varied by *APOE* status ( $P_{\text{interaction}} < 0.001$ ). In participants without an *APOE* ε4 allele, the HR of all-cause dementia or vascular dementia associated with an optimal AHA's Life's Essential 8 score was 0.39 (95% CI, 0.31–0.49) and 0.18 (95% CI, 0.12–0.29), respectively. In participants with at least 1 *APOE* ε4 allele, the HR of all-cause dementia or vascular dementia associated with an optimal AHA's Life's Essential 8 score was 0.71 (95% CI, 0.56–0.90) and 0.41 (95% CI, 0.27–0.63), respectively.
- Greater cardiovascular risk factor burden is associated with increased risk of cognitive decline and dementia.<sup>137,138</sup>
- In CARDIA,<sup>137</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>139</sup> greater Framingham 10-Year Cardiovascular Disease Risk Score was associated with greater late-life cognitive decline ( $-0.064$  [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  $-0.018$ ]).
  - In the Insight 46 cohort, higher Framingham 10-Year Cardiovascular Disease Risk Score in early adulthood (36 years of age) also was associated with lower late-life total brain volume ( $\beta$  per 1% increase in risk score= $-3.6$  mL [95% CI,  $-7.0$  to  $-0.3$ ]) and higher WMH volume (exponentiated  $\beta$  [mean ratio] per 1% increase in risk score= $1.09$  [95% CI,  $1.01$ – $1.18$ ]).<sup>140</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>141</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).
  - Among adults in the ARIC (n=11460) and AGES (n=3907) cohorts over a median follow-up of 22.3 and 10.5 years respectively, participants with a high CVH score in midlife (CVH measured by smoking, BMI, PA, healthy diet, BP, FPG, and TC; high score defined as a score of 10–14 on a 14-point scale in ARIC or score of 8–12 on a 12-point scale in AGES) had a lower risk of incident dementia than participants with a low CVH score (defined as a score of 0–5 in ARIC or a score of 0–4 in AGES) in midlife (HR, 0.60 [95% CI, 0.52–0.69] in ARIC and 0.83 [95% CI, 0.66–0.99] in AGES).<sup>142</sup>
  - The association between cardiovascular risk factors and incident dementia may depend on the cardiovascular risk factors included in the burden score. Among 12412 adults in the NACC dataset (mean age, 71 years), over a mean 65 months of follow-up, participants with vascular-dominant cardiovascular risk factors (diagnoses of hypertension and hyperlipidemia) had higher odds of incident AD than participants without vascular risk factors (OR, 1.74 [95% CI, 1.28–2.36]).<sup>143</sup> Participants with vascular-metabolic cardiovascular risk factors (diagnoses of hypertension, hyperlipidemia, diabetes, and high

BMI) did not differ in the incidence of AD compared with participants without vascular risk factors (OR, 1.30 [95% CI, 0.94–1.80]).

### Chronic Kidney Disease

- Among 90369 adults in the CGPS, of whom 2468 developed dementia over 15 years of follow-up, age- and sex-standardized percentile of eGFR below the median versus above was associated with 9% higher risk of dementia (95% CI, 1%–18% higher).<sup>144</sup> In a meta-analysis of >460000 Scandinavian adults conducted by the same authors, there was a dose-response pattern: Risk of dementia was 1.14 times as high (95% CI, 1.06–1.22) for eGFR 60 to 90 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>, 1.31 times as high (95% CI, 0.92–1.87) for eGFR 30 to 59 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>, and 1.91 times as high (95% CI, 1.21–3.01) for eGFR <30 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> relative to eGFR >90 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>.<sup>144</sup>
- Among 6050 adults in the Whitehall II Study, of whom 306 developed dementia over a mean 10 years of follow-up, eGFR <60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> at baseline was associated with 37% higher risk of dementia (95% CI, 1%–85% higher), and decline in eGFR of  $\geq 4$  mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> over  $\approx 4$  years was associated with 37% higher risk of subsequent dementia (95% CI, 2%–85% higher).<sup>145</sup>
- In a meta-analysis of 16 studies (some longitudinal and some cross-sectional) including >120000 participants, of whom 5488 had or developed cognitive impairment and 1266 had or developed dementia, albuminuria was associated with 1.18 times the odds of cognitive impairment (95% CI, 1.09–1.27), 1.32 times the odds of dementia (95% CI, 1.10–1.58), 1.33 times the odds of AD (95% CI, 1.06–1.67), and 2.32 times the odds of vascular dementia (95% CI, 1.59–3.38).<sup>146</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>147</sup>
- In a secondary analysis of SPRINT, higher serum creatinine was associated with increased risk of incident dementia or amnestic MCI over a median of 4.13 years of follow-up (HR, 1.24 [95% CI, 1.19–1.29] per 1 SD of baseline serum creatinine).<sup>148</sup>
- Among 1354 participants in MAP (mean age, 79 years; 75% female), lower eGFR was associated with higher risk of incident AD (HR, 1.27 [95% CI, 1.09–1.48] for every 1-SD decrease in eGFR).<sup>149</sup> Participants with an eGFR <60 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> were diagnosed with AD a median of 1.57

(95% CI, 0.25–2.89) years sooner than those with normal kidney function.

### SDB/Sleep Apnea

(See also Chapter 13 [Sleep].)

- In a meta-analysis of 18 longitudinal studies ( $N=246\,786$  participants), SDB (including self-reported or objective snoring, sleep apnea, or OSA) 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>150</sup>
- In another meta-analysis of 6 longitudinal studies (follow-up between 3 and 15 years), SDB (defined as AHI  $\geq 15$  or based on *ICD-9* codes) 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>151</sup>
- Pooling data from 5 prospective cohort studies with up to 5 years of follow-up ( $N=5946$ ; age range, 58–89 years; 31.5% female; ARIC, CHS, FHS, Osteoporotic Fractures in Men Study, and Study of Osteoporotic Fractures), the Sleep and Dementia Consortium found that adults with mild to severe OSA (AHI  $\geq 5$ ) had worse global cognition (pooled  $\beta=-0.06$  [95% CI, -0.11 to -0.01];  $P=0.01$ ) compared with the reference group (AHI  $< 5$ ).<sup>152</sup>
- Greater OSA severity, based on AHI parameters, was associated with decreased cerebrospinal fluid  $\beta$ -amyloid 42 over 2 years in a community-based sample of adults with normal cognition ( $N=208$ ; 62% females).<sup>153</sup> There was also a trend, although nonsignificant, between OSA severity and cortical Pittsburgh compound B–positron emission tomography uptake.
- Sleep apnea, assessed by AHI or oxygen desaturation index, 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>154</sup> and with brain WMH, most notably periventricular frontal and dorsal WMH volumes ( $N=529$  participants; age, 52 years; 53% females).<sup>155</sup>
- In a retrospective study of Medicare beneficiaries with OSA (*ICD-9* codes;  $N=53\,321$  adults  $\geq 65$  years of age; 41% females), the odds of incident AD and dementia not otherwise specified over 3 years were lower among older adults prescribed treatment for positive airway pressure therapy (OR, 0.65 [95% CI, 0.56–0.76] and 0.69 [95% CI, 0.5–0.85]).<sup>156</sup>
- In a meta-analysis of 9 RCTs ( $N=1901$ ), CPAP treatment was not associated with benefits for cognition; however, study designs were heterogeneous, and all of the interventions were  $\leq 1$  year.<sup>157</sup>

## Social Determinants of Health/Health Equity

### Race and Ethnicity

(See Prevalence, Incidence, Lifetime Risk and Cumulative Incidence, and Secular Trends sections.)

### Sexual Orientation and Gender Identity

- Among 108 152 NHIS participants  $\geq 45$  years of age, 2421 individuals identified as gay, lesbian, bisexual, or something else, and 105 731 identified as straight.<sup>158</sup> Difficulty remembering or concentrating (subjective cognitive impairment) was reported by 24.5% (95% CI, 21.6%–27.8%) of sexual minority individuals compared with 19.1% (95% CI, 18.6%–19.6%) of straight individuals (OR, 1.5 [95% CI, 1.3–1.8], adjusted for age, income, education, race and ethnicity, and survey year). Frequency, severity, and extent of this subjective cognitive impairment were all reported more often by sexual minority individuals. Being “limited in any way” because of difficulty remembering or periods of confusion was reported by 7.3% (95% CI, 6.1%–8.7%) of sexual minority individuals compared with 5.4% (95% CI, 5.2–5.6) of straight individuals (OR, 1.7 [95% CI, 1.4–2.1]).<sup>159</sup> However, cohort data from the Canadian Longitudinal Study on Aging ( $N=36\,849$ ; mean age, 62.1 years) showed no association between sexual orientation and executive function and better performance on memory among lesbian/gay adults ( $\beta=0.22$  [95% CI, 0.08–0.35]) and bisexual adults ( $\beta=0.26$  [95% CI, 0.01–0.50]) compared with heterosexual adults.<sup>160</sup>
- Among 452 transgender adults  $\geq 50$  years of age identified in the OneFlorida Clinical Research Consortium, 3.5% had been diagnosed with ADRD compared with 2.2% of age- and race and ethnicity-matched cisgender adults ( $P=0.07$ ).<sup>161</sup>

### Education

- In a meta-analysis of 31 studies conducted in Latin America, prevalence of dementia among participants without a formal education was 21.4%, whereas prevalence of dementia among participants with at least 1 year of formal education was 9.9%.<sup>162</sup>
- In a meta-analysis of 39 prospective studies including  $>1.4$  million individuals, lowest education level (ie, quintile) was associated with 22% higher risk for cognitive impairment and dementia (95% CI, 10%–25% higher) relative to highest education level; lowest education versus highest education was also associated with higher risk for all-cause dementia (RR, 1.66 [95% CI, 1.20–2.32]).<sup>163</sup>
- In a harmonized cross-national dataset of the HRS family of studies including the HRS, ELSA, MHAS, CHARLS, and LASI ( $N=14\,980$ ; age,  $\geq 65$  years), the association between higher educational attainment and better cognition in late-life was consistently

observed in both high- and middle-income countries. Compared with the reference group of those with lower secondary education, adults with post-secondary education scored better on global cognition overall: males in the United States,  $\beta=0.80$  (95% CI, 0.62–0.99); England,  $\beta=0.55$  (95% CI, 0.39–0.71); Mexico,  $\beta=0.29$  (95% CI, –0.03 to 0.61); China,  $\beta=0.29$  (95% CI, 0.10–0.48); and India,  $\beta=0.54$  (95% CI, 0.35–0.72); and females in the United States,  $\beta=1.00$  (95% CI, 0.84–1.15); England,  $\beta=0.63$  (95% CI, 0.44–0.83); Mexico,  $\beta=0.86$  (95% CI, 0.56–1.15); China,  $\beta=0.77$  (95% CI, 0.58–0.97); and India,  $\beta=0.74$  (95% CI, 0.43–1.04).<sup>164</sup>

- Lower quality of high school education (assessed with a proxy measure, the number of teachers with graduate degrees) was associated with worse phonemic fluency, animal fluency, and immediate recall after 58 years of follow-up ( $\beta$  comparing schools with 0–5 teachers with graduate training versus schools with  $\geq 24$  teachers with graduate training ( $\beta=-0.24$  [95% CI, –0.37 to –0.11];  $\beta=-0.22$  [95% CI, –0.35 to –0.09];  $\beta=-0.20$  [95% CI, –0.32 to –0.08], respectively) in the Project Talent Aging Study (N=2289; mean age, 74.8 years).<sup>165</sup>
- PARs for established potentially modifiable risk factors for dementia among different groups were calculated with 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 ( $P_{\text{interaction with sex}}=0.1880$ ,  $P_{\text{interaction with wealth}}<0.0000$ ).<sup>166</sup>

### Occupation

- Among 10195 adults in studies included in the COSMIC collaboration, high occupational complexity (eg, managers and professionals) versus low (eg, individuals performing simple and routine manual tasks) was associated with 19% longer dementia-free survival time (95% CI, 5%–33% longer).<sup>167</sup> Intermediate occupational complexity (eg, clerical and craft jobs) versus low was associated with 7% longer dementia-free survival time (95% CI, 1% lower–16% higher).
- Among 8941 ELSA participants, low occupational attainment (routine/manual) was associated with 1.60 times the risk of dementia (95% CI, 1.23–2.09) and intermediate occupational attainment with 1.53 times the risk of dementia (95% CI, 1.15–2.06) compared with high occupational attainment (managerial or professional) after adjustment for age and sex.<sup>168</sup>
- In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest occupation level (ie, quintile) was not significantly associated with

risk for cognitive impairment and dementia (RR, 1.06 [95% CI, 0.83–1.36]) relative to highest occupation level or with risk for all-cause dementia (RR, 1.03 [95% CI, 0.77–1.36]).<sup>163</sup>

- In the KHANDEL cohort (N=1536; mean age, 76 years; 29% White participants; mean follow-up, 2.4 years), there were cross-sectional associations between occupational complexity using data and executive function ( $\beta$  highest tertile compared with lowest=0.11 [95% CI, 0.00–0.22]) and semantic memory ( $\beta=0.14$  [95% CI, 0.04–0.25]), as well as between occupational complexity with people and performance on executive function, verbal memory, and semantic memory ( $\beta=0.29$  [95% CI, 0.18–0.40];  $\beta=0.12$  [95% CI, 0.00–0.24];  $\beta=0.23$  [95% CI, 0.12–0.34], respectively).<sup>169</sup>

### Income/Wealth

- In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest income level (ie, quintile) was associated with 21% higher risk for cognitive impairment and dementia (95% CI, 4%–41% higher) relative to highest income level; lowest income versus highest was not significantly associated with risk for all-cause dementia (RR, 1.19 [95% CI, 0.78–1.82]).<sup>163</sup>
- Among 8941 ELSA participants, self-reported household wealth was measured as the total value of home (minus outstanding mortgage), physical items such as jewelry, business assets such as investments, and financial assets, including cash and savings (minus debts and loans).<sup>168</sup> The lowest tertile of wealth was associated with 1.63 times the risk of dementia (95% CI, 1.26–2.12) and middle tertile of wealth with 1.22 times the risk of dementia (95% CI, 0.93–1.60) compared with the highest wealth tertile.
- Cross-national comparisons (N=9465; age,  $\geq 65$  years) of negative wealth shock in late life defined as a loss of wealth  $\geq 75\%$  differed by country. In the United States and China, negative wealth shock was associated with worse cognition ( $\beta=-0.16$  SD units [95% CI, –0.29 to –0.040] and  $\beta=-0.14$  [95% CI, –0.21 to –0.07]), but this association was not significant in England or in Mexico ( $\beta=-0.01$  [95% CI, –0.24 to 0.22] or  $\beta=-0.11$  [95% CI, –0.24 to 0.03]).<sup>170</sup>

### Composite SES

- Composite SES is a measure that incorporates education, occupation, and income levels into an index, with higher values indicating higher SES. In a meta-analysis of 39 prospective studies including >1.4 million individuals, lowest composite SES level (ie, quintile) was associated with 1.75 times the risk for cognitive impairment and dementia (95% CI, 1.37–2.23) relative to highest composite SES level

and with 2.00 times the risk for all-cause dementia (95% CI, 1.27–3.15).<sup>163</sup>

- Adults living in neighborhoods with greater disadvantage, assessed by the Area Deprivation Index, a composite area-based measure of socioeconomic disadvantage, were more likely to develop dementia (reference, lowest quintile of Area Deprivation Index; second quintile aHR, 1.09 [95% CI, 1.07–1.10]; third quintile aHR, 1.14 [95% CI, 1.12–1.15]; fourth quintile aHR, 1.16 [95% CI, 1.14–1.18]; and highest quintile aHR, 1.22 [95% CI, 1.21–1.24]) with adjustment for demographics and psychiatric and medical comorbid conditions in a national, retrospective study of Veterans Health Administration patients (N=1637 484; mean age, 68.6 years; mean follow-up, 11.0 years).<sup>171</sup> Similarly, in the Mayo Clinic Study of Aging (N=4699; mean age, 72.9 years), residence in areas with greater Area Deprivation Index was associated with increased risk of dementia (HR for each decile increase in the Area Deprivation Index state ranking, 1.06 [95% CI, 1.01–1.11]) and slightly greater declines in cognition (annualized rate of change in global cognitive Z score per decile increase in Area Deprivation Index:  $\beta=-0.035$  [95% CI, −0.045 to −0.024]).<sup>172</sup>

#### Geography/Dementia Belt/Rural-Urban

- Among 152 444 HRS participants ≥50 years of age, compared with living in an urban county that had maintained or increased population size over the previous 20 years, living in a rural county that had maintained or increased population size was associated with 0.22-point lower TICS score ( $P<0.01$ ), and living in a rural county that had decreased in population size was associated with 0.36-point lower TICS score ( $P<0.01$ ).<sup>173</sup>
- In a US nationwide ecological study of Medicare beneficiaries from 2008 to 2015, county-level annual prevalence of AD/ADR was ≈0.5 to 1.0 case per 100 population lower in rural counties than in urban counties, whereas county-level annual incidence of AD/ADR was ≈0.4 new case per 100 population higher in rural counties than in urban counties, adjusted for county-level demographic and health care factors.<sup>174</sup>
- Geospatial analysis of HRS data (N=96848; mean age, 75.0 years) indicates that dementia prevalence based on region of residence was greatest in the US South (10.7%–13.6%) and lowest in the Northeast (7.8%–9.3%), with similar patterns for prevalence based on region of birth (13.5%–14.7% and 6.6%–7.0%, respectively). In models adjusted for survey year, demographics, education, and region of residence, birth in the Northeast United States was significantly associated with lower dementia compared with birth in the South (OR, 0.57 [95% CI, 0.49–0.65]).<sup>175</sup>

- Among 20878 participants in REGARDS (age, ≥45 years; 57% female), 79% lived in urban areas, 11.7% in large rural areas, and 8.5% in small rural areas.<sup>176</sup> Small rural versus urban residence had 24% higher odds of incident cognitive impairment (95% CI, 2%–53% higher) adjusted for sociodemographics, health behaviors, and clinical characteristics. Large rural versus urban residence was not associated with incident cognitive impairment.

#### Risk Prediction

- The LIBRA index for predicting dementia includes depression, diabetes, PA, hypertension, obesity, smoking, hypercholesterolemia, CHD, and mild to moderate alcohol use. 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>177</sup>
- Among 4392 adults in MESA, 3 vascular risk scores at baseline—CAIDE score, Framingham Stroke Risk Profile score, and ASCVD-PCE score—were each associated with lower mean scores on 3 cognitive measures obtained 10 years later: CASI, Digit Symbol Coding, and Digit Span.<sup>178</sup> For example, mean CASI score was 2.41 points lower (95% CI, 2.19–2.64), mean Digit Symbol Coding score was 7.46 points lower (95% CI, 6.97–7.95), and mean Digit Span score was 0.95 points lower (95% CI, 0.83–1.07) per 1-SD increment in CAIDE score. These associations varied by race and ethnicity. For example, the association of SD increment in baseline CAIDE score with mean CASI score 10 years later was 1.61 points lower in White individuals (95% CI, 1.28–1.95), 2.52 points lower in Chinese American individuals (95% CI, 1.81–3.24), 2.30 points lower in Black individuals (95% CI, 1.84–2.77), and 3.28 points lower in Hispanic individuals (95% CI, 2.82–3.74).
- Among 34 083 female and 39 998 male patients with AF with no history of dementia, CHA<sub>2</sub>DS<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>179</sup>
- The FDRS includes age, marital status, BMI, stroke/TIA, diabetes, and cancer. The FDRS, which had previously been shown to predict dementia with a C statistic of 0.72 in a general population sample of 2383 adults ≥60 years of age in the FHS,<sup>180</sup>

was shown to have similar accuracy in predicting dementia risk in adults  $\geq 50$  years of age who had newly diagnosed HF ( $n=3052$  [C statistic, 0.69]) and in adults  $\geq 50$  years of age who had newly diagnosed AF ( $n=4107$  [C statistic, 0.73]) in a population-based study in Minnesota.<sup>69</sup>

## Subclinical/Unrecognized Disease

### MRI Abnormalities/Covert Vascular Brain Injury

- MRI measures of brain age were assessed in 2 community-based cohorts of middle-aged and older adults (WHICAP: mean age, 75 years; and Offspring: mean age, 55 years; combined  $N=1467$ ).<sup>181</sup> Cortical thickness in AD-related regions and WMH volume differed significantly by race and ethnicity and life course stage. Among Black participants, age was significantly associated with cortical thickness and WMH similarly at both midlife and late life (cortical thickness:  $\beta=0.001$  [95% CI,  $-0.002$  to  $0.004$ ];  $P=0.64$ ; WMH volume:  $\beta=0.003$  [95% CI,  $-0.010$  to  $0.017$ ];  $P=0.61$ ), suggesting brain changes earlier in the life course. These associations were significant only in late life compared with midlife for Hispanic or Latino older adults (cortical thickness:  $\beta=0.006$  [95% CI,  $0.004$ – $0.008$ ];  $P<0.001$ ; WMH volume:  $\beta=-0.010$  [95% CI,  $-0.018$  to  $-0.001$ ];  $P=0.03$ ) and White participants (cortical thickness:  $\beta=0.005$  [95% CI,  $0.002$ – $0.008$ ];  $P=0.001$ ; WMH volume:  $\beta=-0.021$  [95% CI,  $-0.043$  to  $0.002$ ];  $P=0.07$ ).
- In a meta-analysis of 49 studies including 5409 participants with AD, the pooled prevalence of cerebral microbleeds with 32% (95% CI, 29%–35%).<sup>182</sup> Studies conducted with 3-T MRI detected a greater prevalence of cerebral microbleeds (39% [95% CI, 33%–45%]) than those conducted with 1-T/1.5-T MRI (26% [95% CI, 22%–30%]). Studies conducted with susceptibility-weighted MRI detected a greater prevalence of cerebral microbleeds (45% [95% CI, 38%–52%]) than those conducted with non-susceptibility-weighted MRI (26% [95% CI, 23%–29%]).
- Among 1881 participants, including 539 with incident dementia, in the ARIC Neurocognitive Study, risk of dementia over 25 years of follow-up was 2-fold higher among participants who had a combination of larger (3–20 mm) and smaller ( $<3$  mm) infarcts compared with those who had no infarcts observed on MRI (HR, 2.61 [95% CI, 1.44–4.72]).<sup>183</sup>
- In a meta-analysis of 9 studies, covert brain infarct was associated with decline in cognitive dysfunction on the MMSE (SMD,  $-0.47$  [95% CI,  $-0.72$  to  $-0.22$ ]).<sup>184</sup> In the same meta-analysis, among 4 studies, covert brain infarct was associated with cognitive dysfunction on the MoCA Scale (SMD,  $-3.36$  [95% CI,  $-5.90$  to  $-0.82$ ]).

- Among 630 participants without dementia in the Alzheimer's Disease Neuroimaging Initiative who underwent an assessment for neuropsychiatric symptoms with the Neuropsychiatric Inventory and 3-T MRI at baseline ( $n=631$ ) and follow-up ( $n=616$ ), a higher burden of cerebral small-vessel disease was associated with neuropsychiatric symptoms in follow-up.<sup>185</sup> Lacunar infarcts predicted hyperactivity ( $P=0.0092$ ), psychosis ( $P=0.0402$ ), affective symptoms ( $P=0.0156$ ), and apathy ( $P\leq0.0001$ ). WMHs were associated with hyperactivity ( $P=0.0377$ ) and apathy ( $P=0.0343$ ), whereas cerebral microbleeds correlated with apathy ( $P=0.0141$ ).
- Among 552 dementia- and stroke-free participants from the FHS, lighter sleep, as characterized by longer N1 sleep duration and shorter slow-wave sleep on polysomnography, was associated with higher enlarged perivascular spaces burden in the centrum semiovale on brain MRI (OR of higher burden per minute of N1 sleep, 1.03 [95% CI, 1.10–1.05]), and longer N3 sleep duration was associated with lower enlarged perivascular spaces burden in the centrum semiovale (OR, 0.99 [95% CI, 0.98–1.00]).<sup>186</sup> These findings suggest that sleep architecture may be involved in glymphatic clearance and cerebral small-vessel disease.

### Subclinical Cortical Abnormalities (Not MRI)

- Among 4399 cognitively unimpaired adults 65 to 85 years of age enrolled in the Anti-Amyloid Treatment in Asymptomatic Alzheimer Disease Study, the  $\beta$ -amyloid standard uptake value ratio on positron emission tomography imaging was associated with anxiety scores on the State Trait Anxiety Inventory (range, 6–24) but not depression scores on the Geriatric Depression Scale.<sup>187</sup> For each 0.5-point increase in cortical  $\beta$ -amyloid standard uptake value ratio, the mean anxiety score increased by 0.25 points (95% CI, 0.04–0.53).
- Transcranial magnetic stimulation applied to the primary motor cortex and coupled with electromyography provides a subclinical measure of cortical excitability and plasticity. In a meta-analysis of the value of transcranial magnetic stimulation-derived excitability and plasticity measures to distinguish AD, MCI, and normal cognition, 61 studies ( $n=2728$  participants) included 1454 patients with AD, 163 patients with MCI, and 1111 cognitively normal individuals.<sup>188</sup> Patients with AD had significantly lower resting motor threshold (Cohen  $d=1.05$  [ $P<0.0001$ ]), lower active motor threshold (Cohen  $d=0.77$  [ $P<0.0001$ ]), lower short latency afferent inhibition (Cohen  $d=1.89$  [ $P<0.0001$ ]), lower short-latency intracortical inhibition (Cohen  $d=0.68$  [ $P<0.01$ ]), and lower long-term potentiation-like plasticity (Cohen  $d=1.20$  [ $P<0.0001$ ]) compared with cognitively normal individuals. Patients with MCI

had lower resting motor threshold (Cohen  $d=0.39$  [ $P<0.005$ ]) and lower long-term potentiation-like plasticity (Cohen  $d=0.86$  [ $P<0.05$ ]) compared with cognitively normal individuals.

- In a single-center study, among 288 Chinese patients (mean age, 80.5 years; 60.4% females) with AD, subclinical epileptiform discharge on scalp electroencephalography was present in 57 patients (19.8%).<sup>189</sup> Subclinical epileptiform discharge was associated with greater decline in CASI ( $-9.32$  versus  $-3.52$  points;  $P=0.0001$ ) and MMSE ( $-2.52$  versus  $-1.12$  points;  $P=0.0042$ ) scores at 1 year.

#### **Subclinical Cardiac and Arterial Disease**

- Abnormal P-wave parameters on ECG are associated with brain MRI findings. Among 1715 participants in the ARIC Neurocognitive Study (mean age, 76.1 years; 61% female), including 797 (46%) who had at least 1 abnormal P-wave parameter, abnormal P-wave terminal force in lead 1 was associated with higher odds of cortical infarcts (OR, 1.41 [95% CI, 1.14–1.37]) and lacunar infarcts (OR, 1.36 [95% CI, 1.15–1.63]); prolonged P-wave duration was associated with higher odds of cortical infarcts (OR, 1.30 [95% CI, 1.04–1.63]) and lacunar infarcts (OR, 1.37 [95% CI, 1.15–1.65]).<sup>190</sup>
- Greater arterial stiffness, measured by 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>191</sup>
- Among 623 community-dwelling adults from the Whitehall II Imaging Substudy who underwent multimodal MRI, higher mean arterial pressure throughout midlife ( $\beta=3.36$  [95% CI, 0.42–6.30]) and faster cognitive decline in letter fluency ( $\beta=-0.07$  [95% CI,  $-0.13$  to  $-0.01$ ]) and verbal reasoning ( $\beta=-0.05$  [95% CI,  $-0.11$  to  $-0.001$ ]) were associated with severe small-vessel disease burden in older age.<sup>192</sup>
- In a study that combined longitudinal data from 3 clinical trials (B-Vitamin Atherosclerosis Intervention Trial, Women's Isoflavone Soy Health Trial, and Early Versus Late Intervention Trial With Estradiol), among participants (308 males and 1187 females; mean age, 61 years) free of CVD and diabetes, participants underwent the same standardized protocol for ultrasound measurement of carotid IMT, as well as cognitive assessment, at baseline and 2.5 years. Although no associations were found between carotid IMT and cognitive function at baseline or at 2.5 years, there was a weak inverse association

between carotid IMT at baseline and change in global cognition assessed over 2.5 years ( $\beta=-0.056$  [SE, 0.028] units per 0.1-mm carotid IMT [95% CI,  $-0.110$  to  $-0.001$ ];  $P=0.046$ ).<sup>193</sup> When the analysis was stratified by  $<65$  and  $\geq65$  years of age, the inverse association remained statistically significant for participants in the older age group.

#### **Genetics and Family History**

- AD is highly heritable with a complex genetic architecture. With the use of 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>194</sup>
- Rare forms of early-onset autosomal dominant AD may reflect highly penetrant variations in *APP*, *PSEN1*, or *PSEN2*.<sup>195</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>196,197</sup> Missense variations in *NOTCH3* are largely responsible for cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy, whereas variations in *APP*, *CST3*, or *ITM2B* underlie familial cerebral amyloid angiopathy.
- The heritability of sporadic vascular dementia is estimated to be very low (<1%).<sup>198</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>199</sup>
- The *APOE* ε4 allele also is associated with vascular dementia risk.<sup>200</sup> Among 549 cases with vascular dementia and 552 controls without dementia in Europe, having  $\geq 1$  *APOE* ε4 alleles was associated with 1.85 times the odds of vascular dementia (95% CI, 1.35–2.52), and having  $\geq 1$  *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>201</sup>
- Among 8263 Latino people in the United States, prevalence of  $\geq 1$  *APOE* ε4 alleles (associated with higher risk for late-onset AD) 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>202</sup> Prevalence of  $\geq 1$  *APOE* ε2 alleles (associated with lower risk for late-onset AD) 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

- The largest GWAS of clinically diagnosed AD was performed by the International Genomics of Alzheimer's Project Consortium.<sup>203</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 late-onset AD, 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>204</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*).
- GWASs also have combined clinically diagnosed with proxy AD cases. For example, a study of n=111 326 clinical diagnosed or proxy AD cases and n=677 663 controls identified 75 loci, including 42 new loci.<sup>205</sup> In addition to confirming involvement of amyloid/tau pathways, this study suggested new mechanisms, including the tumor necrosis factor-α pathway. These results also were used to develop new GRSs to predict AD/dementia incidence or progression from MCI to AD/dementia.
- To increase ancestral diversity, a GWAS of AD and ADRD was performed in the Million Veteran Program biobank, restricted to participants of African ancestry (n=4012 cases).<sup>206</sup> To increase statistical power, the authors combined their AD and ADRD GWAS with a proxy dementia GWAS that used survey-reported paternal AD or dementia (n=4385 maternal cases, n=2256 paternal cases). Three loci in *APOE*, *ROBO1*, and *RP11-340A13.2* were identified. *ROBO1* participates in the regulation of axon guidance. Lack of association between *ROBO1* when a strict AD phenotype was examined suggests that this locus may be relevant for dementia more broadly.

### Polygenic Risk Scores

- All-cause dementia GRSs have been used to examine whether lifestyle factors can offset high dementia genetic risk.<sup>207</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 ( $P=0.99$ ).

- A PRS for AD developed from GWASs in a European population was associated with risk of AD in a sample of 1634 Korean participants, of whom 716 had AD (OR of AD per increment in PRS, 1.95 [95% CI, 1.40–2.72]), suggesting that GRSs for AD may be transferable across different ethnic populations.<sup>208</sup>
- In the UK Biobank with 206 646 participants 37 to 73 years of age at baseline and 5750 incident dementia cases over a median of 12.5 years of follow-up, a PRS for dementia based on European ancestry GWAS was categorized into high, medium, and low risk.<sup>209</sup> Progressively higher risk of dementia was seen with high PRS versus low (HR, 1.50 [95% CI, 1.31–1.61]), presence of cardiometabolic disease (HR, 1.70 [95% CI, 1.60–1.82]), combined high PRS with cardiometabolic disease (HR, 2.63 [95% CI, 2.38–2.93]), and presence of *APOE* ε4 genotype (HR, 3.16 [95% CI, 3.00–3.33]).

### Prevention

#### Exercise

- A 2019 randomized, parallel-group, community-based clinical trial of 132 multiracial, multiancestry, cognitively normal individuals (mean age, 40 years) with below-median aerobic capacity in New York found that aerobic exercise, compared with stretching and 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 among those with  $\geq 1$  *APOE* ε4 alleles.<sup>210</sup>
- In a trial of adults  $\geq 65$  years of age with subjective cognitive concerns (N=585), participants were randomized to exercise training, mindfulness-based stress reduction, both exercise training and mindfulness-based stress reduction, or health education. At both 6 and 18 months, there was no difference in executive function or episodic memory among the intervention groups.<sup>211</sup>
- Meta-analyses examining RCTs indicate that PA interventions benefit cognition in both AD (7 RCTs; N=501; with improvement on the MMSE, 0.458 [95% CI, 0.097–0.819]) and MCI (15 RCTs; N=1156; improvement on the MMSE, 0.631 [95% CI, 0.244–1.018]).<sup>212</sup>

#### BP Control

- Among 9361 participants (SPRINT) with hypertension and high cardiovascular risk in the United States and Puerto Rico (mean age, 67.9 years; 35%

females; 58% White individuals, 30% Black individuals, 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 cases versus 18.3 cases per 1000 PY; HR, 0.81 [95% CI, 0.69–0.95]) and the combined rate of MCI or probable dementia (20.2 cases versus 24.1 cases per 1000 PY; HR, 0.85 [95% CI, 0.74–0.97]) but not the risk of adjudicated probable dementia (7.2 cases versus 8.6 cases per 1000 PY; HR, 0.83 [95% CI, 0.67–1.04]) over a total median follow-up of 5.11 years.<sup>213</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 (HR for amnestic MCI, 0.74 [95% CI, 0.64–0.87]; HR for probable dementia, 0.80 [95% CI, 0.57–1.14]).<sup>214</sup>

- A post hoc analysis from the PreDIVA trial (54% females; 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>215</sup>
- In a systematic review of 15 prospective cohort studies and 7 RCTs (N=649 790), treatment with calcium channel blockers and angiotensin II receptor blockers was associated with a reduced risk of incident dementia compared with other antihypertensive classes.<sup>216</sup> For calcium channel blockers, the HR versus ACE inhibitors was 0.84 (95% CI, 0.74–0.95), the HR versus  $\beta$ -blockers was 0.83 (95% CI, 0.81–0.97), and the HR versus diuretics was 0.89 (95% CI, 0.78–1.01). For angiotensin II receptor blockers, the HR versus ACE inhibitors was 0.88 (95% CI, 0.81–0.97), the HR versus  $\beta$ -blockers was 0.87 (95% CI, 0.77–0.99), and the HR versus diuretics was 0.93 (95% CI, 0.83–1.05).
- In a randomized clinical trial of older adults with MCI and hypertension (N=176; mean age, 66 years; 57% females; 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>217</sup>
- In a subset of participants in the International Polycap Study 3 who underwent cognitive assessment (N=2098; mean $\pm$ SD age,  $70.1\pm4.5$  years), treatment with a polypill (antihypertensives and a statin), aspirin alone, or polypill plus aspirin over 5 years did not reduce the risk of cognitive decline or dementia compared with treatment with placebo.<sup>218</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>219</sup>

- In a meta-analysis of 5 RCTs (N=28 008; mean age, 69.1 years; median follow-up, 4.3 years; HYVET, SYST-EUR, PROGRESS, ADVANCE, and SHEP), antihypertensive treatment was associated with reduced risk of incident dementia (aOR, 0.87 [95% CI, 0.75–0.99]).<sup>220</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>221</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 year (95% CI, 0.11–0.19).<sup>222</sup>
- In an observational study of 18 846 older adults (median age, 74 years; 56% females) with no history of cardiovascular events, statin therapy was not associated with risk of dementia, MCI, or cognitive decline.<sup>223</sup>
- A meta-analysis of 14 double-blind trials (4 phase 2 and 10 phase 3) for the PCSK9 inhibitor alirocumab found a low incidence of neurocognitive adverse events, with no significant differences between the alirocumab and control groups and no association between neurocognitive adverse events and LDL-C <25 mg/dL.<sup>224</sup> Another meta-analysis of 35 RCTs for alirocumab and evolocumab similarly found no significant associations between PCSK9 inhibitor use and neurocognitive adverse events (OR, 1.12 [95% CI, 0.88–1.42]).<sup>225</sup>
- A randomized placebo-controlled trial of evolocumab in addition to statin therapy (N=1204; age, 40–85 years) found no significant differences in cognitive function between the evolocumab group and the placebo group.<sup>226</sup> Another RCT (N=22 655) involving evolocumab added to statin therapy found no significant effect on self-reported cognition, even among patients who had LDL-C <20 mg/dL.<sup>227</sup>
- A meta-analysis of 33 RCTs found no association between lipid-lowering treatments (PCSK9 inhibitors, statins, and ezetimibe) and cognitive impairment and no significant effects of low LDL-C levels

on cognitive disorder likelihood or global cognitive performance.<sup>228</sup>

### **Aspirin and Antiplatelet 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=19114; age, 65–98 years; 44% male).<sup>229</sup>
- In a meta-analysis of 11 randomized trials of antiplatelet therapy (N=109 860; mean age, 66.2 years; mean follow-up, 5.8 years), there was no protective benefit for risk of cognitive impairment or dementia (OR, 0.94 [95% CI, 0.88–1.00]; absolute risk reduction, 0.2% [95% CI, –0.4% to 0.009%];  $P=0.0$ ) or cognitive decline (SMD, –0.04 [95% CI, –0.04 to 0.01];  $P_{\text{heterogeneity}}=0.18$ ;  $P=23.1\%$ ).<sup>230</sup>

### **Glycemic Control**

- 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>231</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>232</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>233</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>234</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>235</sup>

- A meta-analysis of RCTs for older adults with MCI (28 RCTs; N=2711; mean $\pm$ SD age, 71.6 $\pm$ 3.4 years; mean $\pm$ SD duration of intervention, 19.8 $\pm$ 14.6 weeks) suggests that compared with single-domain interventions, multidomain interventions, targeting at least 2 nonpharmacological strategies, benefit cognition, including global cognition (20 RCTs; SMD, 0.41 [95% CI, 0.23–0.59]), executive function (17 RCTs; SMD, 0.20 [95% CI, 0.04–0.36]), memory (15 RCTs; SMD, 0.29 [95% CI, 0.14–0.45]), and verbal fluency (8 RCTs; SMD, 0.30 [95% CI, 0.12–0.49]) but not attention (6 RCTs; SMD, 0.13 [95% CI, –0.15 to 0.41]) or processing speed (10 RCTs; SMD, 0.46 [95% CI, –0.04 to 0.96]).<sup>236</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>237</sup> Compared with supportive therapy, behavioral activation also was associated with improvement in executive function and preservation of everyday function.
- SMARRT (N=172; age, 70–89 years; with  $\geq 2$  of 8 targeted risk factors) compared personalized risk reduction, targeting physical inactivity, poorly controlled hypertension, poor sleep, adverse prescription medication use, high depressive symptoms, poorly controlled diabetes, social isolation, and smoking, with a health education control.<sup>238</sup> In this 2-year RCT, participants in the intervention group demonstrated a 74% greater improvement on the composite cognitive score compared with the control group (average treatment effect of SD, 0.14 [95% CI, 0.03–0.25];  $P=0.02$ ).
- A Basque multidomain RCT, GOIZ ZAINDU ("caring early" in Basque), modeled after FINGER, targeted cardiovascular risk factors, nutrition, PA, and cognitive training in older adults (N=125; age,  $\geq 60$  years; CAIDE risk score  $\geq 6$  and poor cognitive performance). In the intervention group, fewer participants experienced decline in executive function Z score after 1 year (40%) compared with the health advice control group (64%; OR, 2.58 [95% CI, 1.17–5.71];  $P=0.019$ ), and fewer intervention participants declined in processing speed Z score (39%) compared with control participants (61%; OR, 2.44 [95% CI, 1.11–5.36];  $P=0.026$ ).<sup>239</sup>
- In the AgeWell.de cluster randomized trial, the multidomain intervention focused on cardiovascular risk factor management, nutrition, PA, social activity,

and cognitive training and was delivered through the German primary care system. Among trial participants ( $N=819$ ; age, 60–77 years; CAIDE risk score  $\geq 9$ ), changes in cognition after 2 years did not differ between the intervention group and the control group receiving health advice and usual care (average marginal effect, 0.010 [95% CI, −0.113 to 0.133]).<sup>240</sup>

## Mortality

### (See Table 16-2)

- In 2022 (unpublished NHLBI tabulations using CDC WONDER<sup>241</sup> and the NVSS<sup>242</sup>):
  - On average, every 1 minute 48 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 292 881 (Table 16-2); the age-adjusted death rate for dementia as an underlying cause of death was 70.4 per 100 000 (Table 16-2), whereas the age-adjusted rate for any mention of dementia as a cause of death was 109.1 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 66.7% of US dementia deaths in 2022.
- Conclusions about changes in dementia death rates from 2012 to 2022 are as follows<sup>241</sup>:
  - The age-adjusted dementia death rate increased 11.2% (from 63.3 per 100 000 to 70.4 per 100 000), whereas the actual number of dementia deaths increased 31.1% (from 223 404 to 292 881 deaths).
  - Age-adjusted dementia death rates increased 9.1% for males and 12.9% for females.
- A mortality risk score for people having probable dementia was developed among 4267 HRS participants who had probable dementia with a mean 82 years of age and median follow-up of 3.9 years; it was then externally validated in NHATS participants.<sup>243</sup> In the external validation, the risk score had an AUC of 73% (95% CI, 70%–76%) for predicting death within 1 year and an AUC of 74% (95% CI, 71%–76%) for predicting death within 5 years. Factors included in this mortality risk score model were age, sex, BMI, smoking status, activities of daily living dependency count, instrumental activity of daily living difficulty count, difficulty walking several blocks, participation in vigorous PA, and chronic conditions (cancer, HD, diabetes, lung disease).

- Among 5989 NHANES participants surveyed in 1999 to 2014 with mortality follow-up to 2015, lower cognitive test scores were associated with higher all-cause mortality rates.<sup>244</sup> For example, a 1-SD decrement on the Digit Symbol Substitution Test was associated with 36% higher (95% CI, 25%–48% higher) mortality rate. There were differences by education level. Among individuals with less than high school education, mortality rates were 46% higher (95% CI, 9%–97% higher) per 1-SD decrement in animal fluency, 34% higher (95% CI, 7%–67% higher) per 1-SD decrement in word list learning, and 38% higher (95% CI, 5%–82% higher) per 1-SD decrement in word list delayed recall; those associations were not observed for individuals with high school diploma or higher education. Similarly, SD decrements in animal fluency, word list learning, and word list delayed recall were associated with higher mortality among low-income individuals but not high-income individuals.

### Mortality in Hospitalized Patients

- In a 5-year retrospective review of 9519 adult patients with trauma, 195 (2.0%) who had a diagnosis of dementia at an American College of Surgeons-verified level I trauma center,<sup>245</sup> patients with dementia ( $n=195$ ) were matched with dementia-free patients ( $n=195$ ) and compared on mortality, ICU length of stay, and hospital length of stay. The comorbidities and complications were similar between the groups (11.8% versus 12.4%). Mortality was 5.1% in both the dementia and control groups. The study found that dementia did not increase the risk of mortality in patients with trauma.
- In a cohort of  $>1$  million Medicare beneficiaries hospitalized in 2016, of whom 211 698 had diagnosed dementia, those with dementia were more likely to die (5.7%) than those without dementia (3.1%) within 30 days after discharge (aOR, 1.21 [95% CI, 1.17–1.24]).<sup>246</sup>
- In an analysis of 3.7 million hospitalizations of adults  $\geq 65$  years of age throughout Italy, of whom 278 149 were patients diagnosed with dementia, those with dementia were more likely to die while in the hospital than those without dementia (age-, sex-, and comorbidity-adjusted OR, 1.98 [95% CI, 1.95–2.00]).<sup>247</sup> Among patients with dementia, the comorbidities most strongly associated with higher risk for in-hospital mortality were HF, pneumonia, and kidney disease.
- Among 7118 patients  $\geq 65$  years of age, including 3559 individuals with dementia and 3559 controls without dementia, admitted to an ED in Italy from 2014 to 2019, in-hospital mortality was more frequent among those with dementia (18.7% versus 16.0%; aHR, 1.13 [95% CI, 1.01–1.27]).<sup>248</sup>

## Complications

### Suicide

- In a national cohort of Medicare fee-for-service beneficiaries  $\geq 65$  years of age with newly diagnosed ADRD ( $n=2667\,987$ ) linked to the National Death Index, the rate of suicide was 26.42 per 100000 PY.<sup>249</sup> The overall standardized mortality ratio for suicide was 1.53 (95% CI, 1.42–1.65). The highest risk for suicide was among those 65 to 74 years of age (SMR, 3.40 [95% CI, 2.94–3.86]) and during the first 90 days after diagnosis. Rural residence and recent mental health, substance use, or chronic pain conditions were associated with increased suicide risk.

### Stroke

- 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 PY (95% CI, 10.6–20.3), incidence of ischemic stroke (11 studies) was 13.0 per 1000 PY (95% CI, 7.6–18.5), and incidence of ICH (16 studies) was 3.4 per 1000 PY (95% CI, 2.3–4.6).<sup>250</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).

### Postoperative Complications

- Among 53 studies ( $N=196\,491$  patients) included in a systematic review and meta-analysis, preoperative cognitive impairment was associated with a significant risk of delirium in patients  $\geq 60$  years of age after noncardiac surgery (25.1% versus 10.3%; OR, 3.84 [95% CI, 2.35–6.26]).<sup>251</sup> Cognitive impairment was also associated with an increased risk of discharge to assisted care (44.7% versus 38.3%; OR, 1.74 [95% CI, 1.05–2.89]) and postoperative complications (40.7% versus 18.8%; OR, 1.85 [95% CI, 1.37–2.49]).

### Frailty

- In a meta-analysis of 16 studies of patients  $\geq 65$  years of age living with dementia in acute care, community, and residential care settings, the prevalence of frailty (variously defined) ranged from 50.8% to 91.8% in acute care settings across studies (overall 77.6% in 6 studies for which detailed data were available).<sup>252</sup>

### Falls

- Unexplained falls are those that occur not because of slips or trips, with no clear reason for the fall. Among 2108 community-dwelling adults  $\geq 65$  years of age, cognitive impairment was associated with higher odds of unexplained falls (OR, 1.38 [95% CI, 0.99–1.93]), especially when coupled with mobility impairment (OR, 2.92 [95% CI, 1.73–4.92]) or with orthostatic hypotension (OR, 3.03 [95% CI,

1.85–4.97]); the combination of all 3 conditions—cognitive impairment, mobility impairment, and orthostatic hypotension—was associated with the highest odds of falls (OR, 4.33 [95% CI, 2.59–7.24]) compared with having none of the 3 conditions.<sup>253</sup>

### Mobility

- In a registry-based longitudinal study in Sweden, among 23 759 patients  $>50$  years of age with a nonpathological hip fracture previously able to walk, 25% of patients with dementia lost their ability to walk compared with 7% of those with no cognitive dysfunction.<sup>254</sup> After adjustment for several other risk factors, dementia was associated with an increased risk of loss of walking ability at 4 months (OR, 1.80 [95% CI, 1.57–2.06]).

### Instrumental Activities of Daily Living

- 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>255</sup>

### Sleep

- In a meta-analysis of 24 studies of polysomnographic changes in patients with AD compared with healthy control subjects, patients with AD had significant reductions in total sleep time (SMD, -0.60 [95% CI, -0.86 to -0.34]), sleep efficiency (SMD, -0.96 [95% CI, -1.36 to -0.57]), and percentage of slow-wave sleep (SMD, -0.86 [95% CI, -1.14 to -0.58]) and rapid eye movement sleep (SMD, -0.77 [95% CI, -1.14 to -0.40]), as well as increases in sleep latency (SMD, 0.45 [95% CI, 0.29–0.61]), wake time after sleep onset (SMD, 0.74 [95% CI, 0.38–1.10]), number of awakenings (SMD, 0.55 [95% CI, 0.25–0.86]), and rapid eye movement latency (SMD, 0.35 [95% CI, 0.13–0.58]).<sup>256</sup> Decreased slow-wave sleep and rapid eye movement sleep were significantly associated with the severity of cognitive impairment.

### Periodontitis

- In a retrospective cohort study ( $n=8640$  patients with dementia without prior periodontitis and 8640 propensity score-matched control individuals without dementia), 2670 patients with dementia developed periodontitis.<sup>257</sup> The risk of periodontitis was significantly higher in those with dementia compared with those without dementia (aHR, 1.92 [95% CI, 1.77–2.08]).

**Pseudobulbar Affect**

- In a series of meta-analyses of the prevalence of uncontrolled episodes of crying and laughing (pseudobulbar affect) in patients with neurodegenerative disorders, the prevalence of pseudobulbar affect in AD was 16.4% (95% CI, 7%–25%).<sup>258</sup>

**Health Care Use****Dementia Care**

- A structured dementia care program was examined with regard to health care use and cost outcomes.<sup>259</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.

**Stroke Care**

- 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 compared with 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>260</sup> Preexisting MCI compared with 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 compared with 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 464710 patients with AIS in the Japanese Diagnosis Procedure Combination Database, including 57905 who had dementia, those with dementia were less likely to receive intravenous thrombolysis (5.2% versus 6.9%; aOR, 0.79 [95% CI, 0.76–0.82]) and more likely to receive early rehabilitation as acute care (76.1% versus 73.0%; aOR, 1.06 [95% CI, 1.04–1.09]).<sup>261</sup>
- 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>262</sup>

**Hospital Admission and Readmission**

- Among 490 community-dwelling people living with dementia with a family caregiver in the Baltimore, MD, area, 34.4% were hospitalized at least once in the course of 12 months.<sup>263</sup> Infection (22.4%), falls (16.5%), and cardiovascular/pulmonary issues (12.4%) were the leading reasons for hospitalization.
- 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>264</sup>
- Use of ED care and inpatient hospitalization during the past 6 months of life with dementia varies by race and ethnicity. Among 5058 participants in HRS with linked Medicare claims who were diagnosed with dementia and died between 2000 and 2016, ED care was used by 79.7% of Black individuals and 76.8% of Hispanic individuals compared with 70.7% of White individuals ( $P<0.001$ ).<sup>265</sup> Inpatient hospitalization occurred for 77.3% of Black individuals and 77.0% of Hispanic individuals compared with 67.5% of White individuals ( $P<0.001$ ). In addition, completing advance care planning was lower among Black individuals (20.7%) and Hispanic individuals (21.4%) than among White individuals (57.1%); having written instructions to choose all care possible to prolong life was higher among Black individuals (20.8%) and Hispanic individuals (18.4%) than among White individuals (3.9%).

**Telemedicine**

- 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>266</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%).

**Hospice Care**

- Use of hospice care during the past 6 months of life with dementia varies by race, sex, and level of education. Among 5058 participants in HRS with linked Medicare claims who were diagnosed with dementia and died between 2000 and 2016, NH Black individuals had 35% lower odds (95% CI, 22%–45% lower) of using hospice care than NH White individuals.<sup>265</sup> Females had 19% higher odds (95% CI, 5%–35% higher) of using hospice care than males. Individuals with high school education had 17% higher odds (95% CI, 1%–36% higher) and those with more than high school education

had 32% higher odds (95% CI, 13%–54% higher) of using hospice care compared with those with less than high school education.

## Cost

### Total Costs Including Social Care and Informal (Unpaid) Care

- 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>267</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.
- Based on HRS data, in 2016, mean per-patient costs for dementia were \$28 078 (95% CI, \$25 893–\$30 433) for formal medical and long-term care, \$36 667 (95% CI, \$34 025–\$39 473) replacement cost for informal care, and \$15 792 (95% CI, \$12 980–\$18 713) in forgone wages for informal caregivers.<sup>268</sup> Aggregate costs for the United States were estimated at \$196 (95% UI, \$179–\$213) billion for formal care, \$450 (95% UI, \$424–\$478) billion for informal care replacement, and \$305 (95% UI, \$278–\$333) billion in forgone wages in 2020.
- Based on BRFSS, HRS, and NHATS data to quantify the amount of time spent on informal dementia caregiving, the mean annual replacement cost per patient was estimated to be \$42 422 (95% UI, \$35 422–\$49 181), and mean annual forgone wages were estimated to be \$10 677 (95% UI, \$8 611–\$12 904) in 2019.<sup>269</sup>

### Health Care Costs

- Estimated US health care spending on dementias more than doubled from \$38.6 (95% CI, \$34.1–\$42.8) billion in 1996 to \$79.2 (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>270</sup>
- Among 2779 HRS participants with incident dementia, mean Medicare spending in the quarter during which the diagnosis occurred was \$13 794, which was \$8400 more ( $P<0.001$ ) than mean Medicare spending of \$5394 in the quarter before the diagnosis.<sup>271</sup> The additional costs in the quarter containing the diagnosis were not significantly different (all group differences  $P>0.1$ ) for females (+\$7899) versus males (+\$9248), for NH Black

individuals (+\$8709) versus NH White individuals (+\$8388), for college graduates (+\$7265) versus those with less than college graduation (+\$8639), and for those living in rural areas (+\$8849) versus those living in nonrural areas (+\$8666).

- Based on 3653 HRS participants with dementia linked to Medicare claims data for 1992 to 2015, compared with demographically matched HRS participants without dementia, mean Medicare cost attributable to dementia was \$15 632 (95% CI, \$12 780–\$18 588) during the first 5 years after diagnosis, with \$9288 (95% CI, \$8241–\$10 357), or 59%, occurring during the first year after diagnosis.<sup>272</sup>
- Among 3619 HRS participants with incident dementia, during the first 8 years after diagnosis, mean estimated total out-of-pocket spending on medical costs was \$22 795 (95% CI, \$21 236–\$24 398), which was \$8751 more (95% CI, \$7354–\$10 217) than the expected mean 8-year total out-of-pocket spending without dementia of \$14 044 (95% CI, \$13 544–\$14 597).<sup>273</sup> Additional out-of-pocket spending attributed to dementia was much higher for NH White individuals (mean, \$16 766 [95% CI, \$14 305–\$19 380]) than for Black or Hispanic individuals (mean, \$853 [95% CI, −\$441 to \$2209]) and was higher for females (mean, \$13 706 [95% CI, \$11 393–\$16 322]) than for males (mean \$5744 [95% CI, \$3815–\$7801]). Additional out-of-pocket spending attributed to dementia and the race, ethnicity, and sex differences were largely the result of out-of-pocket nursing home costs.
- Inpatient hospitalization costs during the past 6 months of life with dementia vary by race and ethnicity. Among 5058 participants in HRS with linked Medicare claims who were diagnosed with dementia and died between 2000 and 2016, mean inpatient hospitalization costs were \$23 279 for Black individuals (95% CI, \$20 690–\$25 868) and \$23 471 for Hispanic individuals (95% CI, \$19 532–\$27 410) compared with \$14 609 for White individuals (95% CI, \$13 800–\$15 418).<sup>265</sup>

### Global Burden

All prevalence and mortality estimates cited here are courtesy of the GBD Study 2021 based on 204 countries and territories and pertain to all types of dementia combined.<sup>274</sup>

### Prevalence: GBD Study 2021

#### (See Table 16-3 and Chart 16-2)

- There were 56.86 (95% UI, 49.38–64.98) million prevalent cases of AD and other dementias in 2021, with 20.75 (95% UI, 17.77–23.80) million among males and 36.10 (95% UI, 31.47–41.12) million among females (Table 16-3).

- In 2021, the highest age-standardized prevalence rates of AD and other dementias among regions were found for East Asia followed by high-income North America, North Africa and the Middle East, tropical Latin America, and central sub-Saharan Africa (Chart 16-2).

### **Mortality: GBD Study 2021**

#### **(See Table 16-3 and Chart 16-3)**

- There were 1.95 (95% UI, 0.51–4.98) million total deaths attributable to AD and other dementias in 2021 (Table 16-3).
- In 2021, among regions, mortality rates estimated for AD and other dementias were highest for central sub-Saharan Africa followed by East Asia. Mortality was lowest for Andean Latin America (Chart 16-3).

## **COVID-19**

### **COVID-19 as a Risk Factor for Cognitive Decline and Dementia**

- 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>275</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 another meta-analysis of 43 studies, prevalence of cognitive impairment ≥12 weeks after COVID-19 diagnosis was 22% (95% CI, 17%–28%).<sup>276</sup>
- In a study of 401 UK Biobank participants who had brain imaging before and after COVID-19 infection and 385 control subjects who had brain imaging at 2 time points on average 2 years apart without COVID-19 infection, those who had COVID-19 experienced 7.8% greater increase in time to complete Trails A (uncorrected  $P=0.0002$ ; family-wise error-corrected  $P=0.005$ ) and 12.2% greater increase in time to complete Trails B (uncorrected  $P=0.0007$ ; family-wise error-corrected  $P=0.002$ ) relative to control subjects without COVID-19. Those with COVID-19 also had significantly reduced gray matter thickness in certain regions, changes in tissue damage biomarker levels, and reduced global brain size, suggesting that COVID-19 infection affected brain structure.<sup>277</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>278</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 and 12 months (95% CI, 9.14–39.51).

- 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>279</sup>

### **Dementia and Breakthrough COVID-19 Infection**

- Dementia was assessed in relation to breakthrough COVID-19 infection in fully vaccinated older adults. Among 225 763 fully vaccinated older adults (mean age, 73.8 years), including 2764 with AD, 1244 with vascular dementia, and 4385 with MCI, after adjustment for comorbidities, risk of breakthrough infection was similar to nondementia for AD (aOR, 1.07 [95% CI, 0.87–1.32]) and vascular dementia (aOR, 1.05 [95% CI, 0.78–1.41]) but was elevated for MCI (aOR, 1.16 [95% CI, 1.00–1.35]).<sup>280</sup>

### **Mortality in Relation to Dementia and COVID-19**

- 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>281</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 (aOR, 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>282</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>283</sup>
- In a 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]).<sup>284</sup>

**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)
At 55 y of age				
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)
At 65 y of age				
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)
At 75 y of age				
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)
At 85 y of age				
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>141</sup> by permission of Oxford University Press. Copyright © 2021 The Authors.

**Table 16-2. Dementia Mortality in the United States**

Population group	Mortality, 2022: all ages*	Age-adjusted mortality rates per 100 000 (95% CI),* 2022
Both sexes	292 881	70.4 (70.1–70.6)
Males	97 470 (33.3%)†	59.7 (59.3–60.1)
Females	195 411 (66.7%)†	76.8 (76.4–77.1)
NH White males	80 270	63.4 (62.9–63.8)
NH White females	159 862	82.6 (82.2–83.1)
NH Black males	7687	62.5 (61.0–63.9)
NH Black females	15 912	69.9 (68.8–71.0)
Hispanic males	6209	45.7 (44.5–46.9)
Hispanic females	13 004	59.2 (58.2–60.2)
NH Asian males	2463‡	30.0 (28.8–31.1)‡
NH Asian females	5128‡	39.8 (38.7–40.9)‡
NH American Indian or Alaska Native	897	39.8 (37.2–42.4)
NH Native Hawaiian or Other Pacific Islander	202	42.5 (36.6–48.5)

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 people 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 decedents, Asian and Pacific Islander decedents, 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, Japanese, and other Asian people.

Source: Mortality: Unpublished National Heart, Lung, and Blood Institute tabulation using NVSS<sup>242</sup> and CDC WONDER.<sup>241</sup>

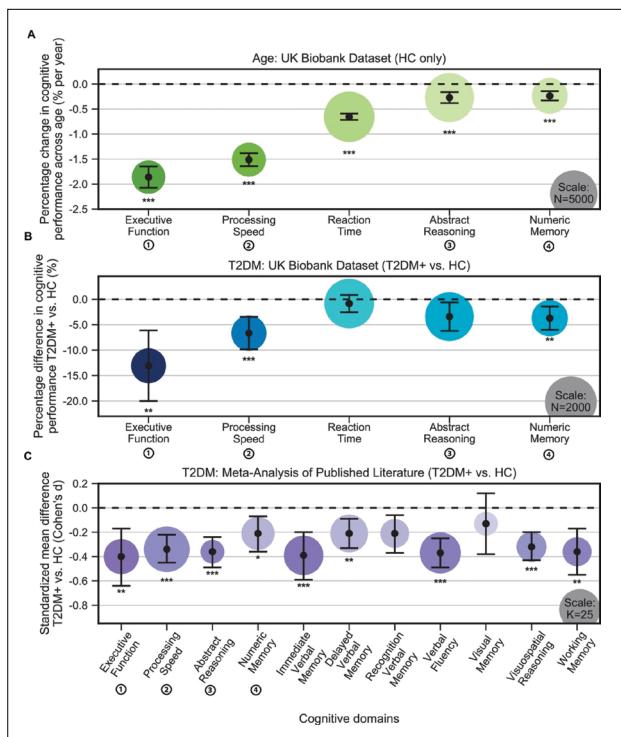
**Table 16-3. Global Mortality and Prevalence of AD and Other Dementias, by Sex, 2021**

	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), 2021	1.95 (0.51 to 4.98)	56.86 (49.38 to 64.98)	0.63 (0.15 to 1.68)	20.75 (17.77 to 23.80)	1.33 (0.36 to 3.32)	36.10 (31.47 to 41.12)
Percent change (%) in total number, 1990–2021	194.39 (176.93 to 220.09)	160.81 (156.09 to 165.90)	212.84 (193.81 to 240.83)	171.06 (164.66 to 176.63)	186.41 (165.67 to 215.47)	155.27 (150.83 to 160.39)
Percent change (%) in total number, 2010–2021	50.32 (44.65 to 57.92)	45.50 (44.03 to 46.99)	54.84 (47.22 to 64.60)	47.16 (45.55 to 48.84)	48.27 (41.70 to 57.63)	44.56 (43.02 to 46.07)
Rate per 100 000, age standardized, 2021	25.16 (6.68 to 64.25)	694.01 (602.88 to 794.08)	20.71 (5.19 to 55.50)	589.47 (507.48 to 678.79)	27.88 (7.48 to 69.79)	769.94 (670.71 to 877.57)
Percent change (%) in rate, age standardized, 1990–2021	0.47 (−3.78 to 6.99)	3.24 (1.75 to 4.23)	2.61 (−2.13 to 9.38)	3.15 (1.19 to 4.43)	1.00 (−5.02 to 9.07)	4.59 (3.36 to 5.63)
Percent change (%) in rate, age standardized, 2010–2021	1.04 (−2.30 to 5.70)	3.03 (2.17 to 3.86)	2.61 (−2.07 to 7.93)	3.00 (2.16 to 3.82)	0.97 (−3.37 to 7.13)	3.53 (2.56 to 4.43)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>274</sup>



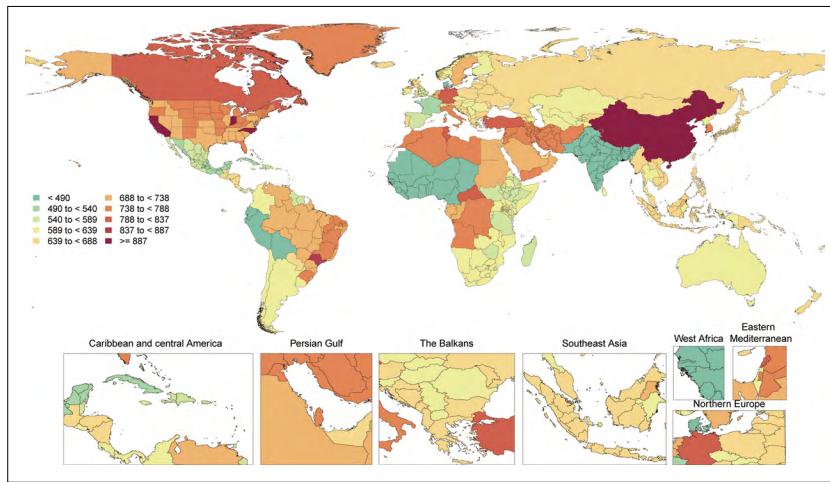
### Chart 16-1. Domain-specific cognitive deficits associated with age and type 2 diabetes.

**A.** In the UK Biobank, among participants without type 2 diabetes, age was associated with statistically significant deficits in executive function, processing speed, abstract reasoning, numeric memory, and reaction time. **B.** In the UK Biobank, type 2 diabetes was associated with statistically significant deficits in executive function, processing speed, abstract reasoning, and numeric memory but not in reaction time. **C.** In a meta-analysis of published literature, type 2 diabetes was associated with statistically significant deficits in executive function, processing speed, abstract reasoning, numeric memory, immediate verbal memory, delayed verbal memory, recognition verbal memory, verbal fluency, visuospatial reasoning, and working memory but not in visual memory.

Error bars are 95% CI. \* $P\leq 0.05$ , \*\* $P\leq 0.01$ , \*\*\* $P\leq 0.001$ , Bonferroni corrected.

HC indicates healthy controls; and T2DM, type 2 diabetes.

Source: Reprinted from Antal et al.<sup>99</sup> Copyright © 2022 The Authors. This article is distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use and redistribution provided that the original author and source are credited.

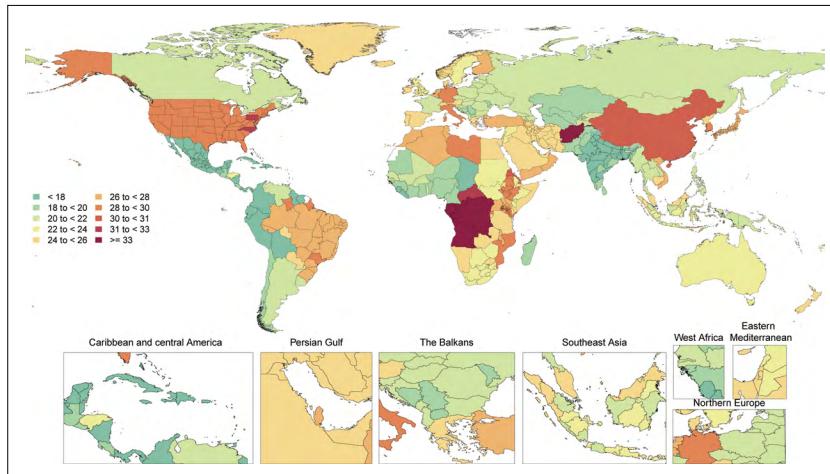


**Chart 16-2. Age-standardized global prevalence rates of AD and other dementias per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study, Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>274</sup>



**Chart 16-3. Age-standardized global mortality rates of AD and other dementias per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study, Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>274</sup>

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## 17. CONGENITAL CARDIOVASCULAR DEFECTS AND KAWASAKI DISEASE

See Tables 17-1 and 17-2 and Charts 17-1 through 17-6

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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 one of the most common birth defects worldwide.<sup>1,2</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>3</sup> on par with what is seen in other chronic pediatric health conditions,<sup>4</sup> as well as deficits in cognitive functioning<sup>5,6</sup> and neurodevelopmental outcomes.<sup>7,8</sup> However, health outcomes generally continue to improve for CCDs, including survival.<sup>9</sup>

### Overall Life Span Prevalence

It is estimated that 13.3 (95% CI, 11.5–15.4) million people globally were living with CCDs in 2019.<sup>10</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. The change was greatest in low- and middle-income countries, attributed to both increasing population growth and improving survival.

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,

The 2025 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 2025. 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.

266 461–331 437; 60%) of these <20 years of age.<sup>11</sup> This figure represents a fairly drastic downshift from the 32nd Bethesda Conference estimate (2000 estimate, 800 000)<sup>12</sup> and estimates provided by the CDC (2010 estimate, 1.4 million adults and 1 million children),<sup>13</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>11</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 prevalence 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>11</sup>

### Birth Prevalence

- In high-income North America, including the United States, the birth prevalence of CCDs is estimated to be 12.3 per 1000 (95% CI, 11.1–13.8) according to 1990 to 2017 data.<sup>11</sup>

### Birth Prevalence of Specific Defects

- The National Birth Defects Prevention Network showed the average birth prevalence of 29 selected major birth defects from 39 population-based birth defects surveillance programs in the United States from 2010 to 2014.<sup>14</sup> These data indicated the following prevalence: atrioventricular septal defect (0.54 per 1000 births), coarctation of the aorta (0.56 per 1000 births), truncus arteriosus (0.067 per 1000 births), double-outlet right ventricle (0.17 per 1000 births), HLHS (0.26 per 1000 births), other single ventricle (0.079 per 1000 births), interrupted aortic arch (0.062 per 1000 births), pulmonary valve atresia/stenosis (0.97 per 1000 births), TOF (0.46 per 1000 births), total anomalous pulmonary venous connection (0.14 per 1000 births), and TGA (0.38 per 1000 births).
- 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>15</sup>

### Risk Factors

- Numerous nongenetic risk factors are thought to contribute to CCDs.<sup>16</sup>

- Maternal exposure to first-trimester anesthesia (between 3 and 8 weeks after conception) may be associated with 1.50 times greater risk of CCDs at birth (95% CI, 1.11–2.03).<sup>17</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>18</sup>
- Maternal lifestyle factors have been associated with increased risk of CCDs.
  - Periconceptional cigarette smoking<sup>19–22</sup> 1 month before conception through 3 months after conception is associated with an increased odds of ASD (OR, 1.7 [95% CI, 1.5–2.0]), truncus arteriosus (OR, 1.7 [95% CI, 1.0–2.7]), any septal defect (OR, 1.5 [95% CI, 1.3–1.7]), double-outlet right ventricle (OR, 1.3 [95% CI, 1.1–2.2]), perimembranous VSD (OR, 1.3, [95% CI, 1.0–1.4]), atrioventricular septal defect (OR, 1.3 [95% CI, 1.0–1.9]), right-sided obstructive lesion (OR, 1.2 [95% CI, 1.0–1.4]), and pulmonary valve stenosis (OR, 1.2 [95% CI, 1.0–1.4]). There was not a significant association between this exposure and truncus arteriosus (OR, 1.2 [95% CI, 0.7–2.1]) and Ebstein anomaly (OR, 1.1 [95% CI, 0.7–1.8]).<sup>23</sup> Exposure to secondhand smoke also has been implicated as a risk factor for CCDs.<sup>21</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>24</sup>
- Maternal health factors have been associated with increased risk of CCDs.<sup>25</sup>
  - 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>26</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 (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>27</sup>
  - A 2019 study has further highlighted the relationship between maternal obesity and congenital

HD.<sup>28</sup> According to a population cohort study of 2050 491 singleton infants born in Sweden between 1992 and 2012, maternal obesity was associated with a greater odds of CCD, with a clear dose-response risk rate between categories of obesity including normal weight (BMI 18.5–<25 kg/m<sup>2</sup>), overweight (BMI 25–<30 kg/m<sup>2</sup>), obese class I (BMI 30–<35 kg/m<sup>2</sup>), obese class II (BMI 35–<40 kg/m<sup>2</sup>), and obese class III (BMI ≥40 kg/m<sup>2</sup>). In particular, a BMI of 35 to <40 kg/m<sup>2</sup> was associated with an OR of 1.51 (95% CI, 1.08–2.12), and a BMI ≥40 kg/m<sup>2</sup> was associated with an OR of 1.85 (95% CI, 1.11–3.08) of TGA. Similarly, a BMI of 30 to <35, 35 to <40, and ≥40 kg/m<sup>2</sup> was associated with an OR of 1.32 (95% CI, 1.09–1.58), 1.60 (95% CI, 1.19–2.15), and 1.87 (95% CI, 1.19–2.95) for aortic arch defect (eg, aortic arch hypoplasia), respectively. A BMI of 30 to <35 kg/m<sup>2</sup> was associated with an OR of 1.64 (95% CI, 1.13–2.38) of single-ventricle heart. Maternal diabetes, including type 1, type 2, and gestational diabetes, is associated with fetal CCDs (OR, 1.94 [95% CI, 1.59–2.35]).<sup>29,30</sup>

- Approximately 2670 (95% UI, 1795–3795) cases of CHDs could potentially be prevented annually if all females in the United States with pregestational diabetes achieved glycemic control before pregnancy.<sup>31</sup> Uncontrolled prenatal diabetes with an HbA1c >8% was associated with a 4-fold greater risk for CCD.<sup>32</sup>
- By 2007, folate deficiency was considered a well-documented risk for CCDs.<sup>33</sup> However, a more recent systematic review did not identify a relationship between folate deficiency and CCDs.<sup>34</sup>
- Maternal viral infections associated with CCDs include hepatitis B virus (OR, 2.21 [95% CI, 1.66–2.95]), coxsackievirus B (OR, 2.21 [95% CI, 1.63–3.00]), human cytomegalovirus (OR, 3.12 [95% CI, 2.44–3.98]), and rubella (OR, 2.62 [95% CI, 1.95–3.51]).<sup>35</sup>
- Maternal medications associated with CCDs include receipt of antihypertensive agents (ACE inhibitors, antiadrenergic agents, β-blockers, calcium channel blockers, diuretics) during the first trimester with variable odds, depending on the lesion type and overall greater odds of CHD (OR, 2.03 [95% CI, 1.46–2.84]).<sup>16</sup>
- Additional medications associated with a greater odds of CCD if taken by females during the first trimester of pregnancy include any antibacterial agents, sulfonamides, nitrofurantoin, quinolones, urinary antiseptic, erythromycin, insulin, fertility drugs, clomiphene, chorionic gonadotropin, non-steroidal anti-inflammatory drugs, benzodiazepines, lithium, anticonvulsants, selective serotonin

reuptake inhibitors (eg, paroxetine), and tricyclic antidepressants.<sup>16</sup>

- Maternal factors associated with a greater odds of CCD included maternal history of a serious health condition 6 months before or during pregnancy (OR, 1.5 [95% CI, 1.1–2.2]) and maternal history of CCD (OR, 2.4 [95% CI, 1.4–4.0]).<sup>16</sup>
- Paternal occupational exposures may also be associated with fetal CCDs.<sup>36</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>37</sup>
  - More recent data from the Japan Environment and Children's Study identified higher risks for CCDs related to paternal exposure to engine oil (OR, 1.68 [95% CI, 1.02–2.77]), lead-like solder (OR, 2.03 [95% CI, 1.06–3.88]), lead-free solder (OR, 3.45 [95% CI, 1.85–6.43]), and microbes (OR, 4.51 [95% CI, 1.63–12.49]).<sup>38</sup>

## Screening

It has been more than 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>39,40</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>41</sup> and several studies have demonstrated the benefit of such screening.<sup>42–44</sup> However, developmental changes in skin physiology and pigmentation require further study because of the potential for overestimation of oxygen saturation in babies of races with darker skin tone (Indian, Black).<sup>45</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>46</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>47</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>48</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>49</sup> with a sensitivity and specificity of pulse oximetry screening for critical CCDs of 100% and 99.7%, respectively.
- A more recent retrospective cohort study of CCD live births between 2004 and 2018 in Massachusetts did not find a reduction in delayed diagnosis once pulse oximetry screening became mandatory.<sup>50</sup> However, in this same study, prenatal screening was associated with improved diagnosis rates. Between 2004 and 2018, prenatal diagnosis of CCD increased by 65% ( $P_{\text{trend}} < 0.001$ ) and delayed diagnosis decreased by 56% ( $P_{\text{trend}} = 0.021$ ).

## Social Determinants of Health/Health Equity

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 lower SES and poverty were associated with higher incidence and prevalence of CCDs; reported associations between lower SES and 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>51</sup>
- The importance of a healthy maternal-fetal environment and social deprivation on CCD incidence cannot be overemphasized. Among >2.4 million infants born in California, the odds of CCD were 31% greater among infants born in neighborhoods in the lowest compared with the highest SES quartile (OR, 1.31 [95% CI, 1.21–1.42]). The odds of CCD were 1.23 times (95% CI, 1.15–1.31;  $P < 0.001$ ) greater among infants born in neighborhoods with the greatest exposure to environmental pollutants (versus the lowest quartile exposure group; OR, 1.23 [95% CI, 1.15–1.31]). Together, the odds of CCD were the highest among infants in the highest quartile for environmental exposure and social deprivation (OR, 1.48 [95% CI, 1.32–1.66];  $P < 0.0001$ ).<sup>52</sup>
- 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>53</sup> Rurality and low material wealth are risk factors for CCD. In a cohort study of 798 173 singleton births, infants living in the most socially deprived neighborhoods (SDI quintile 5) had an 18% increase in the odds of CHD (aOR, 1.18 [95% CI, 1.1–1.26]) compared with those living in quintile 1.<sup>54</sup> Infants living in rural areas had a 13% increase in the odds (aOR, 1.13 [95% CI, 1.06–1.21]) of CHD compared with their counterparts living in urban areas.

- 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 per  $10 \mu\text{g}/\text{m}^3$  [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>55</sup>
- Among infants with HLHS in 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>56</sup> Novel technology such as remote cardiac monitoring during the interstage period (the time between the first and second palliative surgeries) might help to reduce disparities in outcome. Among families from low, middle, and high socioeconomic groups enrolled in a Cardiac High Acuity Monitoring Program, survival was no different among the highest and middle SES groups: mortality OR of 0.997 (95% CI, 0.30–3.36) and OR of 1.7 (95% CI, 0.73–3.94), respectively.<sup>57</sup>
- 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>51</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>58</sup>
- The income status of the neighborhood in which a child lives is associated with increased risk for death after congenital heart surgery and resource use.<sup>59</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.

- Adolescent and adults with CHD residing in the most deprived neighborhoods had higher rates of inpatient admission, ED visits, and outpatient visits. Among children and adults with CCD residing within the most compared with the least deprived communities, there was a 56% greater odds of inpatient admission (OR, 1.56 [95% CI, 1.25–104]), an 86% greater odds of an ED visit (RR, 1.86 [95% CI, 1.47–2.34]), and a 23% greater odds of an outpatient clinic visit (OR, 1.23 [95% CI, 1.11–1.37]).<sup>60</sup>
- 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 and \$80 000.<sup>61</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>58</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>62</sup>
- Gaps in care are common among youths with CCDs. According to results from a single-center study, roughly one-third of youths with CCDs experience a  $>3$ -year gap in clinical care.<sup>63</sup> Factors associated with gaps in clinical care include 14 to 29 years of age (OR, 1.20 [95% CI, 1.06–1.37]), Black race (OR, 1.50 [95% CI, 1.15–1.97]), distance of  $>150$  miles from the hospital (OR, 1.81 [95% CI, 1.00–3.27]), mother's education of high school or less (OR, 1.17 [95% CI, 1.03–1.34]), and low neighborhood-level opportunity (eg, high deprivation; OR, 1.22 [95% CI, 1.02–1.45]).
- Individuals with CCDs who reside within higher-deprivation communities are more likely to have had no health care visits within a 12-month period (OR, 1.5 [95% CI, 1.1–2.1]), more emergency department visits within a 12-month period (OR, 1.6 [95% CI, 1.1–2.3]), more hospitalizations within a 12-month period (OR, 1.6 [95% CI, 1.1–2.3]), and  $>1$  cardiac comorbidity (OR, 1.8 [95% CI, 1.2–2.7]).<sup>64</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>65</sup>
- CCDs can have a heritable component, and parental consanguinity is a known risk factor.<sup>18</sup> There is a greater concordance of CCDs in monozygotic than dizygotic twins.<sup>66</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>67</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>68</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>69</sup>
  - Large chromosomal abnormalities are found in 8% to 10% of individuals with CCDs.<sup>69</sup> For example, aneuploidies such as trisomy 13, 18, and 21 account for 9% to 18% of CCDs.<sup>70</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>71</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>72</sup> The most common copy number variant is del22q11, which encompasses the *TBX1* (T-box transcription factor) gene and presents as DiGeorge syndrome and velocardiofacial syndrome. Others include del17q11, which causes William syndrome.<sup>73</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>69</sup> Carriers of de novo variants also have been reported to have worse transplantation-free survival and a longer extubation duration.<sup>74</sup>
  - Point variants in single genes are found in 3% to 5% of CCDs<sup>69</sup> and include variants in a core group of cardiac transcription factors (*NKX2.5*, *TBX1*, *TBX2*, *TBX3*, *TBX5*, *GATA4*, and *MEF2*,<sup>73,75,76</sup> *ZIC3*, and the *NOTCH1* gene (dominantly inherited and found in ≈5% of cases of bicuspid aortic valve) and related *NOTCH* signaling genes.<sup>77</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>78</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>79</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 intra-genic SNP associated with LV outflow tract defect.<sup>80</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>81</sup> These results suggest that non-coding de novo variants play a significant role in CCDs in addition to coding de novo variants.

- Human induced pluripotent stem cell-derived cardiomyocyte-based experiments examining the role of 6590 noncoding de novo variants revealed that 403 noncoding de novo variants affect cardiac regulatory activity through predominantly increasing enhancer activity.<sup>82</sup>
- A human induced pluripotent stem cell study investigating the role of haploinsufficiency of *TBX5*, a transcription regulator, in the development of CCD revealed a dose-sensitive requirement of *TBX5* for ventricular myocyte differentiation, highlighting the role of *TBX5* haploinsufficiency in the development of VSD.<sup>83</sup>
- Recently, in addition to 14 previously recognized genes associated with CCDs, 7 new genes (*FEZ1*, *MYO16*, *ARID1B*, *NALCN*, *WAC*, *KDM5B*, and *WHSC1*) have been identified as being associated with CCDs.<sup>84</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>85</sup>
- Rare monogenic CCDs also exist, including monogenic forms of ASD, heterotaxy, severe mitral valve prolapse, and bicuspid aortic valve.<sup>73</sup> GWASs and mechanistic studies have supported a causal role of *WNT5A* in TGA and *MUC4* in bicuspid aortic valve disease.<sup>86,87</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>88</sup>
- Genetic variants associated with CCDs may also occur within cancer risk genes.<sup>89</sup>

- There is no exact consensus currently on the role, type, and utility of clinical genetic testing in people with CCDs,<sup>73</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>12,90</sup>
- The diagnostic yield for CCD genetic panels in familial, nonsyndromic cases is 31% to 46% and is even lower in nonfamilial disease.<sup>91,92</sup> Use of whole-exome genetic testing has been shown to improve rates of detection.<sup>93</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>94</sup>

## Mortality

(See Table 17-1 and Charts 17-1 through 17-4)

- In 2017, CCDs were among the top 8 causes of infant mortality in all global regions.<sup>11</sup>
- In 2022, mortality related to CCDs was 3213 deaths (Table 17-1) in the United States, a 5.2% increase from the number of deaths in 2012 (unpublished NHLBI tabulation using NVSS<sup>95</sup>).
- CCDs (*ICD-10* Q20–Q28) were the most common cause of infant deaths resulting from birth defects (*ICD-10* Q00–Q99) in 2022; 23.0% of infants who died of a birth defect had a heart defect (*ICD-10* Q20–Q24; unpublished NHLBI tabulation using NVSS<sup>95</sup>).
- In 2022, the age-adjusted death rate (deaths per 100000 people) attributable to CCDs was 1.0, which is the same as it was in 2012 (unpublished NHLBI tabulation using CDC WONDER<sup>96</sup>).
- Death rates attributed to CCDs decrease as gestational age advances to 40 weeks.<sup>97</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>98</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>99</sup> showed that of 31102 analyzable CCD surgeries in 2018, there were 662 mortalities among the 25608 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>100</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 35998 patients with a median follow-up of 18 years and an overall standardized mortality ratio of 8.3% (95% CI, 8.0%–8.7%).<sup>101</sup>
- In Mexico, 70741 deaths were attributed to CCDs during the years 2000 to 2015, with the standardized mortality rates increasing from 3.3 to 4 per 100000 individuals and mortality rates increasing in the group <1 year of age from 114.4 to 146.4 per 100000 live births.<sup>102</sup>
- Analysis of the NIS database of 20649 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>103</sup>
- A meta-analysis of outcomes for 848 patients with heterotaxy who underwent a Fontan procedure before May 2018 showed survival rates 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>104</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 2022 (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 people, NH White people, and Hispanic people (Chart 17-2). Although there was variability by race, 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 2022 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 2022 (Chart 17-4).
- The US 2022 age-adjusted death rate (deaths per 100000 people) attributable to CCDs was 1.2 for NH White males, 1.4 for NH Black males, 0.9 for Hispanic males, 0.6 for NH Asian males, 0.9 for NH White females, 1.2 for NH Black females, 0.8 for Hispanic females, and 0.5 for NH Asian females (Table 17-1). Infant (<1 year of age) mortality rates

were 29.2 for NH White infants, 36.2 for NH Black infants, 18.6 for NH Asian infants, and 29.0 for Hispanic infants (unpublished NHLBI tabulation using CDC WONDER<sup>96</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>105</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 are associated with higher mortality during the first year of life among infants with critical congenital HD (1.61 [95% CI, 1.042–2.5]).<sup>58</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>106</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>107</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>108</sup>
- According to data from the National Pediatric Cardiology Quality Improvement Collaborative Phase II registry, factors such as gestational age <37 weeks, birth weight <2.5 kg, secondary cardiac lesion, extracardiac anomaly, or genetic syndrome are associated with worse survival.<sup>109</sup> Although the presence of a single high-risk diagnosis is not associated with decreased survival, an incremental increase in the number of high-risk diagnoses is associated with reduced survival to a first birthday (OR, 0.23 [95% CI, 0.15–0.36]). The presence of 3 to 5 high-risk diagnoses is associated with an even greater odds of mortality (OR, 0.17 [95% CI, 0.10–0.30]).

- The personality type of adults with CCDs has been associated with mortality. According to the Dutch National Congenital Corvita registry, adults with type D (distressed) personality had an increased risk for all-cause mortality. After 10 years of follow-up, adults with CCDs and type D personality had survival rate of 82% versus 87% for those with non-type D personality ( $P=0.014$ ).<sup>110</sup>
- Institution of an IHM for infants with HLHS may be beneficial for reducing interstage mortality.<sup>111</sup> Data from the National Pediatric Cardiology Quality Improvement Collaborative have indicated a >40% reduction in interstage 1 mortality, reducing mortality to <2%, in the current era, after changes in practice such as institution of IHM.<sup>112</sup> According to a single-center retrospective study, institution of an IHM compared with a historical control was associated with an average 29% lower predicted probability of interstage death (adjusted probability, –0.29 [95% CI, –0.52 to –0.57];  $P=0.015$ ).<sup>113</sup> However, the sole benefit of IHM remains a major research gap; no RCTs have assessed the role that IHM plays in improvement in interstage mortality and morbidity, and IHM may be only 1 component of the many factors (eg, improved discharge process, care coordination, nutrition) contributing to improved outcomes.<sup>112,113</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>114–116</sup>

- Individuals with CCDs are at increased risk of AF. In an analysis in Sweden including 21 982 patients with CCDs and 219 816 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 control patients without congenital HD.<sup>117</sup> By 42 years of age, ≈8% of patients with CCDs had been diagnosed with AF. Macroreentrant atrial tachycardia is very frequent in adults with congenital HD.<sup>118</sup>
- HF rates are 40%, 25%, and 50% among TOF, coarctation, and TGA/Fontan-repaired adult survivors, respectively.<sup>116</sup>
- Arrhythmia is very common and occurs among 35%, 32%, and 60% of TOF, coarctation, and TGA/Fontan-repaired adult survivors, respectively.<sup>116</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>116</sup>
- Chronic hypoxia, neurohormonal derangements, intraglomerular hemodynamic shifts, ischemia, and nephrotoxins place individuals with CCD at

- increased risk for CKD.<sup>119</sup> According to data from the Swedish National Patient Register and the Cause of Death Register, the risk of CKD is 6.4 times higher in patients with CCD than control subjects (OR, 6.4 [95% CI, 5.65–7.27]).<sup>120</sup>
- Growth failure, in both weight and length, is common among patients with HLHS.<sup>121</sup> According to a secondary analysis of data from a prospective cohort study of growth and neurodevelopment in infants with CCD, infants with single-ventricle physiology compared with healthy infants had lower weight *Z* scores at 3 months ( $-1.64$  versus  $-0.22$ ;  $P<0.0001$ ), 6 months ( $-1.30$  versus  $-0.09$ ;  $P<0.0001$ ), 9 months ( $-0.76$  versus  $0.06$ ;  $P=0.001$ ), and 12 months ( $-0.45$  versus  $0.20$ ;  $P=0.005$ ).<sup>122</sup> Analysis of length *Z* scores demonstrated infants with single-ventricle physiology to be shorter than healthy infants at 3 months ( $-1.21$  versus  $0.15$ ;  $P<0.0001$ ), 6 months ( $-1.02$  versus  $0.22$ ;  $P<0.0001$ ), 9 months ( $-0.71$  versus  $0.28$ ;  $P<0.001$ ), and 12 months ( $-0.59$  versus  $0.10$ ;  $P=0.013$ ) of age.
  - Children with CCDs may be at risk for adverse neurodevelopmental outcomes, including mild to severe motor impairments among 12.3% to 68.6% (interquartile range, 23.4%–52.2%),<sup>123</sup> increased attention-deficit/hyperactivity disorder-related behaviors (mean T score, 57 for inattention and 54 for hyperactivity/impulsivity compared with a normal mean T score of 50;  $P<0.0001$  using Connors-3 testing), difficulties in social interaction (mean T score, 53 compared with a normal mean T score of 50;  $P=0.035$ ), combined attention-deficit/hyperactivity disorder-related symptoms and social interaction problems in 23% of children,<sup>124</sup> and depression or anxiety (OR, 5.23 [95% CI, 3.9%–7.1%]).<sup>125,126</sup>
  - A systematic review and meta-analysis has shown that children with neonatal repair of TGA had normal neurodevelopmental scores at 5 years of age.<sup>127</sup>
  - Among long-term Dutch survivors of CCDs (median follow-up, 45 years), adults had lower educational level ( $P<0.001$ ), occupational level ( $P<0.001$ ), and employment rate ( $P<0.001$ ) but better health-related quality of life, emotional functioning,<sup>128</sup> and executive function<sup>129</sup> compared with normative data from the Dutch population.
  - Infants with single-ventricle physiology are more likely to have poorer fine and gross motor skills at 9 and 18 months compared with infants with other CCDs. Using the Dutch version of the Bayley-III shows that infants with single-ventricle physiology compared with infants with other forms of CCD performed significantly ( $P\le0.05$ ) worse on both fine and gross motor skill assessments at 9 and 18 months. Mean fine motor score for single-ventricle physiology at 9 months was  $9.9\pm1.6$  versus  $10.5\pm1.4$  for

- TGA,  $10.9\pm1.7$  for TOF, and  $11.6\pm1.6$  for aortic arch pathology ( $P=0.046$ ). Mean fine motor skills score for single-ventricle physiology at 18 months was  $9.9\pm2.5$  versus  $11.4\pm1.6$  for TGA,  $11.6\pm1.7$  for TOF, and  $11.9\pm2.4$  for aortic arch pathology ( $P=0.002$ ). Mean gross motor score for single-ventricle physiology at 9 months was  $6.8\pm3.5$  versus  $9.4\pm3.0$  for TGA,  $8.6\pm2.9$  for TOF, and  $8.8\pm2.8$  for aortic arch pathology ( $P=0.001$ ). Last, mean gross motor score for single-ventricle physiology at 18 months was  $7.5\pm3.7$  versus  $10.6\pm3.1$  for TGA,  $10.2\pm2.8$  for TOF, and  $9.6\pm2.6$  for aortic arch pathology ( $P=0.001$ ).<sup>130</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. Among 1020 individuals with adult congenital HD and 497 987 without adult congenital HD, individuals with adult congenital HD had significantly poorer performance on alphanumeric trail making, a measure of visual attention and cognitive flexibility, spending 6.4 seconds longer on alphanumeric trail making (95% CI, 3.0–9.9;  $P=0.002$ ) and 2.5 seconds longer on numeric trail making (95% CI, 0.5–4.6;  $P=0.034$ ), a measure of visual attention and processing speed.<sup>131</sup>
  - In patients with HLHS, an older age at Fontan procedure and a history of sepsis were independent predictors of poor neurocognitive outcomes.<sup>132</sup> According to multivariable linear regression models, sepsis was associated with a lower full-scale intelligence quotient of  $-9.9$  (95% CI,  $-17.0$  to  $-2.90$ ;  $P=0.007$ ), a lower performance intelligence quotient of  $-9.2$  (95% CI,  $-17$  to  $-2.10$ ;  $P=0.012$ ), and a lower verbal intelligence quotient of  $-9.2$  (95% CI,  $-17.02$  to  $-1.90$ ;  $P=0.015$ ). Similarly, a history of Fontan procedure was associated with a lower full-scale intelligence quotient of  $-6.5$  (95% CI,  $-10.4$  to  $-2.80$ ;  $P<0.0001$ ), a lower performance intelligence quotient of  $-6.40$  (95% CI,  $-10.5$  to  $-2.70$ ;  $P<0.0001$ ), and a lower verbal intelligence quotient of  $-5.10$  (95% CI,  $-9.00$  to  $-1.10$ ;  $P=0.013$ ).
  - 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>116</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>116</sup>
  - There are inconclusive data showing an increased risk of serious adverse events from COVID-19 infection in children and adults with CCDs.<sup>133</sup>

- Roughly one-fourth of patients living with a Fontan circulation develop liver cirrhosis throughout adulthood. The cumulative incidence of liver cirrhosis among patients with Fontan circulation is 27.5% (95% CI, 16.9%–34.4%).<sup>134</sup>
- Independently of the severity of the underlying heart defect, adults with congenital HD have an increased risk for anxiety disorder.<sup>135</sup> High New York Heart Association class is associated with a greater odds of anxiety and depression (OR, 2.67 [95% CI, 1.50–4.76]).
- Quality of life can also be affected by CCDs. A low to moderate amount of variation in health-related quality of life among children with CCDs can be attributed to variables such as surgical/ICU factors, demographic factors, and health care use factors, with attributable variance ranging from 24% to 29%.<sup>136</sup> Worse functional class (stage C or D, New York Heart Association class  $\geq 2$ ) was associated with more dissatisfaction with health (OR, 3.44 [95% CI, 1.3–10.4]), whereas no differences were seen in the psychological, social relationship, or environmental domains.<sup>137</sup>

## Health Care Use: Hospitalizations

- In 2021, the total number of first-listed hospital discharges for CCDs for all ages was 41 785.
- 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>138</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>139</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>140</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. Among individuals with CCDs, median ambulatory, physician, nonphysician, ED, prescription, and out-of-pocket ambulatory costs were \$3598 (interquartile range, \$1221–\$9454), \$1120 (interquartile range, \$440–\$2503), \$839 (interquartile range, \$90–\$3413), \$2005

(interquartile range, \$993–\$4035), \$213 (interquartile range, \$13–\$1237), and \$802 (interquartile range, 246–1862); among individuals without CCDs, those costs were \$1068 (interquartile range, \$230–\$3640), \$375 (interquartile range, \$69–\$1083), \$125 (interquartile range, \$0–\$704), \$1583 (interquartile range, \$808–\$3209), \$64 (interquartile range, \$0–\$527), and \$261 (interquartile range, \$33–\$892), respectively ( $P<0.001$  for all comparisons).<sup>141</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>141</sup>

## Cost

- Among pediatric hospitalizations (0–20 years of age) in the HCUP 2009 and 2012 Kids' Inpatient Database<sup>142,143</sup>,
  - Pediatric hospitalizations with CCDs (4.4% of total pediatric hospitalizations) accounted for \$6.6 billion in hospitalization spending (23% of total pediatric hospitalization costs).
  - 26.7% of all CCD costs were attributed to critical CCDs, with the highest costs attributable to HLHS, coarctation of the aorta, and TOF.
  - Median hospital cost was \$51 302 (interquartile range, \$32 088–\$100 058) in children who underwent cardiac surgery, \$21 920 (interquartile range, \$13 068–\$51 609) in children who underwent cardiac catheterization, \$41 34 (interquartile range, \$17 771–\$10 253) in children who underwent noncardiac surgery, and \$23 062 (interquartile range, \$55 29–\$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. Among 59 917 hospitalizations, annual CHD costs increased by 21.6% from CAD: \$99.7 (95% CI, \$89.4–\$110.1) million in 2004 to \$121.2 (95% CI, \$112.8–\$129.6) million in 2013 ( $P<0.001$ ). Costs were higher for children compared with adults. The cost increase was greater in adults (4.5%/y;  $P<0.001$ ) than in children (0.7%/y;  $P=0.006$ ). Adults accounted for 38.2% of costs in 2004 versus 45.8% in 2013 ( $P=0.002$ ). Costs increased most among adults with complex CHD (7.2%/y;  $P=0.001$ ).

Adult males accounted for greater increases in costs relative to females ( $P<0.001$ ). Length of stay was unchanged over time.<sup>144</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. Adjusted average length of stay was shortest in the West and longest in the South (26.1 days [95% CI, 24.0–35.1] versus 34.9 days [95% CI, 31.8–38.1]); average adjusted charges were lowest in the Northeast (\$324 600 [95% CI, \$271 400–\$377 900]) and highest in the West (\$400 500 [95% CI, \$346 700–\$454 300];  $P=0.05$ ).<sup>145</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>146</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. A similar cost reduction was not found for patients with aortic coarctation repair.<sup>147</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>148</sup>
- Cost of CCD care may be affected by center volume. Data from the Pediatric Health Information Systems database show that of 1024 neonates with truncus arteriosus, of whom 495 (48%) were treated at high-volume centers, costs at the 75th percentile were lower at high-volume versus low-volume centers by \$28 456 ( $P=0.02$ ). Patients at high-volume centers had lower median postoperative ventilation days (5 days versus 6 days;  $P<0.001$ ), ICU length of stay (13 days versus 19 days;  $P<0.001$ ), hospital length of stay (23 days versus 28 days;  $P=0.02$ ), and inotropic agent use (3 days versus 4 days;  $P=0.004$ ).<sup>60,149</sup>
- In a nationally comprehensive cohort of patients with CCD, Black race was associated with greater resource use, with higher odds of ED visits compared with White race (OR, 4.19 [95% CI, 1.35–13.04];  $P=0.001$ ).<sup>150</sup>

## Global Burden of CCDs

### (See Table 17-2 and Charts 17-5 and 17-6)

- A total of 3.12 (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>10</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>11</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>151</sup>
- CCDs were responsible for 261 247 deaths globally in 2017 (95% CI, 216 567–308 159), which is a 30% decline from 1990.<sup>11</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>11</sup>
- Based on 204 countries and territories in 2021<sup>152</sup>:
  - The prevalence of congenital heart anomalies was 15.77 (95% UI, 14.04–17.39) million cases (Table 17-2).
  - There were 0.25 (95% UI, 0.21–0.30) million total deaths estimated for congenital heart anomalies worldwide (Table 17-2).
  - Among regions, age-standardized mortality rates of congenital heart anomalies were highest for Oceania, followed by the Caribbean, North Africa and the Middle East, and western sub-Saharan Africa. They were lowest for high-income Asia Pacific, Australasia, and Western Europe (Chart 17-5).
  - The age-standardized prevalence of congenital heart anomalies among regions was highest for high-income Asia Pacific, Central Asia, and Western Europe (Chart 17-6).
- 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>151</sup>
- There are multiple recent estimates on the prevalence of CCDs in China.
  - 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>153</sup> possibly reflecting differences in diagnostic access.
- In another study from China (Zhengzhou, Henan), the overall prevalence of CCDs was 8.44 per 1000 live births during 2014 to 2020.<sup>154</sup>
  - From January to December 2019, among 51 857 newborns born in 11 cities in eastern China, the total birth prevalence of CCDs was 5.79 per 1000 births.<sup>155</sup> Birth prevalence was higher in low-income (6.14 per 1000 births) compared with high-income (5.58 per 1000 births;  $P=0.009$ ) areas.
  - In the Yunnan region of China, differences in CCD prevalence among ethnic groups were found. The overall CCD prevalence was 6.04 cases per 1000 children.<sup>156</sup> The ethnic groups displaying the highest CCD prevalence were the Lisu (15.51 per 1000), Achang (13.18 per 1000), Jingpo (12.32 per 1000), Naxi (9.68 per 1000), and Tibetan (8.57 per 1000).
  - 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>157</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>158</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>159</sup>
  - In Argentina, according to data provided by the national Network of Congenital Anomalies (2009–2018), the prevalence of CCDs was 11.46 (95% CI, 11.02–11.92) per 10 000 births.<sup>160</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>161</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>161</sup>
  - A population-based registry analysis of CCD prevalence in French Guiana found a birth prevalence of

68.4 per 10 000 with live birth prevalence of 65.2 per 10 000.<sup>162</sup>

- Although gains in CCD mortality were seen over the past 3 decades, unfavorable period and cohort effects were found in many countries, raising questions about health care adequacy to care for children with CCDs.<sup>163</sup>
  - India, China, Pakistan, and Nigeria had the highest mortality, accounting for 39.7% of deaths resulting from CCDs globally.
  - During the past 30 years, favorable mortality reductions were generally found in most high-SDI countries like South Korea (net drift,  $-4.0\%/\text{y}$  [95% CI,  $-4.8\%/\text{y}$  to  $-3.1\%/\text{y}$ ]) and in many middle-SDI countries like Brazil ( $-2.7\%$  [95% CI,  $-3.1\%$  to  $2.4\%$ ]) and South Africa (95% CI,  $-2.5\%$  [ $-3.2\%$  to  $-1.8\%$ ]).
  - However, 52 of 129 countries had either increasing trends (net drifts  $\geq 0.0\%$ ) or stagnated reductions ( $\geq -0.5\%$ ) in mortality.

## Kawasaki Disease

### **ICD-9 446.1; ICD-10 M30.3.**

KD is an acute inflammatory illness characterized by fever, rash, nonexudative limbal-sparing conjunctivitis, extremity changes, red lips and strawberry tongue, and a swollen lymph node. The most significant consequence of this vasculitis is coronary artery aneurysms, which can result in coronary ischemic events and other cardiovascular outcomes in the acute period or years later.<sup>164</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>165,166</sup>

#### **Prevalence**

- KD is the most common cause of acquired HD in children in the United States and other high-income countries.<sup>167</sup>

#### **Incidence**

- A review of HCUP/Kids' Inpatient Database for KD hospitalizations in children <18 years of age in the United States during 2009 to 2012 revealed 10 486 hospitalizations for KD of 12 678 005 total hospitalizations. The incidence of KD was estimated at 6.35 per 100 000.<sup>168</sup>
- The incidence of KD was estimated at 20.8 per 100 000 US children <5 years of age in 2006.<sup>169</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>169</sup>
- Although KD can occur into adolescence (and rarely adulthood), 76.8% of US children with KD are <5 years of age.<sup>169</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 children (17.5 per 100 000 children <5 years of age) and Hispanic children (15.7 per 100 000 children <5 years of age), and is least common in White children (12.0 per 100 000 children <5 years of age).<sup>169</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>170</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 children, 86.9 for Native Hawaiian children, 83.2 for Chinese children, 64.5 for Filipino children, and 13.7 for White children.<sup>170</sup>
- There are seasonal variations in KD that may track other respiratory and enteric viruses<sup>171</sup>; KD is more common during the winter and early spring months, except in Hawaii, where no clear seasonal trend is seen.<sup>169,170</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>172</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>173</sup>
- KD rarely recurs. Recurrences constitute 2% to 4% of total KD cases in both the United States and Japan,<sup>174</sup> and the incidence of first recurrence among children with a history of KD has been reported as 6.5 per 1000 PY in Japan (2007–2010) and 2.6 per 1000 PY in Canada (2004–2014).<sup>175,176</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>169</sup>

### Genetics/Family History/Risk Factors

- GWASs have identified loci in *FCGR2A*, *FAM167-BLK*, *CD40*, *IHGV3-66*, HLA class II region, *NAALADL2*, and *ZFHX3* to be associated with KD.<sup>177–181</sup> Recently, a novel locus (intergenic variant rs6017006) has been identified to be

associated with coronary artery aneurysm in patients of European descent with KD.<sup>182</sup>

- Various 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>165,181,183</sup>
- Advanced maternal age ( $\geq 35$  years of age; 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>184</sup>
- Certain types of air pollution, both prenatally and during early life, may contribute to the development of KD in children. The strongest risk related to carbon monoxide (parts per million) is during pregnancy (OR, 1.67 [95% CI, 1.23–2.28];  $P=0.001$ ) and after delivery (1.61 [95% CI, 1.16–2.22];  $P=0.004$ ).<sup>185</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  $\approx 4\%$  for aneurysms defined by absolute dimensions).<sup>167</sup> Aspirin is routinely used for its anti-inflammatory and antiplatelet effects, but it does not reduce the incidence of coronary artery aneurysms.<sup>186</sup>
- On the basis of a Cochrane review, adding 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>187</sup>
- Treatment of IVIG resistance is currently not standardized. A multicenter comparative-effectiveness trial including 30 US hospitals and 103 patients (4 weeks–17 years of age) showed that infliximab compared with a second dose of IVIG resulted in shorter fever duration ( $1.5 \pm 1.4$  days versus  $2.5 \pm 2.5$  days) and shorter hospitalization ( $3.2 \pm 2.1$  days versus  $4.5 \pm 2.5$  days). No difference was found in coronary artery outcomes.<sup>188</sup>
- Cyclophosphamide may arrest further coronary artery dilation in those with severe and progressive coronary artery enlargement after KD.<sup>189</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>190,191</sup>

### Complications of KD

In the acute phase (up to  $\approx 6$  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>192</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>167</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>193</sup>
  - A recent study showed that younger age (OR, 0.94 [95% CI, 0.90–0.99]), IVIG nonresponse (OR, 6.70 [95% CI, 1.80–24.50]), and noncoronary cardiac events (OR, 3.20 [95% CI, 1.10–8.70]), in particular in very young children (<6 months), may also increase risk for more severe KD with coronary artery aneurysms (OR, 2.18 [95% CI, 1.25–3.80]).<sup>194</sup>
  - In Latin America, children <6 months of age were more likely to have delayed diagnoses (OR, 0.17 [95% CI, 0.08–0.35]) and less obvious clinical features (oral changes: OR, 0.26 [95% CI, 0.12–0.58]; cervical lymphadenopathy: OR, 0.28 [95% CI, 0.14–0.28]; extremity changes: OR, 0.45 [95% CI, 0.23–0.88]; complete KD: OR, 0.24 [95% CI, 0.13–0.47]) and were at greater risk of developing coronary artery aneurysm (OR, 11.25 [95% CI, 3.87–36.25]), even after controlling for day of treatment initiation.<sup>195</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>196–198</sup> Mortality is related to thrombosis or rupture of rapidly expanding aneurysms or, less commonly, shock or macrophage activation syndrome with multiorgan failure.<sup>198,199</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>200</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>190,201</sup>
- In a large prospective study across 16 Latin American countries and 64 participating pediatric centers including 1853 patients with a new KD diagnosis, delayed admission (>10 days after symptom onset) occurred in 16%, 25% had incomplete KD, and 11% were IVIG resistant.<sup>202</sup> Of 671 who had coronary artery  $Z$  scores reported, 21% had coronary artery aneurysms and 4% had giant coronary artery aneurysms. Maximal coronary artery  $Z$  score  $\geq 2.5$  mm at presentation was alone most prognostic of coronary aneurysm at follow-up (AUC, 0.84 [95% CI, 0.80–0.88]).
  - 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>203</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 2022, US mortality attributable to KD was 14 patients for all-cause mortality and 11 deaths for underlying mortality (unpublished NHLBI tabulation using CDC WONDER<sup>96</sup>).

### Health Care Use

- In 2021, there were 3400 principal and 5145 all-listed diagnoses hospital discharges for KD (HCUP<sup>204</sup> unpublished NHLBI tabulation).
- A Canadian study found that children with KD compared with control subjects had higher rates of hospitalization (adjusted rate ratio, 2.07 [95% CI, 2.00–2.15]), outpatient visits (adjusted rate ratio, 1.30 [95% CI, 1.28–1.33]), and ED visits (adjusted rate ratio, 1.22 [95% CI, 1.18–1.26]) throughout follow-up.<sup>205</sup> Within 1 year after discharge, 717 children with KD (15.6%) were rehospitalized, 4587 (99.8%) had  $\geq 1$  outpatient physician visits, and 1695 (45.5%) had  $\geq 1$  ED visits.
- Patients with KD also had higher composite health care costs after discharge (eg, median cost within 1 year [Canadian dollars], \$2466 [KD cases] versus \$234 [comparators]).<sup>205</sup>

### Global Burden of KD

- The annual incidence of KD is highest in Japan, at 264 per 100 000 children <5 years of age in 2014, followed by South Korea at 134.4 per 100 000 children <5 years of age in 2014 and Taiwan at 82.7 per 100 000 in children <5 years of age.<sup>206</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>207</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>208</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>176,209–213</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>214</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-CoV-2 infection or exposure, multisystem organ involvement, and exclusion of alternative 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>215</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-CoV-2 infection.<sup>216</sup>
- Since May 2020, the CDC has been tracking reports of MIS-C. As of June 2, 2024, 9684 cases and 79 attributable deaths (0.81%) have been reported. Median age of cases was 9 years of age; 56% of cases that have ethnicity information available have occurred in children who are Hispanic or Latino or Black (2398 cases); 98% tested positive for SARS-CoV-2 (reverse transcriptase–polymerase chain reaction, serology, or antigen test); and 60% of reported patients were male.<sup>217</sup>
- Some data suggest that the risks of MIS-C have changed over the course of the SARS-CoV-2

pandemic. The CDC reported that early in the COVID-19 pandemic, MIS-C occurred in ≈1 of every 3000 to 4000 children and adolescents with SARS-CoV-2 infection, but the incidence has become more rare, decreasing from 2020 to 2023. A multicenter, international, cross-sectional study collected the MIS-C incidence from the participant regions and countries for the period of July 2020 to November 2021.<sup>218</sup> Over 2 subsequent 4-week periods of measurement in a reference population of 17906 432 children, a significant decrease of MIS-C/COVID-19 cases was found globally ( $P<0.001$ ).

- A meta-analysis showed that the pooled OR for MIS-C in vaccinated children compared with unvaccinated children was 0.4 (95% CI, 0.03–0.06).<sup>219</sup>
- A meta-analysis of patient characteristics in MIS-C shows that more males (55.8% [95% CI, 50.3%–61.2%]) are affected, most patients (79.1% [95% CI, 70.8–85.5]) require ICU admission, nearly one-third of patients (29.2% [95% CI, 19.9%–40.5%]) require mechanical ventilation, and a small number (7.6% [95% CI, 4.1%–13.8%]) require extracorporeal membrane oxygenation.<sup>220</sup>
- Risk of MIS-C may vary with ethnicity, with apparently higher risk among those of African descent.<sup>221,222</sup>
- A potential association has been found in 2 studies between severe vitamin D deficiency and severe disease in children presenting with MIS-C.<sup>223,224</sup>
- There is also an association with obesity and the severity of MIS-C. In Poland, among 306 children with MIS-C, children with obesity had a higher rate of incomplete recovery (OR, 4.2 [95% CI, 1.4–12.1]).<sup>225</sup>
- In England during the Alpha wave, MIS-C occurred in 0.038% (interquartile range, 0.037%–0.041%) of pediatric SARS-CoV-2 infections; during the Delta wave, MIS-C occurred in 0.026% (interquartile range, 0.025%–0.029%).<sup>226</sup>
- Among 903 cases of MIS-C in Brazil, the RR of death caused by MIS-C was 5.29 (95% CI, 2.83–9.87;  $P<0.001$ ) times higher in adolescents from 15 to 19 years of age compared with children 0 to 4 years of age. In addition, residency in the North region, a region with poorer health and economic indicators, was a risk factor for death (RR, 3.72 [95% CI, 1.29–10.74];  $P=0.008$ ).<sup>227</sup>
- Multiple follow-up studies have been published on the cardiac outcomes of children who had MIS-C. In a single-site study, residual cardiac disease among patients with MIS-C 6 months after presentation was 10.3%.<sup>228</sup> A similar longitudinal study showed MR persisted in 7.5% at 6 months and that coronary artery dilatation persisted in 5.2% at 6 months.<sup>229</sup>

**Table 17-1. CCDs in the United States**

Population group	Estimated prevalence, 2010, all ages	Mortality, 2022, all ages*	Age-adjusted mortality rates per 100 000 (95% CI)*, 2022
Both sexes	2.4 million	3213	1.0 (1.0–1.0)
Males	...	1758 (54.7%)†	1.1 (1.1–1.2)
Females	...	1455 (45.3%)†	0.9 (0.8–0.9)
NH White males	...	1078	1.2 (1.1–1.2)
NH White females	...	844	0.9 (0.8–1.0)
NH Black males	...	277	1.4 (1.2–1.6)
NH Black females	...	257	1.2 (1.1–1.4)
Hispanic males	...	306	0.9 (0.8–1.0)
Hispanic females	...	265	0.8 (0.7–0.9)
NH Asian males	...	49‡	0.6 (0.4–0.7)‡
NH Asian females	...	41‡	0.5 (0.3–0.6)‡
NH American Indian or Alaska Native people	...	22	1.1 (0.7–1.6)
NH Native Hawaiian or Pacific Islander		10	Unreliable (0.8–3.0)

CCD indicates congenital cardiovascular defect; ellipses (...), data not available; and NH, non-Hispanic.

\*Mortality for Hispanic people, NH American Indian or Alaska Native people, 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 under-reporting on death certificates of American Indian or Alaska Native decedents, Asian decedents, Pacific Islander decedents, 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.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Gilboa et al.<sup>13</sup> Mortality (for underlying cause of CCDs): unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System<sup>95</sup> and CDC WONDER.<sup>96</sup> These data represent underlying cause of death only.

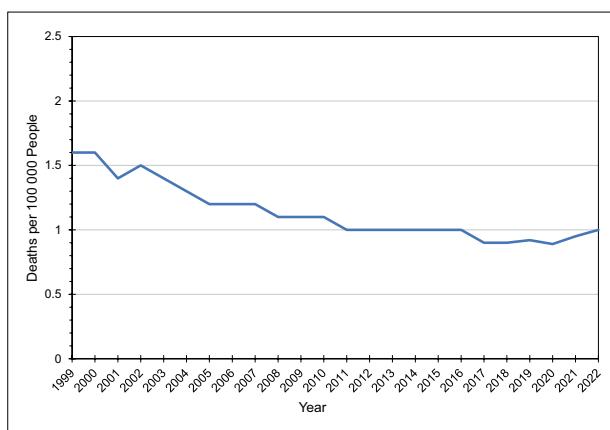
**Table 17-2. Global Mortality and Prevalence of Congenital Heart Anomalies, by Sex, 2021**

	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), 2021	0.25 (0.21 to 0.30)	15.77 (14.04 to 17.39)	0.14 (0.11 to 0.18)	7.72 (6.86 to 8.52)	0.11 (0.09 to 0.14)	8.05 (7.15 to 8.90)
Percent change (%) in total number, 1990–2021	−52.58 (−63.16 to −20.09)	33.83 (31.88 to 35.67)	−54.29 (−65.96 to −17.31)	31.54 (29.65 to 33.47)	−50.25 (−61.52 to −1.19)	36.10 (34.01 to 38.21)
Percent change (%) in total number, 2010–2021	−30.29 (−40.27 to −13.40)	10.46 (9.47 to 11.35)	−31.21 (−42.31 to −8.58)	9.40 (8.34 to 10.45)	−29.08 (−38.64 to −8.13)	11.50 (10.48 to 12.48)
Rate per 100 000, age standardized, 2021	3.86 (3.19 to 4.70)	210.70 (187.92 to 232.48)	4.18 (3.31 to 5.42)	204.17 (181.75 to 225.77)	3.51 (2.74 to 4.29)	217.20 (193.26 to 240.16)
Percent change (%) in rate, age standardized, 1990–2021	−54.63 (−64.72 to −24.20)	0.56 (−0.27 to 1.42)	−56.02 (−67.23 to −21.08)	−0.17 (−1.03 to 0.71)	−52.70 (−63.42 to −6.51)	1.32 (0.36 to 2.31)
Percent change (%) in rate, age standardized, 2010–2021	−28.61 (−39.03 to −11.13)	0.81 (−0.01 to 1.49)	−29.30 (−40.85 to −6.03)	0.17 (−0.76 to 0.95)	−27.67 (−37.42 to −6.14)	1.46 (0.64 to 2.31)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

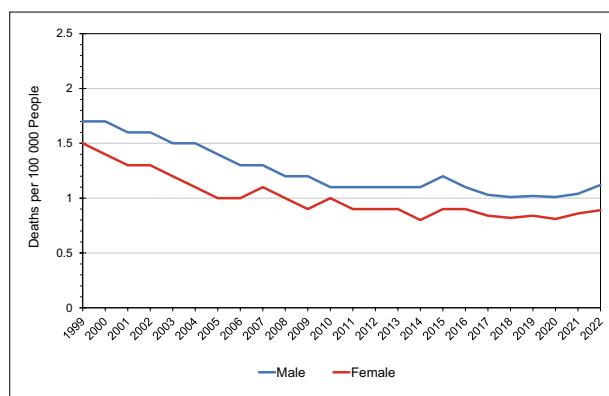
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>152</sup>



**Chart 17-1. Trends in age-adjusted death rates attributable to CCDs, United States, 1999 to 2022.**

CCD indicates congenital cardiovascular defect.

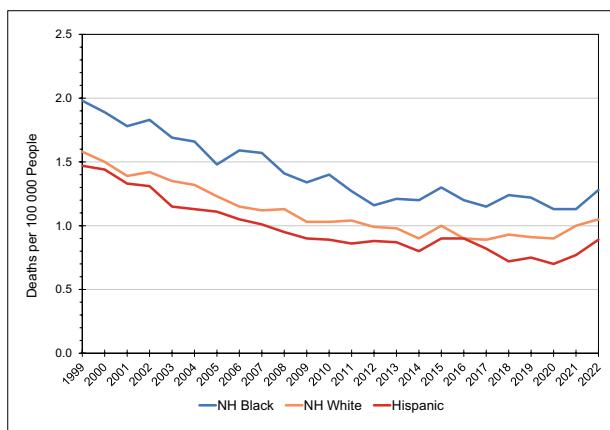
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>96</sup>



**Chart 17-3. Trends in age-adjusted death rates attributable to CCDs, by sex, United States, 1999 to 2022.**

CCD indicates congenital cardiovascular defect.

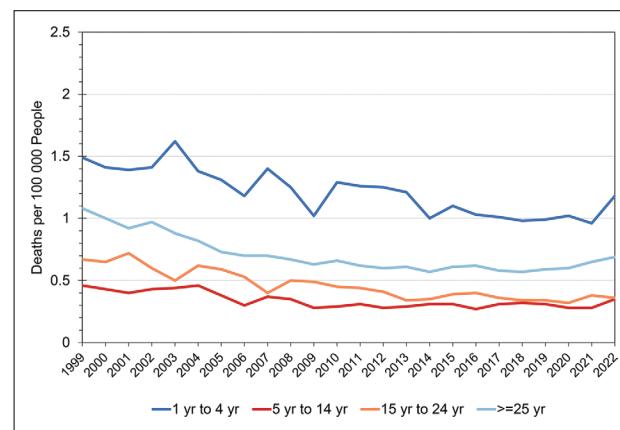
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>96</sup>



**Chart 17-2. Trends in age-adjusted death rates attributable to CCDs, by race and ethnicity, United States, 1999 to 2022.**

CCD indicates congenital cardiovascular defect; and NH, non-Hispanic.

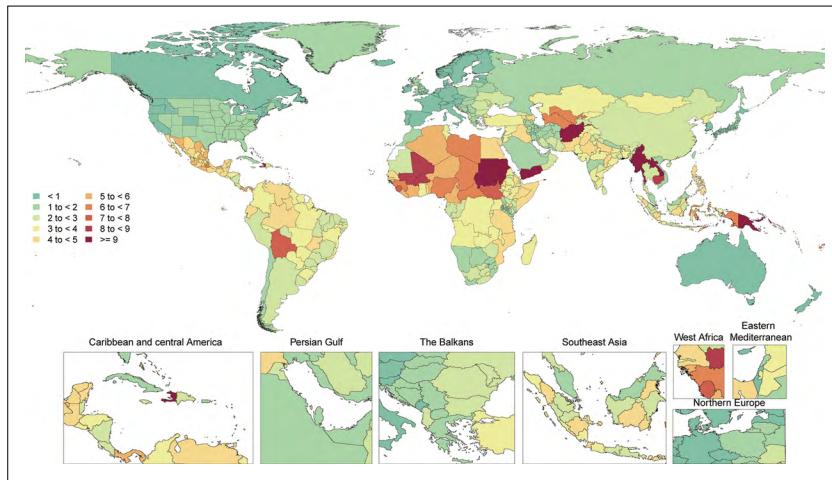
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>96</sup>



**Chart 17-4. Trends in age-specific death rates attributable to CCDs, by age at death, United States, 1999 to 2022.**

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>96</sup>

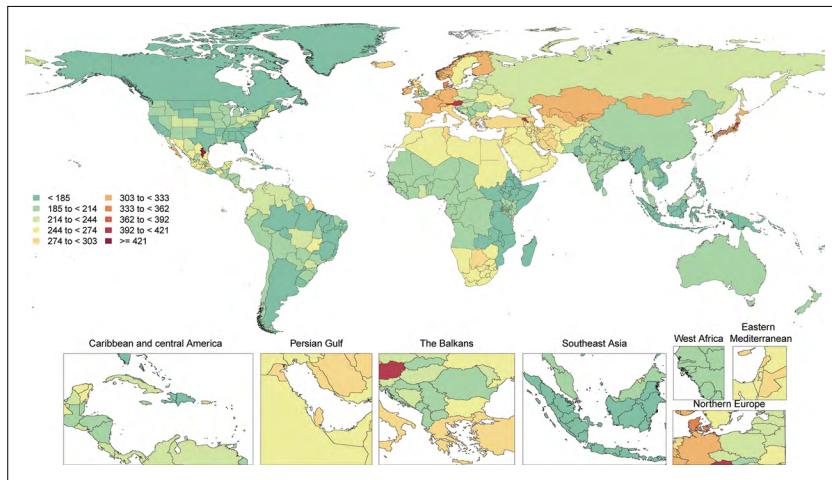


**Chart 17-5. Age-standardized global mortality rates of congenital heart anomalies per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>152</sup>



**Chart 17-6. Age-standardized global prevalence rates of congenital heart anomalies per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

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## 18. DISORDERS OF HEART RHYTHM

See Table 18-1 and Charts 18-1 through 18-16

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### Arrhythmias (Disorders of Heart Rhythm)

2022, United States: Underlying cause mortality—57 725. Any-mention mortality—659 234.

2021, United States: Hospital discharges—604 679.

### Bradyarrhythmias

**ICD-9 426.0, 426.1, 427.81; ICD-10 I44.0 to I44.3, I49.5**

2022, United States: Underlying cause mortality—1700. Any-mention mortality—10 251.

2021, United States: Hospital discharges—98 230.

### 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

- Mobitz II second-degree atrioventricular block is rare in healthy individuals (<0.003%),<sup>4</sup> whereas Mobitz I (Wenckebach) is observed in 1% to 2% of healthy individuals <20 years of age, especially during sleep.<sup>5</sup> In a population-based sample of Chinese adults (N=15 181 402), the age- and sex-standardized prevalence of second-degree atrioventricular block was reported as 0.18% (95% CI, 0.17%–0.18%) but was not further classified as Mobitz I or II.<sup>6</sup>

##### Third-Degree or Complete Heart Block

- The prevalence of complete (third-degree) atrioventricular block is low. The prevalence was 0.11% in a

The 2025 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 2025. 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.

Swedish population-based sample (N=6 113 761).<sup>7</sup> The age- and sex-standardized prevalence of third-degree heart block in a population-based sample of Chinese adults (N=15 181 402) was 0.04% (95% CI, 0.03%–0.04%).<sup>6</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 ≥80 years of age.<sup>8</sup> In a larger Brazilian cohort (N=1 557 901), the prevalence of complete atrioventricular block was far less (0.04%).<sup>4</sup>
- In a post hoc analysis of the LOOP randomized trial, high-grade atrioventricular block was identified in 115 of 6004 trial participants, all of whom were ≥70 years of age and had hypertension, diabetes, HF, or prior stroke.<sup>9</sup>
- Atrioventricular block of varying degrees is reported in 8.6% of patients hospitalized with acute COVID-19 infection.<sup>10</sup> The prevalence appears higher in Asia (22.7%) than in Europe (8.1%) and North America (7.0%).

#### Risk Factors

- Sex and race and ethnicity may impart varying risk. In individuals from MESA (N=1252) without recognized CVD or CVD risk factors, PR-interval reference ranges in individuals ≥65 years of age were reported as 176 milliseconds (32 milliseconds) in males and 162 milliseconds (22 milliseconds) in females of White race; 178 milliseconds (31 milliseconds) in males and 160 milliseconds (19 milliseconds) in females of Black race; and 162 milliseconds (17 milliseconds) in males and 163 milliseconds (18 milliseconds) in females of Hispanic ethnicity.<sup>11</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>5</sup>
- Long sinus pauses and atrioventricular block can occur during sleep apnea, which may be reversible with treatment of the condition.<sup>12</sup> In a meta-analysis of 10 studies (N=1 077), the estimated prevalence of daytime atrioventricular nodal disease in individuals with sleep apnea was 6.07% (95% CI, 2.53%–13.87%) and nighttime prevalence (11 studies, N=2 177) was 9.94% (95% CI, 3.96%–22.82%).<sup>12</sup>
- In multivariable-adjusted analysis including adjustment for competing risk, a full sibling with a history of complete atrioventricular block is associated with a 3-fold increased risk of the condition (HR, 2.91 [95% CI, 2.43–3.49]). In contrast, the risk is 1.5-fold

increased in those with a half-sibling with the condition (HR, 1.51 [95% CI, 0.56–4.10]).<sup>7</sup>

- In a Finnish population-based cohort, risk factors for complete atrioventricular block were older age (HR per 5-year increment, 1.34 [95% CI, 1.16–1.54]), male sex (HR, 2.04 [95% CI, 1.19–3.45]), history of MI (HR, 3.54 [95% CI, 1.33–9.42]), and history of HF (HR, 3.33 [95% CI, 1.10–10.09]).<sup>13</sup> Modifiable risk factors were hypertension (HR per 10–mm Hg increase in SBP, 1.22 [95% CI, 1.10–1.34]) and fasting glucose (HR per 20–mg/dL increase, 1.22 [95% CI, 1.06–1.49]).

### Complications

- In the LOOP study, which enrolled individuals 70 to 90 years of age without AF, a PR interval with a duration <120 or >200 milliseconds was associated with an HR of 1.46 (95% CI, 1.14–1.86) for the development of AF.<sup>14</sup>
- In a population-based Finish cohort, a PR interval with duration >220 milliseconds was associated with 3-fold increased risk of SCD (HR, 3.23 [95% CI, 1.88–5.54]), which was attenuated with inclusion of additional electrocardiographic variables (HR, 2.10 [95% CI, 1.20–3.68]).<sup>15</sup>
- 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>16</sup>

## Sinus Node Dysfunction

### Prevalence and Incidence

- In a post hoc analysis of the LOOP randomized trial, SND was identified in 270 of 6004 trial participants, all of whom were ≥70 years of age and had hypertension, diabetes, HF, or prior stroke.<sup>9</sup>
- Bradycardia (including SND) has been reported in 12.8% of patients hospitalized with acute 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>10</sup>
- A survey of 3846 patients hospitalized with acute COVID-19 infection at 2 London institutions revealed only 6 patients requiring permanent pacemaker implantation (4 implantations were indicated for Mobitz II 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, particularly degenerative fibrosis of sinus nodal tissue) or extrinsic (caused by depression of sinus node function by external factors such as drugs or autonomic influences).<sup>18</sup>
- In the CHS and ARIC studies, factors associated with incident SND included White race versus Black race (Black participants: HR, 0.59 [95% CI, 0.37–0.98]), higher BMI, height, prevalent hypertension, lower heart rate, right bundle-branch block, NT-proBNP, cystatin C, and history of a major cardiovascular event.<sup>19</sup>

### Family History and Genetics

- Bradycardia and atrioventricular block have a heritable component. Data from the Danish Civil Registry, including 4648204 individuals of whom 26880 patients received a first-time pacemaker because of atrioventricular block, showed that the adjusted rate ratio for atrioventricular block was 2-fold higher than the general population if an individual had a first-degree relative who received a pacemaker for atrioventricular block (RR, 2.1 [95% CI, 1.8–2.5]).<sup>20</sup>
- 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>21</sup> *SCN5A*,<sup>22</sup> *RYR2*,<sup>23</sup> *KCNJ3*,<sup>24</sup> and *KCNJ5*<sup>25</sup>) and variants in *ANK2*<sup>26</sup> and *TRPM4*<sup>27</sup> have been associated with SND in families and sporadic cases with severe forms of disease.
- An examination of the diagnostic yield of targeted genetic screening with a panel of 102 genes associated with inherited cardiac diseases among young patients (<50 years of age) who received a pacemaker for atrioventricular block of unknown cause showed that 5% of the 226 patients included in the study harbored a pathogenic/likely pathogenic variant in genes associated with atrioventricular block.<sup>28</sup>

### Complications

- A large (N=1 692 157) 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>29</sup>

## SVT (Excluding AF and Atrial Flutter)

### ICD-9 427.0; ICD-10 I47.1

2022, United States: Underlying cause mortality—251. Any-mention mortality—2539.

2021, United States: Hospital discharges—37 065.

### Prevalence, Incidence, and Risk Factors

- Analysis of health claims data (IBM MarketScan Commercial Research database) from 2008 to 2016 identified the prevalence of documented SVT (including AF/atrial flutter) as 428.9 (95% CI, 418.0–440.1) per 100 000 individuals in females and 227.2 (95% CI, 218.9–235.8) in males.<sup>30</sup> An analysis conducted in an integrated health care delivery system from 2010 to 2015 reported the prevalence of SVT as 140.2 (95% CI, 100.1–179.2) per 100 000 individuals and the incidence as 72.7 (95% CI, 52.5–91.8) per 100 000 individuals.<sup>31</sup> SVT in both studies was more common in females than males.
- An analysis of the nationally representative Nationwide Emergency Department Sample from 2016 to 2018 (N=20.6 million) identified that SVT (excluding AF/atrial flutter) accounted for 2.4% of ED visits in females and 1.5% in males.<sup>32</sup>
- A global registry of acute COVID-19 infections reported that 9.7% of patients hospitalized with acute COVID-19 infection had SVTs other than AF or flutter.<sup>10</sup> The prevalence of SVT was reported as 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>33</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 in 60 genes. Variants were present predominantly in the ion channel genes such as sodium (*SCN1A*, *SCN2B*, *SCN3A*, *SCN4A*, *SCN5A*, *SCN8A*, *SCN9A*, and *SCN10A*) and calcium (*RYR2*, *RYR3*, *CACNB2*, *ATP2A2*, *CACNA1C*, *CACNA1D*, *CACNA1I*, and *CACNA1G*) handling genes and *HCN1–4*, which has been associated with sinoatrial nodal dysfunction.<sup>34</sup>
- A European ancestry–based GWAS meta-analysis for atrioventricular nodal reentry tachycardia, including 2011 individuals with atrioventricular nodal reentry tachycardia and 316 815 control subjects, identified loci within or near cardiomyocyte genes (*TTN*, *MYH6*, *NKX2–5*) as associated with atrioventricular nodal reentry tachycardia.<sup>35</sup>
- Patients with arrhythmogenic right ventricular cardiomyopathy can often present with ventricular arrhythmias. The Clinical Genome Resource Gene Curation Expert Panel appraised the 26 genes reportedly associated with arrhythmogenic right ventricular cardiomyopathy 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 arrhythmogenic right ventricular cardiomyopathy.<sup>36</sup>

### Complications

- 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>37</sup>
- In a Swedish study of 214 patients (51% females) with paroxysmal SVT undergoing ablation, females had a longer history of symptomatic arrhythmia ( $16.2 \pm 14.6$  years versus  $9.9 \pm 13.1$  years), were more likely to report not being taken seriously when consulting for their symptoms (17% versus 7%), and were more symptomatic after 6 months of ablation than males.<sup>38</sup>

### Types of SVT

- Individuals with SVT (N=2260) in a registry in Singapore from 2010 to 2018 had a mean age of  $45 \pm 18$  years. The most common SVT was atrioventricular nodal reentry (57%) followed by atrioventricular reentry (37%) and atrial tachycardia (6%). Generalizability may be limited because all individuals included in the registry underwent catheter ablation.<sup>39</sup>
- In children, atrioventricular reentrant tachycardia has been identified as the most common SVT mechanism (66%–68% of SVT cases), and the remainder of the patients had predominantly atrioventricular nodal reentrant tachycardia (24%–32%).<sup>40,41</sup>

### WPW Syndrome

#### Prevalence

- WPW syndrome refers to the presence of ventricular preexcitation on the ECG combined with a related arrhythmia (SVT). A WPW electrocardiographic pattern (ventricular preexcitation) was observed in 44 of 34 965 adults in a population-based Chinese cohort. In males, the prevalence was 0.14% in those 20 to 44 years of age, 0.04% in those 45 to 59 years of age, and 0.02% in those  $\geq 60$  years of age. In females, the prevalence was 0.12%, 0.04%, and 0.05% in these age groups, respectively.<sup>42</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>43</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>44</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 referents 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>45</sup>
- Asymptomatic adults with ventricular preexcitation appear to be at no increased risk of sudden death compared with the general population.<sup>44</sup> Although there are rare exceptions, the majority of patients who experience cardiac arrest in association with WPW have had symptomatic SVT.
- An administrative health claims analysis quantified the prevalence of WPW syndrome in children (1–18 years of age) as 0.03% (8733/26684581) over a median follow-up 1.6 years (interquartile range, 0.7–2.9 years).<sup>46</sup> Of those without CHD or cardiomyopathy, the incidence of a life-threatening event (defined as VF or cardiac arrest) was 0.8 events per 1000 PY.
- A multicenter international survey of 1589 individuals ≤21 years of age (mean, 13 years of age) with preexcitation identified that 15% had nonpersistent (intermittent) preexcitation.<sup>47</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**

2022, United States: Underlying cause mortality—28936. Any-mention mortality—233 966.

2021, United States: Hospital discharges—442909.

#### **Prevalence**

#### **(See Chart 18-1)**

- Prevalence of AF in the United States is estimated to increase from ≈5.2 million in 2010 to 12.1 million in 2030.<sup>48</sup> An analysis of 5 medical claims datasets used data from 2012 to 2017 to estimate the prevalence of AF in 2015 in the United States as 6.6 million individuals.<sup>49</sup>
- The prevalence of AF in Greenland in 2022 was estimated from electronic health records and

prescription-based data and determined as 1.8% (95% CI, 1.6%–1.9%) in males and 1.0% (95% CI, 1.3%–1.5%) in females. In those age ≥70 years, the prevalence increased to 11.9% (95% CI, 10.3%–13.6%) and 10.1% (95% CI, 8.6%–11.8%), respectively.<sup>50</sup>

- In an integrated regional health care system, the incidence of AF increased from 4.74 (95% CI, 4.58–4.90) per 1000 PY 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>51</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 18-1).<sup>52</sup>
- An analysis of Medicare data identified the annual prevalence of AF among American Indian and Alaska Native beneficiaries from 2015 to 2019 as stable, being 9.4% in 2015 and 9.3% in 2019.<sup>53</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>54</sup>
- Although the prevalence of undiagnosed AF is unknown, investigators used data from 2015 derived from 5 US medical claims datasets to estimate that 591 000 of ≈5.6 million cases, ie, 11%, were undiagnosed.<sup>49,55</sup>

#### **Incidence**

- Comparison of AF incidence across studies is challenged by differing methods with regard to population studied, restriction by age or comorbidity, and statistical approaches to population-based standardization.
- A secondary analysis of a trial conducting screening for AF in at-risk older adults determined that the incidence of AF among 14 960 individuals was 23.7 per 1000 PY (95% CI, 21.0–26.7).<sup>56</sup> AF incidence increased with age (14.2 per 1000 PY at 65–69 years of age to 50.8 per 1000 PY at ≥85 years of age).
- 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 PY during this 10-year observation period.<sup>54</sup>
- A population-based study in England determined that incident AF increased from 247 per 100 000 PY in 1998 to 322 per 100 000 PY in 2017 in

age- and sex-standardized models, yielding an aIRR of 1.30 (95% CI, 1.27–1.33).<sup>57</sup> An analysis of the California State HCUP databases reported that the incidence of AF in American Indian people in the state of California was similar to that in White people and higher than in Black people, Asian people, and Hispanic people.<sup>58</sup>

### Lifetime Risk and Cumulative Risk

(See Chart 18-2)

- In the ARIC study, the lifetime risk of AF was estimated as 36% (95% CI, 32%–38%) in White males, 30% (95% CI, 26%–32%) in White females, 21% (95% CI, 13%–24%) in Black males, and 22% (95% CI, 16%–25%) in Black females.<sup>59</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>60</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>61</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>62</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 18-2).<sup>63</sup>

### Secular Trends

- In an integrated health care system, standardized AF incidence rates increased from 4.74 (95% CI, 4.58–4.90) cases per 1000 PY in 2006 to 6.82 (95% CI, 6.65–7.00) cases per 1000 PY in 2018. The foremost increase in incidence was in those ≥85 years of age.<sup>51</sup> From 2006 to 2018, individuals with AF were more likely to have high BMI (1351/3389 [39.9%] in 2006–2008 versus 4504/9214 [48.9%] in 2015–2018), hypertension (2764 [81.6%] in 2006–2008 versus 7937 [86.1%] in 2015–2018), and ischemic stroke (328 [9.7%] in 2006–2008 versus 1455 [15.8%] in 2015–2018) but less likely to have CAD (1533 [45.2%] in 2006–2008 versus 3810 [41.4%] in 2015–2018). Incidence rates of AF increased in all diagnostic settings and priority pairings.

- 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 PY). 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>54</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>64</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>65</sup>

### Risk Factors

- The highest PAF for AF was for hypertension followed by BMI, smoking, cardiac disease, and diabetes in ARIC. A large health claims analysis conducted in Japan of individuals 20 to 75 years of age (N=2 597 441, spanning 2005–2020) compared the effect of age on AF risk over 3.3±2.5 years of follow-up. In younger individuals (20–49 years of age), the modifiable risk factors of obesity, WC, hypertension, and diabetes were associated with greater risk than in those 50 to 59 or 60 to 75 years of age. For example, in multivariable-adjusted analysis, diabetes in individuals 20 to 49 years was associated with an HR of 1.35 (95% CI, 1.18–1.55) for incident AF compared with 1.10 (95% CI, 1.01–1.21) and 0.93 (95% CI, 0.84–1.03) in those 50 to 59 and 60 to 75 years of age, respectively.<sup>66</sup>
- An analysis in the FHS related electrocardiographic age (determined by deep neural networking to estimate chronological age from the electrocardiogram) to AF.<sup>67</sup> In 9877 FHS participants with 34 948 ECGs, every 10-year increase of electrocardiographic age was associated with 23% increase in AF risk (HR, 1.23 [95% CI, 1.17–1.29]).

### BP and Hypertension

- In a single-center study (N=47 772), SBP >140 mmHg was associated with increased risk of AF in Black individuals (HR, 1.14 [95% CI, 1.03–1.27]) and Hispanic individuals (HR, 1.18 [95% CI, 1.06–1.31]) but not NH White individuals (HR, 0.92 [95% CI, 0.83–1.02]) over 3.3 mean years of follow-up.<sup>68</sup> The PAR (percent) for SBP >140 mmHg and the development of AF was 4.9 (95% CI, 1.3–8.2), 4.6 (95% CI, 1.8–7.2), and –3.0 (95% CI, –7.0 to 0.5), respectively.
- 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– mmHg increase in SBP and DBP was associated with an increased risk of 4.3% and 4.6%, respectively, of incident AF.<sup>69</sup>

- In a systematic review of studies evaluating the relationship between hypertension and AF, the summary RR was 1.50 (95% CI, 1.42–1.58;  $P=98.1\%$ ; n=56 studies) for people with hypertension compared with those without hypertension (1 080 611 cases, 30 539 230 participants).<sup>70</sup> In 37 studies, a 20-mmHg increase in SBP was associated with 1.18 (95% CI, 1.16–1.21) and a 10-mmHg increase in DBP with a 1.07 (95% CI, 1.03–1.11) increased risk of AF. The dose-response curve between SBP and AF was linear.

### 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>71</sup>
- The association of weight loss and bariatric surgery on AF and its subtypes has been studied in observational studies and clinical trials.<sup>72</sup> In a limited-sized cohort (N=220) of morbidly obese individuals, reversal of AF type occurred in 92 individuals (71%) who underwent gastric bypass compared with 36 (56%) who underwent sleeve gastrectomy and 13 (50%) who received gastric banding.
- In a large, prospective Norwegian cohort (N=43 602), individuals with BMI 25.0 to 29.9 or ≥30 kg/m<sup>2</sup> had increased risk of AF over a mean 8.1-year follow-up (HR, 1.18 [95% CI, 1.03–1.35] and HR, 1.59 [95% CI, 1.37–1.84], respectively) than those with BMI <25.0 kg/m<sup>2</sup>.<sup>73</sup> High levels of PA slightly attenuated the association of obesity and AF.
- 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>74</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>75</sup>

- Genetic associations of obesity have been related to risk of AF. 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>76</sup> A mendelian randomization study summarized data from 6 GWASs to relate SNPs associated with adult and childhood obesity, waist-to-hip ratio, childhood BMI, and birth weight to AF.<sup>77</sup> The analysis concluded that 1-SD increases in adult obesity, childhood BMI, and birth weight were associated with 13%, 18%, and 26% higher risks of AF.

### 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/d 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>78</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>79</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>80</sup>
- A meta-analysis of 4 studies determined that individuals with type 1 diabetes had a higher risk of AF (HR, 1.30 [95% CI, 1.15–1.47]) than referents without type 1 diabetes.<sup>81</sup> Subgroup analyses determined that females had an increased AF risk (HR, 1.50 [95% CI, 1.26–1.79]) compared with males and those <65 years of age had increased risk (HR, 1.45 [95% CI, 1.21–1.74]) compared with those ≥65 years of age.
- 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>82</sup>

## Activity and Exercise (See Chart 18-3)

- A meta-analysis of 15 studies ( $N=1\,821\,422$ ) identified an inverse nonlinear relation between weekly PA and AF risk.<sup>83</sup> Results were most robust describing the decreased risk of AF in individuals exercising up to 50 METs of task-hours per week; data are limited for higher levels of PA.
- 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 18-3).<sup>84</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>85</sup> A second meta-analysis of 11 studies ( $N=1\,901\,833$ ) concluded that cross-country skiing was not associated with increased risk of AF (RR, 0.93 [95% CI, 0.80–1.07]), noting significant heterogeneity across studies ( $P=94.0\%$ ).<sup>86</sup>
- A meta-analysis of 23 observational studies included 1 930 725 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 the most physically active females had a decreased risk (RR, 0.91 [95% CI, 0.84–0.99]) for AF.<sup>87</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>88</sup>
- Individuals with congenital HD are at increased risk of AF. In an analysis in Sweden including 21 982 individuals with congenital HD and 21 9816 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>89</sup> By 42 years of age,  $\approx 8\%$  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>90</sup> CKD,<sup>91</sup> and moderate or heavy alcohol consumption.<sup>92</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  $\geq 2$  drinks with an OR of 3.58 (95% CI, 1.63–7.89) relative to the absence of alcohol use.<sup>93</sup> In an n-of-1 clinical trial ( $N=446$ ), those identifying alcohol as a trigger for AF ( $n=43$ ) reported 1.8-fold increased odds of AF with alcohol exposure (OR, 1.77 [95% CI, 1.20–2.69]).<sup>94</sup>
  - In a meta-analysis of 9 observational studies ( $N=5436$ ), moderate to high alcohol use was associated with increased risk of AF recurrence after catheter ablation (OR, 1.45 [95% CI, 1.06–1.99]) compared with no or little alcohol use.<sup>95</sup>
- Sleep disorders:
  - Meta-analyses have consistently reported the association between the sleep apnea–hypopnea syndrome and a 1.4-fold increased risk of AF. After adjustment for confounders, 2 meta-analyses, both of 8 studies, reported that sleep apnea–hypopnea is associated with an RR of 1.40 (95% CI, 1.12–1.74)<sup>96</sup> and 1.38 (95% CI, 1.24–1.54)<sup>97</sup> for AF.
  - 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>98</sup>
  - A meta-analysis of 6 studies identified a significant association between short sleep duration (defined as  $\leq 6$  h/night in 5 studies and  $\leq 5$  h/night in 1 study) and AF (RR, 1.06 [95% CI, 1.02–1.11]).<sup>99</sup> Further mendelian randomization analysis relating genetic loci associated to short sleep duration did not determine a relation to AF risk (OR, 0.98 [95% CI, 0.88–1.09]).
  - In a prospective, urban-dwelling Japanese cohort ( $N=6898$ ), short sleep ( $\leq 6$  hours) and irregular sleep (eg, night-shift work) were associated with increased risks of AF (HR, 1.34 [95% CI, 1.01–1.77] and HR, 1.63 [95% CI, 1.16–2.30], respectively) compared with moderate sleep (7 hours) in multivariable-adjusted analyses over a median of 14.5 years of follow-up.<sup>100</sup>
- Air pollution  
(See Charts 18-4 and 18-5):
  - A systematic review and meta-analysis of 18 studies reported short-term and long-term

associations of air pollution with AF.<sup>101</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.

- A nationwide, time-stratified case-crossover study using air pollution data from 322 cities in China observed an increased incidence of symptomatic AF and SVT in the 24 hours after higher pollutant exposure (Chart 18-4).<sup>102</sup> The change in the odds of onset of symptomatic AF associated with a 10- $\mu\text{g}/\text{m}^3$  (1 mg/m<sup>3</sup> for CO) increase in air pollutant concentrations during lag 0 to 24 hours was 0.6% (95% CI, 0.2%–1.1%) for PM2.5, 1.6% (95% CI, 0.8%–2.4%) for NO<sub>2</sub>, and 5.7% (95% CI, 1.8%–9.8%) for CO.
- 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/d) was not associated with AF risk (HR, 0.79 [95% CI, 0.49–1.28]) compared with no or rare coffee ingestion.
- A follow-up examination of the REGARDS study (n=8977) did not identify an association between Mediterranean diet score (OR, 1.03 [95% CI, 0.95–1.11] per SD) or plant-based dietary pattern (OR, 1.03 [95% CI, 0.94–1.12] per SD) and AF.<sup>104</sup> In addition, less healthy eating was not associated with incident AF during an average 9.4-year follow-up.
- An analysis of the UK Biobank (N=201 856) combined dietary recall of fruit juice and soft drink consumption with the PRS for AF developed in the cohort (Chart 18-5).<sup>105</sup> Over a median of 9.9-years follow-up, consumption of >2 L/wk of SSBs and ASBs was associated with increased risk of AF in multivariable-adjusted analyses including demographic, social, clinical, and genetic risk factors (HR, 1.10 [95% CI, 1.01–1.20], 1.20 [95% CI, 1.10–1.31], respectively) compared with nonconsumption of SSBs or ASBs. Consumption of >2 L/wk of fruit juice was not associated with increased risk of AF (HR, 1.05 [95% CI, 0.96–1.14]) compared with nonconsumption. However, consumption of ≤1 L/wk of fruit juice was associated with reduced risk of AF (HR, 0.92 [95% CI, 0.87–0.97]) compared with nonconsumption.

- 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>106</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 ≥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>107</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>108</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>109</sup>
- AF frequently occurs secondary to other comorbidities.
  - Among 11 239 patients undergoing isolated CABG at 5 sites in the United States between 2002 and 2010, the risk-adjusted incidence of AF was 33.1%, which did not vary significantly over the observation period.<sup>110</sup>
  - A secondary analysis of the PARAGON-HF trial (N=4776) identified that 1552 had AF at trial enrollment. Those with AF at enrollment had 1.3-fold increased risk (RR, 1.31 [95% CI, 1.11–1.54]) of HF hospitalization, the primary outcome of the trial, compared with those without AF.<sup>111</sup>
  - A meta-analysis of 13 studies (N=52 959) reported that new-onset AF has been observed in 10.9% (95% CI, 7.2%–15.3%) of patients undergoing noncardiac general surgery.<sup>112</sup>
  - A meta-analysis of 13 studies (N=225 841) determined that new-onset AF during sepsis was associated with ≈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>113</sup>
  - AF is a common occurrence in hospitalized patients with acute COVID-19 infection. A meta-analysis of 14 studies (N=17 435) 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>114</sup> An international registry of patients hospitalized with COVID-19 reported that AF was the most common arrhythmia in COVID cases, occurring in 509 of 827 events (61.5%).<sup>10</sup> A meta-analysis of 12 studies (N=13 124) identified that new-onset AF during COVID-related hospitalization was associated with increased in-hospital mortality (RR, 1.86 [95% CI, 1.54–2.24]),<sup>115</sup> albeit limited by significant heterogeneity ( $P=72\%$ ).

- Limited literature has investigated the associations between cancer and its treatment with risk of AF. A random-effects meta-analysis of 19 anticancer drugs used as monotherapy included 191 clinical trials (47.1% randomized) of 16 anticancer drugs used in 26 604 individuals.<sup>116</sup> Summary annualized AF incidence rates ranged from 0.26 (95% CI, 0.11–0.63) to 4.92 (95% CI, 2.91–8.31) per 100 PY in those receiving chemotherapy and 0.25 per 100 PY (95% CI, 0.10–0.65) in those in the placebo arms. 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>117</sup> A meta-analysis of 6 studies (N=533 514) 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>118</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

### See Chart 18-6

- Study of social determinants and AF remains limited.<sup>119</sup>
- In an analysis of a large regional health care system, individuals (N=28 858) 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>120</sup>
- An administrative data analysis of individuals with AF in Ontario, Canada, determined that residence in the fifth quintile of neighborhood-based material deprivation was associated with increased 1-year risk of death (HR, 1.16 [95% CI, 1.13–1.20]), stroke (HR, 1.16 [95% CI, 1.07–1.27]), bleeding (HR, 1.16 [95% CI, 1.13–1.25]), and HF (HR, 1.14 [95% CI, 1.11–1.18]) compared with residence in the first quartile.<sup>121</sup>
- An analysis of the Nationwide Readmission Database using data from 2010 to 2019 determined that individuals categorized as having health-related social needs according to *ICD* coding were less likely to

undergo catheter ablation than those without such coding.<sup>122</sup> The analysis may be limited by misclassification and underreporting bias in that there were 3 650 995 hospitalizations for AF during the study time frame with only 1.2% (95% CI, 1.2%–1.3%) having health-related social needs according to *ICD* coding, consequently likely underestimating the prevalence of health-related social needs.

- Further analysis of administrative data in Ontario, Canada, of individuals with AF determined that residence in the fifth quintile of neighborhood-based material deprivation was associated with decreased 1-year likelihood of primary care visits (HR, 0.91 [95% CI, 0.89–0.92]), cardiology visits (HR, 0.84 [95% CI, 0.82–0.86]), receipt of echocardiography (HR, 0.97 [95% CI, 0.96–0.99]), or ambulatory electrocardiographic monitoring (HR, 0.89 [95% CI, 0.87–0.91]). The authors concluded that universal health care systems may still have substantial disparities in health care access.<sup>121</sup>
- An analysis of an administrative claims study of individuals with prevalent AF (N=336 736) 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>123</sup>
- A claims-based analysis (N=28 779) related social measures derived at the 3-digit US zip code level to 180- and 360-day adherence to oral anticoagulation from 2016 to 2020 (Chart 18-6).<sup>124</sup> The analysis determined that geospatially derived, community-based estimate of health literacy, summarized as a social risk score, was associated with decreased anticoagulation persistence at 180 days (OR, 0.80 [95% CI, 0.76–0.83]), where persistence was calculated as the number of days for which an individual had claims for an oral anticoagulant prescription. The analysis further reported that health literacy was associated with decreased likelihood of a proportion of days covered of ≥0.80 (OR, 0.81 [95% CI, 0.76–0.87]). The analysis is limited by use of the 3-digit zip code.
- In an analysis in the community-based ARIC study, AF incidence decreased with progressively increased categories of income and education.<sup>59</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 of 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 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 ( $\le \$19\,999/y$ ) had 2.0-fold greater hospitalization risk (OR, 2.11 [95% CI, 1.08–4.09]) compared with those in the highest income category ( $\ge \$100\,000/y$ ).<sup>125</sup>
- A Danish population-based study of individuals with incident AF who underwent catheter ablation (N=9728) examined social factors and AF recurrence after ablation.<sup>126</sup> Lower education (HR, 1.09 [95% CI, 1.02–1.17]), income (HR, 1.14 [95% CI, 1.06–1.22]), and living alone (HR, 1.07 [95% CI, 1.00–1.13]) were associated with AF recurrence during a median 1.4-year follow-up (quartile 1–3, 0.4–6.3 years) after ablation. These associations were no longer significant after adjustment for comorbid conditions and treatment with antiarrhythmic medications.
- A meta-analysis of 5 studies (N=132 431) determined that individuals of Black race were less likely to receive oral anticoagulation than those of White race (OR, 0.86 [95% CI, 0.75–0.98]).<sup>127</sup> Heterogeneity of the pooled estimate was high ( $P=85\%$ ) with further analysis suggesting that the heterogeneity was attributable to type of anticoagulant (ie, warfarin or DOAC); differences by race were not observed in studies reporting warfarin use, whereas individuals of Black race were less likely compared with those of White race in studies reporting DOAC use.

### Risk Prediction of AF

- Investigation of AHA's Life's Essential 8 in relation to AF remains limited. Several studies have examined CVH as determined by Life's Simple 7 in relation to AF:
  - 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 people 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>128</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>129</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>130</sup>

- A similar analysis in the MESA cohort reported a 27% lower risk of AF over a median follow-up of 11.2 years (interquartile range, 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>131</sup>
- ARIC,<sup>132</sup> FHS,<sup>133</sup> and WHS<sup>134</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, LA enlargement), diabetes, BP (SBP and hypertension treatment), and presence of CVD (CHD, HF, valvular HD). In contrast, the HARMS<sub>2</sub>-AF score had an AUC of 0.782 (95% CI, 0.775–0.789) in the UK Biobank for 5-year risk prediction of AF and validation in FHS with an AUC of 0.757 (95% CI, 0.735–0.779).<sup>135</sup>
- A CHARGE-AF risk prediction model for AF has been validated in a US multiancestry patient cohort,<sup>136</sup> in MESA,<sup>137</sup> in a UK cohort (EPIC Norfolk),<sup>138</sup> in a post-CABG cohort,<sup>139</sup> and in a large nationwide primary care database in the Netherlands.<sup>140</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>141</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 FHS examining lifetime risk of AF identified that the prevalence of AF risk factors increased gradually with age. At an index age of 55 years, lifetime AF risk was 37.0% (95% CI, 34.3%–39.6%).<sup>63</sup> Lifetime AF risk was 23.4% (95% CI, 12.8%–34.5%) for those with an optimal risk profile, 33.4% (95% CI, 27.9%–38.9%) in those with a borderline risk profile, and 38.4% (95% CI, 35.5%–41.4%) in those with an elevated risk profile. At index ages of 65 and 75 years, the gradient of AF lifetime risk was similar.

### 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.
- A meta-analysis reported that atrial high-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>142</sup>

- A meta-analysis of 9 studies (N=42 958) determined that individuals with low atrial high-rate episode burden as detected by an implanted device had an HR of 1.20 (95% CI, 1.03–1.41) for stroke or systemic embolism compared with those without atrial high-rate episodes.<sup>143</sup> In contrast, those with a high burden of atrial high-rate episodes had an HR of 2.52 (95% CI, 1.46–4.37) relative to those without atrial high-rate episodes.

### **Community Screening for Undiagnosed AF**

(See Charts 18-7 and 18-8)

- 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>144</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>145</sup>
- The prevalence of undiagnosed AF in the community is unknown. Using Medicare and commercial claims data, investigators have estimated that in 2009 ≈0.7 million (13.1%) of the ≈5.3 million AF cases in the United States were undiagnosed. Of the undiagnosed AF cases, investigators estimated that 698 900 were undiagnosed, including 535 400 (95% CI, 331 900–804 400) in individuals ≥65 years of age and 163 500 (95% CI, 17 700–400 000) in individuals 18 to 64 years of age.<sup>146</sup>
- A multicenter study conducted in France enrolled individuals (N=336) with palpitations and CHADS<sub>2</sub>-VASC scores ≥2 in males and ≥3 in females to 14-day electrocardiographic monitoring.<sup>147</sup> AF was detected in 14% of the cohort with detection occurring in the first 24 hours of monitoring in 23.4% in whom the arrhythmia was ascertained.
- A single-center study examined duration of monitoring for AF detection after ischemic stroke or TIA in 379 individuals at a median of 63 years of age (interquartile range, 55–73 years).<sup>148</sup> There were 10 cases of AF detected, with 7 in the first 48 hours of monitoring (IR, 1.85% [95% CI, 0.74%–3.81%]; number needed to screen, 54) and 3 additional cases with duration of monitoring from 48 hours to 14 days (IR, 0.83% [95% CI, 0.17%–2.42%]; number needed to screen, 121).
- A multicenter, open-label, randomized trial of individuals ≥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>149</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 (18/434 [4.1%] versus 4/422 [0.9%]; risk difference, 3.2% [95% CI, 1.1%–5.3%]).<sup>149</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>150</sup> Over a median follow-up of 64.5 months (interquartile range, 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 (interquartile range, 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 ≈4% reduced risk for the composite outcome (HR, 0.96 [95% CI, 0.92–1.00]).<sup>151</sup> Post hoc analysis concluded that this screening approach was cost-effective; screening of 1000 older adults resulted in 10.6 (95% CI, –22.5 to 1.4) fewer strokes.<sup>152</sup>
- An artificial intelligence algorithm analyzed 494 042 ECGs, all in sinus rhythm, obtained from 142 310 patients with and without paroxysmal AF.<sup>153</sup> The model had an accuracy of 78.1% (95% CI, 77.6%–78.5%), area under the receiver-operating characteristic curve of 0.87 (95% CI, 0.86–0.87), and area under the precision recall curve of 0.48 (95% CI, 0.46–0.50). In a cohort with an AF prevalence of 3%, the area under the precision recall curve decreased to 0.21 (95% CI, 0.18–0.24). In a cohort with AF prevalence of 30%, this figure increased to 0.76 (95% CI, 0.75–0.78).
- A cluster randomized trial examined point-of-care screening with a single-lead ECG in 16 primary care clinics.<sup>154</sup> Of 30 715 individuals enrolled, 1.72% of 15 393 individuals randomized to screening were diagnosed with AF compared with 1.59% of 15 322 individuals randomized to the control arm at 1-year follow-up (risk difference, 0.13% [95% CI, –0.16% to 0.42%]; Chart 18-7).

- Screening for AF has been evaluated as cost-effective.
    - A meta-analysis of 26 studies determined that population-based (n=13), opportunistic (n=4), targeted (n=6), and mixed-methods screening (n=3) were superior to no screening. However, only 5 studies were categorized as moderate usefulness for policy, and none of the included studies advocated a policy direction on implementation of the results.<sup>155</sup>
    - In Canada's single-payer health care environment, screening for AF with a single-lead ECG was determined to improve health outcomes and cost savings.<sup>156</sup> A model identified that screening 2929 301 individuals identified 127 670 cases of AF and estimated avoidance of 12 236 strokes with a gain of 59 577 QALYs (0.02 per patient) over the lifetime of screened individuals.
    - A post hoc analysis of the STROKESTOP study (N=27 975, all ≥75 years of age, invited to participate in AF screening performed with a handheld ECG for 30 seconds twice daily for 14 days or control) calculated 77 gained life-years and 65 gained QALYs per 1000 individuals invited to the screening group and incremental costs estimated as €1.77 million (\$1.92 million using the average 2023 exchange rate) lower in the screening group.<sup>152</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>157</sup>
    - The US Preventive Services Task Force has concluded that evidence for screening for AF in individuals ≥50 years of age remains lacking.<sup>158</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 ≥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 ≥65 years of age, 926 for 60 to 64 years of age, and 1089 for <60 years of age.<sup>159</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 compared with 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>160</sup>
  - A meta-analysis of 9 RCTs (N=85 209) examining systematic screening, opportunistic screening, and no screening determined that any AF screening (systematic or opportunistic) was associated with higher detection of AF (1.8% versus 1.3%; RR, 2.10 [95% CI, 1.20–3.65]) than no screening.<sup>161</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>162</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 18-8); the threshold varies depending on the presence of other stroke risk factors.<sup>163</sup>

### **Family History and Genetics**

- AF is found to be a common presentation in certain monogenic genetic cardiomyopathies, for example, in individuals with *PRKAG2*- or *TTN*-related cardiomyopathy.<sup>164,165</sup>
- A prospective observational cohort study has noted that among individuals of predominantly European ancestry with early-onset AF (<66 years of age), the prevalence of disease-associated pathogenic/likely pathogenic variants in cardiomyopathy- and arrhythmia-associated genes was 10.1%.<sup>166</sup> The prevalence of the pathogenic/likely pathogenic variants was highest among patients with an AF diagnosed before 30 years of age (≈17%) and was lowest among those diagnosed with AF after 60 years of age (≈7%). Similarly, a study of 227 probands with early AF of African and Hispanic descent showed that 7.0% of the study population

carried a pathogenic/likely pathogenic variant in a curated list of 60 AF genes.<sup>167</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>168</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>169</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>170</sup> Another GWAS of >1 000 000 individuals identified 111 independent genes associated with AF, many of which are near deleterious variants that cause more serious heart defects or near genes important for striated muscle function and integrity.<sup>171</sup>
- Whole-exome/genome sequencing studies have identified rare variants in additional genes associated with AF, including *MYL4*,<sup>172</sup> and loss-of-function variants in *SCN4B* and *KCNA5*, a conserved gene that encodes the voltage-gated Kv1.5 potassium channel.<sup>173,174</sup> Loss-of-function variants in the titin gene have been associated with early-onset AF.<sup>175,176</sup>
- Combinations of these genetic variants for AF are predictive of the 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>62</sup>
- Proteomic studies have identified proteins identified with incident AF. For example, in the ARIC study, 4668 participants were followed up for  $5.7\pm1.7$  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];  $P=2.91\times10^{-45}$  per doubling of NT-proBNP). After further adjustment for medication use and glomerular filtration rate, 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>177</sup>

- It is unclear whether genetic markers of AF could improve risk prediction for AF over models that include only clinical factors.<sup>134</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>178</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>179</sup>
- A multiancestry meta-analysis of GWASs for AF including >1 000 000 individuals led to the discovery of 35 new loci. *IL6R* has been identified as a putative causal gene for AF on the basis of transcriptome-wide association analysis indicating the role of the immune response in the pathogenesis of AF. A GRS developed from the multiancestry GWAS meta-analysis predicted the risk of cardiovascular and stroke mortality. A 1-SD increase in GRS was associated with increased odds of cardioembolic stroke (OR, 1.36 [95% CI, 1.13–1.63]) in individuals without diagnosed AF.<sup>180</sup>
- GWASs also have been conducted with variations 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>181</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>182</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>183</sup>

- A UK Biobank–based analysis including 1546 cases and 41 593 controls examining the contribution of rare and common genetic variants to AF risk revealed that 0.44% of individuals carried rare loss-of-function high-proportion spliced-in variants in the *TTN* gene.<sup>184</sup> Carriers of *TTN* variants had higher odds of AF (OR, 6.15;  $P=3.26\times 10^{-14}$ ).<sup>184</sup> Among *TTN* variant carriers, 14% had AF compared with 9.3% of individuals in the top 0.44% of the AF PRS.<sup>184</sup>
- A multiancestry study using data from the All of Us Research Program, including 38 154 individuals of African ancestry and 105 904 individuals of European ancestry, demonstrated that carrying a high-proportion spliced-in *TTN* truncating variant was associated with a similar increase in the risk of AF in individuals of European (aHR, 1.96 [95% CI, 1.58–2.43]) and African (aHR, 2.42 [95% CI, 1.52–3.85]) ancestry.<sup>185</sup>
- An integrative approach combining genomic, epigenomic, and transcriptomic data led to the identification of 1931 potential AF genes with multiple genes implicated in the development and regulation of cardiac muscle tissue.<sup>186</sup> The integration of multiomics approach yielded a heritability estimate of 18.9% (95% CI, 18.2%–19.5%).
- Functional studies incorporating pluripotent stem cell–derived cardiomyocytes and murine gene-knockout studies demonstrated that the *ZFHX3* gene, a transcription factor encoding gene at the 16q22 locus, is causative in the development of AF. In animal models, loss of *ZFHX3* was associated with changes in action potential duration, conduction velocity, and atrial enlargement compared with the wild-type control.<sup>187</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>188</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>189</sup>
- A meta-analysis of 14 studies (N=1812 422) examined the association of PA with risk of AF in females.<sup>83</sup> The analysis identified that AF risk

reduced progressively with any level of weekly PA. Limitations of the analysis include underrepresentation of studies with individuals exercising 70 METs of task-hours/wk and absence of follow-up of PA assessment.

#### **Secondary Prevention of AF: Observational Data**

- Data support the importance of risk factor modification for secondary prevention of AF recurrence and improved symptoms.
  - Individuals with overweight and obesity 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 ( $0.74\pm 1.3$  versus  $1.05\pm 1.60$ ), cardioversions ( $0.89\pm 1.50$  versus  $1.51\pm 2.30$ ), and ablation procedures ( $0.60\pm 0.69$  versus  $0.72\pm 0.86$ ) 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>190</sup>
- Randomized data supporting the role of CPAP in primary prevention of AF in individuals with SDB are limited, and most attention has focused on secondary prevention.<sup>191,192</sup> In a small, parallel-arm randomized clinical trial (n=109), there was no difference in percent time in AF between intervention participants randomized to CPAP use and those receiving usual care (difference in time in AF between intervention and control,  $-0.6\%$  [95% CI,  $-2.1$  to  $0.9$ ]).<sup>192</sup>
- 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>193</sup>

### **Prevention: Randomized Data**

#### **Primary Prevention of AF: Randomized Data**

- An analysis of SPRINT participants without AF at trial initiation (n=8022) determined that those randomized to the intensive BP-lowering arm (SBP <120 mmHg) had decreased AF risk (HR, 0.74 [95% CI, 0.56–0.98]) over a median 3.8-year follow-up compared with those randomized to the standard BP-lowering arm (SBP <140 mmHg).<sup>194</sup>
- A meta-analysis of individuals with HF enrolled in 6 placebo-controlled trials of SGLT-2 inhibitors (N=9467) reported that those randomized to the SGLT-2 arm had reduced risk of incident AF (RR, 0.62 [95% CI, 0.44–0.87]).<sup>195</sup>
- A meta-analysis of 14 studies (N=2883) observed that pretreatment with statins reduced the risk of post-operative AF (OR, 0.71 [95% CI, 0.60–0.85]) after

cardiothoracic surgery.<sup>196</sup> However, sensitivity analysis excluding studies identified as having bias did not demonstrate that initiation of statins before cardiothoracic surgery was associated with reduced likelihood of postoperative AF (OR, 0.87 [95% CI, 0.71–1.07]).

- A meta-analysis of 8 studies (N=1885) demonstrated that colchicine administration was associated with reduced risk of AF in individuals undergoing cardiac surgery (RR, 0.70 [95% CI, 0.59–0.82]).<sup>197</sup>

### Secondary Prevention of AF: Randomized Data

#### See Chart 18-9

- An Australian multisite, open-label, controlled trial randomized 140 adults who consumed ≥10 drinks of alcohol per week with a history of AF and in sinus rhythm at baseline either to abstain from alcohol or to continue their usual alcohol consumption.<sup>198</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%;  $P=0.01$ ).
- An open-label, parallel-group RCT randomized individuals with PAF and AHI ≥15 to 5 months of treatment with CPAP (n=55) or control (n=54).<sup>192</sup> The adjusted between-group difference in AF burden as measured by loop recorder was −0.63 (95% CI, −2.55 to 1.30).
- RCTs have determined that colchicine does not reduce likelihood of AF recurrence after catheter ablation or noncardiac surgery.<sup>199,200</sup>
- Small trials have examined the effects of exercise and PA in individuals with AF. A multicenter, randomized, open-label trial randomized individuals with AF after cardioversion to intensified pharmacological therapies and cardiac rehabilitation (n=119) or conventional therapy (n=126).<sup>201</sup> At the 1-year follow-up, 75% of intervention participants were in sinus rhythm (determined by 7-day Holter monitoring) compared with 63% of conventional therapy participants (OR, 1.77 [95% CI, 1.02–3.05]). In a second trial, individuals randomized to receive an exercise and PA intervention for 6 months achieved significant improvement in AF symptoms (mean difference, −2.0 [95% CI, −3.7 to −0.3]) at 6 months.<sup>202</sup> The study conducted rhythm monitoring for 4 days at baseline and 6 and 12 months in all participants and reported that randomization to the intervention arm was associated with reduced risk of AF (HR, 0.50 [95% CI, 0.33–0.78]; Chart 18-9).

### Awareness

- A study from Kaiser Permanente in California examined the relationship between AF diagnosis

(2006–2009) and self-report questionnaire data (2010). Of 12517 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>203</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 anti-coagulant 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>204</sup>
- Treatment for subclinical AF (ie, AF duration 6 minutes–24 hours as detected by pacemaker or defibrillator) was evaluated in a double-blind RCT (N=4012) comparing the effectiveness of apixaban with aspirin.<sup>205</sup> After a mean follow-up of  $3.5 \pm 1.8$  years, apixaban was associated with 37% decreased risk of stroke or systemic embolism (HR, 0.63 [95% CI, 0.45–0.88]).
- 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>206</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, there are substantive opportunities to improve oral anticoagulation for stroke prevention in individuals with AF.<sup>207</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>208</sup>
  - An analysis in the PINNACLE registry also reported that receipt of warfarin compared with a DOAC varied significantly by type of

insurance: Patients with military, private, and Medicare insurance were more likely to receive newer anticoagulants than individuals with Medicaid or other insurance.<sup>209</sup>

- A randomized trial tested the effect of an alert embedded in the electronic health record on anti-coagulation prescribing targeting primary care clinicians.<sup>210</sup> In the limited-sized trial ( $N=562$ ), the alert improved anticoagulation therapy (11% [33/314] versus 5% [12/248]; OR, 2.31 [95% CI, 1.17–4.87]).
- A meta-analysis of inappropriate dosing of DOACs ( $N=15$  studies) concluded that underdosing was associated with an increased risk of all-cause mortality (HR, 1.28 [95% CI, 1.10–1.49]) and overdosing with an increased risk of major bleeding (HR, 1.41 [95% CI, 1.07–1.85]).<sup>211</sup> Further analysis ( $N=12$  studies) determined that age, history of bleeding, hypertension, HF, and low creatinine clearance were related to underdosing of DOAC. Underdosing had a null effect on bleeding risk, whereas overdosing was associated with increased risk of major bleeding (HR, 1.41 [95% CI, 1.07–1.85]).
- 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>212</sup>
- The prevalence of individuals with frailty (defined with 5 different measures to identify frailty) with AF has prompted attention toward provision of oral anticoagulation in a population at high risk for stroke and falls or bleeding. A systematic review of frailty included 12 studies ( $N=212\,111$ ) comprising individuals 77 to 85 years of age, of whom 56% were categorized as frail; 52% of individuals categorized as frail received anticoagulation compared with 67% of those categorized as not frail.<sup>213</sup>

### *Disparities in Treatment*

#### (See Chart 18-10)

- Racial differences in access to oral anticoagulation have been identified.
  - 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 individuals and NH White individuals (OR, 1.02 [95% CI, 0.88–1.18]).<sup>214</sup>

- An analysis of the ORBIT-AF II population ( $N=12\,417$ ), of whom 646 (5.2%) were of Black race and 671 (5.4%) were of Hispanic ethnicity, determined in multivariable-adjusted analysis that Black individuals (OR, 0.75 [95% CI, 0.56–0.99]) were significantly less likely to receive oral anti-coagulation than White individuals.<sup>215</sup> This difference was attenuated by adjustment for social and economic factors (OR, 0.78 [95% CI, 0.59–1.04]). The difference between Hispanic and White individuals was not significant.
- An analysis of the GWTG-AFIB registry ( $N=69\,553$ ) determined that Black individuals were less likely than White individuals to be discharged on oral anticoagulation (OR, 0.75 [95% CI, 0.68–0.84]).<sup>216</sup> In 16\,307 individuals with 1-year follow-up data, the risks of bleeding (HR, 2.08 [95% CI, 1.53–2.83]), stroke (HR, 2.07 [95% CI, 1.34–3.20]), and mortality (HR, 1.22 [95% CI, 1.02–1.47]) were higher in Black individuals compared with White individuals.
- In the Florida Puerto Rico AF Stroke Study, a registry of individuals with ischemic stroke and AF ( $N=24\,040$ ), Black individuals were more likely to receive warfarin at hospital discharge after stroke (OR, 1.22 [95% CI, 1.07–1.40]) compared with references of White race.<sup>217</sup> In contrast, Black race was not associated with likelihood of receipt of a DOAC compared with White race. Likewise, Hispanic ethnicity was not associated with likelihood of receipt of warfarin or DOAC compared with White race.
- An administrative data analysis of individuals in Ontario, Canada, determined that residence in the fifth quintile of neighborhood-based material deprivation was associated with decreased 1-year likelihood of cardiology visits (HR, 0.84 [95% CI, 0.82–0.86]), anticoagulation (HR, 0.97 [95% CI, 0.95–0.98]), receipt of an echocardiogram (HR, 0.97 [95% CI, 0.96–0.99]), cardioversion (HR, 0.80 [95% CI, 0.76–0.84]), or ablation (HR, 0.45 [95% CI, 0.30–0.67]; Chart 18-10).<sup>121</sup>

### *Role of Coordinated Care*

- A systematic review and meta-analysis identified 3 studies of coordinated systems of care that included 1383 patients.<sup>218</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.

### Shared Decision-Making

(Chart 18-11)

- Shared decision-making for initiation of anticoagulation is a Class 2b recommendation per professional society guidelines.<sup>55</sup> A toolkit examined the efficacy of a novel tool for shared decision-making in a multisite trial ( $N=1001$ ) and determined the instrument yielded a 7-point, clinically meaningful reduction in the median 1-month decisional conflict score in those randomized to the intervention (9.4 [minimum, 0; maximum, 81.3]) compared with the control (16.4 [minimum, 0; maximum, 81.3]), reaching statistical significance (Mann-Whitney  $U$  statistics, 0.550;  $P=0.007$ ).<sup>219</sup> At 6 months, the median decisional conflict scores were 6.2 (minimum, 0; maximum, 81.3) in those randomized to the intervention compared to 10.9 (minimum, 0; maximum, 90.6) in those randomized to the control (Chart 18-11).
- A second clinical trial ( $N=922$ ) compared implementation of a decision aide in standard care.<sup>220</sup> Patient involvement in decision-making (assessed through video recordings) scores were significantly higher in the intervention arm (adjusted mean difference, 4.2 points [95% CI, 2.8–5.6]). No significant between-arm difference was found in encounter duration (intervention arm,  $32\pm16$  minutes; standard care arm,  $31\pm17$  minutes; adjusted mean between-arm difference, 1.1 minutes [95% CI, –0.3 to 2.5]).

## Mortality

**ICD-9 427.3; ICD-10 I48.**

(See Chart 18-12)

- In 2022, AF was the underlying cause of death in 28936 people and was listed on 233966 US death certificates (any-mention mortality; unpublished NHLBI tabulation using NVSS<sup>221</sup>).
- The AAMR attributable to any mention of AF was 6.9 per 100000 people in 2022 (95% CI, 6.8–7.0; unpublished NHLBI tabulation using CDC WONDER<sup>222</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>223</sup>
- The GBD Study indicates increases in sex-specific, age-standardized mortality estimates across US states between 1990 and 2017.<sup>224</sup> The greatest

percentage increases were as follows: for males, Mississippi (+26.4%), Oklahoma (+24.9%), Idaho (+24.8%), and New Hampshire (+22.4%); and for females, Oregon (+54.6%), Montana (+46.7%), Utah (+42.5%), and Nebraska (+40.5%).<sup>224</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>225</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 18-12).<sup>54</sup> The 2-year risk of all-cause mortality decreased by 30% for 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>226,227</sup> MI,<sup>228</sup> pre-CABG,<sup>229</sup> post-CABG<sup>230</sup> (long term), aortic valve replacement (transcatheter or surgical),<sup>231,232</sup> PAD,<sup>233,234</sup> and stroke.<sup>235</sup>
  - Individuals with AF have increased mortality with concomitant HF, including HFpEF<sup>236</sup> and HFrEF.<sup>236</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 associated with prevalent AF (RR, 1.19 [95% CI, 1.03–1.38];  $P_{\text{interaction}}<0.001$ ).<sup>237</sup> A population-based analysis of administrative data ( $N=52\,447$ ) determined that individuals with AF had 3.3-fold increased 3-year mortality risk after incident HF (95% CI, 3.08–3.43).<sup>238</sup>
  - AF is also associated with an increased risk of death in individuals with other conditions, including diabetes,<sup>239,240</sup> and critical illness in the ICU<sup>241</sup>; in individuals after primary PCI<sup>242</sup>; and in individuals  $\geq 80$  years of age with hypertension.<sup>243</sup>
- In the ARIC study, the rate difference for all-cause mortality for individuals with versus without AF per 1000 PY 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>244</sup>
- There was substantial variation in mortality with AF in US counties from 1980 to 2014.<sup>245</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 >90th percentile were clustered in Oregon; California; Utah; Idaho; northeastern Montana; areas east of Kansas City, MO; and southwest West Virginia.<sup>245</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 [interquartile range, 3–9 days]) compared with those with private insurance (4 days [interquartile range, 2–8 days]).<sup>246</sup>
- Serial cross-sectional analyses of annual US death certificate data for cardiovascular mortality identified an increase in AAMR per 100 000 population in those diagnosed with AF from 18.0 (95% CI, 17.8–18.2) in 2011 to 22.3 (95% CI, 22.0–22.4) in 2018.<sup>247</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>248</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>249</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 (interquartile range, 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>250</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>251</sup>

### Complications

#### 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>252</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 the ARIC study (N=14 941), incident AF was associated with adjusted increased risk of extracranial systemic emboli (HR, 3.58 [95% CI, 3.28–8.44]) compared with those without AF.<sup>252</sup> Risk of embolism increased with higher CHADS-VASc score (HR per 1-point increase, 1.24 [95% CI, 1.05–1.47]).

#### 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>253</sup>
- Before the widespread use of anticoagulant drugs, after accounting for standard stroke risk factors, AF was associated with a 4- to 5-fold increased risk of ischemic stroke. Although the RR of stroke associated with AF ( $\approx$ 3- to 5-fold increased risk) has not varied substantively with advancing age, the proportion of strokes attributable to AF has increased significantly. In the FHS, AF accounted for  $\approx$ 1.5% of strokes in individuals 50 to 59 years of age and  $\approx$ 23.5% in those 80 to 89 years of age.<sup>254</sup>
- In Medicare analyses that were adjusted for comorbidities, Black people (HR, 1.46 [95% CI, 1.38–1.55];  $P<0.001$ ) and Hispanic people (HR, 1.11 [95% CI, 1.03–1.18];  $P<0.001$ ) had a higher risk of stroke than White people with AF.<sup>255</sup> The increased risk persisted in analyses adjusted for anticoagulant therapy status. Additional analyses from the Medicare registry demonstrated that the addition of Black race to the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system significantly improved the prediction of stroke events among patients with newly diagnosed AF who were  $\geq$ 65 years of age.<sup>256</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>257</sup>
- In patients with COVID-19 in a global database, risk of ischemic stroke and other thromboembolic complications was higher in those with AF compared with those without AF (9.9% versus 7.0%; RR, 1.41 [95% CI, 1.26–1.59]).<sup>258</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>223</sup>

### Cognition and Dementia

- A meta-analysis of 11 prospective studies including 112876 participants with normal baseline cognition and without acute stroke reported an adjusted 34% (HR, 1.34 [95% CI, 1.24–1.44]) higher incidence of dementia in individuals with AF compared with those without AF.<sup>259</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>260</sup> A third meta-analysis of 6 studies including ≈1.6 million individuals determined that the association of AF varied by age (RR, 1.06 [95% CI, 0.55–2.06] in those <65 years of age and RR, 1.50 [95% CI, 1.00–2.26] in those <70 years of age).<sup>261</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>262</sup> Furthermore, in adjusted analyses of all the vascular brain features, large noncortical or cortical infarcts had the strongest association with reduced MoCA 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, MoCA, 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 AF.<sup>263</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 (interquartile range, 199–978 days) of follow-up observation.<sup>264</sup>
- A systematic review (10 studies; N=342 624) determined that receipt of a DOAC was associated with

reduced risk of dementia compared with receipt of warfarin over 0.3 to 3.7 years of follow-up (HR, 0.88 [95% CI, 0.80–0.98];  $P=0.75$ ).<sup>265</sup> Of note, this finding was heterogeneous by the geographic region in which studies were conducted; a significant difference in dementia risk in those receiving DOAC studies was identified in studies conducted in Asia (n=4) or North America (n=1; HR, 0.81 [95% CI, 0.68–0.86] and HR, 0.85 [95% CI, 0.76–0.98], respectively) but not those conducted in Europe (n=6; HR, 0.96 [95% CI, 0.81–1.14]).

- A cross-sectional analysis of a Swiss AF registry (N=1490) determined that compared with no exercise, once-weekly exercise was associated with reduced probability of ischemic infarct (OR, 0.78 [95% CI, 0.63–0.98]), moderate to severe WMH (OR, 0.78 [95% CI, 0.62–0.99]), and higher brain volume ( $\beta=1.40$  [95% CI, 0.65–2.15]).<sup>266</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 and diminished quality of life.<sup>267</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; interquartile range, 62–92) compared with males (mean, 83; interquartile range, 69–94).<sup>268</sup> A smaller, single-center study (N=339) identified that females with AF reported worse physical and social function than males with the condition.<sup>269</sup>

### Falls

- AF has been associated with increased risk of falls. A meta-analysis of 7 studies (N=36 444) concluded that individuals with AF have 1.2-fold increased risk of falls (OR, 1.20 [95% CI, 1.07–1.33]) relative to those without AF. Heterogeneity of studies was limited ( $P=37\%$ ).<sup>270</sup>

### Heart Failure

(See Charts 18-13 and 18-14)

- AF and HF share many antecedent risk factors, and ≈40% of people with either AF or HF will develop the other condition.<sup>88,271</sup>
- In the community, estimates of the incidence of HF in individuals with AF ranged from 3.3<sup>271</sup> to 5.8<sup>272</sup> per 100 PY of follow-up. In Olmsted County, Minnesota, in individuals with AF, the incidence of HFpEF was 3.3 per 100 PY of follow-up (95% CI, 3.0–3.7), which was more common than HFrEF (2.1 [95% CI, 1.9–2.4]).<sup>272</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>273</sup>

- A prospective, multicenter registry (N=13 133) compared outcomes with (n=1854) or without (n=11 279) HF in individuals with AF treated with a DOAC (edoxaban).<sup>274</sup> Individuals with HF had higher annual event rates of major bleeding (1.73%/y versus 0.86%/y, respectively) and mortality (8.30%/y versus 3.17%/y) than those without (Chart 18-13).
- An analysis in the REGARDS study (N=25 787) determined that cohort participants with AF (n=1896) had multivariable-adjusted increased risk of HFrEF (HR, 1.87 [95% CI, 1.38–2.54]) and HFpEF (HR, 1.65 [95% CI, 1.20–2.28]) over a 14-year follow-up (Chart 18-14).<sup>275</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>276</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>276</sup>
- For individuals with AF in ARIC,<sup>244</sup> a higher risk of MI was observed in Black people 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>277</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 ESKD compared with no AF (74 versus 64 per 1000 PY of follow-up).<sup>278</sup>
- A multinational consortium of 81 cohorts (N=24 353 175) determined that in those with CKD (n=605 596), AF was associated with increased risk of requiring renal replacement therapy (n=93 600; HR, 1.37 [95% CI, 1.05–1.77]).<sup>279</sup>

### *SCD and VF*

- 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>280</sup>

- An analysis of a French national database (N=3 381 472) determined that over a 5.4-year median follow-up (interquartile range, 5.0–5.8 years), individuals with AF had a greater multivariable-adjusted risk (HR, 1.17 [95% CI, 1.11–1.23]) for ventricular arrhythmias than those without AF.<sup>281</sup> A mediation analysis identified the odds of cardiac arrest mediated by AF-associated ventricular arrhythmias as an OR of 1.04 (95% CI, 1.04–1.04).

### *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>282</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>283</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>284</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 showed 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>285</sup>

### *Hospitalizations and Ambulatory Care Visits*

- According to HCUP data,<sup>286</sup> in 2021, there were 442 909 hospital discharges with AF and atrial flutter as the principal diagnosis (unpublished NHLBI tabulation).

- There were 8 365 000 physician office visits (NAMCS, unpublished NHLBI tabulation)<sup>287</sup> in 2019 and 677 971 ED visits in 2021 for AF and atrial flutter (HCUP,<sup>286</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>288</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 PY. 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>289</sup>
- A retrospective analysis of administrative data using MarketScan Research Databases (N=3 398 490) identified that individuals with AF (n=156 732) had 9 (95% CI, 8.96–9.12) ambulatory visits, 0.3 (95% CI, 0.33–0.34) inpatient admissions, and 2.7 (95% CI, 2.71–2.77) prescribed medications more than those without AF.<sup>290</sup> Among those with AF, patients living in rural areas had 1.99 fewer (95% CI, −2.26 to −1.71) and 0.05 more (95% CI, 0.02–0.8) emergency department visits than patients with AF living in metropolitan areas.

## 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 (95% CI, \$24.6–\$33.8) billion in 2016 dollars.<sup>291</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%.
- 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, \$12 895, and \$41 420 for lower-middle-, middle-, and high-income economies, respectively.<sup>292</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 total.<sup>293</sup>

## Global Burden of AF

**(See Table 18-1 and Charts 18-15 and 18-16)**

- Based on 204 countries and territories in 2021<sup>294</sup>:
  - The total number of global deaths estimated for AF/atrial flutter was 0.34 (95% UI, 0.29–0.37) million, with 0.13 (95% UI, 0.12–0.15) million among males and 0.20 (95% UI, 0.17–0.23) million among females (Table 18-1). Among regions, age-standardized mortality estimated for AF was highest for Australasia followed by Western Europe. Mortality was lowest for Central Asia and high-income Asia Pacific (Chart 18-15).
  - Globally, 52.55 (95% UI, 43.14–64.96) million individuals had prevalent AF/atrial flutter in 2021, with 27.90 (95% UI, 23.03–34.65) million among males and 24.65 (95% UI, 20.03–30.93) million among females (Table 18-1).
  - Age-standardized prevalence of AF among regions was highest for high-income North America, Australasia, and Western Europe. North Africa and the Middle East had the lowest age-standardized prevalence rates (Chart 18-16).
- 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%;  $P<0.001$ ). In this cohort, HF deaths (30%) exceeded deaths attributable to stroke (8%).<sup>295</sup>

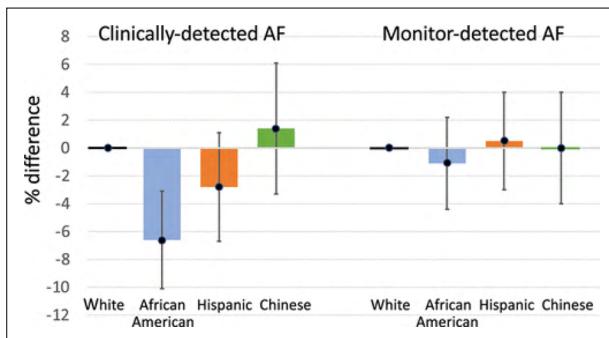
**Table 18-1. Global Mortality and Prevalence of AF, by Sex, 2021**

	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), 2021	0.34 (0.29 to 0.37)	52.55 (43.14 to 64.96)	0.13 (0.12 to 0.15)	27.90 (23.03 to 34.65)	0.20 (0.17 to 0.23)	24.65 (20.03 to 30.93)
Percent change (%) in total number, 1990–2021	195.92 (166.25 to 226.52)	136.57 (128.15 to 148.08)	215.63 (184.37 to 263.52)	142.76 (132.38 to 154.48)	184.22 (152.85 to 216.52)	129.93 (121.22 to 141.15)
Percent change (%) in total number, 2010–2021	46.62 (39.16 to 53.56)	40.62 (38.03 to 43.13)	49.68 (40.07 to 60.28)	39.70 (36.94 to 42.32)	44.67 (36.12 to 53.36)	41.68 (39.08 to 44.12)
Rate per 100,000, age standardized, 2021	4.36 (3.69 to 4.75)	620.51 (511.36 to 768.88)	4.44 (3.94 to 4.81)	728.88 (601.91 to 895.81)	4.29 (3.53 to 4.80)	529.12 (430.79 to 663.14)
Percent change (%) in rate, age standardized, 1990–2021	2.92 (−6.01 to 12.35)	0.64 (−3.28 to 5.75)	5.65 (−3.74 to 19.94)	0.15 (−4.10 to 5.80)	1.07 (−8.97 to 11.90)	−0.08 (−3.89 to 5.01)
Percent change (%) in rate, age standardized, 2010–2021	−0.83 (−5.50 to 3.71)	1.96 (0.33 to 3.35)	0.10 (−5.90 to 6.74)	0.66 (−1.02 to 1.97)	−1.42 (−7.24 to 4.53)	3.16 (1.51 to 4.71)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

AF indicates atrial fibrillation; GBD, Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>294</sup>

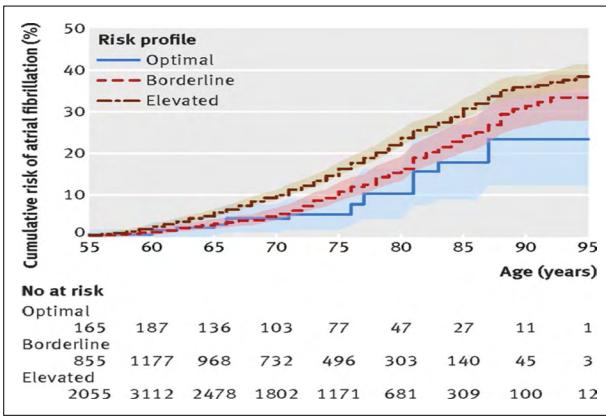


**Chart 18-1. Adjusted percent difference in AF prevalence compared with White individuals for clinically detected AF (2000–2018) and monitor-detected AF (2016–2018) in the MESA Study.**

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.

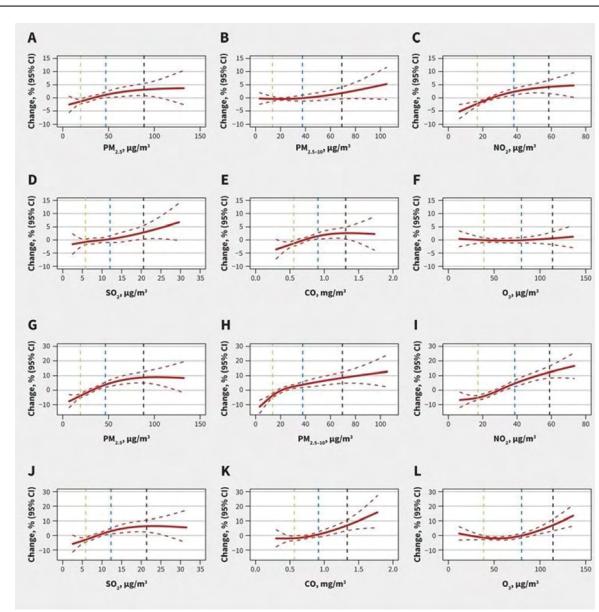
AF indicates atrial fibrillation; HF, heart failure; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; and SBP, systolic blood pressure.

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**Chart 18-2. 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>63</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/>.

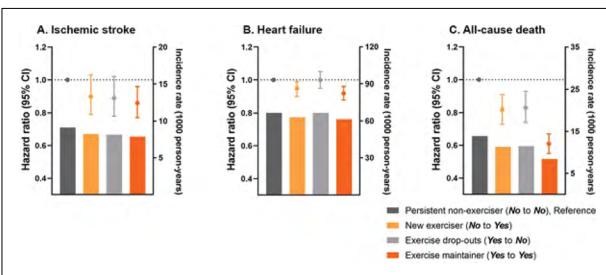


**Chart 18-4. Nationwide, time-stratified case-crossover analysis of air pollution data spanning 2015 to 2021 from 322 cities in China in relation to presentation with symptomatic AF or SVT.**

Exposure-response curves for the concentrations of 6 air pollutants and AF (A-F) and SVT (G-L). The associations are presented as percentage change in the odds of the outcome compared with the odds at the median concentration over a lag period of 0 to 24 hours. Solid red lines represent the point estimates; intervals between dashed red lines represent 95% CIs. The other dashed lines represent the concentration of air pollutants (green, 25th percentile; blue, 75th percentile; black, 95th percentile).

AF indicates atrial fibrillation; CO, carbon monoxide; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM<sub>2.5</sub>, particulate matter with an aerodynamic diameter  $\leq 2.5 \mu\text{m}$ ; PM<sub>2.5-10</sub>, particulate matter with an aerodynamic diameter between 2.5 and 10  $\mu\text{m}$ ; SO<sub>2</sub>, sulfur dioxide; and SVT, supraventricular tachycardia.

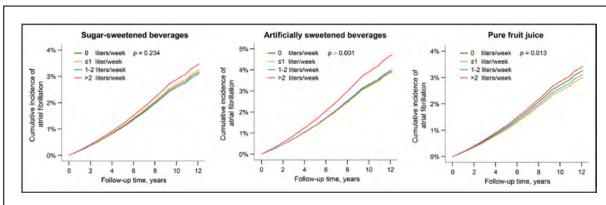
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**Chart 18-3. Retrospective analysis conducted in the Korean National Health Insurance Service of individuals (N=66 692) with newly diagnosed AF who underwent self-reported exercise assessment 2 years before and after AF diagnosis, 2010 to 2016.**

**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. 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>84</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.

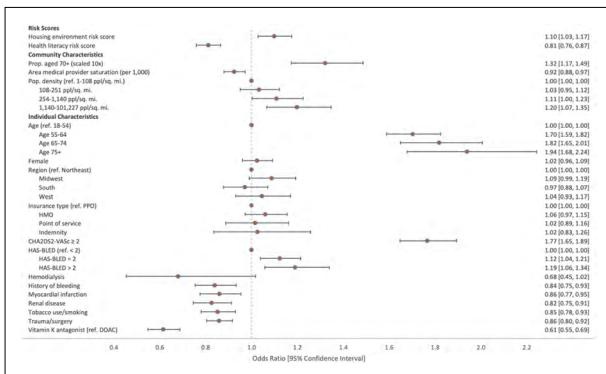


**Chart 18-5. Multivariable-adjusted cumulative incidence of AF according to consumption of SSBs, ASBs, and pure fruit juice.**

The unit of beverages consumption is liter per week. Models were adjusted for age; sex; ethnicity (White/others); education level (university or college degree/others); the Townsend deprivation index; alcohol consumption; current smoking; ideal PA level; sleep duration; BMI; SBP; TC; eGFR; OSA; CHD; HF; diabetes; the PRS for AF; and the consumption of vegetables, fruits, red meat, processed meat, coffee, total fat, total sugar, and total energy and mutually adjusted for 2 additional beverages.  $P$  value was for the log-rank test.

AF indicates atrial fibrillation; ASB, artificially sweetened beverage; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; OSA, obstructive sleep apnea; PA, physical activity; PRS, polygenic risk score; SBP, systolic blood pressure; SSB, sugar-sweetened beverage; and TC, total cholesterol.

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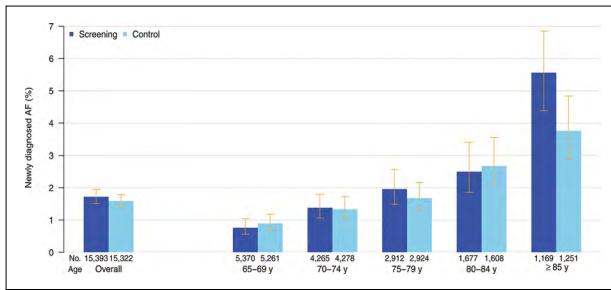


**Chart 18-6. Multivariable-adjusted regressions of associations between community-level (determined by US 3-digit zip code) and patient-level (determined from IQVIA PharMetrics Plus claims data from January 2016–June 2020) characteristics and proportion of days covered at 360 days.**

Risk scores are continuous variables on a 1–5 scale, where 1=little to no risk, 2=low risk, 3=moderate risk, 4=high risk, and 5=severe risk. Community characteristics are measured at the 3-digit ZIP code (ZIP-3) level. Proportional community-level measures are scaled by a factor of 10. For example, a 1-unit increase in "Prop. aged 70 and older" is equivalent to a 10% increase in the prevalence of residents aged  $\geq 70$  years in the ZIP-3 area. Other measures represent median or mean values.

DOAC indicates direct-acting oral anticoagulant; HAS-BLED, atrial fibrillation bleeding risk score (hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, elderly, drug and alcohol use); HMO, health maintenance organization; pop, population; ppl, people; PPO, preferred provider organization; prop, proportion; and ref, referent group.

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**Chart 18-7. Proportion of adults by age category with newly diagnosed AF by screening (n=15 393) at a primary care visit compared with control subjects (n=15 322) who were not screened in a single US health care system: VITAL-AF RCT.**

Error bars indicate 95% CI.

AF indicates atrial fibrillation; RCT, randomized controlled trial; and VITAL-AF, Screening for Atrial Fibrillation Among Older Patients in Primary Care Clinics.

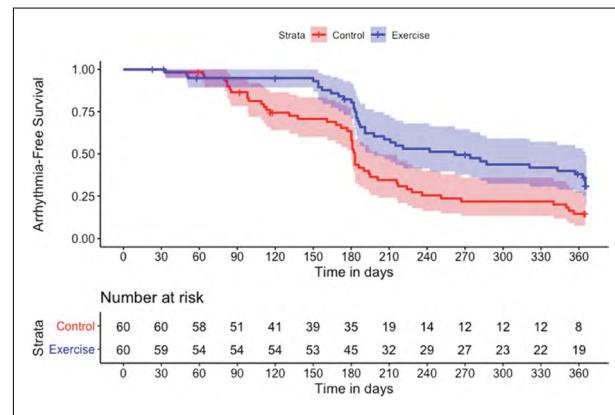
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Maximum Daily AF Duration	CHA2DS2-VASc Score				
	0	1	2	3-4	$\geq 5$
No AF	<b>0.33%</b> n=2922 (13.4%)	<b>0.62%</b> n=2151 (9.9%)	<b>0.70%</b> n=4554 (20.9%)	<b>0.83%</b> n=7164 (32.9%)	<b>1.79%</b> n=4977 (22.9%)
AF 6 min–23.5 h	<b>0.52%</b> n=3381 (15.5%)	<b>0.32%</b> n=4 events	<b>0.62%</b> n=17 events	<b>1.28%</b> n=42 events	<b>2.21%</b> n=36 events
AF >23.5 h	<b>0.86%</b> n=1572 (7.2%)	<b>0.50%</b> n=3 events	<b>1.52%</b> n=19 events	<b>1.77%</b> n=28 events	<b>1.68%</b> n=13 events

**Chart 18-8. Risk of stroke and systemic embolism in nonanticoagulated patients (N=21 768) by AF duration and CHA2DS2-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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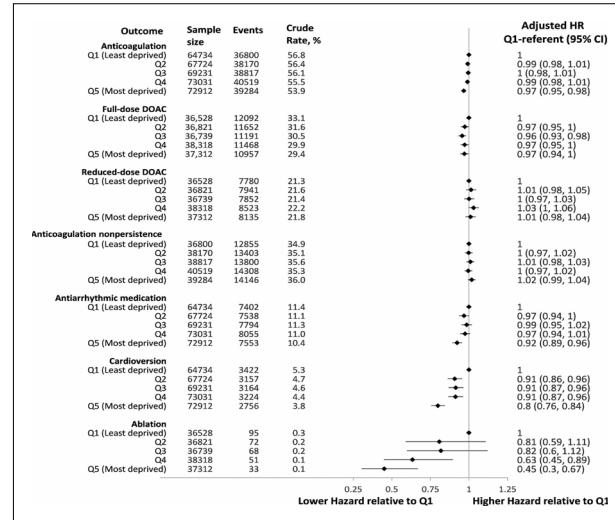


**Chart 18-9. An exercise and PA program in patients with AF: the ACTIVE-AF RCT.**

Proportion of study participants free from arrhythmia during the trial follow-up.

ACTIVE-AF indicates A Lifestyle-based Physical Activity Intervention for Patients with Symptomatic AF; AF, atrial fibrillation; PA, physical activity; and RCT, randomized controlled trial.

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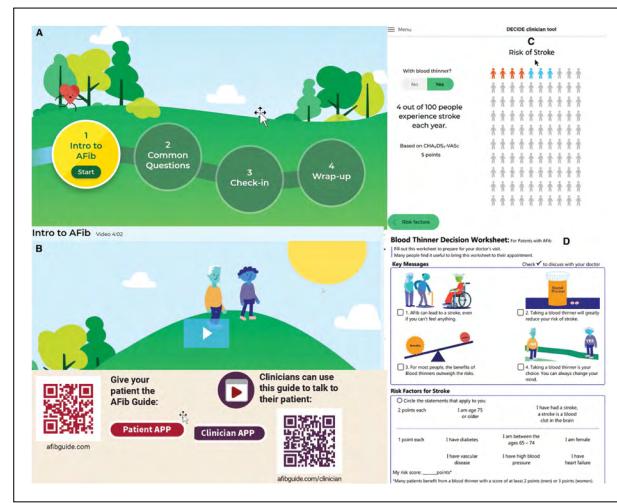


**Chart 18-10. Treatment and interventions related to AF within 1 year of incident diagnosis by quintile of material deprivation in the Canadian province of Ontario.**

HRs with 95% CIs for therapies and treatment relevant for AF.

Material deprivation derived from Ontario, Canada, census tract-level indices (mean population, 400–700 people) with analysis conducted at the individual level. AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; HR, hazard ratio; and Q, quintile.

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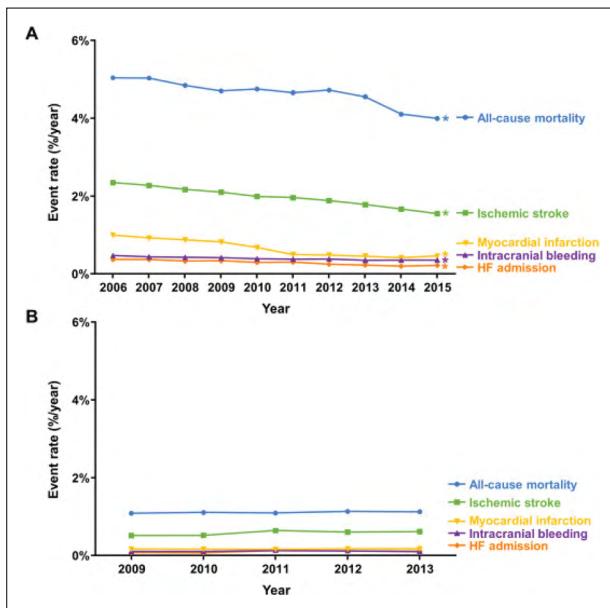


**Chart 18-11. Randomized comparative-effectiveness trial of individuals ≥18 years of age with nonvalvular AF conducted at 5 US sites (December 18, 2019–August 17, 2022) to evaluate a shared decision-making pathway for stroke prevention.**

**A**, Screenshot of patient web app navigation screen leading to 4 parts of the video: (1) patient video, (2) frequently asked questions, (3) brief quiz, and (4) worksheet. **B**, Screenshot of opening scene of patient video with animated characters who take the journey to decide about anticoagulation for AF stroke prevention. **C**, Screenshot of an example of stroke reduction estimate based on AF stroke risk that the clinician may use through the clinician web app. **D**, First page of the worksheet given to the patient to indicate key messages. The second page (not shown) has space for questions that the patient has for the clinician visit. **E**, QR codes to the patient tool and clinician tool.

AF/Afib indicates atrial fibrillation; app/APP, application; and RCT, randomized controlled trial.

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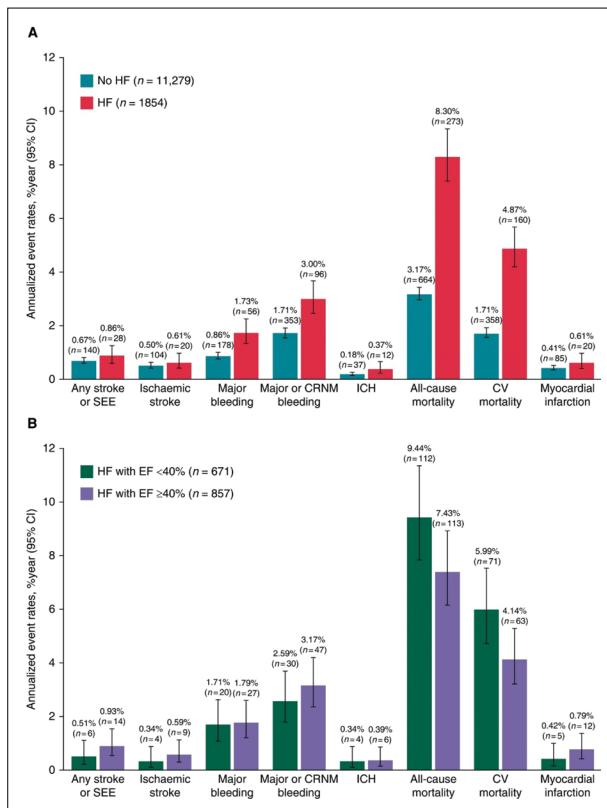


**Chart 18-12. Temporal trends of the 1-year adverse event rates from 2006 to 2015 in (A) 679 416 adults with newly diagnosed AF and (B) those without AF in the Korean National Health Insurance Service database.**

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.  $P_{\text{trends}} < 0.001$ .

AF indicates atrial fibrillation; and HF, heart failure.

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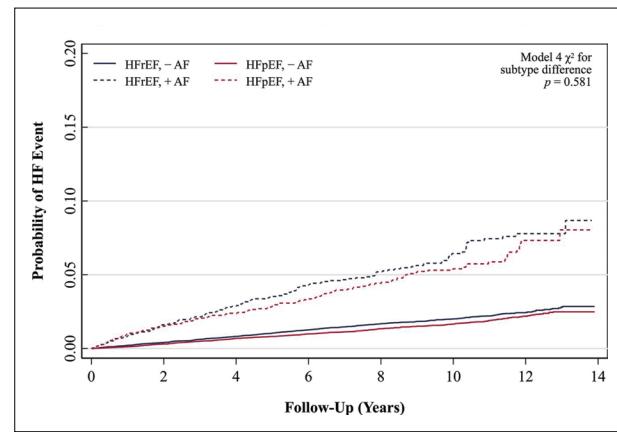


**Chart 18-13. Two-year clinical outcomes for participants in the ETNA-AF-Europe multinational registry in Europe, Japan, Korea, and Taiwan, stratified by HF and EF status from 2015 to 2020.**

**A**, Patients with or without HF. **B**, Patients with HF and EF <40% or ≥40%. For 326 patients with HF, the EF was not documented.

CRNM indicates clinically relevant nonmajor; CV, cardiovascular; EF, ejection fraction; ETNA-AF-EU, Edoxaban Treatment in Routine Clinical Practice For Patients With Non-Valvular AF; HF, heart failure; ICH, intracranial hemorrhage; MI, myocardial infarction; and SEE, systemic embolic events.

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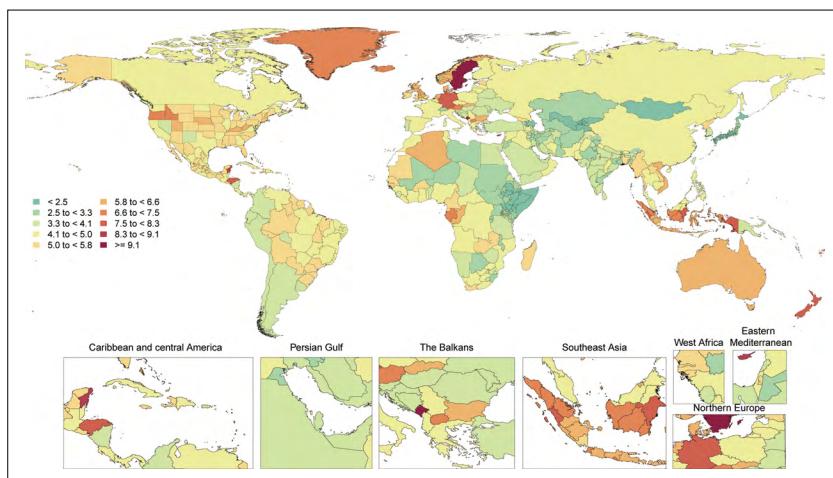


**Chart 18-14. Kaplan-Meier estimates for incident HFpEF or HFrEF by concomitant AF status in the REGARDS Study (N=25 787).**

Prevalent AF ascertained by baseline ECG or participant self-report of diagnosis. Analysis of HF subtype difference adjusted for age, sex, race, income, education, geographic region, smoking history, SBP, diabetes, BMI, LDL, LVH by ECG, eGFR, baseline CHD status and CHD as a time-varying covariate, and medications.

AF indicates atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; and SBP, systolic blood pressure.

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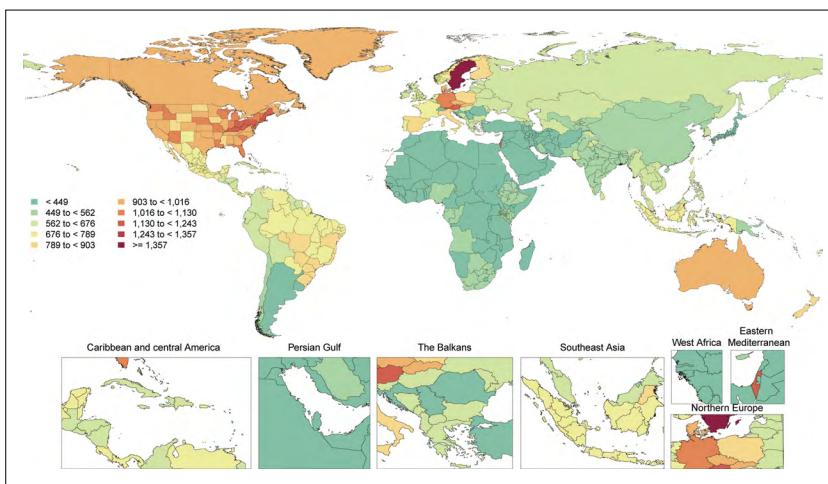


**Chart 18-15. Age-standardized global mortality rates of AF and atrial flutter per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

AF indicates atrial fibrillation; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

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**Chart 18-16. Age-standardized global prevalence rates of AF and atrial flutter per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

AF indicates atrial fibrillation; and GBD, Global Burden of Diseases, Injuries, and Risk Factors.

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## 19. SUDDEN CARDIAC ARREST, VENTRICULAR ARRHYTHMIAS, AND INHERITED CHANNELOPATHIES

*See Tables 19-1 through 19-7 and Charts 19-1 through 19-5*

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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.**

2022, United States: Underlying cause mortality—19 171. Any-mention mortality—41 7957.

### Tachycardia

**ICD-9 427.0, 427.1, 427.2; ICD-10 I47.1, I47.2, I47.9.**

2022, United States: Underlying cause mortality—1291. Any-mention mortality—11 380.

### Sudden Cardiac Arrest

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; an ILCOR consensus statement recommends categorizing cardiac arrest into events with external causes (drowning, trauma, asphyxia, electrocution, and drug overdose) or events with 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. To that end, this chapter addresses

The 2025 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 2025. 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.

epidemiology and statistics pertaining to adult OHCA, adult IHCA, pediatric OHCA, pediatric IHCA, SCA/SCD not associated with location, and special circumstances in separate subheadings for ease of use.

### OHCA in Adults

#### *Incidence and Cause*

*(See Tables 19-1 through 19-3)*

- The ongoing CARES registry<sup>3</sup> estimates the incidence of EMS-treated OHCA among individuals of any age in >2300 EMS agencies in the United States. Differences in bystander intervention and survival by race and ethnicity, sex, and neighborhood characteristics are listed in Table 19-1.
- Incidence of EMS-treated OHCA in US people of any age is 83.4 individuals per 100 000 population according to the 2023 CARES registry, with great variation between states (range, 47.3–138.6; Table 19-2).
- In 2023, location of OHCA in adults was most often a home or residence (71.0%) followed by public settings (18.2%) and nursing homes (10.7%; Table 19-3).<sup>3</sup>
- The initial recorded cardiac rhythm was VF, VT, or shockable by an automated external defibrillator in 17.8% of EMS-treated adult OHCAs in 2023 (Table 19-3).
- 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>4</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.
- In a Swedish study that integrated data from 3 national registries between 2007 and 2021, 5.2% of the 66 261 cardiac arrests were attributable to poisoning. The most common cause of poisoning was polysubstance use.<sup>5</sup>
- Among 608 OHCAs with a cardiac cause 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>4</sup>
- OHCA has been attributed to various causes, including cardiac (53%), respiratory (18%), neurological (3%), toxicological (6%), other (9%), and

unknown (11%), in a multihospital health network observational study.<sup>6</sup>

### COVID-19 Effects on OHCA Incidence

The COVID-19 pandemic has had multiple effects on the 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>7</sup> Compared with the pre-COVID-19 control period, individuals experiencing OHCA during COVID-19 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, non-shockable rhythms) during the COVID-19 period compared with the control period.
- 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 1 million residents) and very high COVID-19 mortality (adjusted mean difference, 28.7 [95% CI, 26.7–30.6] per 1 million residents).<sup>8</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>9</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 ≥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>10</sup>
- 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=10 992), mortality was 85% compared with 62% for the control periods.<sup>11</sup>
- In a Swiss study, a significant contribution to the increase in OHCA was attributable to delay in seeking care for AMI. A delay in symptom onset to contact with the medical system was measured during the COVID-19 pandemic compared with control (112 minutes versus 60 minutes;  $P=0.049$ ).<sup>12</sup>
- In a 2024 meta-analysis, a total of 49 882 patients in 10 studies were analyzed to explore the incidence of OHCA, rates of bystander CPR, and survival outcomes during the first wave of the pandemic compared with prepandemic data.<sup>13</sup> In regions where weekly COVID-19 incidence was highest (>136/100 000 per week), OHCA incidence increased significantly, and patients had lower odds of bystander CPR (OR, 0.49 [95% CI, 0.29–0.81];  $P=0.005$ ) compared with prepandemic rates.
- In a large US registry, rates of sustained ROSC after OHCA were, on average, 28% lower during the first wave of the pandemic (March 16–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>8</sup> The decline in sustained ROSC 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-19 mortality.<sup>8</sup>

### Secular Trends

- 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>14</sup> Rates of ROSC also increased from 6.31 to 9.99 per 100 000.
- 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>15</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 nationwide study in Japan analyzed patients with OHCA who arrested and were defibrillated by laypeople between 2005 and 2019.<sup>16</sup> In this cohort, the RR reduction and NNT of compression-only CPR were 7.6% and 22.1, respectively, for favorable neurological outcomes with the exception of the years 2005 and 2013.

### Risk Factors

- The first 3 to 6 months after AMI are considered 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 PY (if everyone were followed up for 90 days; 0.19% at 30 days or 228 per 100 000 PY).<sup>17</sup>
- MI with OHCA or cardiac arrest in the ED occurred in 9682 of 252 882 patients (3.8%) 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>18</sup>
  - Of 4729 patients with STEMI in Los Angeles County, California, from 2011 to 2014, 422 (9%) had OHCA.<sup>19</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>20</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>21</sup> Similar findings were reported recently from Israel and Italy.<sup>22,23</sup>

## Sex

Variability in survival and neurological recovery after OHCA by sex has been reported by the following 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, 1 study found that females have equivalent or higher rates of survival to hospital discharge or to 30 days relative to males.<sup>24</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>25</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>26</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 contrast to the previous studies, 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>27</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]).

- Data from the German Resuscitation Registry found that 20 344 women (34.6%) and 38 454 men (65.4%) were resuscitated after OHCA between 2006 and 2022.<sup>28</sup> Women received less mechanical CPR (OR, 1.22 [95% CI, 1.13–1.32];  $P<0.001$ ) and less targeted temperature control (OR, 1.08 [95% CI, 1.00–1.17];  $P<0.05$ ), which may have contributed to better neurological outcomes for men at discharge (Cerebral Performance Category 1 or 2; OR, 1.1 [95% CI, 1.015–1.191];  $P=0.021$ ).

## Social Determinants of Health/Health Equity

- A study of the NIS from 2006 through 2018 identified patients with OHCA who survived to hospital admission and IHCA.<sup>29</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 of age versus 65.9 years of age;  $P<0.001$ ), 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 dataset 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>30</sup> At a zip code level, each additional \$10 000 above the 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 compared with the FPL (ie, \$20 650 in 2007 to \$24 300 in 2017 for a family of 4) had 14.62 fewer arrests ( $P<0.001$ ).<sup>31</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 a meta-analysis examining race including 53 507 Black patients (22.4%) who experienced OHCA, Black race was associated with worse outcomes.<sup>32</sup> The study revealed significantly worse outcomes on all measures in Black patients, including survival to hospital discharge (OR, 0.81 [95% CI, 0.68–0.96];  $P=0.01$ ), ROSC (OR, 0.79 [95% CI, 0.69–0.89];  $P=0.0002$ ), and good neurological outcomes (OR, 0.80 [95% CI, 0.68–0.93];  $P=0.003$ ).
- 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>33</sup>
- In King County, Washington, the presence of more pharmacies or medical facilities was not associated with lower rates of OHCA or shorter response times; in fact, OHCA was more common in census tracts with more pharmacies or other medical facilities (OR, 1.28 [95% CI, 1.03–1.59]).<sup>34</sup>
- In an analysis of 347 705 SCDs in the United States between 1999 and 2019 from CDC WONDER, AAMRs were higher in rural than in urban counties.<sup>35</sup> In urban counties, rates of SCD declined from 1999 through 2013 (–0.05 [95% CI, –0.09 to –0.01]) but then increased through the end of the study period (0.08 [95% CI, 0.03–0.12]). In rural counties, AAMRs attributable to SCD declined throughout the study period, but the rate of decline slowed after 2013 (–0.29 versus –0.14). AAMRs for urban-dwelling males increased from 2013 onward from 4.8 to 5.7 per 100 000 population. AAMRs for rural-dwelling males were unchanged from 2013 onward: 9.3 versus 9.3 per 100 000 population. AAMRs 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>15</sup>
- The incidence of OHCA per 100 000 PY was 30.9 in women and 87.1 in men in an OHCA registry from a Dutch province.<sup>36</sup> Compared with the highest household income quintile, the aHR to experience OHCA from the second highest to the lowest household income quintiles ranged from 1.24 (95% CI, 1.01–1.51) to 1.75 (95% CI, 1.46–2.10) in women and from 0.95 (95% CI, 0.68–1.34) to 2.30 (95% CI, 1.74–3.05) in men.

### Awareness and Treatment

- 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>37</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>38</sup>; 68% of citizens in Victoria, Australia<sup>39</sup>; and 61.1% of laypeople in the United Kingdom<sup>40</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>41</sup>
- Laypeople with knowledge of automated external defibrillators include 69.3% of people in the United Kingdom and 66% in Philadelphia, PA.<sup>40,42</sup> A total of 58% of Philadelphia respondents<sup>42</sup> but only 2.1% of UK respondents<sup>40</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>43</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>44</sup>
- Laypeople in the United States initiated CPR in 40% of OHCA in CARES 2022 data.<sup>3</sup>

- Layperson CPR rates in Asian countries range from 10.5% to 40.9%.<sup>45</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>46</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>47</sup> or in predominantly Hispanic neighborhoods (OR, 0.62 [95% CI, 0.44–0.89]) than in high-income White neighborhoods.<sup>48</sup>
- Examining 2013 to 2019 CARES data shows that 32.2% of arrests occurred in Black individuals or Hispanic individuals. Black individuals and Hispanic individuals were less likely to receive layperson CPR at home (aOR, 0.74 [95% CI, 0.72–0.76]) and in public (aOR, 0.63 [95% CI, 0.60–0.66]) compared with White individuals with OHCA.<sup>49</sup> This disparity persisted despite the racial makeup of the community in which they arrested and the economic strata.
- Layperson CPR rates varied from 1.3% to 72% in an international study including 35 communities across 25 countries.<sup>50</sup> Rates of layperson CPR correlated with gross domestic product per capita (0.772;  $P<0.01$ ;  $r^2=0.596$ ). Socioeconomically advantaged communities most likely have more resources to provide CPR education.

### Mortality

(See Tables 19-2 through 19-4)

- Based on a total of 139 822 OHCA in 2023, there was variation in survival to hospital discharge between states reporting data (range, 7.5%–15.0%; Table 19-2). Survival to hospital discharge after EMS-treated adult OHCA was 10.2% in the 2023 CARES registry on the basis of 135 723 adult cases (Table 19-3). Survival to hospital discharge with good functional status was 8.1% in 2023.<sup>3</sup>
- Survival to hospital admission after EMS-treated nontraumatic OHCA in 2023 was 26.1% for all presentations, with higher survival rates in public places (38.0%) and lower survival rates in homes/residences (24.6%) and nursing homes (15.8%) in the 2023 CARES registry (Table 19-4).
- 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>51</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>52</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>19</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>53</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  $1.9\pm1.0$  hours of hospital arrival.<sup>54</sup> Presumed causes of OHCA were identified in 39%. Potentially life-threatening complications of resuscitation were identified in 13% of cases.
- A meta-analysis was conducted to explore long-term survival from OHCA attributable to a suspected cardiac cause.<sup>55</sup> In 11 800 patients with OHCA, the median survival for patients surviving to hospital discharge was 5 years (interquartile range, 2.3–7.9 years). Survival to 10 years after hospital discharge was 63.9% (95% CI, 62.3%–65.4%).

### Treatment

- Immediate coronary angiography compared with 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>56</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>57</sup>
- A multicenter RCT of 530 patients resuscitated from OHCA with no evidence of STEMI compared outcomes with immediate and delayed coronary angiography.<sup>58</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>59</sup> and neuron-specific enolase,<sup>60–62</sup> correlate with poorer outcomes.
- Guidelines recommend targeted temperature management to prevent hypoxic-ischemic brain damage in patients with coma after cardiac arrest.<sup>63</sup> However, the benefit of this treatment has been questioned. An open-label RCT of 1861 comatose adults resuscitated after OHCA with a cardiac cause 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.<sup>64</sup> A meta-analysis of multiple trials also found a lack of benefit of hypothermia in individuals with OHCA.<sup>65</sup> ILCOR recommends temperature control for comatose survivors of OHCA to a temperature of  $<37.7^{\circ}\text{C}$ ; however, the ideal target temperature for other subgroups remains unclear.<sup>66</sup>

- Markers of systemic inflammation are commonly elevated in comatose patients resuscitated from OHCA, and higher levels are associated with poorer outcomes. In an RCT of tocilizumab, an interleukin-6 receptor antibody, patients resuscitated from OHCA had 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>67</sup>
- An RCT conducted with a 2×2 factorial design explored optimal BP targets (mean arterial pressure, 63 mmHg versus 77 mmHg)<sup>68</sup> and optimal oxygen targets (arterial oxygen [ $\text{PaO}_2$ ], 9–10 kPa [68–75 mmHg] or 13–14 kPa [98–105 mmHg]<sup>69</sup>) in resuscitated patients with OHCA with presumed cardiac cause of arrest. The measured outcome was a composite outcome of death at hospital discharge with a Cerebral Performance Category of 3 or 4. To assess optimal BP, 789 patients were randomized to the 2 arms. There was no difference in the primary outcome event (HR, 1.08 [95% CI, 0.84–1.37];  $P=0.56$ ) between the 2 target BPs. In assessment of the optimal oxygen target between the liberal and restrictive strategies, no difference was found in the primary outcome event between the 2 oxygen targets (HR, 0.95 [95% CI, 0.75–1.21];  $P=0.69$ ).
- A multicenter RCT randomized 1700 patients from 63 ICUs in 17 countries to 24 hours of mild hypercapnia (target partial pressure of arterial carbon dioxide, 50 to 55 mmHg) or normocapnia (target partial pressure of arterial carbon dioxide, 35 to 45 mmHg).<sup>70</sup> There was no difference in the primary outcome of attaining a favorable neurological outcome at 6 months (RR, 0.98 [95% CI, 0.87–1.11];  $P=0.76$ ).
- In a single-center RCT of 256 adults with a witnessed OHCA of presumed cardiac origin without ROSC, 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>71</sup> However, the trial was possibly under-powered to detect a clinically relevant difference.

### Other Outcomes

- Functional recovery continues over the first 6 to 12 months after OHCA in adults.<sup>72,73</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>74</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±SD of  $714\pm1013$  days.<sup>75</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>76</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 was found in 18 caregivers (14%) at 12 months.<sup>77</sup>
- Among OHCA survivors, the prevalence of depression (19%), anxiety (26%), and posttraumatic stress disorder (20%) is significant, highlighting the need for further screening, prevention, and treatment options.<sup>78</sup>
- Among 7321 patients with OHCA in Taiwan who survived to ICU admission, 281 (3.84%) had new-onset HF.<sup>79</sup> Strong predictors of new-onset HF were age (60–75 years of age; 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]).

### 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>80</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>81</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.

- In a systematic review accounting for 133 981 patients with EMS-witnessed OHCA treated in 33 countries, the incidence of EMS-treated cases was 4.1 in 100 000 PY (95% CI, 3.5–4.7 per 100 000 PY).<sup>82</sup> Survival to hospital discharge or at 30 days from arrest was 20% in shockable rhythms and 6% in nonshockable rhythms. Significant global variation was appreciated.

## IHCA in Adults

### Incidence

(See Tables 19-3 and 19-5)

- 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>83,84</sup>
- Incidence of IHCA among 15 953 rapid response team calls in Australia was 159 cases in 152 individuals or 0.62 IHCA per 1000 multiday admissions (interquartile range, 0.50–1.19).<sup>85</sup>
- In the HCUP NIS for 2021 (unpublished NHLBI tabulation):<sup>86</sup>
  - There were 28 655 hospital discharges with a primary diagnosis of cardiac arrest.
  - There were 321 670 hospital discharges with all-listed diagnoses of cardiac arrest.
  - There were 191 632 ED discharges with a principal diagnosis of cardiac arrest.
- 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 between 2006 and 2018.<sup>87</sup>
- After data from GWTG-R were combined with Medicare data from 2014 to 2017, 38 630 patients with IHCA were analyzed to determine the incidence of IHCA of Medicare beneficiaries and hospital variation in IHCA.<sup>88</sup> The median risk-adjusted IHCA incidence was 8.5 per 1000 admissions (95% CI, 8.2–9.0 per 1000 admissions). IHCA incidence varied across hospitals after adjustment for differences in case-mix index, from 2.4 per 1000 admissions to 25.5 per 1000 admissions (interquartile range, 6.6–11.4; median OR, 1.51 [95% CI, 1.44–1.58]). Higher case-mix index, higher nurse staffing, and teaching status were associated with less incidence of IHCA.
- In the Swedish Intensive Care Registry and the Swedish Cardiopulmonary Registry, the incidence of IHCA within the ICU was 16.1 per 1000 admissions.<sup>89</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>90</sup>

- A smaller single-center study found that IHCA within the first 48 hours after PCI for STEMI occurred in 11% (44) of 403 patients reviewed.<sup>91</sup>
- IHCA incidence was 320 of 21 337 patients (1.50%) with ACS admitted to 3 hospitals in China from 2012 to 2016.<sup>92</sup>
- According to 2023 GWTG data, location of adult IHCA was the ICU in 41.1%, operating room in 2.2%, ED in 17.8%, and noncritical care areas in 38.7% of 40 837 events at 404 hospitals (Table 19-3).
- Initial recorded cardiac rhythm was VF or VT in 14.4% of adult IHCA in 2023 GWTG data (GWTG-R, unpublished data, 2023; Table 19-3).
- Additional adult IHCA quality of care data from GWTG-R 2023 are listed in Table 19-5 and Chapter 26 (Quality of Care).
- 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>93</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>94–97</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>98</sup>

### COVID-19 Effects on IHCA Incidence

- 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>99</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.
- Compared with 2016 to 2019, patients in the United Kingdom who experienced IHCA during the first wave of the pandemic were younger, male, and of underrepresented race (Asian, Black, multiracial, other).<sup>100</sup> Higher hospital COVID-19 burden was associated with decreased survival to hospital discharge (OR, 0.95 [95% CI, 0.93–0.98];  $P<0.001$ ).

### 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>101</sup>
- Early warning score systems using both clinical criteria and vital signs identified hospitalized patients

with a higher risk of IHCA<sup>102</sup> (see also IHCA incidence).

- 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>103</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>104</sup>

### Mortality

(See Table 19-3 and Chart 19-1)

- Survival to hospital discharge was 23.6% of adult patients with pulseless IHCAs in GWTG 2023 data (Table 19-3 and Chart 19-1). Among survivors, 79.2% had good functional status (Cerebral Performance Category 1 or 2) at hospital discharge.
- According to data from the GWTG-R registry, there was an increase in survival to hospital discharge in patients who arrested in the ICU between 2006 and 2018.<sup>105</sup> Increases in both ROSC (unadjusted rate, 55.0%–65.4%; aOR per year, 1.04 [95% CI, 1.03–1.05]) and survival to hospital discharge (unadjusted rate, 16.7%–20.5%; aOR per year, 1.03 [95% CI, 1.03–1.04]) were measured.
- 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>106</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>87</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>107</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>108</sup>
- A propensity-matched analysis of 2000 to 2018 data from 497 US hospitals participating in the AHA GWTG-R registry examined the use of epinephrine before defibrillation for treatment of IHCA with a shockable rhythm.<sup>109</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>110</sup> The active treatment group experienced significantly higher rate of ROSC (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).

### Other Outcomes

- 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>111</sup>
- In a single-center study, 102 patients experienced IHCA; 50 survived the arrest event and 47 survived to hospital discharge with a good neurological outcome (mRS score, 0–3).<sup>112</sup>

### Global Burden of Disease

- Hospitals in Beijing, China, reported an IHCA incidence of 17.5 events per 1000 admissions.<sup>113</sup>
- Among 353 adults after IHCA in 6 Kenyan hospitals in 2014 to 2016, 16 (4.2%) survived to hospital discharge.<sup>114</sup>

## OHCA in Pediatric Patients

### Incidence

(See Table 19-3)

- In 2023, the location of EMS-treated OHCA was home for 83.0% of children in the CARES data. The location was a public place for 16.7% of the children (Table 19-3).<sup>3</sup>
- The annual incidence of pediatric OHCA was 8.7 per 100 000 population in Western Australia from 2011 to 2014.<sup>115</sup>

### Secular Trends

- 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.<sup>116</sup> The incidence was even lower among children <1 year of age.
- 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>116</sup> Survival to hospital discharge increased from 9.4% to 17.7%.

### Awareness and Treatment

- In an English study of 2363 pediatric OHCA events, layperson CPR was performed in 69.6% of cases

(1646) overall.<sup>117</sup> There was variability in provision of CPR across the different regions studied.

- According to data from a multicenter prospective observational registry in Japan between 2014 and 2019, there were significant increases in the rates of bystander-initiated CPR (50.6% to 62.3%;  $P=0.003$ ) and epinephrine (adrenaline) administration (from 2.4% to 6.9%;  $P=0.014$ ).<sup>118</sup> However, the rate of advanced airway management decreased (from 17.7% to 8.8%;  $P=0.003$ ) and overall 1-month survival did not change.
- Despite the majority of pediatric cardiac arrests being secondary to respiratory pathogenesis, few studies have examined the neurological recovery when conventional CPR (ventilation and compression) is applied versus compression-only CPR.<sup>119</sup> In this observational study from a nationwide Japanese registry, neurologically favorable 1-month survival rate with no bystander CPR was 2.4%, with compression-only CPR was 3.2%, and with conventional CPR was 6.6% ( $P<0.01$ ). With multivariable logistic regression, conventional CPR was associated with higher neurologically favorable 1-month survival than compression-only CPR (OR, 1.98 [95% CI, 1.03–3.81]).

### Mortality

(See Table 19-6)

- Survival to hospital discharge was 7.4% for 1587 children <1 year of age, 14.1% for 1225 children 1 to 12 years of age, and 18.5% for 854 children 13 to 18 years of age in CARES 2023 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>120</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>121</sup>

## IHCA in Pediatric Patients

### Incidence

(See Tables 19-3 and 19-5)

- Of 722 events of IHCA in children (1–<18 years of age) at 108 hospitals, 47.5% occurred in the ICU, 5.8% in the operating room, 19.8% in the ED, and 26.7% in noncritical care areas per 2023 GWTG data (Table 19-3). Of the 1274 IHCA events in infants (<1 year of age) at 104 hospitals, 57.4%

occurred in the ICU, 4.5% in the operating room, 4.7% in the ED, and 33.4% in noncritical care areas per the 2023 GWTG data (Table 19-3).

- Additional ICHA in pediatric patients quality of care data from 2023 GWTG-R are listed in Table 19-5 and Chapter 26 (Quality of Care).
- 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 dataset of 10078 pediatric ICU admissions from 2011 to 2013.<sup>122</sup>
- In a registry of 23 cardiac ICUs in the Pediatric Critical Care Consortium that included 15908 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>123</sup>
- In a meta-analysis that included 131724 children with cardiac disease admitted to an ICU, 5% (95% CI, 4%–6%) experienced IHCA with in-hospital mortality reaching 51% (95% CI, 42%–59%).<sup>124</sup>
- Initial recorded cardiac arrest rhythm was VF or VT in 8.8% of 722 child (>1–<18 years of age) events at 108 hospitals in GWTG-R in 2023 and 1.9% of 1274 infant (<1 year of age) events at 104 hospitals (Table 19-3).
- In a secondary analysis of the ICU-RESUS trial, investigators found that in 1276 patients, 184 (16.3%) had a prearrest diagnosis of PH and 101 of 184 patients (54.9%) were receiving inhaled nitric oxide at the time of their IHCA.<sup>125</sup>
- 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>126</sup>

### Secular Trends

(See Chart 19-1)

- Survival to discharge after pulseless IHCA in pediatric patients (children and infants 0–18 years of age) increased from 18.9% to 45.2% between 2000 and 2023 in GWTG data (Chart 19-1).
- 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>127</sup> The improvement in survival plateaued after 2010.

### Mortality

(See Table 19-3)

- Survival to hospital discharge after pulseless IHCA was 42.2% in children 1 to <18 years of age and 45.9% in infants <1 year of age per 2023 GWTG data (GWTG-R, unpublished data; 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>122</sup>
- In 429 pediatric IHCA events, survival before and during the COVID-19 pandemic was similar (52% versus 60%;  $P=0.12$ ).<sup>128</sup>

### Global Burden of Disease

- Perioperative cardiac arrest and mortality vary between middle- and low-income countries. The global incidence of cardiac arrest that occurred perioperatively was 2.54 (95% CI, 2.23–2.84) per 1000 anesthetic events, and mortality was 41.18 (95% CI, 35.68–46.68) per 1000 anesthetic events.<sup>129</sup>

## SCA or SCD When Location Is Not Specified

### Lifetime Risk and Cumulative Incidence

(See Table 19-7 and Chart 19-2)

- SCD appeared among the multiple causes of death on 12.7% of death certificates in 2022 (417 957 of 3 279 857; Table 19-7). Because some people survive SCA, the lifetime risk of cardiac arrest is even higher.
- In 2022, infants had a higher incidence of SCD (12.1 per 100 000) than older children (1.3–2.3 per 100 000). Among adults, risk of SCD increased exponentially with age, surpassing the risk for infants by 35 to 39 years of age (16.8 per 100 000; Chart 19-2).

### Secular Trends

(See Charts 19-3 and 19-4)

- 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 [ $n=641$ ; 2003–2004] and REDINSCOR I [ $n=1710$ ; 2007–2011]).<sup>130</sup> This reduction in SCD was associated with more frequent use of  $\beta$ -blockers (85% versus 71%), mineralocorticoid antagonists (64% versus 44%), ICDs (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, increased to 111.2 in 2021, and decreased to 99.6 in 2022 (Chart 19-3).
- In a community-based survey of out-of-hospital SCD, only one-half of the sudden deaths had no specific findings at autopsy. In these cases, the mechanism of death was classified as arrhythmic. However, approximately one-half of the sudden unexpected deaths in each study had specific

findings at autopsy, supporting a nonarrhythmic mechanism for the sudden death, including AMI, cardiac rupture, acute HF, and acute pulmonary embolus (Chart 19-4). In addition, acute neurological events and occult drug overdoses were common in the San Francisco community study. EMS data were available for the San Francisco community study. When the initial rhythm recorded by EMS was VT or VF, the autopsy findings were likely to be consistent with sudden arrhythmic death, whereas when the initial finding was pulseless electric activity, the autopsy was likely to result in a classification of nonsudden arrhythmic death.

### 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>131</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 of 360 (3.9%) had SCD and 16 (4.4%) had major ventricular arrhythmias (SCA or ICD intervention) during a median follow-up of 152 months.<sup>132</sup> Events were associated with larger LA 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 (HR, 1.47 [95% CI, 1.07–2.03];  $P=0.02$  and HR, 1.89 [95% CI, 1.25–2.87];  $P=0.003$ ) and frequent ventricular premature depolarizations (HR, 1.38 [95% CI, 1.00–1.90];  $P=0.046$  and HR, 1.78 [95% CI, 1.19–2.66];  $P=0.005$ ) with total and cardiovascular mortality, respectively, but no relation to SCD.<sup>133</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>134</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 ≈50% increased risk of SCD compared with patients without prior MI.<sup>135</sup>

- Alcohol consumption was not associated with increased risk of ventricular arrhythmia but was associated with SCD in a longitudinal study of 408 712 individuals over a follow-up time of 11.5 years.<sup>136</sup>

### Age

**(See Chart 19-2)**

- In 2022, 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 ≥10 years of age with each 5-year age category through 84 years of age (Chart 19-2).

### Sex

- 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, and March 1, 2014.<sup>137</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%;  $P<0.01$ ).

### Race and Ethnicity

- In the ARIC study, 215 of 3832 Black participants (5.61%) and 332 of 11 237 White participants (2.95%) experienced SCD during 27.4 years of follow-up.<sup>138</sup> The sex-adjusted HR for SCD comparing Black participants with White participants was 2.12 (95% CI, 1.79–2.51), and the fully adjusted HR was 1.38 (95% CI, 1.11–1.71).
- In 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>137</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 patients with hypertension without evidence of coronary or cerebrovascular disease at entry who were followed up for an average of 10.3 years.<sup>139</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).
- In a cohort of 233 970 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>140</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>141</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>142</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>143</sup>
- A French database of all hospitalized patients in 2013 was queried. In total, 3 345 638 patients were categorized into having AF or not having AF.<sup>144</sup> The incidence (2.23%/y versus 0.56%/y) and risk (HR, 3.657 [95% CI, 3.604–3.711]) of ventricular arrhythmia and cardiac arrest were higher in patients with AF compared with patients without AF.
- Risk of SCD in the general population ≥45 years of age who were initially free of CVD when recruited in 1987 to 1993 and followed up for a subsequent 10 years was associated with male sex, Black race, diabetes, current smoking, and SBP.<sup>145</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>145</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>146</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>147</sup>
- In a meta-analysis that included 17 studies with 11 895 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>148</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>149</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>150</sup>
- Among 12 241 ARIC study participants, of whom 346 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>151</sup>
- Among 20 177 participants in the ARIC study followed up for 14 years (median), the incidence of SCD was 1.86 per 1000 PY. 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>152</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>153</sup>

### Social Determinants of Health/Health Equity

- In the ARIC study, 215 of 3832 Black participants (5.61%) and 332 of 11 237 White participants (2.95%) experienced SCD during 27.4 years of follow-up.<sup>138</sup> The sex-adjusted HR for SCD comparing Black participants with White participants was 2.12 (95% CI, 1.79–2.51), and the fully-adjusted HR was 1.38 (95% CI, 1.11–1.71).
- Survival and neurological recovery after cardiac arrest are worse in White Hispanic individuals, Black individuals, and Asian individuals compared with White individuals.<sup>154</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.

### Mortality

(See Table 19-7)

- In 2022, primary-cause SCD mortality was 19 171, and any-mention SCD mortality in the United States was 417 957 (Table 19-7). The any-mention age-adjusted annual rate was 99.6 (95% CI, 99.3–99.9) SCDs per 100 000 population (unpublished NHLBI tabulation).<sup>155</sup>
- 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>156</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.

### Complications

- Survivors of cardiac arrest experience multiple medical problems related to critical illness, including impaired consciousness and cognitive deficit. Functional impairments are associated with reduced

function, reduced quality of life, and shortened life span.<sup>157,158</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>159</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>160</sup>
- Of 141 individuals who survived hospitalization after SCA, 41 (72%) returned to work by 12 months.<sup>159</sup>
- In a meta-analysis of 35 studies including 7186 survivors, the incidence of first recurrence of cardiac arrest was 15.24% (95% CI, 11.01%–19.95%; mean follow-up time,  $41.3 \pm 29.3$  months) and of second recurrence was 35.03% (95% CI, 19.65%–51.93%; mean follow-up,  $161.1 \pm 54.3$  months).<sup>161</sup> Shockable initial rhythm increased the incidence of first recurrence of cardiac arrest ( $P=0.01$ ).

## Special Circumstances

### Opioid-Associated Cardiac Arrest

- The incidence of opioid-associated OHCA has been increasing with the overall rise in prevalence of synthetic opioids in the United States since 2013.<sup>162</sup>
- Most estimates are based on EMS-treated events and do not account for those individuals who were left untreated by EMS after opiate overdose.<sup>162</sup>
- Two publications from large North American datasets estimate the incidence of opioid-associated OHCA at 2% of the total OHCA population; however, recent smaller studies with the benefit of greater depth of chart review estimate that this incidence is closer to 6% to 15% of all OHCAs.<sup>131,163,164</sup>

### Sports-Related Cardiac Arrest

- Sports-related SCAs accounted for 39% of SCAs among those  $\leq 18$  years of age, 13% among those 19 to 25 years of age, and 7% among 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>165</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>166</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>167</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>168</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>169</sup> Only 2 deaths were reported among 1 116 271 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>170</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>166</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 LOTS (6.0%).<sup>171</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  $\pm$  SD age was  $47 \pm 15$  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  $\geq 35$  years of age.<sup>172</sup>
- Preparticipation screening of 5169 middle and high school students (mean  $\pm$  SD age,  $13.06 \pm 1.78$  years) from 2010 to 2017 revealed high-risk cardiovascular conditions in 1.47%.<sup>173</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).
- 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>167</sup>

### Maternal Cardiac Arrest

- 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>174</sup>

## Epilepsy and Cardiac Arrest

- In a global cohort of 271 172 patients with epilepsy, the 30-day risk of cardiac arrest in patients after a seizure was 0.9%.<sup>175</sup>

## Specific Ventricular Arrhythmias and Inherited Channelopathies

### 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>176-178</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>179</sup>
- Among 228 unexplained SCA, whole-exome sequencing of 184 genes associated with SCD or cardiomyopathy identified a pathogenic/likely pathogenic variant in 23 survivors (10%). Among the 23 pathogenic/likely pathogenic variants identified, 13 variants (57%) were present in cardiomyopathy genes but were not associated with a diagnosis of cardiomyopathy at the time of arrest.<sup>180</sup>
- Genetic testing for *SCN5A* rare variants with a minor allele frequency <0.005 in 60 patients with SCA revealed that 5 (8.3%) carried an *SCN5A* rare variant.<sup>181</sup> All 5 variants identified were categorized as variants of unknown significance.<sup>181</sup> However, whole-cell patch clamp studies showed that the Asp872Asn *SCN5A* variant was associated with PR prolongation and early repolarization.<sup>181</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%), arrhythmogenic cardiomyopathy (4%), and Brugada syndrome (3%).<sup>182</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>183</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%, arrhythmogenic cardiomyopathy 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>184</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>185</sup> Among 127 adults, diagnoses included idiopathic VF (44.1%), arrhythmogenic bileaflet mitral valve (14.2%), acquired LQTS (9.4%), LQTS (7.9%), and J-wave syndromes such as Brugada (3.9%). Among 53 children, diagnoses included LQTS (28.3%), CPVT (20.8%), idiopathic VF (20.8%), HCM (5.7%), and triadin knockout syndrome (5.7%).
- Among 225 patients of resuscitated SCA, 115 (51%) had an inherited cardiac disease. The identified inherited cardiac diseases included LQTS (42%), HCM (24%), Brugada syndrome (14%), CPVT (8%), and arrhythmogenic cardiomyopathy (8%).<sup>186</sup>

### 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>187</sup> However, the oligogenic nature of genetic determinants of SCA requires further evaluation.
- Although SCA GWASs are limited, investigations have been conducted with multiple electrocardiographic traits used 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>188</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>189</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>190,191</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>192</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>193,194</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>195</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>196</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>197</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>198</sup>
- Genetic testing for LQTS among 281 families had a diagnostic yield for genetic variants of 47%.<sup>199</sup> Nearly a third of patients with acquired LQTS are reported to carry pathogenic congenital LQTS variants.<sup>200</sup>
- However, some studies have called into question whether previously identified LQTS genes are truly causative.<sup>201,202</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>203</sup>
- GWASs have identified additional rare and common variants in genes associated with QT interval,<sup>201</sup>

suggesting that individuals with long QT who are variant negative could have a polygenic inheritance.

- Common genetic variants may explain ≈15% of the susceptibility to LQTS. A 68-SNP PRS for the QT interval had a higher score in genotype-negative (no disease-causing rare variant identified) patients compared with genotype-positive patients, supporting a polygenic basis for LQTS in genotype-negative patients. In genotype-negative patients, the third (OR, 3.74;  $P=4.2\times10^{-6}$ ) and fourth (OR, 6.13;  $P=4.8\times10^{-11}$ ) quartiles of the PRS score were associated with a higher odds of LQTS compared with the first quartile.<sup>204</sup>
- 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>205</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>206</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>207</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>208</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>209</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>210</sup>

- Reappraisal of the 17 LQTS genes led to the classification of 3 genes (*KCNQ1*, *KCNH2*, *SCN5A*) as definitive genes causing LQTS and 4 genes (*CALM1*, *CALM2*, *CALM3*, *TRDN*) as having definitive or strong evidence for causality in LQTS with atypical features; 1 gene (*CACNA1C*) had moderate evidence for causing LQTS, and the other genes had limited evidence for causing LQTS.<sup>211</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>212</sup>
- Prevalence of a QTc interval <320 milliseconds in a population of 41 767 young, predominantly male Swiss conscripts was 0.02%,<sup>213</sup> which was identical to the prevalence in a Portuguese sudden death registry.<sup>214</sup>
- Prevalence of QT interval ≤340 milliseconds in 99 380 unique patients ≤21 years of age at the Cincinnati Children's Hospital between 1993 and 2013 was 0.05%.<sup>215</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>216</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>217</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>218</sup> Prevalence was higher in males (0.9%) than in females (0.1%).<sup>219</sup>

- Among 678 patients with Brugada syndrome from 23 centers in 14 countries, patients whose first documented arrhythmic event was SCA had a mean±SD age of 39±15 years, whereas age at the first documented arrhythmic event in patients with prophylactic defibrillator implantation was 46±13 years.<sup>220</sup>
- In a multicenter retrospective study of 770 patients with Brugada syndrome, 177 (23%) were female.<sup>221</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 a mean follow-up of 122 months, 2.8% of females versus 7.1% of males ( $P=0.04$ ) experienced appropriate ICD 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>222</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>223</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>224</sup>
- Variants in the *PKP2* gene that causes arrhythmogenic cardiomyopathy have been reported to cause an arrhythmogenic phenotype in the absence of overt structural disease<sup>225</sup> and may be implicated in Brugada syndrome.<sup>226</sup>
- Apart from identifying 10 new loci, a GWAS meta-analysis for Brugada syndrome supported by functional studies has elucidated the causal role of *MAPRE2* in the pathogenesis of Brugada syndrome.<sup>227</sup>
- The large proportion of sporadic cases and variable penetrance in *SCN5A* carriers has suggested a more complex pattern of penetrance. PRS-based analysis for Brugada syndrome supports that the disease threshold varies between individuals depending on the contributions of rare variants

of *SCN5A*, common risk alleles, and exposure to sodium channel blockade.<sup>227</sup>

- A reappraisal of 21 genes associated with Brugada syndrome for clinical validity led to the classification of only *SCN5A* as definitive evidence for causing Brugada syndrome, and the other 20 were classified as limited evidence for causing Brugada syndrome.<sup>228</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 (eg, 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>229</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>230</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>231</sup>
- Incidence of SCA in children with ≥2 CPVT gene variants was 11 of 15 (73%).<sup>232</sup> VT or exertional syncope occurred in 3 of the children (20%), and only 1 (7%) was asymptomatic.

### Arrhythmogenic RV Dysplasia/Arrhythmogenic Cardiomyopathy

- Arrhythmogenic RV dysplasia or arrhythmogenic cardiomyopathy is a form of genetically inherited structural HD that presents with fibrofatty replacement of the myocardium, which increases risk for palpitations, syncope, and sudden death attributable to VT.<sup>233</sup>
- Twelve arrhythmogenic cardiomyopathy loci have been described (*ARVC1*–*ARVC12*).<sup>234</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 arrhythmogenic cardiomyopathy.<sup>235</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>236</sup>

#### Complications

- In a cohort of 301 patients with arrhythmogenic cardiomyopathy from a single center in Italy, the probability of a first life-threatening arrhythmic event was 14% at 5 years, 23% at 10 years, and 30% at 15 years.<sup>237</sup>
- In a pooled analysis examining 5485 patients, rates of SCD were 0.65 per 1000 (95% CI, 0.00–6.43;  $P=0.00$ ) in those with an ICD placed and 7.21 (95% CI, 2.38–13.79;  $P=0.00$ ) in the non-ICD cohort.<sup>238</sup> Patient characteristics identified individuals at a higher risk of life-threatening arrhythmia: age at presentation (aHR, 0.98 [95% CI, 0.97–0.99]), male sex (2.08 [95% CI, 1.29–3.36]), RV dysfunction (6.99 [95% CI, 2.17–22.49]), QRS fragmentation (6.55 [95% CI, 3.33–12.90]), T-wave inversion (1.12 [95% CI, 1.02–1.24]), syncope at presentation (2.83 [95% CI, 2.40–4.08]), and previous nonsustained ventricular tachyarrhythmia (2.53 [95% CI, 1.44–4.45]).
- In a cohort of 502 patients with arrhythmogenic cardiomyopathy, younger patients (<50 years versus >50 years of age) were more likely to present with SCA (5% versus 2%) or SCD (7% versus 6%).<sup>239</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>240</sup>
- 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>241</sup>
- In a pooled analysis of 98 studies and N=70 510 patients (431 407 patient-years), contemporary SCD rates from 2015 to present were 0.32%/y and significantly lower compared with 2000 or earlier (incidence rate, 0.32% [95% CI, 0.20%–0.52%] versus incidence rate, 0.73% [95% CI,

0.53%–1.02%), respectively.<sup>242</sup> Reported SCD rates for HCM were lowest in North America (incidence rate, 0.28% [95% CI, 0.18%–0.43%]) and highest in Asia (incidence rate, 0.67% [95% CI, 0.54%–0.84%]).

### **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>243</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>244</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>243</sup>
- Among 11 956 residents of rural Liaoning Province, China, who were  $\geq 35$  years of age, 1.3% had ERP, with a higher prevalence in males (2.6%) than females (0.2%).<sup>245</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, LA enlargement, right atrial enlargement, short PQ interval, and ventricular pre-excitation WPW syndrome.<sup>246</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>247</sup>
- The consensus panel<sup>244</sup> and others have identified certain electrocardiographic characteristics associated with increased risk for VF: ERP in the inferior and lateral electrocardiographic leads and J waves associated with horizontal or down-sloping ST segments (as opposed to rapidly ascending ST segments).<sup>248</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>249</sup>

- Shocks from an automatic ICD 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>250</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>251</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>252–254</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>255</sup>
- A review of the NIS from 2012 to 2014 identified 46 289 patients with a diagnosis of sarcoidosis. VT was recognized in 2.29% of all patients with sarcoidosis compared with 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 patients with sarcoidosis was 0.72%.<sup>256</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>257</sup>
- Prevalence of sustained VT in patients with LV aneurysm after MI is reported at 10%.<sup>258</sup>
- Monomorphic VT occurred in 9 of 342 patients (2.6%) at a median of 1 day (interquartile range,

0.25–4.75 days) after PCI for chronic total occlusion of a coronary artery.<sup>259</sup>

- During a mean follow-up period of 85 months, sustained VT was observed in 13 of 250 patients (5.2%) and monomorphic VT in 9 of 250 patients (3.6%) with congenital LV aneurysms or diverticula.<sup>260</sup>

### Polymorphic VT/VF

#### Prevalence and Incidence

- In the setting of AMI, the prevalence of polymorphic VT was 4.4%.<sup>261</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>257</sup>

### Complications

- In the setting of AMI, polymorphic VT is associated with increased mortality (17.8%).<sup>261</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>262</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>263</sup>

**Table 19-1. Differences in Bystander Interventions and Survival After OHCA by Race, Ethnicity, Sex, and Neighborhood Characteristics, CARES, United States, 2023**

	Nontraumatic pathogenesis survival rates	Bystander intervention rates	
	Overall survival to hospital discharge	CPR	Public AED use
Total	14 299/139 822 (10.2%)	43 736/106 193 (41.2%)	2228/19 099 (11.7%)
Race and ethnicity			
American Indian/Alaska Native	37/546 (6.8%)	185/451 (41.0%)	10/82 (12.2%)
Asian	371/3880 (9.6%)	1330/3050 (43.6%)	65/477 (13.6%)
Black/African American	2750/30 286 (9.1%)	7646/22 026 (34.7%)	351/3723 (9.4%)
Hispanic/Latino	1209/12 177 (9.9%)	3879/9771 (39.7%)	173/2014 (8.6%)
Native Hawaiian/Pacific Islander	76/653 (11.6%)	229/533 (43.0%)	6/103 (5.8%)
White	7679/70 459 (10.9%)	23 164/53 257 (43.5%)	1260/9386 (13.4%)
Unknown	2177/21 821 (10.0%)	7303/17 105 (42.7%)	363/3314 (11.0%)
Sex			
Male	9403/88 079 (10.7%)	28 445/68 741 (41.4%)	1849/14 862 (12.4%)
Female	4891/51 700 (9.5%)	15 281/37 420 (40.8%)	379/4222 (9.0%)
Neighborhood racial composition			
≥70% White	6478/59 111 (11.0%)	20 121/45 269 (44.4%)	953/7503 (12.7)
≥40% Black	1726/20 079 (8.6%)	5102/15 317 (33.3%)	193/2329 (8.3%)
Integrated	6095/60 632 (10.0%)	18 513/45 607 (40.6%)	1082/9267 (11.7%)
Neighborhood median household income			
<\$40 000 annually	1434/15 617 (9.2%)	3866/11 867 (32.6%)	172/2325 (7.4%)
\$40 000–\$80 000 annually	6787/67 673 (10.0%)	20 499/51 026 (40.2%)	923/8980 (10.3%)
>\$80 000 annually	5657/52 756 (10.7%)	19 319/40 324 (45.4%)	893/52 756 (13.1%)

Bystander CPR rate excludes 9-1-1 responder–witnessed, nursing home, and health care facility arrests. Public AED use rate excludes 9-1-1 responder–witnessed, home/residence, nursing home, and health care facility arrests. Sex was missing for 38 cases. Race is unknown for 16.2% of CARES cases in the 2022 dataset 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>3</sup>

**Table 19-2.** Variation in EMS-Treated OHCA in Selected States, United States, 2023

	OHCA incidence					Nontraumatic cause survival rates		Bystander intervention rates	
	CARES cases reported	CARES population catchment	Total state population	% population covered	Incidence rate (per 100 000)	Overall survival to hospital discharge (%)	Utstein survival (%)	CPR (%)	Public AED use (%)
National	139 822	167 583 783	333 287 557	50.30%	83.4	10.2	32.8	41.2	11.7
State									
Alaska	519	610 324	733 583	83.2%	85.0	11.2	35.4	75.2	10.6
California	25 324	32 898 701	39 029 342	84.3%	77.0	8.4	32.1	41.8	9.1
Colorado	3542	4 800 582	5 839 926	82.2%	73.8	10.8	35.6	43.9	10.8
Connecticut	2387	2 851 771	3 626 205	78.6%	83.7	8.4	31.7	25.4	6.1
Delaware	1298	1 018 396	1 018 396	100.0%	127.5	10.8	33.9	41.7	7.8
Hawaii	1591	1 440 196	1 440 196	100.0%	110.5	12.6	36.8	39.7	12.7
Maine	1159	1 385 340	1 385 340	100.0%	83.7	8.7	25.9	43.6	6.5
Michigan	8671	8 832 727	10 034 113	88.0%	98.2	8.6	29.1	38.9	13.0
Minnesota	3408	4 777 014	5 717 184	83.6%	71.3	11.7	32.2	37.8	9.1
Mississippi	1596	2 257 986	2 940 057	76.8%	70.7	7.7	18.3	40.8	13.2
Missouri	3223	3 137 940	6 177 957	50.8%	102.7	9.0	29.9	38.2	10.7
Montana	692	1 002 301	1 122 867	89.3%	69.0	11.3	30.3	42.8	7.8
Nebraska	717	1 166 752	1 967 923	59.3%	61.5	14.8	40.2	49.2	12.1
Nevada	2288	2 967 081	3 177 772	93.4%	77.1	13.6	40.9	55.7	20.5
North Carolina	8989	9 673 545	10 698 973	90.4%	92.9	11.6	30.4	40.3	11.4
Oregon	3183	3 966 389	4 240 137	93.5%	80.2	13.7	34.7	55.9	10.7
Pennsylvania	7106	9 157 463	12 972 008	70.6%	77.6	8.8	31.1	36.5	13.5
Utah	1600	3 380 800	3 380 800	100.0%	47.3	10.1	31.5	38.9	9.9
Vermont	506	647 064	647 064	100.0%	78.2	7.5	13.2	47.0	16.7
Washington	5021	7 626 214	7 785 786	98.0%	65.8	15.0	44.3	53.2	12.3
Wisconsin	3214	3 485 171	5 892 539	59.1%	92.2	11.0	33.8	39.9	15.2
District of Columbia	931	671 803	671 803	100.0%	138.6	10.5	44.3	31.6	11.0

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: Data derived from CARES.<sup>3</sup>

**Table 19-3. Characteristics of and Outcomes for OHCA (CARES) and IHCA (GWTG-R), United States, 2023**

	OHCA*			IHCA		
	Adults (>18 y)	Children (1–18 y)	Infants (<1 y)†	Adults (>18 y)	Children (1–18 y)	Infants (<1 y)
Females	37.0	40.0	43.9	40.6	47.4	47.2
Males	63.0	60.0	56.0	59.4	52.6	52.7
Survival to hospital discharge	10.2	15.9	7.4	23.6	42.2	45.9
Good functional status at hospital discharge‡	8.1	12.8	5.7	79.2	70.9	79.6
Initial pulseless rhythm§						
VF/VT/shockable	17.8	9.5	2.5	14.4	8.8	1.9
PEA	22.1	16.8	13.5	55.4	39.1	21.2
Asystole	51.7	63.6	74.6	21.3	26.9	16.0
Unknown	...	...	...	7.6	7.7	7.9
Public setting	18.2	16.7	8.3	...	...	...
Home	71.0	83.0	91.7	...	...	...
Nursing home	10.7	0.3	0.0	...	...	...
Public AED use	11.7	19.2	2.5	...	...	...
Arrest in ICU	...	...	...	41.1	47.5	57.4
Arrest in operating room	...	...	...	2.2	5.8	4.5
Arrest in ED				17.8	19.8	4.7
Noncritical care area				38.7	26.7	33.4

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; GWTG-R, Get With The Guidelines—Resuscitation; 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 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=332).

†Stillborn neonates and perinatal newborns born without signs of life are not CARES cases and are not entered into the registry.

‡Good functional status is defined as discharge Cerebral Performance Category of 1 or 2 in adults or Pediatric Cerebral Performance Category of 1 or 2 in pediatrics.

§Does not include initial rhythms of bradycardia with poor perfusion.

||Inclusion criteria: an OHCA. 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>3</sup> and are based on 135 723 EMS-treated OHCA adult cases, 2079 EMS-treated OHCA pediatric cases (1–18 years of age), and 1587 EMS-treated OHCA infant cases (<1 year of age) with known hospital outcome data in 2023. IHCA data are from GWTG-R (unpublished AHA tabulation) 2023 and are based on 40 837 adult IHCAs in 404 hospitals, 722 child (≥1–<18 years of age) IHCAs in 108 hospitals, and 1274 infant (<1 year of age) IHCAs in 104 hospitals.

**Table 19-4. Outcomes of EMS-Treated Nontraumatic OHCA in Adults (>18 Years of Age), CARES, United States, 2023**

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 (135 723)	26.1	10.2	8.1	61.0
Home/residence (96 429)	24.6	8.8	6.9	64.3
Nursing home (14 540)	15.8	3.9	1.6	75.1
Public setting (24 752)	38.0	19.3	16.7	49.2
Unwitnessed (69 242)	16.6	4.5	3.3	72.6
Bystander witnessed (50 216)	34.7	15.4	12.6	55.7
9-1-1 responder witnessed (16 265)	40.2	18.2	14.6	54.7
Shockable presenting rhythm (24 192)	47	28.7	25.2	48.9
Nonshockable presenting rhythm (111 518)	21.6	6.2	4.4	71.4
Layperson CPR (41 943)†	28.5	12.5	10.5	56.2
No layperson CPR (60 504)	22.7	7.6	5.8	66.7

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=293).

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 derived from CARES.<sup>3</sup>

**Table 19-5. Quality of Care of Patients With IHCA Among GWTG-R Hospitals, United States, 2023**

	Adults (≥18 y)	Children (≥1y-<18 y)*	Infants (<1 y)*
Event outside critical care setting	38.7	26.7	33.4
Hospital survival to discharge for IHCA outside the ICU	16.6	22.2	23.6
End-tidal CO <sub>2</sub> monitoring used during arrest (all IHCA events)	34.7	55.4	40.2

Values are mean percentages.

GWTG-R is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

GWTG-R indicates Get With The Guidelines—Resuscitation; ICU, intensive care unit; and IHCA, in-hospital cardiac arrest.

Source: Unpublished American Heart Association tabulation, GWTG-Resuscitation.

\*Includes children and infants with initial rhythms of bradycardia with poor perfusion.

**Table 19-6. Outcomes of EMS-Treated Nontraumatic OHCA in Children and Infants, CARES, United States, 2023**

Age group, y (n)	Survival to hospital admission	Survival to hospital discharge	Survival with good neurological function (CPC 1 or 2)	In-hospital mortality*
<1 (1587)	18.5	7.4	5.7	60.2
1–12 (1225)	31.6	14.1	10.5	55.3
13–18 (854)	37.7	18.5	16.2	50.9

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=36). 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>3</sup>

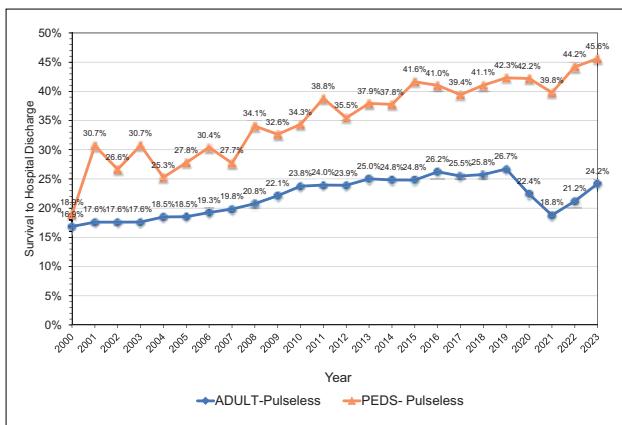
**Table 19-7. SCA Mortality, United States, 2022 (ICD-10 I46.0, I46.1, I46.9, I49.0)**

Population group	No. of deaths as underlying cause, 2022, all ages	Underlying cause age-adjusted mortality rates per 100 000 (95% CI), 2022	Any-mention mortality, 2022, all ages	Any-mention age-adjusted mortality rates per 100 000 (95% CI), 2022
Both sexes	19 171	4.6 (4.5–4.6)	41 7957	99.6 (99.3–99.9)
Males	10 622	5.7 (5.5–5.8)	22 2334	120.7 (120.2–121.2)
Females	8 549	3.7 (3.6–3.7)	19 5623	82.5 (82.1–82.8)
NH White males	7 605	5.6 (5.4–5.7)	15 2654	112.7 (112.1–113.3)
NH White females	6 089	3.6 (3.5–3.7)	13 2636	76.4 (76.0–76.8)
NH Black males	1 913	10.9 (10.4–11.4)	3 1415	183.1 (180.9–185.2)
NH Black females	1 658	6.9 (6.6–7.2)	2 9940	124.6 (123.2–126.0)
Hispanic males	712	3.4 (3.1–3.7)	2 4714	130.0 (128.2–131.7)
Hispanic females	526	2.2 (2.0–2.4)	2 1236	89.7 (88.5–90.9)
NH Asian males*	252	2.7 (2.4–3.0)	9577	104.5 (102.4–106.6)
NH Asian females*	191	1.5 (1.3–1.8)	8702	69.7 (68.2–71.2)
NH American Indian/Alaska Native*	74	2.8 (2.2–3.5)	2 650	103.8 (99.7–107.8)
NH Native Hawaiian or Pacific Islander*	34	5.6 (3.8–7.8)	866	147.3 (137.2–157.3)

ICD-10 indicates International Classification of Diseases, 10th Revision; NH, non-Hispanic; and SCA, sudden cardiac arrest.

\*Mortality for Hispanic people, NH American Indian or Alaska Native people, 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 under-reporting on death certificates of American Indian or Alaska Native decedents, Asian decedents, Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

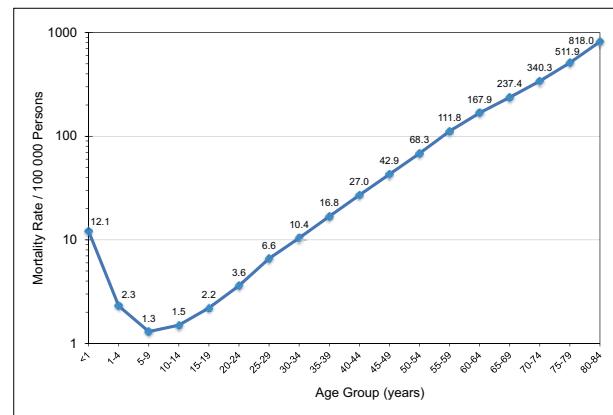
Sources: Any-mention cause and underlying cause data derived from the National Vital Statistics System<sup>264</sup> and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database.<sup>155</sup>



**Chart 19-1. Temporal trends in survival to hospital discharge after IHCA in adults and children in GWTG-R from 2000 to 2023, United States.**

GWTG-R indicates Get With The Guidelines—Resuscitation; IHCA, in-hospital cardiac arrest; and PEDS, pediatrics.

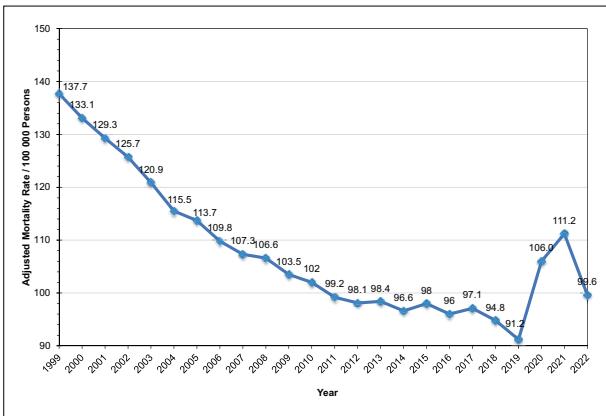
Source: GWTG-R; unpublished American Heart Association data.



**Chart 19-2. Age-specific mortality rates for any mention of SCD, by age, United States, 2022.**

SCD indicates sudden cardiac death.

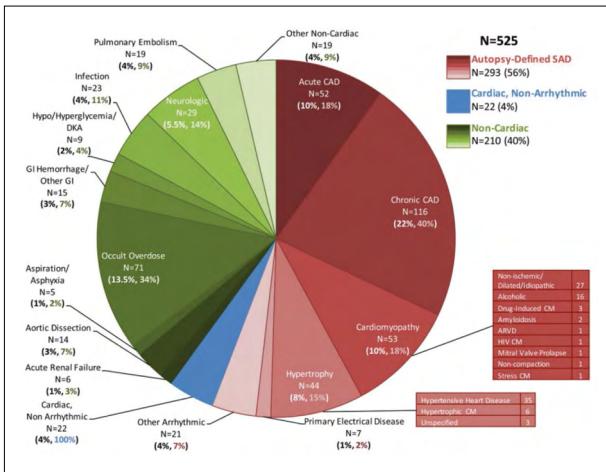
Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research database.<sup>155</sup>



**Chart 19-3. Age-adjusted mortality rates for any mention of SCD, United States, 1999 to 2022.**

SCD indicates sudden cardiac death.

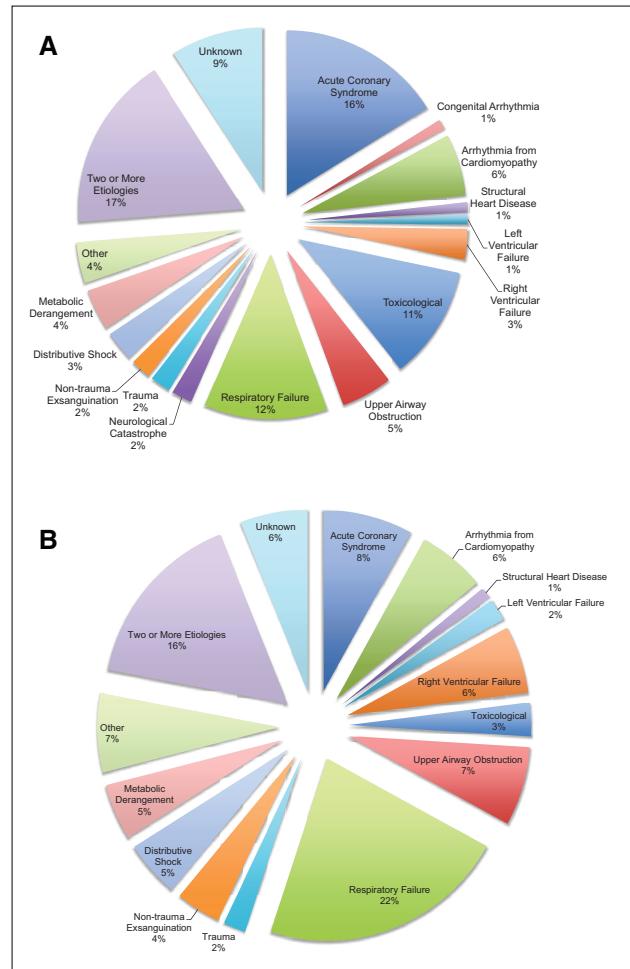
Source: Data derived from Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiological Research.<sup>155</sup>



**Chart 19-4. Adjudicated causes of autopsied WHO-defined SCDs.**

Adjudicated causes of autopsied WHO-defined SCDs after review of comprehensive medical records, EMS records, complete autopsy, toxicology, and postmortem chemistries. Autopsy-defined SADs had no identifiable extracardiac (eg, 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 from Tseng et al.<sup>265</sup> Copyright © 2018 American Heart Association, Inc.



**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>131</sup>

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## 20. SUBCLINICAL ATHEROSCLEROSIS

**See Charts 20-1 through 20-6**

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Multiple complementary imaging modalities facilitate the detection and quantification of atherosclerosis at different stages and within various vascular beds. Early identification of subclinical atherosclerosis can guide preventive care, including lifestyle modifications and medical treatment (eg, aspirin, antihypertensives, lipid-lowering therapy, GLP1-RA) to prevent clinical manifestations of atherosclerosis such as MI, stroke, or PAD. Several modalities can be used for assessing atherosclerosis, including noncontrast chest CT, CCTA, B-mode ultrasound, brachial artery reactivity testing, aortic and carotid MRI, and tonometric measurement of vascular compliance.

Among these modalities, the role of CAC in assessing cardiovascular risk is particularly well established. The 2018 Cholesterol Clinical Practice Guideline<sup>1</sup> and the 2019 CVD Primary Prevention Clinical Practice Guidelines<sup>2</sup> recommend using a CAC score to guide decisions on statin therapy in intermediate-risk or selected borderline-risk adults (10-year ASCVD risk, 5%–19%). This approach is advised if statin therapy decisions remain uncertain after 10-year ASCVD risk is estimated and risk enhancers are considered. The US-based National Lipid Association<sup>3</sup> also recommends the use of CAC to guide preventive strategies for ASCVD risk reduction, as do professional organizations around the globe such as those in Europe, Canada, China, Australia, and the United Kingdom.<sup>4</sup>

This chapter begins with a focus on coronary atherosclerosis followed by statistics on carotid atherosclerosis and includes statistics on other subclinical atherosclerosis imaging studies. The chapter prioritizes discussion of social determinants of health and health equity in relation to subclinical atherosclerosis. Furthermore, the last section of the chapter provides statistics on subclinical atherosclerosis in relation to healthy lifestyle behaviors and preventive medications.

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The 2025 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 2025. 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.

## Coronary Atherosclerosis

### Background

- CAC quantifies the calcified atherosclerotic burden within the coronary arteries using noncontrast CT and correlates strongly with the total plaque burden (both calcified and noncalcified). CAC is classically reported with an Agatston score based on the total area of calcium deposits and the density of coronary calcium.
- CCTA is a contrasted CT scan that can visualize calcified and noncalcified atherosclerotic and assesses for coronary artery lumen narrowing.

### Prevalence and Risk Factors

#### (See Charts 20-1 through 20-4)

- The NHLBI's MESA, a study of White adults, Black adults, Chinese adults, and Hispanic adults, measured CAC in 6814 participants 45 to 84 years of age (mean, 63 years), including White men and women ( $n=2619$ ), Black men and women ( $n=1898$ ), Hispanic men and women ( $n=1494$ ), and Chinese men and women ( $n=803$ ).<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 females 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.
- On average, the prevalence of CAC among women is comparable to that among men who are 10 to 15 years younger (Chart 20-1).<sup>6</sup>
- The prevalence of atherosclerosis increases with age:
  - In a harmonized dataset analysis of 19725 Black individuals and White individuals 30 to 45 years of age from CARDIA, the CAC Consortium, and the Walter Reed Cohort, the prevalence of CAC  $>0$  among White males, Black males, White females, and Black females was 26%, 16%, 10%, and 7%, respectively (Chart 20-2).
  - Among MESA participants 60 to 70 years of age, the prevalence of CAC was  $\approx 44\%$  for women and 68% for men (unpublished tabulation using MESA data<sup>7</sup>).
  - Among MESA and ARIC participants  $\geq 75$  years of age, the prevalence of CAC was 85% for women and 90% to 95% for men, and for participants  $\geq 90$  years of age, there was a  $>95\%$  prevalence of CAC regardless of sex.<sup>8</sup>

- To illustrate 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>9</sup>
  - Overall, in the population (mean age, 58 years; 50% female), 85% of individuals were free of any CAC, and even in individuals >75 years of age, 65% remained free of CAC. These unique data emphasize the importance of modifiable risk factors and that coronary atherosclerosis typically can be avoided by maintaining a low lifetime burden of CAD risk factors.<sup>9</sup>
- In US adults who are free of CAC at baseline, subsequent development of CAC is strongly correlated with a person's risk factor profile. In 3116 MESA participants (58±9 years of age; 63% women) 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>10</sup> A rescanning interval of 3 years was suggested for high-risk individuals and 6 to 7 years for low-risk individuals.
- 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>11</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.
- In 2359 asymptomatic adults (including 47% Hispanic) of the Miami Heart Study who underwent CCTA, 49% of participants had coronary plaque, 6% had stenosis ≥50%, and 7% had plaques with high-risk features (Chart 20-3).
- In SCAPIS, among 25 182 middle-aged individuals without known CHD who underwent CCTA, 42% had coronary atherosclerosis and 5.2% had ≥50% stenosis.<sup>12</sup> Among those with CAC=0, 5.5% had noncalcified atherosclerosis and 0.4% had ≥50% stenosis.
- Studies have identified APO, obesity, elevated lipoprotein(a), and inflammatory disorders as being associated with calcified or noncalcified coronary atherosclerosis:
  - Among 10528 females in Sweden with ≥1 deliveries in 1973 or later who later participated in an imaging study at a median of 57.3 years of age in 2013 to 2018, atherosclerosis was present by CCTA in 32.1% (95% CI, 30.0%–34.2%) of females with a history of any APO.<sup>13</sup> This prevalence was higher compared with females without any history of APO (prevalence difference, 3.8% [95% CI, 1.6%–6.1%]; PR, 1.14 [95% CI, 1.06–1.22]).
  - In 937 apparently healthy asymptomatic family members of individuals with premature ASCVD, high lipoprotein(a) levels were associated with CAC ≥100 (OR, 1.79 [95% CI, 1.13–2.83]).<sup>14</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>15</sup>
- The 10-year trends in CAC progression among individuals without clinical CVD in MESA were assessed (Chart 20-4).
  - The mean age at the baseline examination was 67 years; 47.4% were men. Detectable CAC was evaluated in White participants, Black participants, Hispanic participants, and Chinese participants, with >50% prevalence at baseline.
  - CAC severity was also evaluated at baseline and 10 years. After adjustment for age, gender, ethnicity, and type of CT scanner, the proportion of participants with no CAC decreased over time from 40.7% to 32.6% ( $P=0.007$ ). The proportions increased from 29.9% to 37.0% ( $P=0.01$ ) for those with CAC 1 to 99 and from 14.7% to 17.7% ( $P=0.14$ ) for those with CAC 100 to 399, whereas the proportion with CAC ≥400 decreased from 9.1% to 7.2% ( $P=0.11$ ).

### CAC and Incidence of ASCVD Events (CHD and Stroke)

(See Charts 20-5 and 20-6)

- The NHLBI's MESA reported the association of CAC with incident CHD events over a median follow-up of 3.9 years among a population-based sample of 6722 individuals (39% White participants, 27% Black participants, 22% Hispanic participants, and 12% Chinese participants).<sup>16</sup>
  - Chart 20-5 shows the HRs associated with CAC scores of 1 to 100, 101 to 300, and >300 compared with CAC=0 after adjustment for standard risk factors. People with CAC 1 to 100 had ≈4 times greater risk, and those with CAC scores >100 were 7 to 10 times more likely to experience a CHD event than those without CAC.
  - CAC provided similar predictive value for CHD events in White individuals, Chinese individuals, Black individuals, and Hispanic individuals (HRs ranging from 1.15–1.39 for each doubling of CAC).
- In an analysis of 66 636 participants from the CAC Consortium, higher CAC scores were associated with an increased risk of SCD with a nearly 5-fold

increased risk for individuals with CAC  $\geq 1000$  (subdistribution HR, 4.9 [95% CI, 2.6–9.9]).<sup>17</sup>

- In 13 397 low-risk younger adults 30 to 49 years of age of the Walter Reed Cohort, a CAC score  $>100$  was associated with an HR of 5.16 (95% CI, 3.29–8.10) for MI, 3.14 (95% CI, 2.26–4.36) for MACEs (MI, stroke, or CVD death), 1.73 (95% CI, 1.01–2.97) for stroke, and 2.08 (95% CI, 1.13–3.82) for all-cause mortality.<sup>18</sup>
- In analysis of 4511 participants without known CAD who were compared with 438 individuals with a prior ASCVD event in the CONFIRM international registry, there was a similar MACE event rate of  $\approx 53$  per 1000 PY for individuals with CAC  $>300$  and those with a history of ASCVD. Over a median of 4 years follow-up, there was a similar cumulative incidence of MACEs for individuals with CAC  $>300$  or a prior ASCVD event ( $P=0.329$ ; Chart 20-6).
- In MESA, individuals with a very high CAC score  $\geq 1000$  ( $n=257$ ) had a MACE rate of 3.4 per 100 PY, which was similar to the secondary prevention population in the FOURIER trial who had a prior ASCVD event plus at least 1 additional major or 2 minor ASCVD risk factors.<sup>19</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>20</sup>
- During 13.2 years of follow-up in asymptomatic individuals from the MESA study ( $n=4512$ ; 61.9 years of age; 52.5% women; 36.8% White, 29.3% Black, 22.2% Hispanic, and 11.7% Chinese), an independent association with ASCVD risk was observed for elevated lipoprotein(a) levels (HR, 1.29 [95% CI, 1.04–1.61]) and elevated CAC scores (score of  $\geq 100$  versus 0: HR, 2.66 [95% CI, 2.07–3.43]).<sup>21</sup> No lipoprotein(a)-by-CAC interaction was observed. This study noted similar findings when the same analyses were performed with the Dallas Heart Study cohort.

### CAC Progression and Risk

- In MESA, for participants with CAC=0, 84% had the continued absence of CAC, and among the 16% with incident CAC, the median progression was 2.2 Agatston units per year. Among MESA participants with CAC  $>0$  at baseline, 85% had progression of CAC with an average CAC progression of 29 Agatston units/y over a median follow-up of 7.6 years. Among those with CAC  $>0$  at baseline, there was a stepwise increased cumulative incidence of CHD with higher annual CAC progression, and for every 100–Agatston units annual increase, there was a 1.3 (95% CI, 1.1–1.5) higher adjusted hazard for total CHD events.<sup>22</sup>
- In a MESA study of 2759 postmenopausal women, 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>23</sup>

### Social Determinants of Health/Health Equity in CAC and Coronary Atherosclerosis

In addition to the differences by race and ethnicity detailed previously, differences in CAC or associations with CAC have been described by factors such as sex, unemployment, and exposure to air pollution:

- In 1125 Black participants in the CARDIA study, exposure to a low versus high level of neighborhood-level racial residential segregation in young adulthood was associated with a lower risk of developing midlife CAC (rate ratio, 0.52 [95% CI, 0.28–0.98]).<sup>24</sup> This association was attenuated and lost significance after adjustment for cardiovascular risk factor burden (rate ratio, 0.56, [95% CI, 0.29–1.09]).
- 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 women but not men (PR, 1.00 [95% CI, 0.91–1.08]).<sup>25</sup>
- In 312 females (mean age, 50.8 years), after adjustment for potential confounders, depression, health behaviors, and CVD risk factors, psychosocial well-being was not significantly associated with CAC progression.<sup>26</sup> However, among the 134 females with baseline CAC  $>0$ , well-being was associated with less CAC progression (RR, 0.921 [95% CI, 0.852–0.995];  $P=0.037$ ).
- 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>27</sup>
- 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>28</sup> Similar associations were observed for NO<sub>2</sub>.

### CAC, Carotid IMT, CT Angiography, and Risk Prediction

- In MESA, the investigators reported the follow-up of 6779 men and women in 4 ethnic groups over 9.5 years and compared the predictive utility of carotid IMT, carotid plaque, and CAC (presence and burden).<sup>29</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, gender, 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.
- In 4724 participants of the Suita study of middle-aged to older adults with carotid ultrasound, 2722 of whom had follow-up ultrasounds, prevalent and incident common carotid artery plaque was associated with incident CVD (incident plaque HR, 1.95 [95% CI, 1.14–3.3] for CVD and HR, 2.01 [95% CI, 1.01–3.99] for stroke).<sup>30</sup>
- In the CONFIRM study, coronary atherosclerosis presence, extent, and severity quantified by CT angiography improved risk prediction over traditional risk factors (C statistic, 0.64 versus 0.73;  $P=0.008$ ).<sup>31</sup>
- Although CT angiography can measure coronary artery stenosis, the total burden of atherosclerosis is the primary predictor of CVD risk. In a study of 23 759 patients from the Western Denmark Heart Registry, patients with obstructive coronary artery stenosis did not have a higher risk compared with those with nonobstructive coronary artery stenosis and a similar CAC score.<sup>32</sup> For example, the CVD and mortality event rate per 1000-PY follow-up for patients with CAC  $\geq 100$  to 399 and obstructive CAD was 17.3 (95% CI, 14.5–20.6) compared with 17.9 (95% CI, 14.8–21.7) for patients with CAC  $\geq 100$  to 399 and nonobstructive CAD.
- 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>33</sup> This score was externally validated in the AWHS of males of similarly age.
- Conversely, a number of studies have demonstrated that the absence of atherosclerosis is strongly predictive of low CVD risk.<sup>34–36</sup> In a study of 6814 participants from the MESA cohort, CAC=0 was associated with the lowest risk for CVD and had the greatest downward change in net reclassification index of 13.8 compared with the next largest net reclassification index of 4.9 for carotid IMT  $<25$ th percentile.<sup>37</sup>

## 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 early manifestation of atherosclerosis because thickening precedes the development of atherosclerotic plaque.

- Carotid IMT methods may vary by the 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.
- Accurate measurement of carotid IMT requires a skilled ultrasonographer because mean IMT values for middle-aged patients are generally  $<1$  mm<sup>38</sup> and vary during the cardiac cycle.<sup>39</sup>
- Carotid IMT is greater with older age and in men compared with women of the same age. Thus, a  $\geq 75$ th percentile carotid IMT thickening is commonly considered to identify high ASCVD risk.<sup>40</sup>
- Stroke risk was 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>41</sup>

### Prevalence and Risk Factors

- Gender and race differences have been demonstrated in carotid IMT. In 518 healthy Black males and females 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>42</sup> In MESA and a large cross-continent cohort of individuals of African, Asian, White European, and Hispanic ancestry, Black people had the thickest carotid IMT (particularly common carotid, 0.91 mm) of all 4 ethnic groups.<sup>43</sup> Chinese participants had the lowest carotid IMT (0.83 mm), in particular in the internal carotid, of the 4 ethnic groups.
- Adverse risk factors in early childhood and young adulthood are implicated in the early development of atherosclerosis. In the Bogalusa Heart Study (mean,  $32\pm3$  years of age), 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 step-wise increases in mean carotid IMT levels.<sup>42</sup> Higher BMI and LDL-C levels measured at 4 to 7 years of age were associated with increased risk for carotid IMT  $>75$ th percentile in young adulthood.<sup>44</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>45</sup> Increased trajectory of lipids from 5 to 45 years of age measured in 1201 individuals in the Bogalusa Heart Study was also associated with midlife IMT compared with stable low lipid levels.<sup>46</sup>

- In 9388 US and Finnish individuals with longitudinal measurement of CVD risk factors and carotid IMT, CVH declined from childhood to adulthood and was associated with IMT thickening.<sup>47</sup>

### Social Determinants of Health/Health Equity in Carotid IMT and Vascular Disease

- In the FAMILIA trial of 436 socioeconomically challenged young adults who underwent carotid and femoral vascular ultrasound, subclinical atherosclerosis was present in 12.6% of NH Black individuals versus 6.6% of Hispanic individuals, with higher risk for prevalent disease (OR, 3.45 [95% CI, 1.44–8.29];  $P=0.006$ ) and multivascular disease ( $P=0.026$ ) in analyses adjusted for CVD risk factors, as well as lifestyle and SES factors.<sup>48</sup>
- In the biracial HANDLS study of 2270 adults, interaction analyses demonstrated a race-by-SES effect whereby individuals who 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>49</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>50</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  $\text{IMT}_{\text{max}}$ ,  $\text{IMT}_{\text{mean-max}}$ , and  $\text{IMT}_{\text{mean}}$ , respectively; all  $P<0.0001$ ).<sup>51</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 of IMT in follow-up ( $P=0.002$ ).<sup>52</sup>
- Several studies from cohorts including ELSA-Brasil, Mexican-Teachers Cohort, and an urban US cohort suggest that psychosocial well-being is associated with lower IMT, whereas serious financial difficulty, psychosocial stress, and racial discrimination are associated with subclinical vascular disease, including elevated IMT.<sup>53–55</sup>

### Risk Prediction

- 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>56</sup> In MESA<sup>56</sup> and CHS participants,<sup>57</sup> the upper quartile and quintile were associated with 2- to 3-fold increased risks for CVD, respectively, including MI and stroke. Among  $>13000$  participants in ARIC, carotid IMT was associated with incident HF<sup>58</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>59</sup>

- The presence of carotid plaque is a stronger risk factor for incident CVD (HR, 1.61 [95% CI, 1.17–2.21]) than carotid IMT thickness (HR, 1.20 [95% CI, 0.94–1.52]).<sup>29</sup>

### Genetics and Family History

- Substantial evidence demonstrates the heritability of subclinical atherosclerosis. Studies leveraging twin data and family cohorts indicate that genetic factors significantly influence the development of both carotid artery IMT and CAC. Heritability estimates for carotid artery IMT range up to 59%, whereas  $\approx 40\%$  to 50% of the variation in CAC quantity is attributable to genetic influences.<sup>60,61</sup> Even the progression of CAC has a heritable component, albeit at a smaller magnitude ( $h^2=14\%$ ).<sup>62</sup>
- There is evidence for genetic control of subclinical atherosclerosis, with several loci identified that are associated with CAC and carotid artery IMT in multiancestry and racial populations.<sup>63–67</sup> The identified genes and variants indicated that there are considerable shared genetic components with subclinical disease and other risk factors.<sup>68–70</sup>
- CHARGE Consortium investigators identified 8 unique genetic loci that contributed to carotid IMT in 71 128 individuals and 1 novel locus for carotid plaque in 48 434 individuals.<sup>65</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>67</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>67</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 and overt CVD and CVD risk factors.
- Ancestrally diverse populations can enable identification of novel subclinical atherosclerosis loci. In a study of N=7894 unrelated participants from sub-Saharan Africa, a carotid IMT GWAS identified 2 novel loci for mean-maximum carotid IMT (*SIRPA* and *FBXL17*) and sex-specific loci at *SNX29*, *LARP6*, and *PROK1*.<sup>71</sup> These loci may influence

macrophage activity (*SIRPA*), vascular endothelial growth (*PROK1*), and collagen synthesis (*LARP6*).

- A 48-SNP GRS for type 2 diabetes was associated with carotid plaque and ASCVD events in ≈160 000 individuals, suggesting a causal role between genetic predisposition to type 2 diabetes and ASCVD.<sup>72</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>73</sup>

### **Arterial Stiffness and CVD**

- In a study of 12 170 patients hospitalized with SARS-CoV-2 in the SEMI-COVID-19 network in Spain, arterial stiffness, defined as pulse pressure  $\geq 60$  mmHg, conferred a 27% greater odds of in-hospital mortality after multivariable adjustment for comorbidities.<sup>74</sup>
- 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>75</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>76</sup>
- In 440 Black participants in the JHS (mean age,  $59\pm 10$  years; 60% female), 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.<sup>77</sup>
- 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>78</sup>
  - In the ARIC-NCS 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>79</sup>
  - FHS investigators also previously demonstrated that arterial stiffness is related to brain aging, with structural brain abnormalities and progression of these abnormalities as occur in AD.<sup>80-83</sup>

### **Flow-Mediated Dilation 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 flow-mediated dilation was observed.<sup>84</sup>

### **Comparison of Measures of Subclinical Atherosclerosis**

- 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, 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 NRI (0.659) compared with other subclinical markers, including family history, ABI, IMT, and CRP.<sup>85</sup> Similar findings also were noted in the Rotterdam Study, in which addition of CAC score had the largest improvement in risk prediction among 12 CHD risk markers.<sup>86</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>37</sup> After accounting for CVD risk factors, absence of CAC had the strongest negative predictive value with an adjusted mean $\pm$ SD diagnostic likelihood ratio of  $0.41\pm 0.12$  for all CHD and  $0.54\pm 0.12$  for CVD followed by carotid IMT  $<25$ th percentile (diagnostic likelihood ratio,  $0.65\pm 0.04$  and  $0.75\pm 0.04$ , respectively).

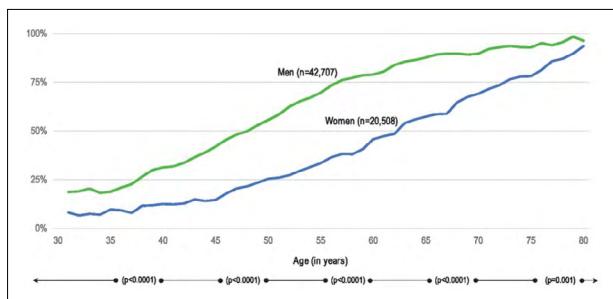
### **Subclinical Atherosclerosis and Healthy Lifestyle/Preventive Medications**

- 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 5-year NNT: The estimated 5-year NNT for preventing 1 CVD event across dyslipidemia categories in the MESA cohort ranged from 23 to 30 in those with CAC  $\geq 100$ .<sup>35</sup> A very high 5-year NNT 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 5-year NNT 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>87</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 a 5-year NNT lower than the number needed to harm (for CAC  $\geq 100$ , 5-year NNT, 140 versus 518).<sup>88</sup> In individuals with CAC=0, the 5-year NNT of 1190 was much higher than the 5-year NNT 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 were  $\geq 5\%$ .<sup>89</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>90</sup> The incremental cost-effective ratio improved in the male,  $>60$  years of age, and  $\geq 7.5\%$  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.
- Measurement of CAC has the potential to inform the use of GLP1-RA therapy. In a study pooling 1125 participants from the MESA, CARDIA,

and DHS cohorts who had diabetes without prior CVD, the NNT with a GLP1-RA to prevent 1 CVD event over 5 years was 3-fold higher for participants with CAC=0 (NNT, 280) compared with those with CAC  $>100$  (NNT, 85).<sup>91</sup>

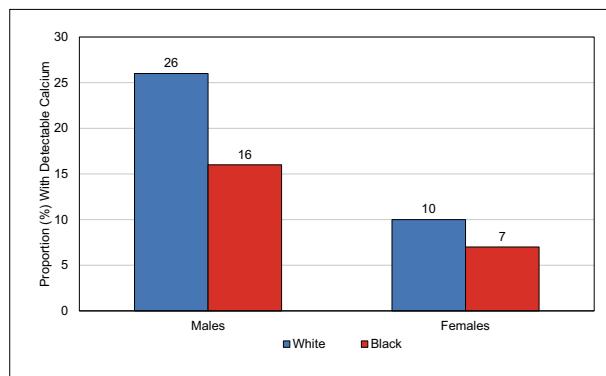
- Optimal lifestyle habits in youth and adulthood are associated with lower subclinical atherosclerosis:
  - In overweight and obese children 6 to 13 years of age, greater nut consumption was independently associated with lower carotid IMT ( $\beta=0.135$  mm;  $P=0.009$ ).<sup>92</sup>
  - In a cohort of older females, a diet high in vegetables, particularly cruciferous vegetables, was associated with lower carotid IMT.<sup>93</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>94</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>95</sup>
  - In the FHS, higher midlife-estimated cardiopulmonary 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>96</sup>



**Chart 20-1. Proportion of women and men with detectable CAC (score  $>0$ ) across 30 to  $\geq 80$  years of age from the CAC Consortium, 1991 to 2010.**

CAC indicates coronary artery calcium.

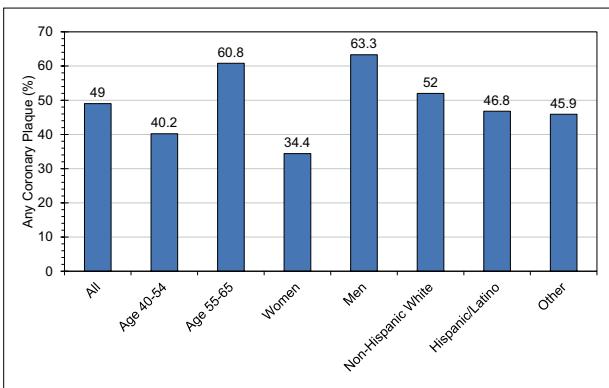
Source: Reprinted from Shaw et al,<sup>6</sup> by permission of Oxford University Press. Published on behalf of the European Society of Cardiology. All rights reserved. Copyright The Author(s) 2018.



**Chart 20-2. Prevalence (percent) of detectable CAC by sex and race among 19,725 asymptomatic individuals 30 to 45 years of age without known ASCVD pooled from CARDIA (1995–2001), the CAC Consortium (1992–2011), and the Walter Reed Cohort (1997–2009).**

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcification; and CARDIA, Coronary Artery Risk Development in Young Adults.

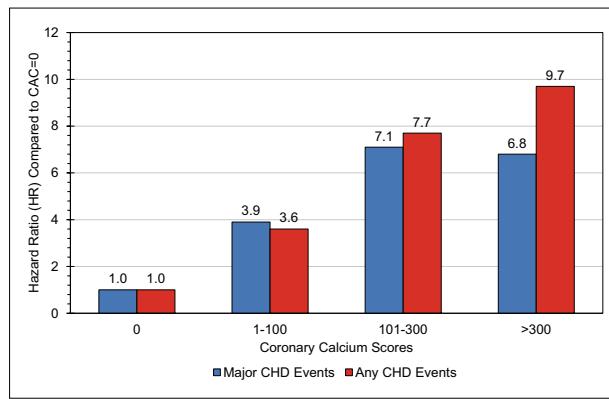
Source: Data derived from Javid et al.<sup>97</sup>



**Chart 20-3. Presence of any coronary plaque by CCTA in an asymptomatic US population of 2359 individuals in the Miami Heart Study at Baptist Health South Florida, 2015 to 2018.**

CCTA indicates coronary CT angiography.

Source: Reprinted from Nasir et al.<sup>98</sup> Copyright 2022, with permission from American College of Cardiology Foundation.

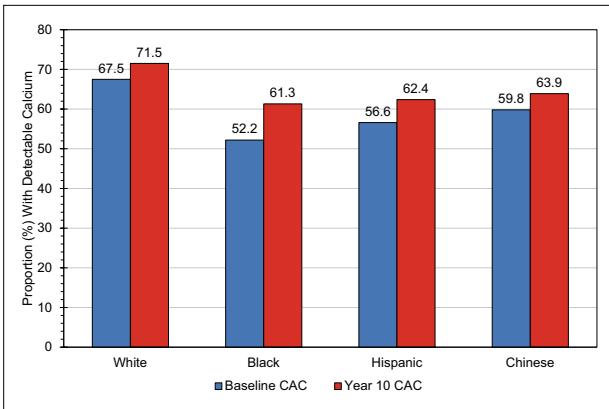


**Chart 20-5. HRs for CHD events associated with CAC scores: US adults 45 to 84 years of age (reference group, CAC=0) in MESA, baseline examination 2000 to 2002.**

Baseline examination in 2000 to 2002 with a 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.

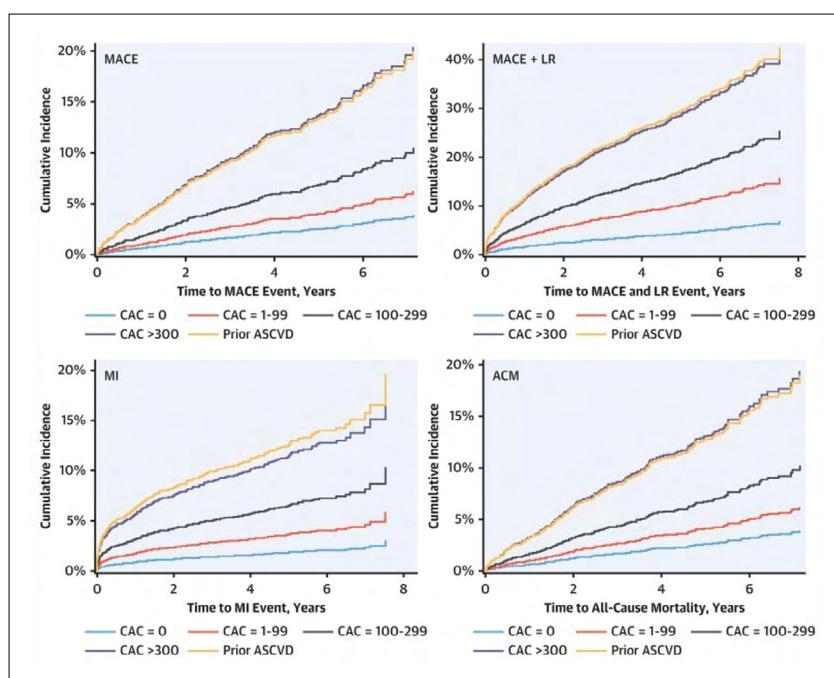
Source: Data derived from Detrano et al.<sup>16</sup>



**Chart 20-4. 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>5,99</sup>



**Chart 20-6. Cumulative incidence of MACEs by CAC score compared with patients with a prior ASCVD event in the CONFIRM registry, 2005 to 2009.**

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CONFIRM, Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry; LR, likelihood ratio; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

Source: Reprinted from Budoff et al.<sup>100</sup>

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## 21. CORONARY HEART DISEASE, ACUTE CORONARY SYNDROME, AND ANGINA PECTORIS

**See Tables 21-1 through 21-3 and Charts 21-1 through 21-8**

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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)**

- In an analysis of data on 17 266 adults with a history of CHD from NHIS 2006 to 2015, the prevalence of premature CHD (<65 years of age for females and <55 years of age for males) was higher among Asian Indian adults ( $aOR, 1.77 [95\% CI, 1.05–2.97]$ ) and other Asian adults ( $aOR, 1.68 [95\% CI, 1.17–2.42]$ ) than White adults.<sup>1</sup>
- On the basis of data from NHANES 2017 to 2020,<sup>2</sup> an estimated 20.5 million Americans  $\geq 20$  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  $\geq 20$  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  $\geq 18$  years of age.<sup>3</sup>
- According to data from NHANES 2017 to 2020 (unpublished NHLBI tabulation),<sup>2</sup> the overall

prevalence of MI is 3.2% in US adults  $\geq 20$  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>2</sup> the overall prevalence of angina is 3.9% in US adults  $\geq 20$  years of age (Table 21-2).
- Data from the BRFSS 2022 survey indicate that 4.5% of respondents had been told that they had had an MI. The highest age-adjusted prevalence was in West Virginia (6.1%), and the lowest was in Colorado (2.8%; Chart 21-3; unpublished NHLBI tabulation using BRFSS<sup>4</sup>).
- In the same survey in 2022, 4.4% of respondents had been told that they had angina or CHD. The highest age-adjusted prevalence was in Mississippi (5.8%), and the lowest was in Colorado (2.5%; Chart 21-4).<sup>4</sup>

#### Incidence

- Approximately every 40 seconds, an American will have an MI (AHA computation based on incidence data from the ARIC study of the NHLBI<sup>5</sup>).
- On the basis of data tabulated by the NHLBI from the 2005 to 2014 ARIC study<sup>5</sup>:
  - Approximately 720 000 Americans will have a new coronary event (defined as first hospitalized MI or CHD death), and  $\approx 335\,000$  will have a recurrent event.
  - The estimated annual incidence of MI is 605 000 new attacks and 200 000 recurrent attacks. Of these 805 000 first and recurrent events, it is estimated that 170 000 are silent (without significant symptoms).
  - Average age at first MI is 65.6 years for males and 72.0 years for females.
- 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>6</sup>

#### Secular Trends

- In a study of the 2010 to 2019 National Readmission Database, among 592 015 30-day readmissions and 787 008 ninety-day readmissions after index AMI hospitalization, 30-day and 90-day all-cause readmission rates after AMI decreased from 12.8% to 11.6% ( $P=0.0001$ ) and 20.6% to 18.8% ( $P=0.0001$ ), respectively.<sup>7</sup> Downward trends were observed in both pre-HRRP (2010–2012) and post-HRRP periods (2013–2015, 2016–2019).

The 2025 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 2025. 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.

However, the mean length of stay (4.54–4.96 days;  $P=0.0001$ ) and adjusted total cost (\$13449–\$16938;  $P=0.0001$ ) for 30-day all-cause readmission increased over the decade.

- In a retrospective study of 2881 746 PCIs for MI from the NIS 2008 to 2019, the use of intravascular ultrasound-guided PCI increased by 309.9% (6180 versus 25 330;  $P_{\text{trend}}<0.001$ ), whereas optical coherence tomography-guided PCI increased by 548.4% (246 versus 1595;  $P_{\text{trend}}<0.001$ ).<sup>8</sup> The percentage of intravascular ultrasound and optical coherence tomography use in PCIs increased from 3.4% to 8.7% and 0.0% to 0.6%, respectively ( $P_{\text{trend}}<0.001$ ). Intravascular imaging-guided PCI was associated with lower odds of in-hospital mortality (aOR, 0.66 [95% CI, 0.60–0.72];  $P<0.001$ ), suggesting a significant increase in use and improved outcomes.
- Among Medicare beneficiaries between 2002 and 2011, the rates of MI hospitalization declined from 1485 to 1122 per 100 000 PY.<sup>9</sup>
  - The rates of MI as the primary reason for hospitalization decreased over time (from 1063 to 677 per 100 000 PY between 2002 and 2011). The percentage of MIs that were attributable to a primary reason for hospitalization decreased from 72% to 60% between 2002 and 2011.
  - However, the rates of MI as a secondary reason for hospitalization increased (from 190 to 245 per 100 000 PY). 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>10</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 $\pm$ SD age, 65.7 $\pm$ 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 ( $-10.5\%$ ;  $P_{\text{trend}}<0.001$ ) between 2010 and 2017. In the same period, outpatient PCI rates increased from 33.8 to 66.7 per 100 000 ( $+97.1\%$ ;  $P_{\text{trend}}<0.001$ ), whereas inpatient PCI rates declined from 226.4 to 166.2 per 100 000 ( $-26.6\%$ ;  $P_{\text{trend}}<0.001$ ).<sup>11</sup>

### Admissions and Mortality Trends

- 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>12</sup> A similar multisite study in France observed a reduction in STEMs (IRR, 0.72 [95% CI, 0.62–0.85]) and NSTEMIs (IRR, 0.64 [95% CI, 0.55–0.76]) when the 4 weeks before and after lockdown were compared.<sup>13</sup>

- In a cohort of 1533 patients admitted with AMI (STEMI and NSTEMI) in a large health system in Washington, DC, and Maryland between March 1, 2020, and June 30, 2020, 86 had confirmed COVID-19. Furthermore, 20.0% of patients (n=17) 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>14</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>15</sup>
- An observational analysis of ED and inpatient data among patients with HF (n=21 262) or AMI (n=6165) from 12 hospital health systems across the St. Louis metropolitan area found that patient volume decreased for AMI during COVID-19 (6.1–6.6 events/d before COVID-19, 4.9–5.5 events/d during COVID-19;  $P<0.001$ ).<sup>16</sup> However, the proportion of patients with STEMI increased during COVID-19 (32.5%–37.6%) compared with before COVID-19 (29.0%–29.3%;  $P=0.005$ ). Furthermore, in-hospital mortality increased for AMI (OR, 1.46 [95% CI, 1.21–1.76]) and STEMI (OR, 2.57 [95% CI, 2.24–2.96]) during the pandemic.
- A meta-analysis comparing AMI admissions during the COVID-19 pandemic with pre-COVID-19 levels found 35% fewer AMI hospitalizations during COVID-19 compared with the pre-COVID-19 period (OR, 0.65 [95% CI, 0.56–0.74];  $P=99\%$ ;  $P<0.001$ ; 28 studies).<sup>17</sup> Hospitalizations also declined for STEMI (OR, 0.71 [95% CI, 0.65–0.78];  $P=93\%$ ;  $P<0.001$ ; 22 studies) and NSTEMI (OR, 0.66 [95% CI, 0.58–0.73];  $P=95\%$ ;  $P<0.001$ ; 14 studies) during COVID-19 compared with before COVID-19.<sup>17</sup> Another meta-analysis of 79 articles across 57 countries found that during the height of the COVID-19 pandemic, the IRR of STEMI hospitalizations decreased (0.80 [95% CI, 0.76–0.84];  $P<0.05$ ) over the reference period. However,

there was significant heterogeneity across studies ( $P=89\%$ ;  $P<0.0001$ ).<sup>18</sup> There was an inverse association between IRRs for STEMI admissions and hospital bed availability in each country ( $P<0.05$ ).

### Social Determinants of Health/Health Equity

- Data from the NIS October 2017 to December 2018 including 294 540 hospitalizations among adults with type 2 MI were analyzed for racial differences in clinical outcomes.<sup>19</sup> Compared with White individuals, individuals of other races and ethnicities (Native American, Asian or Pacific Islander, and other underrepresented racial and ethnic groups) had higher in-hospital mortality (aOR, 1.17 [95% CI, 1.03–1.33];  $P=0.016$ ) and longer length of stay (adjusted parameter estimate, 0.59 [95% CI, 0.22–0.97];  $P=0.002$ ).
- In a 2013 to 2018 cross-sectional cohort study of 289 376 patients with STEMI and 843 046 patients with NSTEMI  $\geq 66$  years of age from the United States, Canada, England, the Netherlands, Taiwan, and Israel, Patients with high income (those living in an area [eg, postal code] in the top 20% of the income distribution) had lower 30-day mortality (1–3 percentage points) and 1-year mortality (up to 9.1 percentage points in Israel for STEMI [95% CI, –16.7 to –1.6]) compared with patients with low income (those living in areas in the bottom 20% of the distribution).<sup>20</sup> Patients with high income also had higher rates of cardiac catheterization and PCI (1–6 percentage points), lower 30-day readmission rates (1–3 percentage points), and shorter hospital stays (0.2–0.5 days) across all 6 countries.
- A longitudinal cohort study examined racial and cohort differences in the relationship between debt and MI risk in the HRS 1992 to 2018.<sup>21</sup> The study compared the prewar cohort (born 1931–1941,  $N=8698$  in 1992) and Baby Boomers (born 1948–1959,  $N=6792$  in 2010). Higher unsecured debt was associated with increased MI risk for Black adults, especially Baby Boomers (aHR, 1.11;  $P<0.001$ ) and during recessions (aHR, 1.05;  $P<0.001$ ). Higher mortgage debt was associated with lower risk for White Baby Boomers (aHR, 0.97;  $P<0.001$ ) but not Black Baby Boomers (aHR, 1.13;  $P<0.001$ ).
- In an observational cohort study of 135 358 patients with STEMI in California EDs from 2010 to 2019, uninsured patients had lower odds of interfacility transfer compared with insured patients (aOR, 0.93 [95% CI, 0.88–0.98];  $P=0.01$ ) after adjustment for time trends, patient factors, and hospital characteristics, including PCI capabilities.<sup>22</sup>
- In a retrospective study of 9 million adults with NSTEMI (72%) and STEMI (28%) from 2005 through 2019, no significant improvement was found in the use of diagnostic angiograms, PCI, and CABG for Asian and Pacific Islander individuals, Black individuals, Hispanic individuals, and Native American individuals, compared with White individuals over 15 years ( $P>0.05$ ), except for CABG in STEMI for Black individuals versus White individuals (difference, 2.6% to 1.4%;  $P=0.03$ ).<sup>23</sup>
- In an analysis of data from 72 173 census tracts ( $N=308\,243\,060$ ) in the 2018 BRFSS, higher social vulnerability index, a measure of a neighborhood's risk for deleterious outcomes in the event of natural disasters or disease outbreaks, was associated with higher CHD prevalence ( $\beta=0.0520$ ; SE, 0.0008;  $R^2=0.57$ ;  $P<0.0001$ ) when accounting for census-tract median age.<sup>24</sup>
- 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>25</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 HRRP, 0.79 [95% CI, 0.63–0.97];  $P=0.03$ ; after the HRRP, 0.80 [95% CI, 0.68–0.95];  $P=0.01$ ) but not in high-performing hospitals.<sup>26</sup>
- 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];  $P_{\text{interaction}}=0.02$ ).<sup>27</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% (interquartile range, 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>28</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>29</sup>

- In a retrospective cohort study of Medicare fee-for-service patients ( $N=453\,783$ ) 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>30</sup> Yet, at the most socioeconomically disadvantaged—serving practices, patients had higher odds of being admitted for unstable angina (aOR, 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 the 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>31</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 compared with referents.<sup>32–34</sup> Among Medicare beneficiaries, participation in cardiac rehabilitation is lower among females (18.9%) compared with males (28.6%; adjusted PR, 0.91 [95% CI, 0.90–0.93]) and among Hispanic adults (13.2%) and NH Black adults (13.6%) compared with NH White adults (25.8%; adjusted PR, 0.63 [95% CI, 0.61–0.66] and 0.70 [95% CI, 0.67–0.72], respectively).<sup>32</sup> Likewise, in the BRFSS 2011 to 2015, participants in cardiac rehabilitation were less likely to be female (OR, 0.76 [95% CI, 0.65–0.90]), Black (OR, 0.70 [95% CI, 0.53–0.93]), uninsured (OR, 0.53 [95% CI, 0.37–0.75]), and less educated (OR, 0.47 [95% CI, 0.37–0.61]) compared with the referents.<sup>33</sup> In Optum's Clininformatics database ( $N=107\,199$ ), cardiac rehabilitation attendance was 31% lower for Asian adults (95% CI, 27%–36%), 43% lower for Hispanic adults (95% CI, 40%–45%), and 19% lower for Black adults (95% CI, 16%–22%) after adjustment.<sup>34</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>35</sup>
- A study of 2 182 903 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>36</sup>
- In a subset of SILVER-AMI, a community-based longitudinal study of older adults ( $N=1345$ ,  $\geq 75$  years of age), there was no association between neighborhood walkability scores and hospital-free survival time or physical or mental health.<sup>37</sup>
- REGARDS investigators tabulated the 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>38</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 (interquartile range, 6.6–12.7 years). 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>38</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 compared with White individuals were less likely to undergo coronary angiography (61.9% versus 70.2% versus 73.1%) and PCI (44.6% versus 53.0% versus 58.1%;  $P<0.001$ ).<sup>39</sup>
- A systematic review of 181 studies conducted primarily in high-income countries found that lower socioeconomic position (education, income, insurance, occupation, or composite) was associated with higher incidence of ACS (IRR, 1.1–4.7), higher prevalence of ACS (OR, 1.8–3.9), higher odds of receiving suboptimal medical care (OR, 1.1–10.0), and higher mortality after ACS (HR, 1.1–4.13).<sup>40</sup>

**Risk Prediction**

- In a prospective study of 128 322 males and 135 103 females from the UK Biobank study, higher serum levels of sex hormone-binding globulin were associated with a decreased risk of CHD in both males (aHR per 1–log nmol/L increase, 0.88 [95% CI, 0.83–0.94]) and females (aHR, 0.89 [95% CI, 0.83–0.96]).<sup>41</sup> A meta-analysis of 216 417 males and 138 282 females from 11 studies showed that higher sex hormone-binding globulin levels were associated with decreased CHD risk in males (aRR, 0.81 [95% CI, 0.74–0.89]) and females (aRR, 0.86 [95% CI, 0.78–0.94]) when the highest quartile was compared with the lowest quartile.<sup>41</sup>
- Two large cohort studies (MESA, N=1991; Rotterdam Study, N=1217) examining adults 45 to 79 years of age (median: MESA, 61 years of age; Rotterdam Study, 67 years of age) demonstrated that incorporating a CAC score significantly improved risk discrimination compared with a traditional risk factor model alone (MESA: change in C statistic, 0.09; Rotterdam Study: change in C statistic, 0.06). Notably, the addition of a PRS did not yield a similar improvement.<sup>42</sup>
- 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>43</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 ≥10% were 3.8 [4.3], 7.1 [6.4], 8.3 [8.7], and 18.9 [18.7], respectively).<sup>44</sup>
- In 14 169 patients with ASCVD risk <5% and self-reported family history of CHD from the multicenter CAC Consortium followed up for ≈12 years, those with CAC scores >100 had a >10-fold higher risk of CHD mortality than patients with CAC=0 (HR, 10.4 [95% CI, 3.2–33.7]).<sup>45</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>46</sup> This risk was not significantly higher among adults <40 years of age but was significantly higher among adults >40 to 50 years of age (aHR, 2.97 [95% CI, 1.32–6.69]), 50 to 60 years of age (aHR, 5.08 [95% CI, 2.68–9.63]), 60 to 70 years of age (aHR, 1.89 [95% CI, 1.08–3.31]), and ≥70 years of age (aHR, 2.43 [95% CI, 1.33–4.46]) compared with their age counterparts with CAC=0.
- Among 66 636 asymptomatic adults in the CAC Consortium, those with extremely high CAC scores (≥1000) had higher adjusted risk of CVD (HR, 5.04 [95% CI, 3.92–6.48]), CHD (HR, 6.79 [95% CI, 4.74–9.73]), all-cause mortality (HR, 2.89 [95% CI, 2.53–3.31]), and cancer (HR, 1.55 [95% CI, 1.23–1.95]) than those with CAC=0.<sup>47</sup> Moreover, those with CAC ≥1000 had higher adjusted risk of CVD (HR, 1.71 [95% CI, 1.41–2.08]), CHD (HR, 1.84 [95% CI, 1.43–2.36]), all-cause mortality (HR, 1.51 [95% CI, 1.33–1.70]), and cancer (HR, 1.36 [95% CI, 1.07–1.73]) than those with CAC scores of 400 to 999.
- Among 16 289 adults (6526 males, 9763 females) in the HCHS/SOL, WC cut points of >102 cm in males (current joint interim statement criterion) and >97 cm (9 points above the joint interim statement criterion) in females provide optimal discrimination for CHD (evidence of prior MI from ECG or self-report of MI, angina, or coronary procedures).<sup>48</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 ≤5 corresponding to a predicted mortality rate of <0.1% and a score of ≥27 associated with mortality rate of >85%.<sup>49</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>50</sup>

- In a cohort of 272 307 White adults in the UK Biobank study, the integrated PRS, PCE, and PRS-enhanced PCE were compared to predict incident CAD cases.<sup>51</sup> The C statistics for the integrated PRS, PCE, and PRS-enhanced PCE were 0.640 (95% CI, 0.634–0.646), 0.718 (95% CI, 0.713–0.723), and 0.753 (95% CI, 0.748–0.758), respectively. The addition of the integrated PRS to the PCE at a 7.5% risk threshold yielded an NRI of 0.117 (95% CI, 0.102–0.129) for cases and –0.023 (95% CI, –0.025 to –0.022) for controls (overall, 0.093 [95% CI, 0.08–0.104]). Among the incident CAD cases, 14.2% were correctly reclassified to the higher-risk category, and 2.6% were incorrectly reclassified to the lower-risk category.
- The T2-risk score, a risk stratification tool for predicting the primary outcome of death or future MI among patients with type 2 MI, was derived from the High-STEACS trial (2013–2016), the APACE study (2006–2018), and single-center consecutive patients at a hospital in Stockholm (2011–2014).<sup>52</sup> The T2-risk score, which includes age, IHD, diabetes, HF, myocardial ischemia on ECG, anemia, heart rate, eGFR, and maximal cardiac troponin concentration, had good discrimination (AUC, 0.76 [95% CI, 0.73–0.79]) for the primary outcome and was well calibrated. The T2-risk score improved discrimination over the Global Registry of Acute Coronary Events 2.0 risk score in all cohorts.

## **Genetics and Family History**

### **Family History as a Risk Factor**

- Among adults ≥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>2</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>2</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>53</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>54</sup> Of note, estimated heritability was operative throughout the life span but more prominently at younger ages of death, particularly for males.
- 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 processes (ie, cellular adhesion, leukocyte migration and atherosclerosis, coagulation and inflammation, and vascular smooth muscle cell differentiation) in the arterial wall.<sup>55</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>56</sup> The primary SNP at 9p21.3 is common; 50% of the population of European ancestry is estimated to harbor 1 risk allele, and 23% harbor 2 risk alleles.<sup>57</sup>
  - A meta-analysis of 22 studies (N=35 872 cases; N=95 837 controls) identified the 10-year HD risk for a male 65 years of age with two 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>57</sup>
- GWASs have identified multiple loci associated with CAD implicating pathways in blood vessel morphogenesis, lipid metabolism, nitric oxide signaling, inflammation, and basic cellular processes governing the cell cycle,<sup>58</sup> division/replication, and growth. One large, ancestrally diverse GWAS included n=243 392 CAD case and n=849 686 control MVP participants.<sup>59</sup> After meta-analysis with predominantly European ancestry GWASs from CARDIoGRAMplusC4D and the UK Biobank, this GWAS identified 33 novel loci. Further meta-analysis with Biobank Japan and inclusion of MVP

Black participants and Hispanic participants identified 66 novel loci. These loci did not demonstrate heterogeneity across ancestral populations. Most of these novel loci (58%) were associated with CAD risk factors (eg, blood lipids, BP, diabetes, obesity, or smoking). Large-scale collaborative genetic studies of CAD ( $n=72\,868$  cases and  $n=120\,770$  controls) focused on the coding regions of the genome (exons) have identified additional loci, including loss-of-function variants in *ANGPTL4* (angiopoietin-like 4), which is an inhibitor of lipoprotein lipase.<sup>60</sup> These variants are associated with low plasma triglycerides and high HDL-C.

- A study of X chromosome genetic variation in  $>500\,000$  multiancestry individuals from the TOPMed Consortium 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 reduced odds for CHD and type 2 diabetes.<sup>61</sup> Every additional rs5942634-T allele, the lead cholesterol-lowering variant in chromosome Xq23, was associated with estimated ORs of 0.98 (95% CI, 0.96–0.99) for CHD and 0.97 (95% CI, 0.96–0.99) for type 2 diabetes.
- Hematopoietic somatic variants (clonal hematopoiesis of indeterminate potential) that accumulate with age are also 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>62</sup> Clonal hematopoiesis of indeterminate potential itself has germline genetic determinants.<sup>63</sup>

### Clinical Utility of Genetic Markers

- Studies have shown that patients with early-onset MI have a higher proportion of high PRS than those with FH variants; for example,  $\approx 2\%$  carry a rare FH genetic variant, whereas  $\approx 17\%$  have a high PRS.<sup>64</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>65</sup>
- A summary of the 5 most highly cited studies of PRS concluded that the change in C statistic with the addition of PRS to the standard risk model improves the C statistic by  $-0.001$  to  $0.021$  and that PRS has a limited contribution to primary prevention of CAD.<sup>66</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 PRS 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>67</sup>
- Studies suggest that the addition of a PRS contributes modestly to clinical risk prediction. In the UK Biobank with  $>350\,000$  participants, the change in C statistic for incident CAD prediction between a PCE and GRS model was 0.02 (95% CI, 0.01–0.03) with an overall NRI of 4.0% (95% CI, 3.1%–4.9%).<sup>68</sup> In the ARIC and MESA studies, adding a GRS to the PCE 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>69</sup> In an East Asian cohort ( $N=41\,271$ ), addition of a PRS including 540 genetic variants to clinical risk factors had an NRI for CAD of 3.2% (95% CI, 0.9%–5.8%).<sup>70</sup>
- GRSs derived from 1 ancestry may have limited generalizability to individuals of different ancestries, necessitating the development of GRSs that are ancestry specific.<sup>71</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]) that outperformed previous scores based on European ancestral populations.<sup>72</sup>

### Awareness, Treatment, and Control

#### Awareness of Warning Signs and Risk for HD

- 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>73</sup> Compared with adults born in the United States, adults born in Europe, Russia, Africa, the Middle East, the Indian subcontinent, Asia, and Southeast Asia were likely to be aware of all 5 MI symptoms in the NHIS 2017 cycle.<sup>74</sup>
- Data from an online survey of US females ( $\ge 25$  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  $\ge 65$  years of age. Moreover, NH Black females (OR, 0.31 [95% CI, 0.19–0.49]) and Hispanic females (OR, 0.14 [95% CI, 0.07–0.28]) 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>75</sup>

#### Time of Symptom Onset and Arrival at Hospital

- 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>76</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 meta-analysis of 56 studies ( $N=384\,452$ ) concluded that individuals with STEMI presenting during off-hours had similar short-term (RR, 1.07 [95% CI, 1.00–1.14]), midterm (RR, 1.00 [95% CI, 0.95–1.05]), and long-term (RR, 0.95 [95% CI, 0.86–1.04]) mortality compared with those presenting during regular working hours.<sup>77</sup>
- 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>78</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>79</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>80</sup>
- Analysis of a multinational registry of PCI for STEMI that included 109 high-volume centers determined that in 2020 the incidence of PCI was significantly less than in 2019 (IRR, 0.84 [95% CI, 0.83–0.86]), accompanied by increased likelihood of door-to-balloon time  $>30$  minutes (OR, 1.1 [95% CI, 1.03–1.17]).<sup>81</sup>

#### Operations and Procedures

- In 2021, an estimated 444 730 PCIs, 184 000 CABGs, 110 245 carotid endarterectomy and stenting procedures, and 84 020 pacemaker and defibrillator procedures were performed for inpatients in the United States (unpublished NHLBI tabulation using HCUP<sup>82</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>83</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 (interquartile range, 50.7–60.3 months).<sup>84</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>85</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>86</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>87</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>88</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>89</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 [interquartile range, 7–25 minutes] versus 28 minutes [interquartile range, 18–39 minutes]), shorter door-to-device time (median, 40 minutes [interquartile range, 30–51 minutes] versus 52 minutes [interquartile range, 41–65 minutes]), and lower in-hospital mortality (2.8% versus 3.4%;  $P=0.01$ ).<sup>90</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>91</sup>

#### *Secular Trends in Procedures*

- In an analysis of the NIS, among patients ≥70 years of age with non-ST-segment–elevation ACS or STEMI, the proportion of patients undergoing PCI increased from 7.3% in 1998 to 24.9% in 2013 in those with non-ST-segment–elevation ACS and from 11% in 1998 to 35.7% in 2013 in those with STEMI.<sup>92</sup>
- 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>11</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 ( $-10.5\%$ ;  $P_{trend}<0.001$ ). 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 ( $+15.0\%$ ;  $P_{trend}<0.001$ ).
- 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>93</sup>

- In a Swedish population–based registry (N=4085), PCI for unprotected left main CAD increased from 121 procedures in 2005 to 589 in 2017.<sup>94</sup> The risk of major adverse cardiovascular and cerebrovascular events was 44% less in 2017 compared with 2005 (HR, 0.56 [95% CI, 0.41–0.78]).

#### *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>33</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 ≥36 sessions. Participation decreased with increasing age and was lower in females, Hispanic people, Asian people, those eligible for dual Medicare/Medicaid coverage, and those with ≥5 comorbidities.<sup>32</sup>
- A systematic review of 9 studies concluded that home-based cardiac rehabilitation is cost-effective, albeit recognizing heterogeneity across studies, limited duration of follow-up, and absence of consideration of diversity of cardiac rehabilitation participants.<sup>95</sup>
- In an administrative analysis of individuals eligible for cardiac rehabilitation (N=107 199), 28 433 (26.5%) attended cardiac rehabilitation.<sup>34</sup> After adjustment, compared with White individuals, the probability of attending cardiac rehabilitation was 31% lower for Asian individuals (95% CI, 27%–36%), 19% lower for Black individuals (95% CI, 16%–22%), and 43% lower for Hispanic individuals (95% CI, 40%–45%).
- 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 ( $-5.1\pm6.5$  kg versus  $-0.8\pm3.8$  kg [mean±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>96</sup>

- In an observational study ( $N=1120$ ) of individuals with IHD, the 1-year mortality risk did not differ between those who accepted home-based cardiac rehabilitation ( $n=490$ ) compared with those who did not (HR, 0.67 [95% CI, 0.31–1.45]).<sup>97</sup> In contrast, during a median follow-up of 4.2 years, those who participated in home-based cardiac rehabilitation had an HR of 0.64 (95% CI, 0.45–0.90) compared with those who declined.

### Mortality

(See Table 21-1)

- In an observational study using the NIS and National Readmission Database between 2017 and 2019, which compared Takotsubo syndrome ( $n=43\ 335$ ), type 1 MI ( $n=2035\ 055$ ), and type 2 MI ( $n=639\ 075$ ), mortality risk was lower in Takotsubo syndrome compared with type 1 MI (aOR, 0.3;  $P<0.001$ ) and type 2 MI (aOR, 0.3;  $P<0.001$ ). Type 1 MI had higher mortality (aOR, 1.2;  $P<0.001$ ) than type 2 MI.<sup>98</sup>
- In a meta-analysis of 81 studies involving 157 439 patients with COVID-19, those with preexisting CHD had a higher risk of mortality (OR, 2.45 [95% CI, 2.04–2.94];  $P<0.001$ ), severe/critical COVID-19 (OR, 2.57 [95% CI, 1.98–3.33];  $P<0.001$ ), ICU/coronary care unit admission (OR, 2.75 [95% CI, 1.61–4.72];  $P=0.002$ ), and lower odds of discharge/recovery (OR, 0.43 [95% CI, 0.28–0.66];  $P<0.001$ ) compared with those without preexisting CHD.<sup>99</sup>
- In a propensity score-matched analysis of 159 890 STEMI hospitalizations from the 2020 NIS database, 1.38% had concurrent COVID-19.<sup>100</sup> These patients had higher in-hospital mortality (17.8% versus 9.1%) and lower rates of same-day PCI (63.6% versus 70.6%) and CABG (3.0% versus 6.8%) compared with those without COVID-19. However, COVID-19-positive patients with STEMI receiving same-day PCI had lower odds of in-hospital mortality (aOR, 0.42 [95% CI, 0.20–0.85]).
- In a meta-analysis of 4 retrospective, nonrandomized, observational cohort studies among 184 951 patients  $\geq 18$  years of age diagnosed with NSTEMI, early treatment (administered within 24 hours) with  $\beta$ -blockers was associated with a significant reduction in in-hospital mortality compared with no  $\beta$ -blocker treatment (OR, 0.43 [95% CI, 0.36–0.51];  $P=0.0022$ ).<sup>101</sup>
- On the basis of 2022 mortality data (unpublished NHLBI tabulation using NVSS<sup>102</sup>):

- CHD mortality was 371 506 (Table 21-1), and CHD any-mention mortality was 595 121.
- MI mortality was 103 905 (Table 21-1). MI any-mention mortality was 151 312.
- From 2012 to 2022, the annual death rate attributable to CHD declined 16.9%, whereas the actual number of deaths stayed relatively the same (unpublished NHLBI tabulation using CDC WONDER<sup>103</sup>).
- The age-adjusted death rates for CHD and MI by sex, race, and ethnicity can be found in Table 21-1.
- In 2022, 79% of CHD deaths occurred out of hospital. According to US mortality data, 294 458 CHD deaths occurred out of hospital or in hospital EDs in 2022 (unpublished NHLBI tabulation using CDC WONDER<sup>103</sup>).
- The estimated average number of YLL because of an MI death was 14.6 in 2022 (unpublished NHLBI tabulation using CDC WONDER<sup>103</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>5</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>26</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>104</sup>
- Other data indicate that the rapid increase in the population  $\geq 65$  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  $\geq 65$  years of age combined with the slowing of the decrease in HD mortality resulted in an increase in the absolute number of HD deaths since 2011 (50 880 deaths; 8.5% total increase). However, the age-adjusted mortality for CHD continued to decline (2.7% annualized decrease) and the absolute number of CHD deaths declined (2.5% total decrease over the time period) between 2011 and 2017.<sup>105</sup>
- An analysis of those enrolled in Medicare Advantage or traditional Medicare from 2009 to 2018 presenting with STEMI ( $n=557\ 309$ ) and NSTEMI ( $n=1\ 670\ 193$ ) identified significant 30-day

mortality rate differences in 2009 that were no longer present in 2018.<sup>106</sup> In 2018, the 30-day mortality for STEMI was 17.7% in those with Medicare Advantage and 17.8% in those with traditional Medicare (difference, 0.0 percentage points [95% CI, -0.7 to 0.6]); for NSTEMI, the 30-day mortality rate was 10.9% in those with Medicare Advantage and 11.1% in those with traditional Medicare (difference, -0.2 percentage points [95% CI, -0.4 to 0.1]).

- 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>107</sup>
- In extended follow-up (median, 5.7 years), ISCHEMIA participants randomized to an initial invasive strategy did not have increased mortality (HR, 1.00 [95% CI, 0.85–1.18]) compared with those randomized to an initial invasive strategy.<sup>108</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>109</sup>
- An NIS analysis spanning 2004 to 2018 determined that females had a higher incidence of mortality after PCI than males (1.12% mortality compared with 0.78%).<sup>110</sup>
- A prospective analysis of data on 5064 Black adults in the JHS between 2019 and 2021 found that participants with CHD (HR, 1.59 [95% CI, 1.22–2.08]), diabetes (HR, 1.50 [95% CI, 1.22–1.85]), or stroke (HR, 1.74 [95% CI, 1.24–2.42]) had higher risk for all-cause mortality compared with those with no cardiometabolic morbidities.<sup>111</sup> Those with ≥2 cardiometabolic morbidities had higher risk of all-cause mortality with the highest risk among those with diabetes, stroke, and CHD (HR, 3.68 [95% CI, 1.96–6.93]).

### 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 females admitted with STEMI had decreased survival to discharge compared with males (OR, 0.63 [95% CI, 0.52–0.76]).<sup>112,113</sup> Females experience longer door-to-balloon times and lower rates of GDMT 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 males and females.<sup>114</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>115</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>116</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.
- An analysis conducted in the CARDIA study (N=5112) with a median follow-up >33 years identified that premature CVD risk in Black participants was attenuated after adjustment for lifestyle, neighborhood, and socioeconomic factors.<sup>117</sup> For example, the 2.4-fold increased CVD risk in Black females (95% CI, 1.71–3.49) relative to White females was no longer significant after adjustment for clinical, lifestyle, socioeconomic, and neighborhood factors.

The largest decreases in the race-specific estimate for CVD risk occurred with adjustment for clinical (87%), neighborhood (32%), and socioeconomic (23%) factors.

- In MESA, an analysis (N=6814) similarly reported that compared with White participants, Black participants had increased risk of mortality (HR, 1.34 [95% CI, 1.19–1.51]), which decreased after adjustment for socioeconomic factors (HR, 1.16 [95% CI, 1.01–1.34]).<sup>118</sup>
- A large regional health care system in Northern California 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 an HR of 1.20 (95%, 1.11–1.30) increased risk of cardiovascular mortality but not stroke or MI.<sup>119</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>83</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>120</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 (interquartile range, 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>121</sup>

### Complications

- A comparison of 2 NIS cohorts of young adults (18–44 years of age) hospitalized with AMI in 2007 and 2017 revealed an overall increased admission rate, with a decline in males (77.1% to 66.1%) and a rise in females (28.9% to 33.9%).<sup>122</sup> Post-AMI complications, including cardiogenic shock (aOR, 1.16 [95% CI, 1.06–1.27]) and SVT (aOR, 3.76 [95% CI, 3.18–4.44]), increased, whereas all-cause mortality was comparable in these 2 time periods. (aOR, 1.01 [95% CI, 0.93–1.10];  $P=0.749$ ).
- 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>123</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>124</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>125</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>126</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>127</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 experienced 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>128</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 (interquartile range, 34–230 days) of time from discharge to recurrent AMI.<sup>129</sup>
- Sudden death after MI is common. A secondary analysis of IMPROVE-IT (N=18 144) determined the cumulative incidence rate of sudden death after MI as 2.47% (95% CI, 2.23%–2.73%) at the 7-year follow-up.<sup>130</sup>

### Age, Sex, Race, and Complications

- On the basis of pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012; unpublished NHLBI tabulation), of those who have a first MI, the percentage with a recurrent MI or fatal CHD within 5 years is as follows:
  - At  $\geq 45$  years of age, 17% of males and 21% of females.

- At 45 to 64 years of age, 11% of White males, 15% of White females, 22% of Black males, and 32% of Black females.
- At 65 to 74 years of age, 12% of White males, 17% of White females, 30% of Black males, and 30% of Black females.
- At  $\geq 75$  years of age, 21% of White males, 20% of White females, 45% of Black males, and 20% of Black females.
- The percentage of people with a first MI who will have HF in 5 years is as follows:
  - At  $\geq 45$  years of age, 16% of males and 22% of females.
  - At 45 to 64 years of age, 6% of White males, 10% of White females, 13% of Black males, and 25% of Black females.
  - At 65 to 74 years of age, 12% of White males, 16% of White females, 20% of Black males, and 32% of Black females.
  - At  $\geq 75$  years of age, 25% of White males, 27% of White females, 23% of Black males, and 19% of NH Black females.
- The percentage of people with a first MI who will have an incident stroke within 5 years is as follows:
  - At  $\geq 45$  years of age, 4% of males and 7% of females.
  - At  $\geq 45$  years of age, 5% of White males, 6% of White females, 4% of Black males, and 10% of Black females.
- The median survival time (in years) after a first MI is as follows:
  - At  $\geq 45$  years of age, 8.2 for males and 5.5 for females.
  - At  $\geq 45$  years of age, 8.4 for White males, 5.6 for White females, 7.0 for Black males, and 5.5 for Black females.
- A systematic review and pooled analysis of 4 CABG trials compared sex differences in outcomes between females ( $n=2714$ ) and males ( $n=10\,479$ ). 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>131</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>109</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>132</sup>

- An Australian registry of individuals who had undergone PCI ( $N=13\,996$ ) from 2008 to 2020 determined that female sex was associated with increased 2-year readmission (HR, 1.29 [95% CI, 1.11–1.48]) compared with male sex.<sup>133</sup>

### Hospital Discharges and Ambulatory Care

#### (See Chart 21-5)

- From 2011 to 2021, the number of inpatient discharges from short-stay hospitals with CHD as the first-listed diagnosis decreased from 1 193 438 to 886 904.
- From 1997 through 2021, the number of hospital discharges for CHD generally declined (Chart 21-5).
- In 2019, there were 14 167 000 physician office visits for CHD (unpublished NHLBI tabulation using NAMCS<sup>134</sup>). In 2021, there were 909 467 ED visits with a primary diagnosis of CHD (unpublished NHLBI tabulation using HCUP<sup>82</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>135</sup>
- In the CathPCI registry, a composite of use of evidence-based medical therapies, including aspirin, P2Y12 inhibitors, and statins, was high (89.1% in 2011 and 93.5% in 2014). However, in the ACTION-GWTG registry, metrics shown to need improvement were defect-free care (median hospital performance rate, 78.4% in 2014), P2Y12 inhibitor use in eligible medically treated patients with AMI (56.7%), and use of aldosterone antagonists in patients with LV systolic dysfunction and either diabetes or HF (12.8%).<sup>123</sup>
- Among 147 600 individuals with premature ASCVD ( $\leq 55$  years of age) receiving care in the Veterans Affairs health care system from October 1, 2014, through September 30, 2015, there were 10 413 females and 137 187 males. In adjusted analyses, females were less likely to receive antiplatelet therapy (OR, 0.47 [95% CI, 0.45–0.50]), any statin (OR, 0.62 [95% CI, 0.59–0.66]), or high-intensity statin (OR, 0.63 [95% CI, 0.59–0.66]) than males.<sup>136</sup>
- Among individuals presenting with an MI or undergoing coronary revascularization in the Veterans Affairs health care system from July 24, 2015, through December 9, 2019 ( $N=81\,372$ ), the proportions receiving lipid-lowering intensification were 33.3% at 14 days, 41.9% at 3 months, and 47.3% at 12 months after hospitalization.<sup>137</sup> Lipid-lowering

intensification was defined as increasing or initiating therapies to achieve LDL target goals of 70 or 100 mg/dL.

- An analysis of the ISCHEMIA trial ( $N=5179$ ) compared days alive out of the hospital or extended care facilities among trial participants classified as having mild/no ischemia, moderate ischemia, or severe ischemia and randomized to invasive or initially conservative management strategies. At 4 years, there was no significant difference between the 2 groups (1415.0 days with conservative management and 1412.2 days with invasive management;  $P=0.65$ ).<sup>138</sup>

### Cost

- The estimated direct cost of CHD in 2020 to 2021 (average annual) was \$52.8 billion (MEPS,<sup>139</sup> unpublished NHLBI tabulation).
- The estimated direct and indirect cost of CHD in 2020 to 2021 (average annual) was \$129.3 billion (MEPS,<sup>139</sup> unpublished NHLBI tabulation).
- MI (\$14.3 billion) and CHD (\$8.7 billion) were 2 of the 10 most expensive conditions treated in US hospitals in 2017.<sup>140</sup>
- In 642 105 Medicare beneficiaries hospitalized for AMI between 2011 and 2014, 30-day episode payments averaged \$22 128 but varied 2-fold across hospitals. Median costs were \$20 207 in the lowest quartile versus \$24 174 in the highest quartile of hospitals.<sup>141</sup>
- In Medicare beneficiaries hospitalized with AMI, the 180-day expenditures increased from an average of \$32 182 per person in 1999 to 2000 to \$36 836 in 2008 and remained relatively stable thereafter, with expenditures of \$36 668 in 2013 to 2014.<sup>142</sup>
- In 11 969 patients with AMI from 233 US hospitals who underwent PCI from 2010 to 2013, average hospital costs were higher for patients with STEMI (\$19 327) compared with patients with NSTEMI (\$18 465;  $P=0.002$ ) and higher among elderly patients (\$19 575 for those  $\geq 65$  years of age versus \$18 652 for those  $< 65$  years of age;  $P=0.004$ ). Forty-five percent of costs were related to the catheterization laboratory, 22% to room and board, 14% to supplies, and 9% to pharmacy costs. At 1 year after discharge, hospital and ED costs averaged \$8037, with three-quarters attributable to hospitalizations (\$61 116 for hospitalizations, \$1334 for outpatient hospital stays, and \$587 for ED visits).<sup>143</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 those with minimally invasive CABG surgery (\$27 906;  $P<0.001$ ) after propensity score matching. There were no significant differences 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>144</sup>

- An observational analysis of data on young adults (18–45 years of age) who underwent PCI in the 2004 to 2018 NIS found that the inflation-adjusted care cost significantly increased from \$21 567 in 2004 to \$24 173 in 2018 ( $P_{\text{trend}}<0.01$ ).<sup>110</sup>

### Global Burden

#### (See Table 21-3 and Charts 21-6 and 21-7)

- Based on 204 countries and territories in 2021<sup>145</sup>:
  - An estimated 8.99 (95% UI, 8.26–9.53) million total deaths attributable to IHD occurred (Table 21-3). Among regions, IHD mortality rates were highest for Central Asia, Eastern Europe, and North Africa and the Middle East. Mortality was lowest for high-income Asia Pacific (Chart 21-6).
  - Globally, it was estimated that 254.28 (95% UI, 221.45–295.49) million people lived with IHD, and it was more prevalent in males than in females (145.31 [95% UI, 125.89–167.45] and 108.97 [95% UI, 95.25–127.39] million people, respectively). North Africa and the Middle East had the highest prevalence rates of IHD among regions, followed by Eastern Europe and South and Central Asia (Chart 21-7).
- 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>146</sup>

### Acute Coronary Syndrome

#### **ICD-9 410, 411; ICD-10 I20.0, I21, I22.**

- In a study of 9450 patients with ACS, a modified GRACE risk score incorporating continuous high-sensitivity cardiac troponin at presentation showed improved discrimination and reclassification for in-hospital (AUC, 0.878 versus 0.780; NRI, 0.097), 30-day (AUC, 0.858 versus 0.771; NRI, 0.08), and 1-year (AUC, 0.813 versus 0.797; NRI, 0.056) all-cause mortality compared with the original GRACE score.<sup>147</sup>
- In a 2019 to 2020 NIS study ( $N=32 355 827$ ), patients with STEMI with COVID-19 had higher mortality (aOR, 3.10 [95% CI, 2.40–4.02];  $P<0.01$ ) and longer length of stay (aOR, 1.66 [95% CI, 1.07–2.25];  $P<0.01$ ), and unstable patients with NSTEMI had longer admission-to-PCI times (0.45 days [95% CI, 0.16–0.76 days];  $P<0.01$ ).<sup>148</sup>
- In 2021, there were 591 129 ACS principal diagnosis discharges. This estimate was derived by adding the principal diagnoses for MI (584 499) to those

- for unstable angina (6630; unpublished NHLBI tabulation using HCUP<sup>82</sup>).
- When all listed discharge diagnoses in 2021 were included, the corresponding number of inpatient hospital discharges was 1 391 719 unique hospitalizations for ACS. Of the total, 1 375 674 were for MI alone, and 16 045 were for unstable angina alone (unpublished NHLBI tabulation<sup>82</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>149</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];  $P_{\text{interaction}} < 0.01$ ).
  - 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 β-blocker. Risk of overall mortality was lower among those who were on a β-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>150</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 ≤35 years of age had higher odds of 30-day mortality (aOR, 5.65 [95% CI, 2.49–12.82];  $P < 0.001$ ).<sup>151</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];  $P \leq 0.01$ ) 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>152</sup>
  - A retrospective analysis of data on 10 019 patients from the Epi-Cardio Registry in Argentina was conducted to examine sex differences in the presentation of ACS.<sup>153</sup> Females were more likely than males

to present with non-ST-segment-elevation ACS (60.3% versus 46.7%;  $P < 0.001$ ). This sex difference was driven mainly by a higher prevalence of ACS with nonobstructive coronary arteries (20.9% versus 6.6%) in young females because ACS without coronary lesions was mostly non-ST-segment-elevation ACS (77.7% versus 22.3%). There was no significant sex difference in the clinical presentation among patients with obstructive CHD.

- Among adults with ACS from the PLATO trial, the ABC-ACS ischemia model for predicting 1-year risk of CVD and MI that included growth differentiation factor 15 and NT-proBNP had greater prognostic value than all candidate variables (C indices, 0.71 and 0.72 in the development and validation cohorts, respectively).<sup>154</sup>
- A retrospective cohort study of 257 948 adults in the NIH Research Health Informatics Collaborative with suspected ACS in the United Kingdom between 2010 and 2017 found a positive and graded association between high-sensitivity CRP level and mortality at baseline.<sup>155</sup> This association persisted after 3 years for those with high-sensitivity CRP of 2.0 to 4.9 mg/L (aHR, 1.32 [95% CI, 1.18–1.48]), 5 to 9.9 mg/L (aHR, 1.40 [95% CI, 1.26–1.57]), and 10 to 15 mg/L (aHR, 2.00 [95% CI, 1.75–2.28]).

## Stable AP

**ICD-9 413; ICD-10 I20.1 to I20.9.**

### Prevalence

(See Table 21-2 and Chart 21-8)

- 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 21-8).
- 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 people but not for NH Black people.<sup>156</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>157</sup>

**Table 21-1. CHD in the United States**

Population group	Prevalence, CHD, 2017–2020, ≥20 y of age	Prevalence, MI, 2017–2020, ≥20 y of age	Mortality,* CHD, 2022, all ages	Age-adjusted mortality rates per 100 000 (95% CI),* CHD, 2022	Mortality,* MI, 2022, all ages	Age-adjusted mortality rates per 100 000 (95% CI),* MI, 2022
Both sexes	20 500 000 (7.1%) [95% CI, 6.1%–8.3%]	9 300 000 (3.2%) [95% CI, 2.5%–4.0%]	371 506	87.6 (87.3–87.9)	103 905	24.5 (24.4–24.7)
Males	11 700 000 (8.7%)	6 100 000 (4.5%)	223 952 (60.3%)†	121.9 (121.4–122.4)	62 571 (60.2%)†	33.3 (33.0–33.6)
Females	8 800 000 (5.8%)	3 200 000 (2.1%)	147 554 (39.7%)†	60.3 (60.0–60.6)	41 334 (39.8%)†	17.2 (17.0–17.3)
NH White males	9.4%	4.8%	172 181	126.8 (126.2–127.4)	48 545	35.3 (34.9–35.6)
NH White females	5.9%	2.2%	112 164	61.9 (61.5–62.3)	31 205	17.7 (17.5–18.0)
NH Black males	6.2%	4.0%	24 839	144.1 (142.2–146.0)	6695	38.2 (37.2–39.1)
NH Black females	6.3%	2.3%	18 264	75.8 (74.7–76.9)	5193	21.5 (20.9–22.1)
Hispanic males	6.8%	3.1%	16 840	90.7 (89.3–92.2)	4664	24.3 (23.5–25.0)
Hispanic females	6.1%	1.9%	10 754	46.7 (45.8–47.6)	3141	13.5 (13.0–14.0)
NH Asian males	5.2%	2.8%	6538‡	70.8 (69.1–72.6)‡	1855‡	19.8 (18.9–20.8)‡
NH Asian females	3.9%	0.5%	4418‡	35.2 (34.1–36.2)‡	1278‡	10.2 (9.6–10.8)‡
NH American Indian or Alaska Native	...	...	1973	76.5 (73.1–80.0)	572	22.3 (20.4–24.1)
NH Native Hawaiian or Pacific Islander			551	94.1 (86.0–102.1)	164	27.1 (22.8–31.3)

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>158</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 people, NH American Indian or Alaska Native people, 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 under-reporting on death certificates of American Indian or Alaska Native decedents, Asian and Pacific Islander decedents, and Hispanic decedents, as well as undercounts of these groups in censuses.

†These percentages represent the portion of total CHD and MI mortality that is for males vs females.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using National Health and Nutrition Examination Survey.<sup>2</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 estimates. These data are based on self-reports. Incidence: Atherosclerosis Risk in Communities study (2005–2014),<sup>5</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>102</sup> and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.<sup>103</sup>

**Table 21-2. AP\* in the United States**

Population group	Prevalence, 2017–2020, ≥20 y of age
Both sexes	10 800 000 (3.9%) [95% CI, 3.3%–4.5%]
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>158</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 tabulation using NHANES.<sup>2</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).

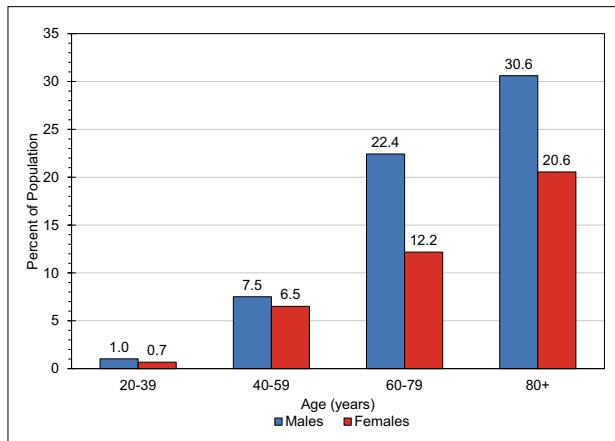
**Table 21-3. Global Mortality and Prevalence of IHD, by Sex, 2021**

	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), 2021	8.99 (8.26 to 9.53)	254.28 (221.45 to 295.49)	5.00 (4.68 to 5.34)	145.31 (125.89 to 167.45)	3.99 (3.54 to 4.32)	108.97 (95.25 to 127.39)
Percent change (%) in total number, 1990–2021	67.53 (58.76 to 75.87)	126.69 (117.83 to 136.62)	78.35 (66.61 to 91.90)	123.62 (115.17 to 132.70)	55.69 (45.92 to 66.83)	130.92 (121.31 to 141.66)
Percent change (%) in total number, 2010–2021	21.03 (15.88 to 26.46)	39.56 (32.12 to 48.00)	22.96 (15.84 to 30.99)	36.63 (29.29 to 44.87)	18.69 (11.82 to 25.33)	43.66 (35.95 to 52.64)
Rate per 100 000, age standardized, 2021	108.73 (99.60 to 115.38)	2,946.38 (2,572.69 to 3,424.32)	136.84 (127.37 to 145.90)	3,610.24 (3,153.05 to 4,164.95)	85.32 (75.90 to 92.31)	2,357.61 (2,063.31 to 2,751.95)
Percent change (%) in rate, age standard- ized, 1990–2021	−31.57 (−34.86 to −28.33)	1.43 (−2.55 to 5.94)	−27.08 (−31.50 to −21.72)	−2.12 (−5.88 to 2.23)	−36.57 (−40.44 to −32.49)	4.76 (0.56 to 9.85)
Percent change (%) in rate, age standard- ized, 2010–2021	−13.02 (−16.59 to −9.23)	2.90 (−2.36 to 8.95)	−11.37 (−16.30 to −5.67)	0.47 (−4.68 to 6.24)	−14.96 (−19.81 to −10.01)	5.99 (0.31 to 12.51)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; IHD, ischemic heart disease, and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>145</sup>

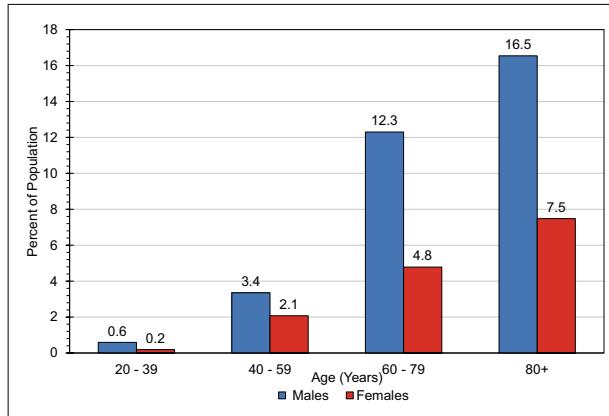


**Chart 21-1. Prevalence of CHD by age and sex, United States (NHANES, 2017–2020).**

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>158</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>2</sup>



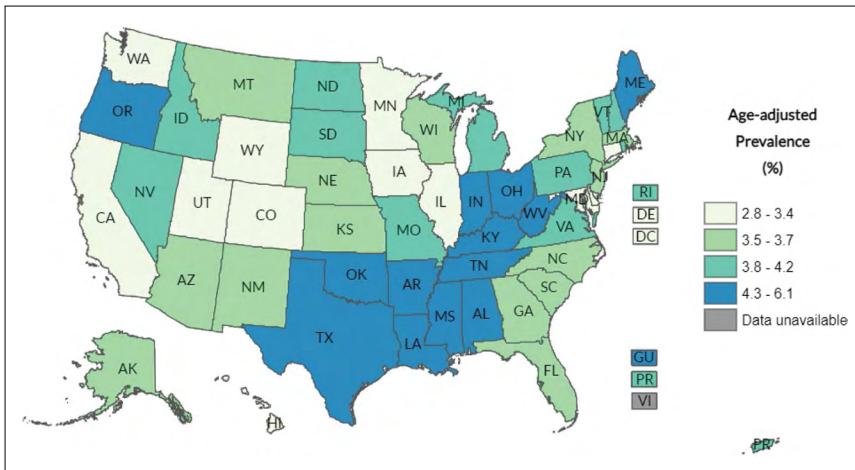
**Chart 21-2. Prevalence of MI by age and sex, United States (NHANES, 2017–2020).**

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>158</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.

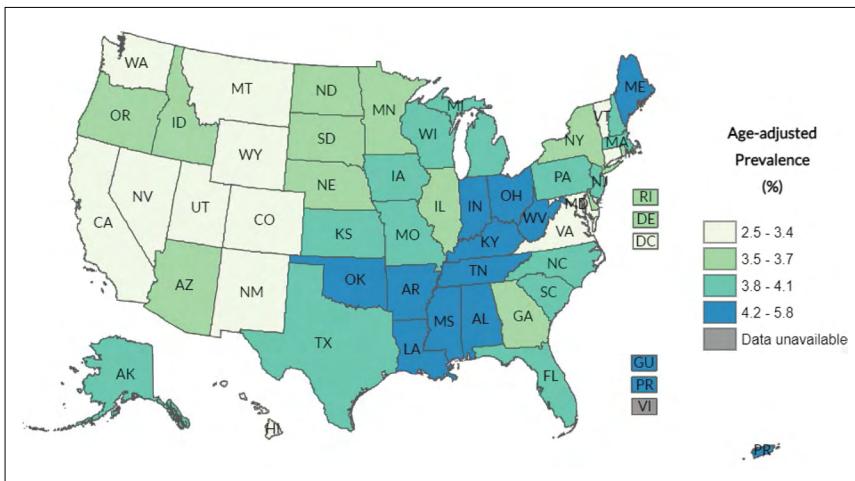
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using NHANES.<sup>2</sup>



**Chart 21-3. "Ever told you had a heart attack (MI)?" Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2022).**

Original chart has been modified to remove white space between map and legend. BRFSS indicates Behavioral Risk Factor Surveillance System; and MI, myocardial infarction.

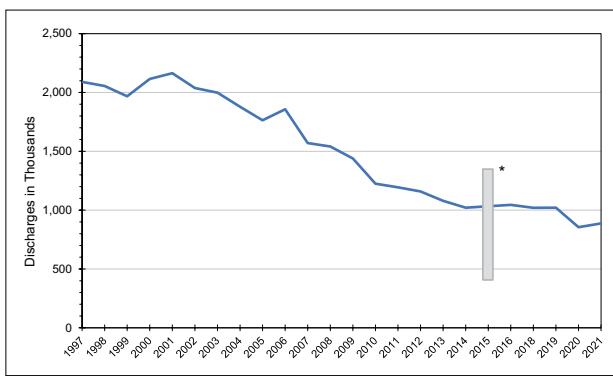
Source: BRFSS prevalence and trends data.<sup>4</sup>



**Chart 21-4. "Ever told you had angina or CHD?" Age-adjusted US prevalence by state (BRFSS prevalence and trends data, 2022).**

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>4</sup>



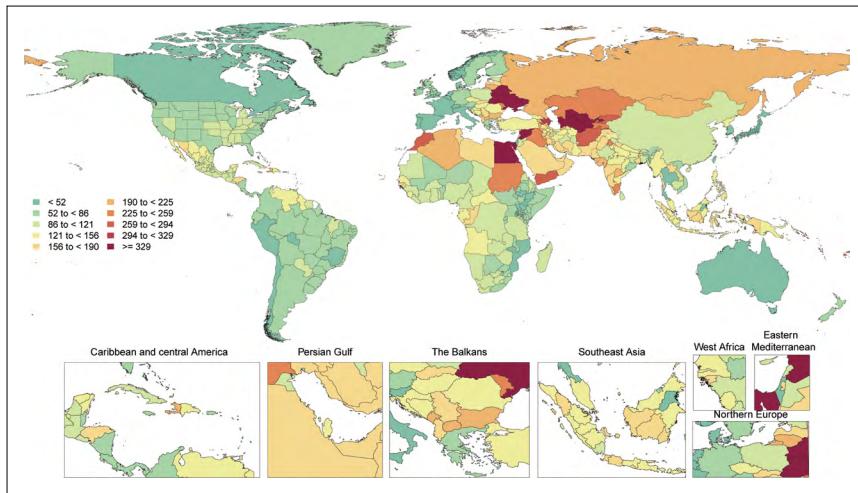
**Chart 21-5. Hospital discharges for CHD, United States (HCUP, 1997–2021).**

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>82</sup>

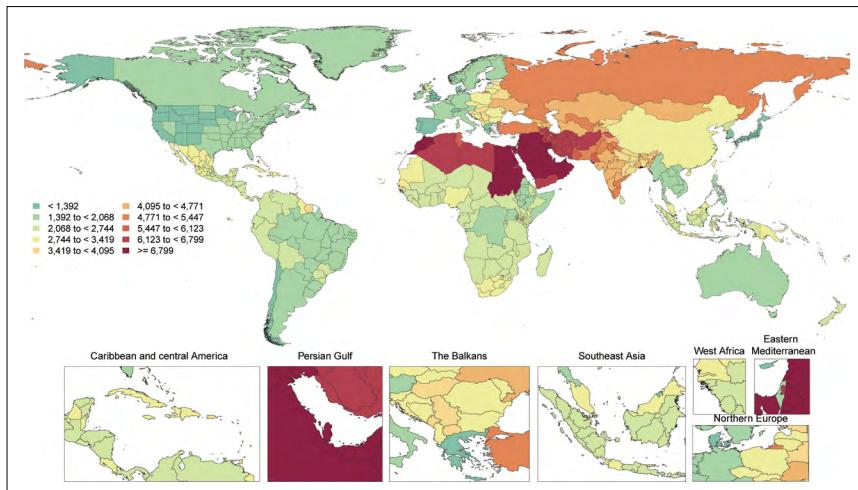


**Chart 21-6. Age-standardized global mortality rates of IHD per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and IHD, ischemic heart disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>145</sup>

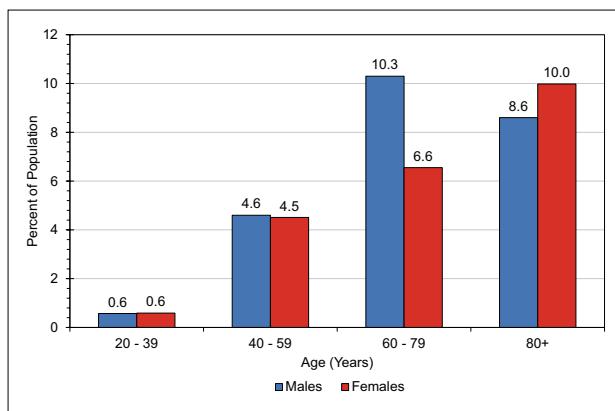


**Chart 21-7. Age-standardized global prevalence rates of IHD per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and IHD, ischemic heart disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>145</sup>



**Chart 21-8. 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>158</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>2</sup>

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## 22. CARDIOMYOPATHY AND HEART FAILURE

**See Tables 22-1 through 22-3 and Charts 22-1 through 22-4**

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### Cardiomyopathy

#### **ICD-9 425; ICD-10 I42**

2022, United States: Underlying cause mortality—19 739. Any-mention mortality—45 314.

Cardiomyopathy diagnoses account for a substantial number of inpatient and outpatient encounters annually.<sup>1</sup> According to HCUP 2021 data<sup>2</sup> for inpatient hospitalizations, cardiomyopathy was the principal diagnosis for 14 770, and it was included among all-listed diagnoses for 1 154 769.

#### **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 primarily encode components of the sarcomere, with variants in *MYH7* and *MYBPC3* (cardiac myosin-binding protein C) being the most common.<sup>3,4</sup> A variant is identifiable in 30% to 60% of cases of familial HCM.
- 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>5</sup> Two-sample mendelian randomization suggests a causal link between increased LV contractility and risk of developing HCM.
- The Sarcomeric Human Cardiomyopathy Registry studied 4591 patients with HCM contributing >24 000 PY 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%

The 2025 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 2025. 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.

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). 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>6</sup>

- A meta-analysis of 98 studies encompassing 70 510 patients with HCM from 1985 to 2020 demonstrated an overall incidence rate of SCD of 0.43%/y (95% CI, 0.37%/y–0.50%/y).<sup>7</sup> This rate decreased over time from 0.73%/y (95% CI, 0.53%/y–1.02%/y) in 1985 to 2000 to 0.32%/y (95% CI, 0.20%/y–0.52%/y) in 2015 to 2020.
- Sex disparities exist in the treatment of HCM. Among 9306 patients with obstructive HCM in the MarketScan database, females were less likely to be prescribed  $\beta$ -blockers (42.7% versus 45.2%;  $P=0.600$ ) or to receive an ICD (1.7% versus 2.6%;  $P=0.005$ ).<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>10</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>11</sup>

#### **Dilated Cardiomyopathy**

- DCM has a prevalence of 1 in 2500, but it is likely underestimated.<sup>12</sup>

- Potential 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>13</sup>
- Among 23 341 participants with HF from 40 countries in the G-CHF registry, 15.4% had idiopathic DCM.<sup>14</sup>
- Many cases of DCM have a genetic cause, called familial DCM.<sup>15</sup> Familial DCM has an estimated prevalence of 30% to 50% among all cases of DCM, and a causal genetic variant has been identified in 10% to 14% of cases.<sup>3,15</sup>
- In a cross-sectional survey of 1220 probands with confirmed DCM and 1693 first-degree relatives who underwent clinical screening, including transthoracic echocardiography, the prevalence of familial DCM was 11.6%.<sup>16</sup>
  - If all living first-degree relatives had been screened, the estimated prevalence of familial DCM was 29.7% (95% CI, 23.5%–36.0%).
  - The estimated prevalence of familial DCM was higher in Black probands compared with White probands (difference, 11.3% [95% CI, 1.9%–20.8%]).
  - With the use of an expanded definition of familial DCM, which included the presence of DCM, LV enlargement, or LV systolic dysfunction without a known cause in at least 1 first-degree relative, the estimated prevalence was 56.9% (95% CI, 50.8%–63.0%).
- Missense and truncating variants in the titin gene have been linked to autosomal dominant cardiomyopathy and to DCM with incomplete penetrance in the general population.<sup>17</sup> Analysis of sequence data in 7855 cases with cardiomyopathy and >60 000 controls revealed a range in penetrance of putative disease variants, which further highlights the challenges in clinical interpretation of variation in cardiomyopathy-associated genes.<sup>18</sup>
- In 186 families who underwent genetic screening because of having a relative with DCM, 37% (95% CI, 30%–45%) were discovered to have a likely pathogenic or pathogenic genetic variant for DCM.<sup>20</sup>
- 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>21</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 arrhythmogenic right ventricular cardiomyopathy.<sup>21</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>17</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>18</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>5,22</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.

### **Genetic Testing**

- 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>16</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. These findings suggest a potential yield of phenotypic screening of first-degree relatives of index DCM cases, especially those identified at a young age. The clinical outcomes in familial DCM have been described recently.<sup>19</sup>

### **Peripartum Cardiomyopathy**

- PPCM is a global problem with significant geographic variation in its incidence.<sup>23</sup> The highest incidence (1 in 102 births) is seen in Nigeria, and the lowest incidence (1 in 15 533 births) is seen in Japan.<sup>24</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>23,25</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>26</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>26</sup>

- In a cohort of 55 804 hospitalized patients with PPCM in the United States, Black individuals (OR, 1.17 [95% CI, 1.15–1.57];  $P < 0.001$ ) and Hispanic individuals (OR, 1.37 [95% CI, 1.17–1.59];  $P < 0.001$ ) were more likely to develop cardiogenic shock than White individuals.<sup>27</sup> Similarly, Black individuals (OR, 1.67 [95% CI, 1.21–2.23];  $P = 0.002$ ) and Hispanic individuals (OR, 2.20 [95% CI, 1.45–3.33];  $P < 0.001$ ) were more likely to have in-hospital mortality than White individuals.
- In a UK case-control study of women with PPCM from 1998 to 2017, the incidence was 2.02 (95% CI, 1.76–2.29) per 10 000 deliveries in Scotland, which was similar to the incidence rate of 2.12 (95% CI, 2.03–2.21) per 10 000 deliveries in England from 2003 to 2017.<sup>28</sup> From 1998 to 2017 in Scotland, 7.7% of women with PPCM died over a median follow-up of 8.3 years, and 30-day mortality was 2.3% (95% CI, 0.9%–5.3%).<sup>28</sup>
- In a global prospective PPCM registry, which included 739 women enrolled between 2012 and 2018 from 49 countries, the 6-month maternal mortality rate was 5.9% overall but negatively correlated with the health expenditure of the countries, defined as a proportion of GDP allocated to health care expenses.<sup>29</sup> Maternal mortality rates at 6 months ranged from 2.0% in high-health-expenditure (>8% GDP) countries, 5.5% in medium-health-expenditure (5%–8% GDP) countries, and 10.0% in low-health-expenditure (<5% GDP) countries ( $P = 0.002$ ).
- In a registry of 535 women with PPCM from 51 countries from 2012 to 2018, overall 1-year mortality was 8.4% with rates varying by region: Europe, 4.9%; Africa, 6.5%; Asia Pacific, 9.2%; and the Middle East, 18.9% ( $P < 0.001$ ).<sup>30</sup> Within 1 year of diagnosis, 14.0% of women had at least 1 rehospitalization, and 3.5% had ≥2 rehospitalizations.
- In many cases of PPCM (47%–66%), LVEF recovers to at least near-normal (≥50%) function and often within 6 months.<sup>30–33</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>34</sup>

## Genetics of PPCM

- 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>34</sup>
- Global mortality from PPCM is 9%<sup>31,35</sup> 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>35</sup>

## Youths

- Since 1996, the Pediatric Cardiomyopathy Registry has collected prospective data on children with cardiomyopathy in New England and central southwestern states.<sup>36,37</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 in children <1 year of age.
  - Annual incidence (cases per 100 000) is higher in Black children (1.47) than in White children (1.06;  $P = 0.02$ ), 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>38</sup> Approximately 9% progress to HF and 12% to SCD over a median follow-up of 6.5 years.<sup>39</sup> Chapter 18 (Disorders of Heart Rhythm) provides statistics on SCD. 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>40</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>41</sup> The 5-year incidence rate of SCD is 3% at the time of DCM diagnosis.<sup>42</sup>
- For all cardiomyopathies seen in children, 5-year transplantation-free survival rate of DCM, HCM, restrictive cardiomyopathy, and LV noncompaction is 50%, 90%, 30%, and 60%, respectively.<sup>43</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>44</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.

### Global Burden of Cardiomyopathy

(See Table 22-1 and Charts 22-1 and 22-2)

- Based on 204 countries and territories in 2021<sup>45</sup>:
  - There were 0.40 (95% UI, 0.37–0.43) million total deaths estimated for cardiomyopathy and myocarditis and an age-standardized mortality rate of 4.89 (95% UI, 4.47–5.26) per 100 000 (Table 22-1).
  - The highest age-standardized death rates among regions estimated for cardiomyopathy and myocarditis were for Eastern Europe followed by central sub-Saharan Africa and Central Asia. Rates were lowest for Andean Latin America (Chart 22-1).
  - Globally, there were 5.26 (95% UI, 4.36–6.09) million prevalent cases of cardiomyopathy and myocarditis and an age-standardized prevalence rate of 65.90 (95% UI, 54.98–76.83) per 100 000 (Table 22-1).
  - Age-standardized prevalence of cardiomyopathy and myocarditis among regions was highest for high-income North America followed by Australasia and Eastern Europe. The lowest prevalence rates were for East Asia and Oceania (Chart 22-2).
- Rates of SCD in patients with HCM vary by geographic region. In a meta-analysis of data from 2015 to 2020, the reported incidence rate per 100 PY was highest in Asia (0.67% [95% CI, 0.54%–0.84%]) followed by Europe (0.37% [95% CI, 0.31%–0.46%]) and North America (0.28% [95% CI, 0.18%–0.43%]).<sup>7</sup>

## Heart Failure

**ICD-9 428; ICD-10 I50. For hospital discharges,  
ICD-10 I50, I11.0, I13.0, I13.2, I09.81**

2022, United States: Underlying cause mortality—87 941. Any-mention mortality—425 147.

2021, United States: Hospital discharges, principal diagnosis—1 200 188

### Prevalence

(See Table 22-2 and Chart 22-3)

- According to data from NHANES 2017 to 2020, 6.7 million Americans ≥20 years of age had HF (Table 22-2), up from the estimate of 6.0 million

in 2015 to 2018 (NHLBI unpublished tabulation using NHANES). The breakdown of HF prevalence by age and sex is shown in Chart 22-3.

- Based on temporal trends, the prevalence of HF is projected to increase further, affecting >8 million people ≥18 years of age by 2030. The total percentage of the population with HF is projected to rise from 2.4% in 2012 to 3.0% in 2030.
- Overall, 1.9% to 2.6% of adults in the United States have HF.<sup>46</sup>

### Incidence

- Of 1 799 027 unique Medicare beneficiaries at risk for HF (median, 73 years of age [interquartile range, 68–79 years]; 56% female), 249 832 had a new diagnosis of HF.<sup>47</sup> HF incidence was 26.5 cases per 1000 beneficiaries in 2016, consistent across subgroups based on sex and race or ethnicity.

### Risk Factors

- Hypertension, smoking, diabetes, and obesity account for 52% of incident HF with PARs as follows<sup>48</sup>: CHD, 20% (23% in males versus 16% in females); hypertension, 20% (28% in females versus 13% in males); cigarette smoking, 14%; obesity, 12%; and diabetes, 12%.
- Data from NHANES show that one-third of US adults have at least 1 HF risk factor.<sup>49</sup>
- Risk factors differ by HF subtype: among 4 community-based studies (CHS, FHS, PREVEND, MESA)<sup>50</sup>:
  - Older age was more strongly associated with incident HFpEF versus HFrEF (subdistribution HR, 1.91 [95% CI, 1.78–2.06] versus 1.69 [95% CI, 1.59–1.81], respectively, per 10-year age increase; *P* for equality=0.02).
  - In contrast, the following risk factors were more strongly associated with incident HFrEF than HFpEF: 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), electrocardiographic 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 (≥75 years of age) individuals:

obesity, 21% versus 13%; hypertension, 35% versus 23%; diabetes, 14% versus 7%; and smoking, 32% versus 1%.<sup>51</sup>

- Lifestyle factors also affect HF risk. Among WHI, MESA, and CHS participants, individuals with more 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>52</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.<sup>53</sup> 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%).

### 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 obesity had the highest PAR among White males and females (21% [95% CI, 15%–27%] and 18% [95% CI, 13%–23%]).<sup>54</sup>
- Sex-specific risk factors for incident HF include disorders of pregnancy (eclampsia/preeclampsia, gestational diabetes), PPCM, polycystic ovarian syndrome, and premature menopause, although the exact contribution of these conditions to the incidence of HF among women is unknown.<sup>55</sup> The penetrance of genetic cardiomyopathies may be influenced by sex with males often more severely affected.

### 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>56</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>57–59</sup> and *CACNB4*.<sup>60</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>61</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>62,63</sup> A transancestry meta-analysis of GWASs including >1 500 000 individuals identified 47 risk loci for all-cause HF. Integrating cardiac MRI intermediary phenotypes into this GWAS led to the identification of 61 loci.<sup>64</sup>
- A large GWAS meta-analysis for HF, including 90 000 cases and 1 000 000 controls, identified 18 novel loci.<sup>65</sup> Mendelian randomization and colocalization analyses identified an additional 10 putatively causal loci associated with HF.<sup>65</sup> According to the GWAS and mendelian randomization proteomics analysis, 7 potential proteins (*CAMK2D*, *PRKD1*, *PRKD3*, *MAPK3*, *TNFSF12*, *APOC3*, and *NAE1*) were identified as drug targets for HF.<sup>65</sup>
- Human induced pluripotent stem cell cardiomyocyte-based functional studies investigating the molecular mechanism of decreased incidence of HF linked to the *BAG3* gene demonstrated that a coding variant (*BAG3*<sup>C151R</sup>) is responsible for the maintenance of myofibrillary integrity and regulation response to proteotoxic stress.<sup>66</sup>
- A single-cell profiling study showed that HCM and DCM share a common final transcriptional pathway at the cellular level. Furthermore, cardiomyopathy was associated with a shift in the macrophage population and the presence of a unique population of activated fibroblasts.<sup>67</sup>
- The genetic basis of specific cardiomyopathies is summarized in the previous Cardiomyopathy section.

### Treatment

- Improvement in survival has been attributed primarily to evidence-based approaches to treat HFrEF, including pharmacotherapies, ICDs, and cardiac resynchronization therapy.<sup>68</sup>
- Based on modeling from clinical trial data, initiation of contemporary GDMT for HFrEF (quadruple therapy with angiotensin receptor/neprilysin inhibitors, ACE inhibitors, or ARBs;  $\beta$ -blockers; mineralocorticoid receptor antagonists; and SGLT-2 inhibitors) may reduce the hazard of cardiovascular death or HF hospitalization in HFrEF 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>69</sup> Treatment efficacy with these classes for the outcome of death is attenuated as LVEF increases, and there is no clear evidence to support  $\beta$ -blockers in HFpEF.<sup>70,71</sup>
- Across jurisdictions, there are significant gaps in the use and dose of GDMT, particularly in females.<sup>72</sup> In an analysis of a US administrative health claims database of 63 759 patients (mean age, 71.3 years;

56.6% male), only 6.2% achieved optimal GDMT within 12 months of HFrEF diagnosis; optimal GDMT was defined as ≥50% of the target dose of evidence-based β-blocker plus ≥50% of the target dose of ACE inhibitors or ARBs or any dose of angiotensin receptor/neprilysin inhibitor plus any dose of mineralocorticoid receptor antagonist.<sup>72</sup> Treatment gaps were wider in female than male patients; relative to males, females with HFrEF had lower use of each GDMT class and of optimal GDMT at every time point at follow-up. In adjusted analyses, female sex was associated with a 23% lower probability of achieving optimal GDMT after diagnosis (HR, 0.77 [95% CI, 0.71–0.83];  $P<0.001$ ). Females were also less likely to receive cardiac resynchronization and intracardiac device therapy than males.

- ICD and cardiac resynchronization therapy reduce all-cause mortality in eligible patients with HFrEF<sup>71,72</sup> but remain underused. Females receive this intervention less frequently than males. In a pooled analysis of 98 cohorts who had received CRT with or without ICD, men received the devices at a median ratio of 3.16 (25th–75th interquartile range, 2.48–3.62) relative to women.<sup>73</sup>

### Mortality

#### Secular Trends

- Among adults ≥75 years of age with HF in the CDC WONDER dataset<sup>74</sup>:
  - AAMR per 100 000 declined from 141.0 in 1999 to 108.3 in 2012 (annual percent change, −2.1 [95% CI, −2.4 to −1.9]), after which it increased to 121.3 in 2019 (annual percent change, 1.7 [95% CI, 1.2–2.2]).
- Across jurisdictions, the COVID-19 pandemic was associated with increased mortality among those with decompensated HF and with a shift in deaths from hospital to community.<sup>75,76</sup> There was an increase in both in-hospital and postdischarge mortality among patients hospitalized with HF despite similar care quality. In the GWTG—Heart Failure registry, in-hospital mortality increased from 2.5% in 2019 to 2020 to 3.0% during 2020 to 2021, with in-hospital mortality as high as 8.2% among those with concurrent COVID-19 infection.<sup>76</sup>

#### Mortality by HF Subtype

- Among 4 community-based cohorts, including CHS, FHS, PREVEND, and MESA, all-cause mortality rates after HF diagnosis were 459 per 10 000 PY among those with HFrEF and 394 per 10 000 PY in individuals with HFpEF.<sup>77</sup>
- Phenotypes based on clinical comorbidities may stratify all-cause death or readmissions with greater discrimination than LVEF categories after hospitalization for HF.<sup>78</sup> In an unsupervised machine-learning cluster analysis of 1693

patients hospitalized for HF and discharged alive, 6 discrete phenogroups characterized by a predominant comorbidity were identified: CHD, valvular HD, AF, sleep apnea, chronic obstructive pulmonary disease, or minimal comorbidities. Phenogroups were LVEF independent, with each phenogroup encompassing a wide range of LVEFs. For the composite outcome of all-cause death or rehospitalization at 6 months, the HRs for phenogroups ranged from 1.25 (95% CI, 1.00–1.58) for AF to 2.04 (95% CI, 1.62–2.57) for chronic obstructive pulmonary disease (log-rank  $P<0.001$ ) relative to the phenogroup with minimal comorbidities. In comparison, LVEF-based classification did not separate patients into different risk categories for composite of all-cause death or rehospitalization at 6 months; ( $P=0.69$ ); relative to patients with LVEF ≤40%, those with LVEF ≥50% had no difference in risk of all-cause death or rehospitalization at 6 months (HR, 1.01 [95% CI, 0.87–1.17];  $P=0.94$ ).<sup>78</sup>

#### CVD Mortality

##### (See Table 22-2)

- Among optimally treated clinical trial patients with HF across the LVEF continuum, 53.5% of deaths were ascribed to CVD causes (of which 33.1% were from HF and 50.6% from SCD), 29.9% to non-CVD causes, and 16.5% to undetermined causes.<sup>79</sup> The proportion of non-CVD death was higher in those with higher EF. In the same analysis, the rate of death per 100 000 patient-years resulting from sudden death, HF, and cardiovascular causes decreased as LVEF increased.
- 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 increased through 2017 (59.3 per 100 000 [95% CI, 58.9–59.6]).<sup>80</sup> There is geographic variation in HF-related CVD mortality, with the highest increases in annual AAMR 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]) compared with the Northeast (0.35 per 100 000 per year [95% CI, 0.03–0.68]).<sup>81</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 ≈1 in 8 deaths in 2021 has HF mentioned on the death certificate (unpublished NHLBI tabulation).<sup>82</sup>
- In 2022, HF was the underlying cause in 87 941 deaths (41 657 males and 46 284 females; Table 22-2).

- The number of deaths attributable to HF was 45.7% higher in 2022 than in 2012 (60 341; unpublished NHLBI tabulation using CDC WONDER).<sup>83</sup>

### **Age, Sex, and Race and Ethnicity Differences in Mortality**

(See Table 22-2)

- Among older adults in the CDC WONDER dataset between 1999 and 2019<sup>74</sup>:
  - Males had consistently a higher AAMR than females throughout the period, with an AAMR of 141.1 in males and 107.8 in females in 2019.
  - NH White adults had the highest overall AAMR (127.2) followed by NH Black adults (108.7), NH American Indian/Alaska Native adults (102.0), Hispanic or Latino adults (78.0), and NH Asian or Pacific Islander adults (57.1).
- 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>84</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>85</sup>
- Underlying cause and any-mention age-adjusted HF mortality rates by gender, race, and ethnicity are listed in Table 22-2.

### **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>86</sup>

### **Health Care Use: Hospital Use**

- In 2019, there were 8 054 000 physician office visits with a primary diagnosis of HF (NAMCS,<sup>87</sup> unpublished NHLBI tabulation). In 2021, there were 1 390 365 ED visits for HF (HCUP,<sup>2</sup> unpublished NHLBI tabulation). In 2021, there were 1 200 188 principal diagnosis hospital discharges for HF (HCUP,<sup>2</sup> unpublished NHLBI tabulation).
- In the NCDR PINNACLE, 1 in 6 patients with HFrEF developed worsening HF within 18 months of diagnosis and was more likely to be Black, to be  $>80$  years of age, and to have greater comorbidity burden; overall, the 2-year mortality rate was 22.5%.<sup>88</sup>
- Outcomes remain poor after hospitalization for HF. In a pragmatic trial of 2 494 patients discharged alive after hospitalization for HF in Canada in 2015 to 2016, 49.1% of patients

were rehospitalized (47.4% of these for HF), an additional 34.1% visited the ED without being rehospitalized, and 15.5% died within 6 months of discharge.<sup>89</sup>

### **Secular Trends**

- In the US 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>90</sup>
- Hospitalizations by HF subtype increased from 2008 to 2018 in the United States for both HFrEF ( $n=283\,193$  to  $n=679\,815$ ) and HFpEF ( $n=189\,260$  to  $n=495\,095$ ).<sup>90</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 sex difference).
- Among 11 806 679 cases of HF hospitalization in the US NIS 2002 to 2016, there was a decrease in adjusted mortality from 6.8% in 2002 to 4.9% in 2016 ( $P_{trend}<0.001$ ), with consistent findings across age, sex, and race.<sup>91</sup> The adjusted mean length of stay decreased from 8.6 to 6.5 days ( $P<0.001$ ), and discharge to a long-term care facility increased from 20.8% to 25.6% ( $P<0.001$ ).

### **Age, Sex, Race, and Socioeconomic Differences**

- Among 4 287 478 weighted hospitalizations in NIS dataset in the United States, the median age was 73.4 years (interquartile range, 62.4–82.9 years), 51.3% of hospitalizations occurred in male patients, and race and ethnicity composition included White individuals (70.0%), Black individuals (17.5%), Hispanic individuals (7.6%), Asian or Pacific Islander individuals (2.2%), and Native American individuals (0.5%). Among the hospitalizations, 33.1% were patients from zip codes in the lowest quartile of national household income (including 0.6% experiencing homelessness).<sup>92</sup> In models adjusted for baseline characteristics, male sex (RR, 1.09 [95% CI, 1.07–1.11]) and low SES (RR, 1.02 [95% CI, 1.00–1.05]) were associated with a higher risk of in-hospital mortality relative to female sex and high SES, whereas Black race (RR, 0.79 [95% CI, 0.76–0.81]) and Hispanic ethnicity (RR, 0.90 [95% CI, 0.86–0.93]) were associated with a lower risk of in-hospital mortality than White race.
- Among 767 180 weighted hospitalizations for HF among young adults  $<50$  years of age in the NIS dataset in the US, Black adults (50.1%) accounted for disproportionately higher HF

hospitalizations compared with White adults (31.9%) and Hispanic adults (12.2%). Nearly half of hospitalizations (45.8%) represented patients from the lowest quartile of national household income.<sup>93</sup>

- 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. Age-adjusted 28-day and 1-year case fatality rates after first-time hospitalized HF were higher among White individuals 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>94</sup>
- In a pragmatic clinical trial of 2494 patients hospitalized for HF in Canada, females were on average ≈5 years older (mean $\pm$ SD age, 80.0 $\pm$ 10.9 years versus 75.4 $\pm$ 12.8 years), more commonly resided in a nursing home (16.2% versus 8.2%), had a 6.89 (5.51–8.28) higher associated mean LVEF,<sup>78</sup> and experienced worse quality of life as measured by the European Quality of Life 5 Dimensions 5 Level Version scores (range, 0–1; 0.37 [95% CI, 0.30–0.44] females versus 0.62 [95% CI, 0.57–0.67] males).<sup>89,95</sup> Event rates were high after index hospitalization; at 3 years of follow-up, 51.4% of patients receiving usual care had died, 80.7% were readmitted for any cause, and 42.3% were readmitted for HF.<sup>96</sup>
- Among those who die or are rehospitalized for any cause after hospitalization for HF, the proportion of cardiovascular deaths or HF hospitalizations decreases as LVEF increases. In a cohort of 1693 patients hospitalized for HF in 2015 to 2016 and discharged alive in Canadian hospitals, patients with LVEF  $\geq$ 50% had a similar risk of all-cause death or rehospitalization at 6 months (HR, 1.01 [95% CI, 0.87–1.17];  $P=0.94$ ), but a lower risk of cardiovascular death or HF rehospitalization (HR, 0.75 [95% CI, 0.62–0.92];  $P=0.005$ ) than those with LVEF  $\leq$ 40%.<sup>78</sup> Among those who died or were rehospitalized for any cause at 6 months, the proportion of cardiovascular deaths or HF hospitalizations was higher in patients with LVEF <40% (61.1%) than in those with LVEF  $>$ 50% (48.4%).
- In the CHARM program, rates of cardiovascular hospitalization were higher among those with LVEF  $\leq$ 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>97</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)

#### Transplant Recipients

- The annual number of transplants in the United States has increased over time from 1676 in 1988 to 4111 in 2022.<sup>98</sup>
- In 2022, the annual transplantation rate was 122.5 per 100 patient-years.<sup>99</sup>
  - Among 3668 adult transplant recipients in 2022, the most common age group (46.6%) was 50 to 64 years of age, 26.9% were female, and 56.4% were White.
  - The demographic characteristics of the typical heart transplant recipient—50 to 64 years of age, male, White—remained unchanged between 2012 and 2022; however, there has been an increase in the proportion of recipients who are 18 to 34 years of age (10.9% to 12.5%),  $\geq$ 65 years of age (17.8% to 20.3%), and of Black race (19.7%–27.0%) or Hispanic ethnicity (7.9% to 11.2%); there has been a decrease in private insurance payers (50.9% to 44.8%). The proportion of recipients who are female remained unchanged between 2012 and 2022 (27.7% to 26.9%).
  - Among 3668 transplant recipients in 2022, the primary diagnosis was cardiomyopathy (64.1%) followed by CAD (25.9%), congenital HD (5.1%), and valvular disease (1.0%), with unknown underlying diagnoses in 3.9%. Coronary disease has become a less common primary diagnosis for heart transplantation over time (38.8% in 2012), and cardiomyopathy remains the most common diagnosis for heart transplantation (54.1% in 2012).
  - Among 3668 transplant recipients in 2022, a majority lived  $<$ 50 miles from the transplantation center (59.2%) and in metropolitan areas (83.6%).
  - A ventricular assist device was present in 35.2% of transplant recipients in 2022, down from 41.4% in 2012.<sup>99</sup>
  - The proportion of transplant recipients who waited  $<$ 90 days for a transplantation increased from 47.6% in 2012 to 65.9% in 2022.
  - Multiorgan transplantation has increased more rapidly than heart transplantation alone. In 2012, 6.0% of heart transplants were combined

with transplantation of other organs, and this increased to 14.0% in 2022. Between 2012 and 2022, heart-kidney transplants increased from 3.7% to 10.5% of total heart transplants, heart-liver transplants increased from 0.9% to 2.0%, and heart-lung transplants changed from 1.3% to 1.2%; the absolute numbers of each type of multiorgan transplants increased substantially during this period in the order in which they are presented here.

### **Transplantation Listings**

- In 2022, a total of 7519 adults were awaiting heart transplantation in the United States, a 28.1% increase from 2011.<sup>99</sup>
- A majority (61.6%) of adult heart transplantation candidates lived <50 miles from the transplantation center in 2022.<sup>99</sup>
- The largest adult age group on the waiting list in 2022 continued to be 50 to 64 years of age (46.7%, followed by 35 to 49 years of age (21.7%), ≥65 years of age (20.3%), and 18 to 34 years of age (11.3%).<sup>99</sup>
- In 2022, more than half of adult heart transplantation candidates were White (56.3%); 28.2% were Black, 10.8% were Hispanic, 3.8% were Asian, 0.4% were Native American, and 0.5% multiracial.<sup>99</sup>
- Among 8747 US adults listed for heart transplantation in the Scientific Registry of Transplant Recipients from 2017 to 2019, 84.7% were from metropolitan, 8.6% were from micropolitan, and 6.6% were from rural settings; >70% were male candidates.<sup>100</sup>
- Time on the waiting list, which is determined by the earliest of transplantation, death, removal, or December 31 of the year, has decreased, and the proportion of candidates waiting <90 days increased from 2011 to 45.8% in 2022.<sup>99</sup>
- The proportion of candidates on the waiting list with a ventricular assist device increased from 22.4% in 2012 to 35.0% in 2022.<sup>99</sup>
- Overall pretransplantation mortality declined from 15 deaths per 100 patient-years in 2011 to 8.7 deaths per 100 patient-years in 2019 and remained steady through 2022. The decrease in pretransplantation mortality has been consistent in all age and race or ethnicity groups other than Asian Americans, who experienced a slight increase with 9.7 deaths per 100 patient-years in 2022 compared with 8.5 deaths per 100 patient-years in 2012.<sup>99</sup>

### **Outcomes After Transplantation**

- In 2022, 6-month, 1-year, 3-year, and 5-year mortality after transplantation were 7.3%, 9.2%, 15.3%, and 19.9%, respectively. Mortality after transplantation has decreased since 2009.<sup>99</sup>

- Five-year survival was modestly lower in those 18 to 34 years of age (78.9%) and ≥65 years of age (77.8%) compared with the other age groups (35–49 and 50–64 years of age, 82.1% and 81.0%, respectively).<sup>99</sup>
- Five-year survival was highest in White transplant recipients (81.9%) followed by recipients identifying as Asian, multiracial, Black, Hispanic, and Native American, ranging from 76.0% to 80.4%.<sup>99</sup>
- Among 32353 adult heart transplant recipients in the United Network for Organ Sharing database, the proportion of Black individuals 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>101</sup> Black individuals had a higher risk of death after transplantation (aHR, 1.14 [95% CI, 1.04–1.24];  $P=0.004$ ) compared with White individuals.
- Among 34198 heart transplant recipients in the International Society for Heart and Lung Transplantation registry between 2004 and 2014, when matched for recipient and donor characteristics, there was no significant difference in survival between male and female recipients.<sup>102</sup> Data from the Scientific Registry of Heart Transplant Recipients 2015 to 2017 also demonstrate no sex differences in survival through 5 years after transplantation.<sup>99</sup>
- Among 15036 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>103</sup> One-year risk-adjusted graft survival ranged from 87% to 92%.

### **Mechanical Circulatory Support**

- The 14th Annual Report from the STS INTERMACS described outcomes of 27 493 patients with a continuous-flow LVAD from 2013 to 2022.<sup>104</sup> During this period, there was a shift to nearly exclusive use of fully magnetically levitated devices.
- In 2022, of 2517 primary LVADs implanted, 99.8% were fully magnetically levitated devices.<sup>104</sup>
- The outcomes of magnetically levitated devices are superior to those of nonmagnetically levitated devices in contemporary (2018–2022) and historical (2013–2017) cohorts.<sup>104</sup>
- Patients supported by a magnetically levitated device ( $n=10920$ ) had a higher 1-year survival of 86% versus 79% and 81% in contemporary and historical nonmagnetically levitated groups, respectively ( $P<0.0001$ ). They also had a higher 5-year survival of 64% versus 44% and 44% in contemporary and historical nonmagnetically levitated groups, respectively ( $P<0.0001$ ).<sup>104</sup>
- Over 5 years, a higher proportion of patients with magnetically levitated devices had freedom from gastrointestinal bleeding (72% versus 60%;

$P<0.0001$ ), stroke (87% versus 67%;  $P<0.0001$ ), and device malfunction/pump thrombus (83% versus 54%;  $P<0.0001$ ) but not device-related infection (61% versus 64%;  $P=0.93$ ) than patients with nonmagnetically levitated support during the contemporary era.<sup>104</sup>

- INTERMACS reported outcomes on 29 143 adults receiving an FDA-approved durable mechanical circulatory support device from 2012 to 2021.<sup>105</sup> During the reported 10-year period, there was not a significant change in the acuity of illness of patients receiving an implant. INTERMACS profiles 1 and 2 still represented approximately half of the population (51% in 2021 versus 54.9% in 2012), with a minority of patients belonging to INTERMACS profile 4 (12.7% in 2021 versus 14.9% in 2012).
- Among LVAD recipients, destination therapy is now the predominant indication (increased from 56.5% in 2018 to 81.1% in 2021), whereas bridge to transplantation is uncommon (decreased from 18.9% in 2018 to 5.3% in 2021).<sup>105</sup>
  - 1-year and 5-year survival was 86.5% and 52.9% for bridge to transplantation, 84.7% and 49.4% for bridge to candidacy, and 70.9% and 42.4% for destination therapy in 2012 to 2021. During this period, there was a consistent improvement in survival for all device indications, with the most striking improvement in destination therapy as the predominant implantation strategy.<sup>105</sup>
  - Improvements in LVAD technology and the use of LVAD as destination therapy have led to more prolonged time on support. Currently, withdrawal from support is the leading cause of death (19.4%), replacing neurological dysfunction (17.9%) in the prior era.<sup>105</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 compared with private insurance (subdistribution HR, 1.57 [95% CI, 1.15–2.16]), although access to transplantation was not different.<sup>106</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;  $P=0.01$ ) relative to females.<sup>107</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 attributed to direct medical costs.<sup>108</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.
- 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>109</sup>
- Data from the US NIS for 4 287 478 primary HF hospitalizations 2014 to 2017 highlight differences in cost of care across demographic groups.<sup>92</sup> The median direct cost of admission was higher in high- than in low-SES groups (\$10 940.40 versus \$9 324.60), male versus female patients (\$10 217.10 versus \$9 866.60), and White versus Black individuals (\$10 019.80 versus \$9 077.20). The median costs increased with SES in all demographic groups, related to greater procedural use.
- Among 11 806 679 HF hospitalizations in the US NIS database between 2002 and 2016, inflation-adjusted mean cost of stay increased from \$14 301 to \$17 925 ( $P<0.001$ ; average annual increase, 1.52%).<sup>91</sup> This trend may have been related to the temporal increase in procedures (echocardiogram, right-sided heart catheterization, use of ventricular assist devices, CABG) and the higher incidence of HF complications (cardiogenic shock, respiratory failure, ventilator, and renal failure requiring dialysis).
- 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>111</sup>

### Global Burden of HF

#### (See Table 22-3 and Chart 22-4)

- Based on 204 countries and territories in 2021<sup>45</sup>:
  - There were 55.50 (95% UI, 49.00–63.84) million prevalent cases of HF and an age-standardized prevalence rate of 676.68 (95% UI, 598.68–776.84) per 100 000 globally (Table 22-3).
  - Among regions, age-standardized prevalence of HF was highest for high-income North America followed by Central Europe, North Africa and the Middle East, and eastern sub-Saharan Africa. The lowest prevalence rates were for high-income Asia Pacific (Chart 22-4).
- In 2019:
  - Adults >70 years of age accounted for 62.2% of the world's HF cases, with female predominance

- in this age group and male predominance in younger adults; 50.3% of those living with HF were females, but age-standardized prevalence was greater in males.<sup>112</sup>
- 69.2% lived in low- and middle-income countries, although the highest age-standardized prevalence was highest in North America and lowest in South Asia.<sup>112</sup> Age-standardized HF prevalence in 2019 was highest in high-income North America (993.84 [95% CI, 866.22–1140.37] per 100 000 in females; 1344.62 [95% CI, 1159.53–1556.54] per 100 000 in males) and East Asia (1001.01 [95% CI, 819.06–1245.62] per 100 000 in females; 991.23 [95% CI, 808.02–1228.71] per 100 000 in males) followed by Oceania and eastern sub-Saharan Africa.<sup>113</sup>
  - There were 5.1 (95% UI, 3.3–7.3) million years lived with disability from HF, distributed equally between the sexes.<sup>112</sup>
  - In sequence, ischemic, hypertensive, and rheumatic HDs were the most common causes of HF in the world. IHD and hypertensive HD were the top causes of HF in males and females, respectively.<sup>112</sup>
  - Between 1990 and 2019<sup>112</sup>:
    - There was a doubling in the global number of HF cases from 27.2 (95% UI, 22.2–33.4) million to 56.2 (95% UI, 46.4–67.8) million, with a doubling in both males and females.

- Accounting for population growth, the age-standardized rate of HF per 100 000 people decreased by 7.1% worldwide, from 766.0 (95% UI, 626.3–936.0) in 1990 to 711.9 (95% UI, 591.1–858.3) in 2019. There were 9.1% (from 864.2 to 785.7) and 5.8% (from 686.0 to 646.1) decreases in age-standardized rates per 100 000 in males and females, respectively.
- High-income regions experienced a 16.0% decrease in age-standardized rates (from 877.5 to 736.8), whereas low-income regions experienced a 3.9% increase (from 612.1 to 636.0), largely consistent across sexes.
- There was a temporal increase in age-standardized HF from hypertensive, rheumatic, and calcific aortic valvular HD, as well as a temporal decrease from IHD, with some regional and sex differences. Age-standardized HF rates from hypertensive HD were largely stable but increased by as much as 22.3% in females in high-middle-SDI regions. Age-standardized prevalence of HF from rheumatic HD increased over time; this was driven by increasing rates in males in low- (5% increase) and low-middle- (9.2% increase) SDI regions and most notably in Andean Latin America (16.7% increase). Despite an overall decrease in the age-standardized HF attributable to IHD, low- and low-middle-SDI regions (including South and Southeast Asia and eastern and western sub-Saharan Africa) experienced increases ranging from 5% to 25% over time; this trend was consistent in both sexes.

**Table 22-1. Global Prevalence and Mortality of Cardiomyopathy and Myocarditis, by Sex, 2021**

	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), 2021	0.40 (0.37 to 0.43)	5.26 (4.36 to 6.09)	0.25 (0.22 to 0.27)	3.03 (2.51 to 3.53)	0.16 (0.14 to 0.17)	2.22 (1.84 to 2.62)
Percent change (%) in total number, 1990–2021	45.67 (33.04 to 59.51)	77.47 (67.74 to 87.17)	63.31 (46.26 to 80.27)	82.04 (72.71 to 91.54)	24.63 (11.99 to 39.24)	71.60 (61.49 to 81.79)
Percent change (%) in total number, 2010–2021	-0.53 (-6.38 to 5.73)	20.11 (13.65 to 26.46)	0.85 (-7.51 to 7.93)	20.27 (13.82 to 25.90)	-2.61 (-9.32 to 4.93)	19.90 (13.12 to 27.15)
Rate per 100 000, age standardized, 2021	4.89 (4.47 to 5.26)	65.90 (54.98 to 76.83)	6.47 (5.86 to 7.07)	78.26 (65.37 to 90.93)	3.46 (3.05 to 3.76)	54.20 (45.01 to 63.96)
Percent change (%) in rate, age standardized, 1990–2021	-37.54 (-42.40 to -32.03)	3.22 (-2.63 to 9.13)	-30.30 (-36.37 to -23.64)	5.97 (0.28 to 11.49)	-46.71 (-51.37 to -41.47)	-0.01 (-6.07 to 6.48)
Percent change (%) in rate, age standardized, 2010–2021	-25.16 (-29.44 to -20.50)	-0.58 (-5.89 to 4.35)	-23.01 (-28.99 to -17.91)	-0.47 (-5.61 to 4.10)	-27.96 (-32.80 to -22.55)	-0.75 (-6.42 to 4.55)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study, Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>45</sup>

**Table 22-2. HF in the United States**

Population group	Prevalence, 2017–2020, ≥20 y of age	Underlying cause mortality, 2022, all ages*	Underlying cause age-adjusted mortality rates per 100 000 (95% CI)*, 2022	Any-mention mortality, 2022, all ages*	Any-mention age-adjusted mortality rates per 100 000 (95% CI), 2022
Both sexes	6 700 000 (2.3%) (95% CI, 1.9%–2.8%)	87 941	21.0 (20.8–21.1)	425 147	101.1 (100.8–101.4)
Males	3 700 000 (2.7%)	41 657 (47.4%)†	24.2 (24.0–24.5)	213 137 (50.1%)†	121.9 (121.3–122.4)
Females	3 000 000 (1.9%)	46 284 (52.6%)†	18.5 (18.3–18.6)	212 010 (49.9%)†	85.6 (85.2–86.0)
NH White males	2.9%	32 820	25.3 (25.0–25.6)	169 070	128.2 (127.6–128.8)
NH White females	1.6%	37 152	19.6 (19.4–19.8)	168 537	90.4 (89.9–90.8)
NH Black males	3.8%	5 101	32.1 (31.2–33.1)	23 112	143.8 (141.8–145.8)
NH Black females	3.3%	5 375	22.7 (22.1–23.3)	23 818	99.8 (98.5–101.1)
Hispanic males	1.8%	2 434	15.0 (14.3–15.6)	13 304	79.3 (77.9–80.8)
Hispanic females	1.6%	2 478	11.0 (10.5–11.4)	12 611	55.2 (54.3–56.2)
NH Asian males	1.4%	835‡	9.7 (9.0–10.4)‡	4 715‡	53.7 (52.1–55.2)‡
NH Asian females	0.5%	883‡	7.0 (6.5–7.5)‡	4 611‡	36.7 (35.7–37.8)‡
NH American Indian or Alaska Native	...	354	14.4 (12.9–16.0)	2 308	92.8 (88.9–96.6)
NH Native Hawaiian or Pacific Islander		94	17.1 (13.7–21.0)	609	108.8 (99.9–117.6)

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>114</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 cause of death listed as HF on death certificates for Hispanic people, NH American Indian or Alaska Native people, 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 decedents, Asian and Pacific Islander decedents, 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 the Mortality section.

†These percentages represent the portion of total mortality attributable to HF that is for males vs females.

‡Includes Chinese people, Filipino people, Japanese people, and other Asian people.

Sources: Prevalence: Unpublished National Heart, Lung, and Blood Institute (NHLBI) tabulation using NHANES.<sup>115</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. Mortality: Unpublished NHLBI tabulation using National Vital Statistics System<sup>82</sup> and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.<sup>83</sup>

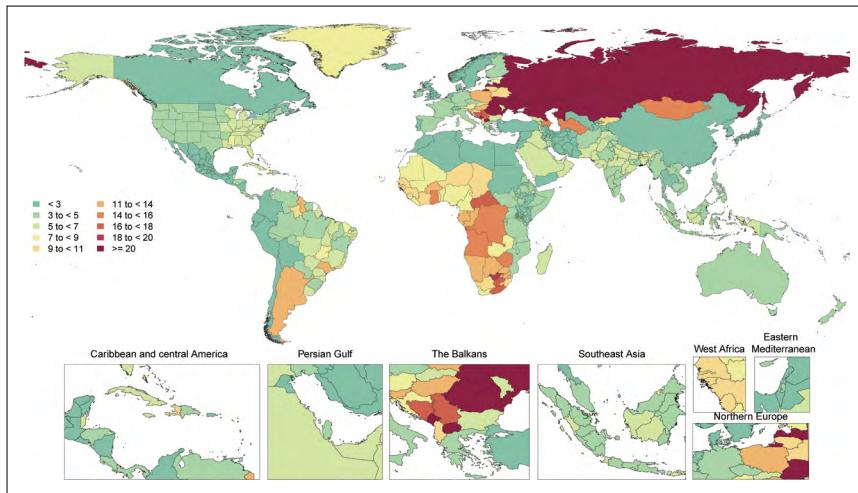
**Table 22-3. Global Prevalence of Heart Failure, by Sex, 2021**

	Prevalence		
	Both sexes (95% UI)	Male (95% UI)	Female (95% UI)
Total number (millions), 2021	55.50 (49.00 to 63.84)	28.59 (25.35 to 32.83)	26.91 (23.72 to 30.98)
Percent change (%) in total number, 1990–2021	118.21 (112.40 to 124.14)	119.11 (112.83 to 125.49)	117.25 (111.26 to 123.99)
Percent change (%) in total number, 2010–2021	33.28 (30.67 to 36.34)	32.28 (29.62 to 35.21)	34.36 (31.31 to 37.50)
Rate per 100 000, age standardized, 2021	676.68 (598.68 to 776.84)	760.78 (673.19 to 874.71)	604.00 (534.95 to 692.29)
Percent change (%) in rate, age standardized, 1990–2021	5.54 (2.70 to 8.49)	4.78 (1.74 to 7.81)	5.57 (2.35 to 8.69)
Percent change (%) in rate, age standardized, 2010–2021	1.02 (−0.54 to 2.73)	0.16 (−1.43 to 1.85)	1.81 (0.00 to 3.59)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

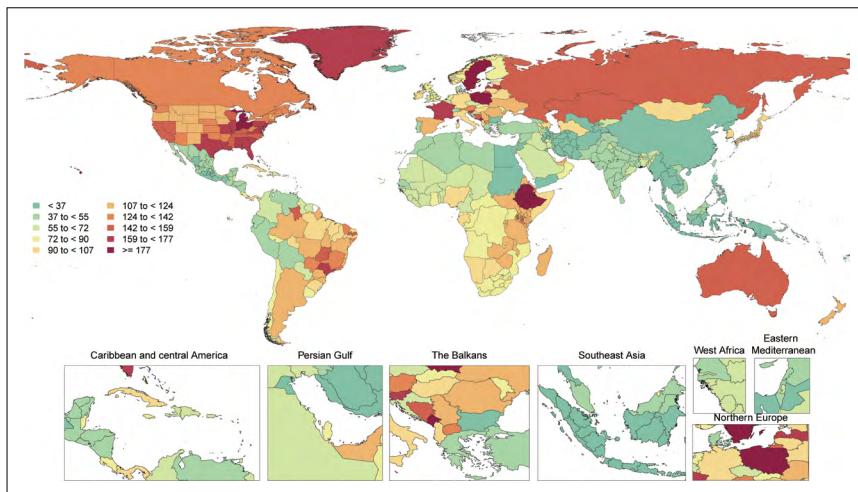
Source: Data courtesy of the GBD Study, Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>45</sup>


**Chart 22-1. Age-standardized global mortality rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

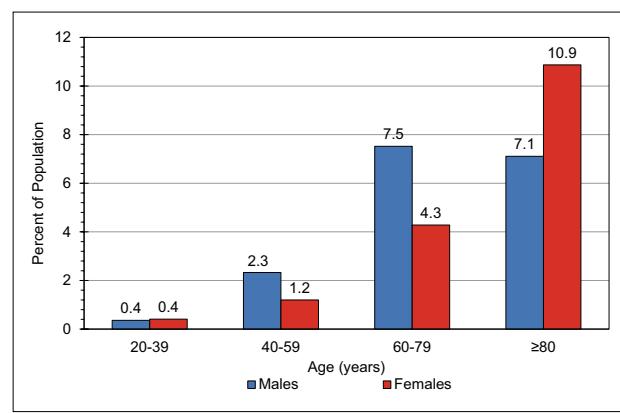
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>45</sup>


**Chart 22-2. Age-standardized global prevalence rates of cardiomyopathy and myocarditis per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

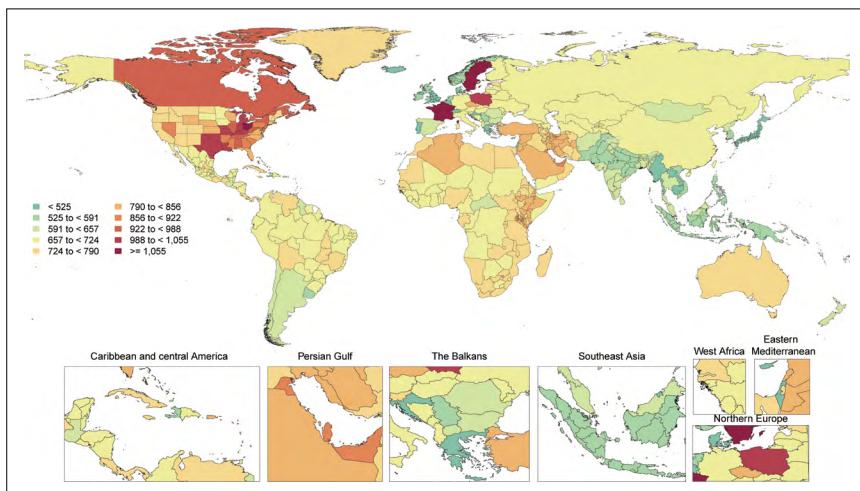
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>45</sup>



**Chart 22-3. Prevalence of HF among US adults  $\geq 20$  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>115</sup>



**Chart 22-4. Age-standardized global prevalence rates of HF per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update.

GBD indicates Global Burden of Disease, Injuries, and Risk Factors; and HF, heart failure.

Source: Data courtesy of the GBD Study, Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>45</sup>

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## 23. VALVULAR DISEASES

**See Tables 23-1 through 23-4 and Charts 23-1 through 23-7**

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Mortality data in this section are for 2022 and based on unpublished NHLBI tabulations using the NVSS<sup>1</sup> and CDC WONDER.<sup>2</sup> Prevalence data are for 2016 and 2017. Hospital discharge data are from HCUP<sup>3</sup> 2021; data included are for inpatients discharged alive, dead, or status unknown. Hospital discharge data for 2021 are based on *ICD-10* codes.

### Valvular HD

#### ***ICD-9 424; ICD-10 I34 to I38.***

2022, United States: Underlying cause mortality—24 102. Any-mention mortality—59 139.

2021, United States: Hospital discharges—145 495.

#### **Prevalence**

- The global prevalence of nonrheumatic VHD in 2021 was 28.4 million with a 95% UI of 26.3 million to 30.6 million.<sup>4</sup>
- Older adults in the ARIC study, a prospective community-based cohort study, underwent protocol echocardiography to classify their aortic and mitral stenotic or regurgitant lesions according to ACC/AHA guidelines.<sup>5</sup> Among 6118 ARIC participants with mean $\pm$ SD age of 76 $\pm$ 5 years (42% male, 22% Black race), at-risk (stage A) left-sided VHD was present in 39%, progressive (stage B) in 17%, and advanced (stage C/D) in 1.1%; 0.7% had previously undergone valve replacement or repair. A graded association was observed between stages A, B, and C/D VHD and risk of all-cause mortality, incident HF, incident AF, and incident CHD but not incident stroke. During the 6.6 years of follow-up, the prevalence of stage C/D VHD increased from 1% to 7%.
- In a US population-based study conducted between October 2011 and June 2014, the prevalence of VHD in 1818 Hispanic/Latino people (mean age,

The 2025 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 2025. 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.

55 years; 57% female) 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>6</sup> There is variation in the cause of VHD across the world. In a prospective cross-sectional study across all 31 provinces in China between 2012 and 2015, the weighted prevalence of VHD based on an analysis of 31 499 adults  $\geq$ 35 years of age was 3.8% (95% CI, 2.6%–5.6%) or an estimated 25 621 503 people. Of those with VHD, 55.1% had rheumatic disease and 21.3% had degenerative disease. The prevalence of VHD increased with age ( $P<0.001$ ) and was not different between males and females ( $P=0.308$ ). VHD was more prevalent in participants with hypertension (5.6% versus 2.8%;  $P<0.001$ ) or CKD (9.2% versus 3.5%;  $P<0.001$ ).

### Aortic Valve Disorders

#### ***ICD-9 424.1; ICD-10 I35.***

2022, United States: Underlying cause mortality—15 817. Any-mention mortality—38 260.

2021, United States: Hospital discharges—110 740.

#### **Prevalence**

- In the MESA study of 6814 participants 45 to 84 years of age free of known CVD in the United States,<sup>7</sup> 77 participants (1.1%) had aortic stenosis on echocardiography; the age-adjusted prevalence of aortic stenosis was highest in White participants (3.5% [95% CI, 2.6%–4.7%]) and Hispanic participants (3.7% [95% CI, 2.5%–5.6%]) with lower prevalence in Black participants (1.8% [95% CI, 1.1%–3.1%]) and Chinese participants (0.3% [95% CI, 0.04%–2.0%]).
- Data from the GBD Study revealed that the global prevalence of calcific aortic valve disease in 2019 was 9 404 080 (95% CI, 8 079 600–10 889 730), and the prevalence of calcific aortic valve disease in the United States was 327 978 730 (95% CI, 285 959 303–369 324 168).<sup>8</sup>
- Globally, there was a 443% increase in the prevalence of calcific aortic valve disease from 1 732 988 (95% CI, 1 431 470–2 074 810) in 1990 to 9 404 080 (95% CI, 8 079 600–10 889 730) in 2019.<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 $\pm$ SD age, 12 $\pm$ 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.<sup>11</sup>

- A meta-analysis of 11 observational studies revealed that among 1177 patients with Turner syndrome, the prevalence of bicuspid aortic valve identified by cardiac MRI or CT was 23.7% (95% CI, 21.3%–26.1%).<sup>12</sup>

### Incidence

- In a population-based cohort study of inpatient, outpatient, and professional claims from a 20% sample of Medicare beneficiaries in the United States between 2010 and 2018, 1513455 patients were diagnosed with aortic stenosis.<sup>13</sup>
  - The aortic stenosis incidence rate for the overall group increased from 13.5 to 17.0 per 1000 between 2010 and 2018 ( $P<0.001$ ).
  - In addition, beneficiaries from underrepresented racial and ethnic groups had significantly lower incidence rates compared with White beneficiaries throughout the study period (91.3% White, 4.5% Black, 1.1% Hispanic, and 3.1% Asian and North American Native).
- Globally, the incident cases of calcific aortic valve disease have increased by 351% from 130821 cases (95% CI, 110700–156020) in 1990 to 589637 cases (95% CI, 512900–677060) in 2019.<sup>9</sup>
- In a retrospective cohort study of 1507 patients from 9 institutions in Japan undergoing hemodialysis, 251 or 17% of patients developed aortic stenosis within a median follow-up of 3.2 years.<sup>14</sup>
- A prospective cross-sectional study of 31 499 people across all 31 provinces in China between 2012 and 2015 reported an aortic regurgitation incidence of 1.2% (95% CI, 0.7%–2.1%) and an aortic stenosis incidence of 0.7% (95% CI, 0.4%–1.1%).<sup>15</sup>

### Lifetime Risk and Cumulative Incidence

- Global incidence and prevalence of calcific aortic valve disease are positively correlated with age. There are 2 peaks in incidence: 1 peak at 70 to 74 years of age and the other at >95 years of age. The prevalence of calcific aortic valve disease peaks at 90 to 94 years of age globally.<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 up 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 CGPS, among 108275 individuals, the risk of developing aortic stenosis was particularly high if BMI was  $\geq$ 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 aortic stenosis diagnosis in 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 BMI of 20 to 22.5 kg/m<sup>2</sup> used as reference.
- In a prospective cohort study of 361930 people with genetic data in the UK Biobank, a total of 1602 participants developed aortic valve stenosis during an 8.4-year follow-up.<sup>18</sup> Cox proportional risk regression models were used to estimate the HRs between 28 modifiable risk factors and aortic valve stenosis.
  - Modifiable risk factors associated with a higher risk of aortic valve stenosis included the following: adiposity (HR, 1.04 [95% CI, 1.05–1.07]), waist-to-hip ratio (HR, 1.03 [95% CI, 1.03–1.04]), BP (HR, 1.10 [95% CI, 1.07–1.14]), pulse pressure (HR, 1.23 [95% CI, 1.19–1.26]), resting heart rate (HR, 1.06 [95% CI, 1.02–1.10]), LDL (HR, 1.10 [95% CI, 1.03–1.18]), urate (HR, 1.02 [95% CI, 1.02–1.03]), CRP (HR, 1.03 [95% CI, 1.02–1.04]), creatinine (HR, 1.04 [95% CI, 1.03–1.05]), glycated hemoglobin (HR, 1.07 [95% CI, 1.06–1.08]), smoking (HR, 1.35 [95% CI, 1.21–1.50]), and insomnia (HR, 1.19 [95% CI, 1.05–1.35]).
  - Genetically predicted 1-SD higher levels of BMI (HR, 1.09 [95% CI, 1.03–1.16]), body fat percentage (HR, 1.17 [95% CI, 1.03–1.33]), LDL (HR, 1.15 [95% CI, 1.08–1.21]), and serum TC (HR, 1.13 [95% CI, 1.02–1.25]) were associated with a higher risk of aortic valve stenosis.
- The CGPS recruited 69988 randomly selected individuals between 2003 and 2015 to evaluate the association between high lipoprotein(a) and high BMI and risk of calcific aortic valve disease.<sup>19</sup>
  - Compared with individuals in the 1st to 49th percentiles for both lipoprotein(a) and BMI, the aHRs for calcific aortic valve disease were 1.6 (95% CI, 1.3–1.9) for the 50th to 89th percentiles of both and 3.5 (95% CI, 2.5–5.1) for the 90th to 100th percentiles of both.
  - The 10-year absolute risk of calcific aortic valve disease was higher in males than in females. The 10-year absolute risk of calcific aortic valve disease in females 70 to 79 years of age with BMI  $\geq$ 30.0 kg/m<sup>2</sup> was 5% for lipoprotein(a)  $\leq$ 42 mg/dL, 7% for lipoprotein(a) 42 to 79 mg/dL, and 9% for lipoprotein(a)  $\geq$ 80 mg/dL.

- The 10-year absolute risk of calcific aortic valve disease in males 70 to 79 years of age with BMI  $\geq 30.0 \text{ kg/m}^2$  was 8% for lipoprotein(a)  $\leq 42 \text{ mg/dL}$ , 11% for lipoprotein(a) 42 to 79 mg/dL, and 14% for lipoprotein(a)  $\geq 80 \text{ mg/dL}$ .
- In a retrospective registry based observational study comprising 23 298 individuals who had their lipoprotein(a) measured between 2003 and 2017 at Karolinska University Laboratory in Stockholm, 489 participants developed calcific aortic valve stenosis.<sup>20</sup> The cohort was divided into deciles of lipoprotein(a) levels.
  - Those with calcific aortic stenosis had significantly higher lipoprotein(a) (117 mg/dL) than those without calcific aortic stenosis (89 mg/dL;  $P < 0.001$ ).
  - For individuals at the 90th percentile for lipoprotein(a) levels, the sex- and age-adjusted HR for development of calcific aortic stenosis was 1.53 (95% CI, 1.08–2.15;  $P = 0.016$ ) compared with those below the 50th percentile.
- A comparison of 2786 patients on dialysis with and without aortic stenosis from 58 hospitals in the Tokai region of Japan between 2017 and 2018 was conducted.<sup>21</sup>
  - Multivariable logistic regression analysis revealed that age (aOR, 1.93 [95% CI, 1.71–2.19];  $P < 0.001$ ), long-term dialysis (aOR, 1.41 [95% CI, 1.21–1.64];  $P < 0.001$ ), and elevated serum phosphorus levels (aOR, 1.16 [95% CI, 1.06–1.28];  $P = 0.001$ ) were associated with mild aortic stenosis.
  - Similarly, age (aOR, 2.51 [95% CI, 2.02–3.12];  $P < 0.001$ ), long-term dialysis (aOR, 1.35 [95% CI, 1.06–1.71];  $P = 0.01$ ), and elevated serum phosphorus levels (aOR, 1.24 [95% CI, 1.07–1.44];  $P = 0.005$ ) were associated with moderate to severe aortic stenosis.
  - In an observational case-control study of 3812 588 people in the Utah Population Database, age and sex-matched controls without aortic or aortic valve disease were identified for individuals with bicuspid aortic valve, TAA, or thoracic aortic dissection.<sup>22</sup> Compared with controls without aortic or aortic valve disease, the risk of concordant diagnosis was elevated in first-degree relatives of individuals with bicuspid aortic valve (HR, 6.88 [95% CI, 5.62–8.43]), first-degree relatives of individuals with TAA (HR, 5.09 [95% CI, 3.80–6.82]), and first-degree relatives of individuals with thoracic aortic dissection (HR, 4.15 [95% CI, 3.25–5.31]). The risk of aortic dissection was higher in first-degree relatives of individuals with bicuspid aortic valve (HR, 3.63 [95% CI, 2.68–4.91]) and in first-degree relatives of patients with thoracic aneurysm (HR, 3.89 [95% CI, 2.93–5.18]) compared with controls.

## Genetics and Family History

- Bicuspid aortic valve is thought to be highly heritable with 47% of the phenotypic variance being explained by genetic variation.<sup>23</sup> Variants in *NOTCH1*, *GATA4*, *GATA5*, *GATA6*, *EXOC4*, *PALMD*, *TEX41*, *FBN1*, *ROBO4*, *MYH6*, and *SMAD6* have been associated with bicuspid aortic valve.<sup>24–31</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>32</sup>
- A GWAS for bicuspid aortic valve including 2236 cases and 11 604 controls identified a novel locus at *MUC4* and replicated previously reported loci at *PALMD*, *GATA4*, and *TEX41* to be associated with bicuspid aortic valve.<sup>33</sup> Approximately 20% of the observed heritability of bicuspid aortic valve may be attributed to a polygenic basis.
- A GWAS in 34 287 individuals of European ancestry for functional aortic area (estimated using cardiac MRI) showed significant associations for variants in *DLEU1*, *CRADD*, and *GOSR2*.<sup>34</sup> A polygenic score developed from this GWAS was shown to be associated with the development of aortic stenosis in an independent population of 308 683 individuals (HR, 1.14 per 1-SD decrease polygenic score;  $P = 0.002$ ).
- 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>35</sup>
- In a GWAS of 1009 individuals undergoing cardiac surgery in Quebec and across Europe between 1993 and 2018,<sup>36</sup> a weighted GRS in each individual, estimated by adding the number of lipoprotein(a)-raising alleles weighted by the effect of each variant on lipoprotein(a) levels, was associated with a higher risk of calcific aortic stenosis (OR, 1.35 [95% CI, 1.10–1.660];  $P = 0.003$ ).
- To investigate the association of hepatic *LPA* expression with calcific aortic valve stenosis, 80 SNPs strongly associated with the expression of *LPA* were examined in 408 403 individuals in the UK Biobank.<sup>37</sup> Of the total cohort, 2574 had calcific aortic valve stenosis (1659 males and 915 females). There was a causal association between hepatic *LPA* expression and calcific aortic valve stenosis in males (OR, 1.27 [95% CI, 1.13–1.43]) and females (OR, 1.22 [95% CI, 1.04–1.44]).
- A GWAS meta-analysis of 5115 cases and 354 072 controls identified *IL6*, *ALPL*, and *NAV1* as susceptibility genes for calcific aortic valve stenosis,<sup>38</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>35,36,39,40</sup> A multiancestry GWAS for calcific aortic valve stenosis conducted in >400 000 individuals identified 6 novel loci (*SLMAP*, *CEL-SR2*, *CEP85L*, *MECOM*, *CDAN1*, and *FTO*).<sup>41</sup> Secondary analysis assessing the pathophysiology of calcific aortic valve stenosis highlighted the role of inflammation, lipid metabolism, calcification, adiposity, and cellular senescence.<sup>41</sup>

- A recent GWAS meta-analysis for calcific aortic stenosis comprising 14 819 cases and 927 044 controls of European ancestry identified 32 loci, of which 20 loci were novel.<sup>42</sup> Transcriptomics-based approaches led to the identification of 5 additional genes associated with calcific aortic stenosis.
- 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>43</sup>
- PCSK9, a key regulator of plasma LDL-C, binds to LDL receptors, leading to their degradation in the liver. Inhibition of PCSK9 leads to an increase in LDL receptors and a decrease in LDL in the blood. A meta-analysis of 10 studies found that the loss-of-function R46L variant in *PCSK9* is associated with a reduced risk of calcific aortic valve stenosis (OR, 0.80 [95% CI, 0.70–0.91];  $P=0.0011$ ).<sup>44</sup>
- To evaluate the association between SBP and risk of valvular disease, 502 602 individuals 40 to 96 years of age in the UK Biobank between 2006 and 2010 were evaluated through mendelian randomization.<sup>45</sup> Each genetically predicted 20-mm Hg increment in SBP was associated with an increased risk of aortic stenosis (OR, 3.26 [95% CI, 1.50–7.10]) and aortic regurgitation (OR, 2.59 [95% CI, 0.75–8.92]).
- To investigate the genetic association of obesity with incident aortic valve stenosis and aortic valve replacement, a mendelian randomization study using 5 genetic variants associated with obesity and including 108 211 individuals from the Copenhagen General Population Study was conducted. The study found that each 1-kg/m<sup>2</sup> increase in BMI was associated with causal RRs for aortic valve stenosis and replacement of 1.52 (95% CI, 1.23–1.87) and 1.49 (95% CI, 1.07–2.08), respectively.<sup>17</sup>

### Treatment

#### Randomized Controlled Trials

- The AVATAR is prospective RCT that evaluated the safety and efficacy of early SAVR in the treatment of asymptomatic patients with severe aortic

stenosis.<sup>46</sup> One hundred fifty-seven patients (mean, 67 years of age; 57% men) across 7 European countries between 2015 and 2020 were randomly allocated to early surgery (n=78) or conservative treatment (n=79). At a median follow-up of 32 months, patients randomized to early surgery had a significantly lower incidence of the primary composite end point of all-cause death, AMI, stroke, or unplanned hospitalization for HF than those in the conservative arm (HR, 0.46 [95% CI, 0.23–0.90];  $P=0.02$ ). Kaplan-Meier estimates of the individual end points of all-cause mortality and HF hospitalization tended to be higher in the conservative compared with the early surgery group but did not reach statistical significance.

- A propensity-matched comparison of pulmonary autograft (Ross procedure; n=434) and bioprosthetic and mechanical aortic valve replacement (n=434) was performed in individuals between 18 and 50 years of age in the mandatory California and New York databases between 1997 and 2014.<sup>47</sup> At 15 years, the actuarial survival after the Ross procedure was 93.1% (95% CI, 89.1%–95.7%), significantly higher than actuarial survival after bioprosthetic aortic valve replacement (HR, 0.42 [95% CI, 0.23–0.75];  $P=0.003$ ) or mechanical aortic valve replacement (HR, 0.45 [95% CI, 0.26–0.79];  $P=0.006$ ). At 15 years, the Ross procedure was associated with a lower cumulative risk of reintervention ( $P=0.008$ ) and endocarditis ( $P=0.01$ ) than bioprosthetic aortic valve replacement. In contrast, the Ross procedure was associated with a higher cumulative incidence of reoperation ( $P<0.001$ ). At 15 years, the Ross procedure also had lower risks of stroke ( $P=0.03$ ) and major bleeding ( $P=0.016$ ) compared with mechanical aortic valve replacement.
- A meta-analysis examined mortality and morbidity in 4812 patients ≥16 years of age undergoing the Ross procedure (n=1991) or mechanical (n=2019) or bioprosthetic (n=802) aortic valve replacement.<sup>48</sup> At a mean follow-up of 7.4 years, all-cause mortality was significantly lower in the Ross procedure group compared with the mechanical aortic valve replacement (HR, 0.58 [95% CI, 0.35–0.97];  $P=0.035$ ) and bioprosthetic aortic valve replacement (HR, 0.32 [95% CI, 0.18–0.59];  $P<0.001$ ) groups.
- The CAVIAAR prospective cohort study enrolled 130 patients who underwent aortic valve remodeling root repair with expansile aortic ring annuloplasty and 131 patients who underwent mechanical composite valve and graft replacement.<sup>49</sup> At 4 years, there was no statistically significant difference in the primary composite outcome of mortality, reoperation, thromboembolic or major bleeding events, endocarditis or operating site infections, pacemaker implantation, and HF between patients

who underwent aortic valve repair and those who had mechanical composite valve and graft replacement (HR, 0.66 [95% CI, 0.39–1.12]). However, there were significantly fewer valve-related deaths (HR, 0.09 [95% CI, 0.02–0.34]) and major bleeding events (HR, 0.37 [95% CI, 0.16–0.85]) in patients who underwent aortic valve repair compared with those who underwent mechanical composite valve and graft replacement.

- SAVR can be performed through either a minimally invasive or full sternotomy approach. A total of 358 patients enrolled in the PARTNER 3 low-risk trial underwent isolated SAVR at 68 centers through either a minimally invasive or full sternotomy approach.<sup>50</sup> The composite end point of death, stroke, or rehospitalization was similar between both groups (16.9% for minimally invasive versus 14.9% for full sternotomy; HR, 1.15 [95% CI, 0.66–2.03];  $P=0.618$ ). At 1 year, there were no significant differences in mortality (2.8% in both minimally invasive and full sternotomy groups;  $P>0.05$ ), stroke (1.9% for minimally invasive versus 3.6% for full sternotomy;  $P>0.05$ ), or rehospitalization (13.3% for minimally invasive versus 10.6% for full sternotomy;  $P>0.05$  for all). Quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire score at 30 days or 1 year, was comparable in both groups ( $P=0.351$ ).
- Between 2014 and 2016, 270 patients from a single center in the United Kingdom were enrolled and randomized to undergo ministernotomy aortic valve replacement ( $n=135$ ) or conventional median sternotomy aortic valve replacement ( $n=135$ ).<sup>51</sup> At a median follow-up of 6.1 years, the composite outcome of all-cause mortality and reoperation occurred in 25 patients (18.5%) in the conventional sternotomy group and in 23 patients (17%) in the ministernotomy group ( $P=0.72$ ).
- The annual volume of TAVR has increased each year since 2011.<sup>52</sup> After the US FDA approval of TAVR for low-risk patients in 2019, the TAVR volume exceeded all forms of SAVR ( $n=72991$  versus  $57\,626$ ).<sup>52</sup> From 2011 through 2018, extreme-risk and high-risk patients remained the largest cohort undergoing TAVR, 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, making up 11.5% of all patients with TAVR.
- Between 2014 and 2018, 913 patients  $\geq 70$  years of age at 34 centers in the United Kingdom with severe, symptomatic aortic stenosis were randomized to either TAVR with any valve and any access route ( $n=458$ ) or SAVR ( $n=455$ ).<sup>53</sup> The median STS mortality risk score of all study participants was 2.6% (interquartile range, 2.0%–3.4%). At 1 year, there were 21 deaths (4.6%) in the TAVR group

and 30 deaths (6.6%) in the SAVR group, with an adjusted absolute risk difference of  $-2.0\%$  (1-sided 97.5% CI,  $-\infty$  to 1.2%;  $P<0.001$  for noninferiority). At 1 year, there were significantly fewer major bleeding events after TAVR compared with surgery (aHR, 0.33 [95% CI, 0.24–0.45]) but significantly more vascular complications (aHR, 4.42 [95% CI, 2.54–7.71]), conduction disturbances requiring pacemaker implantation (aHR, 2.05 [95% CI, 1.43–2.94]), and aortic regurgitation (aHR, 4.89 [95% CI, 3.08–7.75]).

- Despite the increase in TAVR procedures, racial disparities observed in SAVR also exist with TAVR.<sup>54</sup> Among the 70221 patients in the STS/ACC TVT Registry who underwent TAVR between 2011 and 2016, 91.3% were White, 3.8% were Black, 3.4% were Hispanic, and 1.5% were Asian/Native American/Pacific Islander. 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 29351 Medicare and Medicaid patients in this cohort, 1-year adjusted mortality rates were similar in Black individuals and Hispanic individuals compared with White individuals but lower among individuals of Asian/Native American/Pacific Islander race (aHR, 0.71 [95% CI, 0.55–0.92];  $P=0.028$ ). Black individuals 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 276316 patients treated with TAVR who entered the STS/ACC TVT Registry between 2011 and 2019 demonstrated improved temporal trends, with 2018 or 2019 cohorts demonstrating lower event rates than more historic cohorts<sup>52</sup>:
  - Expected risk of 30-day operative mortality (STS Predicted Risk of Mortality score) is 2.5%.
  - The 1-year mortality is 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.
  - Overall in-hospital and 30-day stroke rates are 1.6% and 2.3%, respectively.
  - Incidence of permanent pacemaker implantation at 30 days is 10.8%.
- A study to determine the 5-year outcomes in 18010 patients treated by isolated TAVR or SAVR in the German Aortic Valve Registry between 2011 and 2012<sup>55</sup> showed that patients treated with TAVR ( $n=8942$ ) 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%;  $P<0.0001$ ) than patients treated with SAVR ( $n=9068$ ). 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>55</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>56</sup>
  - The 5-year follow-up results in the US CoreValve High Risk trial revealed 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>57</sup>

#### Intermediate-Risk Patients

- In a cohort of 1746 patients from 87 centers in Europe and North America 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>58</sup> At the 5-year follow up, the primary end point was 31.3% in the TAVR group and 30.8% in the SAVR group (HR, 1.02 [95% CI, 0.85–1.22];  $P=0.85$ ).<sup>59</sup> Moderate to severe paravalvular leak was more common with TAVR than surgery (11 [3.0%] versus 2 [0.7%]; risk difference, 2.37% [95% CI, 0.17%–4.85%];  $P=0.05$ ). Pacemaker implantation rates were higher after TAVR (289 [39.1%] versus 94 [15.1%]; HR, 3.30 [95% CI, 2.61–4.17];  $P<0.001$ ). Last, valve reintervention rates were higher after TAVR (27 [3.5%] versus 11 [1.9%]; HR, 2.21 [95% CI, 1.10–4.45];  $P=0.02$ ).
- SURTAVI Continued Access Study was the single-arm prospective, multicenter, nonrandomized phase

of the primary SURTAVI RCT.<sup>60</sup> Two hundred seventy-five patients enrolled in carotid artery stenting underwent an attempted TAVR at 44 US centers. At the 5-year follow-up, the rate of all-cause mortality or disabling stroke was 29.9% (all-cause mortality, 29.2%; disabling stroke, 3.4%). The rates of reintervention and new permanent pacemaker implantation were 1.1% and 27.6%, respectively. There were no cases of clinical valve thrombosis and 3 cases of valve endocarditis (1.2%). The 5-year mean gradient was 9.16 mmHg, and the 5-year mean effective orifice area was 2.06 cm<sup>2</sup>. Most patients had no or trace aortic regurgitation (87.9%) and no or trace paravalvular leak (89.4%).

- 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>1</sup> Overall, these findings demonstrate that TAVR is a noninferior alternative to SAVR in patients with severe aortic stenosis at intermediate surgical risk.<sup>61,62</sup>
- In a propensity score-matched analysis of 783 matched pairs of intermediate-risk patients who underwent either TAVR from the PARTNER 2 trial or SAVR from the PARTNER 2A trial,<sup>63</sup> all-cause death and disabling stroke at 5 years was 40.2% in patients undergoing TAVR and 42.7% in patients undergoing SAVR (HR, 0.87 [95% CI, 0.74–1.03];  $P=0.10$ ).

#### 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>64</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;  $P=0.02$ ). At 5 years, the Kaplan-Meier estimates for outcomes were as follows: death, 10.0% in the TAVR group and 8.2% in the surgery group; stroke, 5.8% and 6.4%, respectively; and rehospitalization, 13.7% and 17.4%, respectively.<sup>65</sup> The

hemodynamic performance of the valve, assessed according to the mean $\pm$ SD valve gradient, was  $12.8\pm6.5$  mmHg in the TAVR group and  $11.7\pm5.6$  mmHg in the surgery group. A component of the first primary end point (death, stroke, or rehospitalization) occurred in 111 of 496 patients in the TAVR group (22.8%) and in 117 of 454 patients in the surgery group (27.2%; difference, -4.3 percentage points [95% CI, -9.9 to 1.3];  $P=0.07$ ). The second primary end point was a hierarchical composite that included death, stroke, and the number of rehospitalization days, analyzed with the use of a win ratio analysis. The win ratio for the second primary end point was 1.17 (95% CI, 0.90–1.51);  $P=0.25$ .

- In the Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients, a total of 1414 patients with severe aortic stenosis at low surgical risk were randomized to receive either TAVR ( $n=730$ ) or SAVR ( $n=684$ ) between 2016 and 2019.<sup>66</sup> After 1 year of follow-up, Bayesian statistical inference was used to predict that the 2-year 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  $>0.999$ ). After the 2-year follow-up, the primary end point of death or disabling stroke was 4.3% in the TAVR group and 6.3% in the surgery group ( $P=0.084$ ).<sup>67</sup> At 3 years, all-cause mortality or disabling stroke occurred in 7.4% of TAVR patients and 10.4% of surgery patients (HR, 0.70 [95% CI, 0.49–1.00];  $P=0.051$ ).<sup>68</sup> The incidence of mild paravalvular regurgitation was 20.3% in patients undergoing TAVR and 2.5% in surgical patients. The incidence of pacemaker placement was 23.2% in patients undergoing TAVR and 9.1% in surgical patients ( $P<0.001$ ).
- 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>69</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>70</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>71</sup>

### Additional Patient Groups

- In a retrospective observational registry of 923 patients from 12 centers, reductions in LVEF were associated with greater 1-year mortality.<sup>72</sup> The cohort included 146 patients (16%) with LVEF <25%, 425 (46%) with LVEF 25% to 30%, and 352 (38%) with LVEF 31% to 35%.
- In-hospital mortality was similar in the 3 groups: 7 deaths in patients with LVEF <25% (4.8%), 18 deaths in patients with LVEF 25% to 30% (4.2%), and 7 deaths in patients with LVEF 31% to 35% (2.0%;  $P=0.661$ ). One year mortality was increased in those patients with decreased left ventricular function. There were 21 deaths in patients with LVEF <25% (14%), 49 deaths in patients with LVEF 25% to 30% (12%), and 25 deaths in patients with LVEF 31% to 35% (7.1%;  $P=0.024$ ).

### TAVR Techniques

- Although most TAVR valves are implanted using transfemoral access, alternative access techniques for TAVR have been examined. A meta-analysis including 22 observational studies (N=11 896) compared outcomes of patients with transcarotid TAVR access with those of patients with other TAVR access.<sup>73</sup> Compared with transfemoral access, the transcarotid approach had higher mortality at 1 month (3.7% versus 2.6%;  $P=0.02$ ) but lower major vascular complications (1.5% versus 3.4%;  $P=0.04$ ).
- Compared with transaxillary or subclavian artery access, the transcarotid approach had lower major vascular complications (2% versus 2.3%;  $P=0.04$ ) but higher major bleeding (5.3% versus 2.6%;  $P=0.03$ ).
- Compared with transaortic access, the transcarotid approach had lower in-hospital (11.7% versus 1.9%;  $P=0.02$ ) and 1-month (14.4% versus 3.9%;  $P=0.007$ ) mortality.
- Compared with transapical access, the transcarotid approach reduced mortality and risk of major vascular complications or major bleeding; however, this did not reach statistical significance.
- It is interesting that the transcarotid approach did not increase the risk of stroke compared with transfemoral or the other alternative accesses.

### Comparison of Aortic Valve Replacement Techniques

- A meta-analysis compared postoperative outcomes after minimally invasive SAVR using ministernotomy or minithoracotomy with outcomes after conventional SAVR with full sternotomy and TAVR.<sup>68</sup>
- Fifty-six studies including 27 117 patients were analyzed with a random-effects model: 10 397 patients had undergone conventional SAVR with

full sternotomy; 9523 had undergone minimally invasive SAVR with ministernotomy; 5487 had undergone minimally invasive SAVR with minithoracotomy; and 1710 had TAVR.

- Compared with conventional SAVR with full sternotomy, minimally invasive SAVR with ministernotomy was associated with lower rates of 30-day mortality (RR, 0.76 [95% CI, 0.59–0.98]), stroke (RR, 0.84 [95% CI, 0.72–0.97]), acute kidney injury (RR, 0.76 [95% CI, 0.61–0.94]), and long-term mortality (RR, 0.84 [95% CI, 0.72–0.97]) at a weighted mean follow-up duration of 10.4 years.
- Compared with conventional SAVR with full sternotomy, minimally invasive SAVR with minithoracotomy was associated with higher rates of 30-day paravalvular leak (RR, 3.76 [95% CI, 1.31–10.85]) and major bleeding (RR, 1.45 [95% CI, 1.08–1.94]).
- Compared with conventional SAVR with full sternotomy, TAVR was associated with lower rates of 30-day acute kidney injury (RR, 0.49 [95% CI, 0.31–0.77]) but higher permanent pacemaker implantation (RR, 2.50 [95% CI, 1.60–3.91]) and 30-day paravalvular leak (RR, 12.85 [95% CI, 5.05–32.68]).
- In a review of 14 RCTs (with 1395 participants) assessing the effects of minimally invasive aortic valve replacement through a limited sternotomy versus conventional aortic valve replacement through median sternotomy, upper hemisternotomy<sup>74</sup>:
  - had no clear association with mortality (RR, 0.93 [95% CI, 0.45–1.94]);
  - was associated with modest increases in cardiopulmonary bypass time (mean difference, 10.63 minutes [95% CI, 3.39–17.88]) and aortic cross-clamp time slightly (mean difference, 6.07 minutes [95% CI, 0.79–11.35]);
  - was associated with a modest decrease in post-operative blood loss (mean difference, –153 mL [95% CI, –246 to –60]); and
  - was associated with a modest difference in quality of life as measured by the 36-item Short Form Health Survey or any other validated scale (mean difference, 0.03 [95% CI, 0–0.06] and no change in pain scores (SMD, –0.19 [95% CI, –0.43 to 0.04]).
- The WATCH-TAVR trial is a multicenter randomized trial evaluating the safety and effectiveness of concomitant TAVR and LAAO with the WATCHMAN device in patients with AF.<sup>75</sup> Patients were randomized 1:1 to either TAVR with a WATCHMAN device (n=177) or TAVR with medical therapy (n=172) between December 2017 and November 2020 at 34 US centers.
- At 24 months, TAVR with a WATCHMAN device was noninferior to TAVR with medical therapy (HR,

0.86 [95% CI, 0.60–1.22]) for the primary outcome of all-cause mortality, stroke, or major bleeding.<sup>76</sup>

### Mortality

- Calcific aortic valve disease-related death cases increased worldwide from 53 298 (95% CI, 47 760–59 730) in 1990 to 126 827 (95% CI, 105 600–141 390) in 2019.<sup>9</sup>
  - Mortality in patients with calcific aortic valve disease increases exponentially with age, with males having higher mortality than females before 80 years of age.
- Calcific aortic valve disease accounted for 24 826 (95% CI, 20 354–27 718) deaths in the United States in 2019.<sup>8</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 compared with those using watchful waiting (1% at both 4 and 8 years versus 6% at 4 years and 26% at 8 years;  $P=0.003$ ).<sup>77</sup>
- In a study of 2429 patients with severe aortic stenosis, of whom 49.5% were female, the 5-year survival was lower especially in females compared with expected survival ( $62\pm2\%$  versus 71% for females and  $69\pm1\%$  versus 71% for males) and compared with 5-year survival in males despite females having longer life expectancy than males ( $66\pm2\%$  [expected, 75%] versus  $68\pm2\%$  [expected, 70%];  $P<0.001$ ) after controlling for age.<sup>78</sup> Females also were more symptomatic ( $P=0.004$ ) and used aortic valve replacement therapy less often (64.4% versus 69.1%;  $P=0.018$ ).
- In a single-center study of 5994 adults with and without aortic stenosis between 2015 and 2016, the Vmax on transthoracic echocardiography was linearly related to 5-year all-cause mortality (HR, 1.26 [95% CI, 1.19–1.33] for every 100 cm/s of Vmax).<sup>79</sup>
- A meta-analysis of 25 studies comprising 12 143 individuals found that, compared with patients with moderate aortic stenosis, the incidence rate difference of all-cause mortality was –3.9 (95% CI, –6.7 to –1.1) in patients with no or mild aortic stenosis and 2.2 (95% CI, 0.8–3.5) in patients with severe aortic stenosis.<sup>79</sup>
- In an observational echocardiographic multicenter cohort study of 98 565 males and 99 357 females  $\geq 65$  years of age in Australia from 2003 to 2017, 21.0% of males and 18.7% of females had aortic stenosis.<sup>80</sup> The actual 5-year mortality in males and females with normal aortic valves was 32.1% and 26.1%, respectively. In males and females with mild aortic stenosis, this increased to 40.9% and 35.9%, respectively. In males and females with severe

aortic stenosis, this increased 52.2% and 55.3%, respectively.

- A multicenter study of 30 865 US and 217 599 Australian individuals between 2003 and 2017 found that moderate aortic stenosis conferred an increased risk of mortality after adjustment for age and sex (US individuals: HR, 1.66 [95% CI, 1.52–1.80]; Australian individuals: HR, 1.37 [95% CI, 1.34–1.41]).<sup>81</sup>
- Echocardiographic data, including Vmax, from 63 182 Australian and 66 846 US patients  $\geq$ 65 years of age were linked to all-cause deaths in Australia and the United States between 2003 and 2018.<sup>82</sup> Compared with those with Vmax of 1.0 to 1.49 m/s, those with Vmax of 2.50 to 2.99 m/s and 3.0 to 3.49 m/s had HRs of 1.22 (95% CI, 1.12–1.32) and 1.59 (95% CI, 1.36–1.86), respectively, for mortality within 10 years after adjustment for age, sex, left-sided HD, and LVEF.

### Complications

- Sex differences in the complications of bicuspid aortic valve were examined in 992 patients with an echocardiographic diagnosis of bicuspid aortic valve hospitalized at a single center in Beijing between 2008 and 2017.<sup>83</sup> The following complications of bicuspid aortic valve were more common in males than females: aortic regurgitation ( $\geq$ 2+; 39.0% versus 12.8%;  $P < 0.001$ ), only aortic root dilation (3.8% versus 0.8%;  $P = 0.014$ ), and diffuse aortic dilation (25.3% versus 4.3%;  $P < 0.001$ ). The following complications of bicuspid aortic valve were more common in females: moderate to severe aortic stenosis (21.3% versus 45.7%;  $P < 0.001$ ) and only ascending aortic dilation (46.2% versus 61.2%;  $P < 0.001$ ). Sex did not predict early adverse events after aortic valve replacement ( $n = 90$ ; HR, 1.21 [95% CI, 0.74–1.98];  $P = 0.44$ ).
- In a systematic review and meta-analysis of patients with bicuspid aortic valve disease including 8 cohort studies with 5351 patients, bicuspid aortic valve IE occurred with an incidence rate of 48.13 per 10 000 patient-years (95% CI, 22.24–74.02)<sup>84</sup> and a 12-fold increased risk compared with the general population (RR, 12.03 [95% CI, 5.45–26.54]).
- In a prospective study of pregnant individuals with HD from 2 large Canadian tertiary care hospitals in Toronto and Vancouver including 1938 pregnancies, outcomes were examined from 1994 to 2014, and a new risk index to predict maternal cardiac complications was developed.<sup>85</sup> Cardiac complications occurred in 16% of pregnancies and were related primarily to arrhythmias and HF. The overall rates of cardiac complications during pregnancy did not change over the years. In addition, 10 predictors of maternal cardiac complications were identified: 5 general predictors (prior cardiac events

or arrhythmias, poor functional class or cyanosis, high-risk valve disease/left ventricular outflow tract obstruction, systemic ventricular dysfunction, no prior cardiac interventions), 4 lesion-specific predictors (mechanical valves, high-risk aortopathies, PH, CAD), and 1 delivery-of-care predictor (late pregnancy assessment). These 10 predictors were incorporated into a new risk index, CARPREG, to predict maternal cardiac complications.

- 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>86</sup>
- In the multicenter UK TAVR registry of 8652 TAVR procedures performed from 2007 to 2015, there were 205 in-hospital strokes (incidence, 2.4%).<sup>87</sup> 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 included 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 mortality (OR, 5.22 [95% CI, 3.49–7.81];  $P < 0.001$ ) and 1-year mortality (OR, 3.21 [95% CI, 2.15–4.78];  $P < 0.001$ ).
- In a study of all hospitalizations in patients  $\geq$ 18 years of age who underwent TAVR from 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>88</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).

- Duration of RV pacing may be associated with risk of cardiovascular death or HR hospitalization. The PACE-TAVI trial is an international multicenter registry of all patients with TAVR who underwent permanent pacemaker implantation within 30 days of their procedure.<sup>89</sup> The aim of the registry is to evaluate the association of a high percentage of RV pacing with adverse outcomes in patients after TAVR. A total of 377 patients were enrolled, 158 with <40% ventricular pacing and 219 with ≥40% ventricular pacing. After multivariable adjustment, those patients with ≥40% RV pacing had a higher incidence of the primary end point, a composite of cardiovascular mortality or hospitalization for HF (HR, 2.76 [95% CI, 1.39–5.51];  $P=0.004$ ) and cardiovascular death (HR, 3.77 [95% CI, 1.02–13.88];  $P=0.04$ ). The incidence of all-cause death was not significantly different between the 2 groups (HR, 2.17 [95% CI, 0.80–5.90];  $P=0.13$ ).
- In OBSERVANT-II, an observational, prospective, multicenter cohort study, 2753 consecutive patients undergoing TAVR were followed up to investigate the incidence and predictors of 30-day and 6-month postprocedural stroke.<sup>90</sup> The occurrence of a 30-day and 6-month stroke was 1.3% and 2.4%, respectively. Aortic valve predilatation (OR, 2.28 [95% CI, 1.12–4.65];  $P=0.023$ ), diabetes (OR, 3.10 [95% CI, 1.56–6.18];  $P=0.001$ ), and LVEF <50% (OR, 2.15 [95% CI, 1.04–4.47];  $P=0.04$ ) were independently associated with 30-day stroke. Diabetes (subdistribution HR, 2.07 [95% CI, 1.25–3.42];  $P=0.004$ ), preexisting neurological dysfunction (subdistribution HR, 3.92 [95% CI, 1.54–10];  $P=0.004$ ), bicuspid valve (subdistribution HR, 4.75 [95% CI, 1.44–15.7];  $P=0.011$ ), and critical status (subdistribution HR, 3.05 [95% CI, 1.21–7.72];  $P=0.018$ ) were associated with 6-month stroke.
- An observational retrospective study of 1481 patients with TAVR from 6 different European centers aimed to compare the incidence and severity of paravalvular leak and 1-year survival after TAVR with either the EVOLUT PRO or SAPIEN 3 valve.<sup>91</sup> Paravalvular leak occurred more frequently in patients undergoing TAVR with the EVOLUT PRO at prehospital discharge (55.1% versus 37.3%), at 1 month (51% versus 41.4%), and at 1 year (51.3% versus 39.3%). Moderate or severe paravalvular leak occurred in patients receiving EVOLUT PRO and SAPIEN 3 at similar rates of 5.3% and 5.8% before hospital discharge, 4% and 3.1% at 1 month, and 3.2% and 4.9% at 1 year, respectively. There was no significant difference in 1-year survival (HR, 0.73 [95% CI, 0.33–1.63];  $P=0.442$ ).

**Cost**

- In an Australian study, aortic stenosis was associated with 8 more premature deaths in males and 12 more premature deaths in females per 1000 individuals investigated.<sup>80</sup> Per 1000 individuals, this represents 32.5 more QALYs lost in males, representing a societal cost of Australian \$1.40 million, and 57.5 more QALYs lost in females, representing a societal cost of Australian \$2.48 million. Therefore, the estimated societal cost of premature mortality associated with aortic stenosis was Australian \$629 million in males and Australian \$735 million in females.
- In a European study of patients with severe aortic stenosis and intermediate surgical risk, TAVR was associated with an increase of 0.42 years and 0.41 QALYs and lifetime cost savings of €439 compared with SAVR.<sup>92</sup>
- In patients undergoing TAVR with 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>93</sup>
- An economic study of 929 patients with aortic stenosis and low surgical risk randomized to TAVR or SAVR between 2016 and 2017 in the PARTNER 3 trial was conducted.<sup>94</sup> Procedural costs were approximately \$19 000 higher with TAVR; total index hospitalization costs were \$591 more with TAVR compared with SAVR. However, the study found that follow-up costs were lower with TAVR. They found that TAVR led to 2-year cost savings of \$2030 per patient compared with SAVR (95% CI, -\$6222 to \$1816).

**Global Burden****(See Table 23-1 and Charts 23-1 and 23-2)**

- In 204 countries and territories in 2021, there were 13.32 (95% UI, 11.42–15.25) million prevalent cases of calcific aortic valve disease and 0.14 (95% UI, 0.12–0.16) million total deaths attributable to calcific aortic valve disease (Table 23-1). The age-standardized prevalence and death rates were 158.35 (95% UI, 135.92–181.00) and 1.83 (95% UI, 1.54–2.00) per 100 000, respectively.<sup>4</sup> The highest age-standardized death rates of nonrheumatic calcific aortic valve disease among regions were for Western Europe and high-income North America. The lowest rates were for East Asia (Chart 23-1). Among regions, nonrheumatic calcific aortic valve disease prevalence was highest for Western Europe, high-income North America, Central Europe, and Australasia (Chart 23-2).
- Among the causes of HF between 1990 and 2019, calcific aortic valve disease increased by >90% in both males and females.<sup>95</sup>

## Mitral Valve Disorders

### **ICD-9 424.0; ICD-10 I34.**

2022, United States: Underlying cause mortality—2950. Any-mention mortality—7473.

2021, United States: Hospital discharges—31 725.

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**

- See Global Burden section.

#### **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>96,97</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 *GLISI*, *FLNA*, *DCHS1*, *DZIP1*, *TNS1*, and *LMCD1*.<sup>98–102</sup> An updated GWAS meta-analysis using dense imputation coverage revealed several risk loci (*SYT2*, *SRR*, *TSR1*, *SGSM2*, *SIX5*, *DMPK*, and *DMWD*) warranting further functional analysis for these loci.<sup>103</sup>
- Mitral valve prolapse may be seen in syndromes associated with connective tissue diseases such as Marfan syndrome (*FBN1* gene), Loeys-Dietz syndrome (*TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3* genes), and Ehler-Danlos syndrome (*COL5A1*, *COL5A1*, *COL1A1*, *TNXB* genes).<sup>104,105</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>105,106</sup> Nonsyndromic mitral valve prolapse may be seen in carriers of variants in the *MMVP1*, *MMVP2*, *MMVP3*, and *FLNA* genes.<sup>107–109</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>110</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>110</sup>

- Among 3679 young to middle-aged third-generation participants in the FHS with available parental data, 49 (1%) had mitral valve prolapse.<sup>111</sup> Parental mitral valve prolapse was associated with a higher prevalence of mitral valve prolapse in offspring (10/186 [5.4%]) compared with no parental mitral valve prolapse (39/3493 [1.1%]; 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>112</sup>
- A meta-analysis of 6 GWASs for mitral valve prolapse, including 4884 cases and 434 649 controls, identified 14 loci.<sup>113</sup> Transcriptomics-, epigenomics-, and proteomics-based gene prioritization identified *LMCD1*, *SPTBN1*, *LTBP2*, *TGFB2*, *NMB*, and *ALPK3* as candidate genes. A mitral valve prolapse PRS including 1.1 million variants from GWAS meta-analysis was developed. Individuals in the highest quintile had 20% higher odds of mitral valve prolapse compared with individuals in the lower 4 quintiles after accounting for clinical risk factors (OR, 1.20;  $P=2.85\times 10^{-11}$ ).
- A GWAS of mitral annular diameter obtained from a 4-chamber view from 32 220 cardiac MRIs identified 10 loci.<sup>114</sup> The identified loci included possible novel loci (*GOSR2*, *ERBB4*, *MCTP2*, and *MCPH1*) and genes associated with cardiac contractility (*BAG3*, *TTN*, and *RBFOX1*).

#### **Treatment**

##### **(See Chart 23-3)**

- The 2 main percutaneous mitral valve interventions in the United States are TEER and transcatheter mitral valve replacement. Data from the STS/ACC TVT Registry between 2014 and 2020 are reported.<sup>115</sup> A total of 37 475 patients underwent a mitral transcatheter procedure, including 33 878 TEERs and 3 597 transcatheter mitral valve replacements. Annual procedure volumes for TEER 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 TEER 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%, reflecting overall improvements in outcomes over the past several years.
- 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>116</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>117</sup>
- Use of MitraClip procedures has also increased in Asia, although at a slower pace, with the highest increase seen in Japan from 18 procedures in 2011 to 439 procedures in 2018.<sup>118</sup>
- The role of MitraClip in secondary MR has been investigated in 2 published randomized clinical trials, COAPT and MITRA-FR, with divergent results that may be related to differences in sample characteristics, including sample size (614 versus 304, respectively), duration of follow-up (5 years versus 1 year, respectively), and primary end point (rehospitalization versus combined death and rehospitalization for HF; Chart 23-3).<sup>119–121a</sup>
  - 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>120,121a</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 in all-cause mortality at 2 years (29% versus 46.1%; HR, 0.62 [95% CI, 0.46–0.82];  $P<0.001$ ). All-cause mortality at 5 years was 57.3% in the MitraClip group and 67.2% in the medical therapy alone group (HR, 0.72 [95% CI, 0.58–0.89]). Death or hospitalization for HF within 5 years occurred in 73.6% of the MitraClip patients and in 91.5% of the medical therapy alone group (HR, 0.53 [95% CI, 0.44–0.64]). At 5 years, hospitalization for HF was 33.1% per year in the MitraClip group and 57.2% per year in the medical therapy alone group (HR, 0.53 [95% CI, 0.41–0.68]).
  - 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 (83/152 patients [54.6%] versus 78/152 [51.3%] for interventional and conservative management, respectively).
  - The outcomes of transcatheter mitral valve repair versus goal-directed medical therapy were compared using 97 propensity-matched pairs of

patients from the CHOICE-MI registry with secondary MR undergoing either transcatheter mitral valve repair or goal-directed medical therapy.<sup>122</sup> The 2-year rate of HF hospitalization was significantly lower in the transcatheter mitral valve repair group (32.8%) compared with the goal-directed medical therapy group (54.4%; HR, 0.59 [95% CI, 0.35–0.99];  $P=0.04$ ). There was no significant difference in 2-year mortality between the 2 groups: 36.8% in patients with transcatheter mitral valve repair versus 40.8% in patients with goal-directed medical therapy (HR, 1.01 [95% CI, 0.62–1.64];  $P=0.98$ ).

- In a meta-analysis of 15 RCTs and comparative cohort studies, 16 879 patients <70 years of age undergoing mitral valve replacement with either mechanical mitral valve or bioprosthetic mitral valve were compared.<sup>123</sup> Bioprosthetic mitral valve replacement was associated with significantly higher rates of 30-day mortality (RR, 1.53 [95% CI, 1.28–1.83];  $P=0.0006$ ) but no difference in 30-day stroke (RR, 0.70 [95% CI, 0.23–2.12];  $P=0.428$ ). Bioprosthetic valve replacement was associated with higher rates of long-term mortality (RR, 1.28 [95% CI, 1.09–1.50];  $P=0.0054$ ) at a weighted mean follow-up of 14.1 years. No difference was seen between mechanical and bioprosthetic mitral valve replacement for risk of long-term stroke (RR, 0.92 [95% CI, 0.56–1.52];  $P=0.668$ ), reoperation (RR, 1.72 [95% CI, 0.83–3.56];  $P=0.121$ ), or major bleeding (RR, 0.57 [95% CI, 0.28–1.15];  $P=0.10$ ) at a weighted mean follow-up of 11.7, 11.3, and 11.9 years, respectively.
- A systematic review and meta-analysis of 13 RCTs including 1089 patients compared patients who underwent either isolated mitral valve repair or replacement with patients who underwent mitral valve repair or replacement with concomitant surgical ablation for AF.<sup>124</sup> The odds of sinus rhythm were higher in the patients who underwent mitral valve repair or replacement with concomitant surgical ablation at discharge (OR, 9.62 [95% CI, 4.87–19.02];  $P=55\%$ ), at 6 months (OR, 7.21 [95% CI, 4.30–12.11];  $P=34\%$ ), and at 1 year (OR, 8.41 [95% CI, 5.14–13.77];  $P=48\%$ ). Although there was no difference in all-cause mortality, stroke, or thromboembolic events between the 2 groups, the odds of permanent pacemaker implantation were higher in patients who underwent mitral valve repair or replacement with concomitant surgical ablation (OR, 1.87 [95% CI, 1.11–3.17];  $P=0\%$ ).

### Mortality

- According to 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>125</sup>

- 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>126</sup>
- A propensity-matched study was conducted examining patients with MR undergoing either transcatheter mitral valve repair or surgical mitral valve repair between January 1, 2015, and December 31, 2020, from the TriNetX Analytics Research Data Network, a global federated database of electronic health records from 58 health care organizations.<sup>127</sup> During this time period, 1392 patients underwent surgical mitral valve repair and 960 underwent transcatheter mitral valve repair. After 1:1 propensity score matching, a total of 550 patients undergoing surgical mitral valve repair were compared with 550 patients undergoing transcatheter mitral valve repair. Compared with patients undergoing transcatheter mitral valve repair, patients undergoing surgical mitral valve repair had lower risk of mortality at 3 years (HR, 0.42 [95% CI, 0.31–0.56];  $P<0.0001$ ).

### Complications

- In 2017, there were 35 700 (95% CI, 30 500–42 500) degenerative mitral valve deaths globally.<sup>128</sup>
- 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>129</sup>
- In a study using the Nationwide Readmission Database to identify adult patients who underwent TEER from 2014 to 2018,<sup>130</sup> of the 21 323 patients identified, 1615 (7.5%) had major bleeding. Coagulopathy, ESKD, 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];  $P<0.001$ ).

- At 1 year after TEER, as many as 30% of patients have moderate to severe mitral valve regurgitation and an additional 25% have mitral stenosis, which affect survival, symptomatic congestive HF, and need for reintervention.<sup>120,131</sup> The STS Adult Cardiac Surgery Database was used to identify 524 adults who underwent first mitral surgery after TEER from 2014 to 2021.<sup>132</sup> Median time from TEER to mitral valve surgery was 3.5 months. Only 4.5% of mitral valves ( $n=22$ ) could be repaired with >90% ( $n=438$ ) of cases requiring mitral valve replacement. Concomitant tricuspid repair or replacement was performed in 32.8% ( $n=152$ ) with moderate or severe tricuspid regurgitation, and CABG was performed in 12.3% ( $n=57$ ). The 30-day or in-hospital mortality was 10.6% ( $n=49$ ).
- A study of 11 396 Medicare patients who underwent TEER between July 2013 and November 2017 revealed that 548 patients (4.8%) required reintervention after a median time interval of 4.5 months<sup>133</sup>: 294 (53.7%) underwent repeat TEER, and 254 (46.3%) underwent mitral valve surgery. Overall 30-day mortality was 8.6%, and the 30-day composite morbidity was 48.2%. Reintervention with mitral valve surgery after TEER was associated with higher 30-day morbidity (aOR, 4.76 [95% CI, 3.17–7.14]) compared with repeat TEER. Requirement for reintervention was an independent risk factor for long-term mortality (HR, 3.26 [95% CI, 2.53–4.20]).

### Cost

- 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>134</sup>

### Global Burden

(See Table 23-2 and Charts 23-4 and 23-5)

- Based on 204 countries and territories in 2021, there were 15.49 (95% UI, 14.46–16.70) million prevalent cases of degenerative mitral valve disease and 0.04 (95% UI, 0.03–0.04) million total deaths

attributable to degenerative mitral valve disease. The age-standardized prevalence and death rates were 182.13 (95% UI, 169.95–196.07) and 0.46 (95% UI, 0.39–0.51) per 100 000, respectively (Table 23-2). In 2021, the highest age-standardized mortality rates of nonrheumatic degenerative mitral valve disease among regions were for Central Europe. Oceania and East and Southeast Asia had the lowest mortality rates (Chart 23-4). In 2021, among regions, nonrheumatic degenerative mitral valve disease prevalence was highest for high-income North America and Central Asia. The lowest prevalence rates were for regions in sub-Saharan Africa (Chart 23-5).

## Pulmonary Valve Disorders

### **ICD-9 424.3; ICD-10 I37.**

2022, United States: Underlying cause mortality—17. Any-mention mortality—96.

2021, United States: Hospital discharges—970.

- Pulmonic valve stenosis is a relatively common congenital defect, occurring in ≈10% of children with congenital HD.<sup>135</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 (interquartile range, 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>136</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>137</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>138</sup> Transcatheter pulmonic valve implantation of either a Melody or a SAPIEN valve is effective and relatively safe,<sup>138,139</sup> with serious complications occurring in only 3 patients (One-third died and two-thirds required surgical intervention in a study using the NIS database, which included 57 transcatheter pulmonic valve implantation procedures performed in 2012).<sup>140</sup> Surgical pulmonary valve replacement is preferred for native pulmonic valve regurgitation (caused by endocarditis, carcinoid) and is associated with <1% periprocedural mortality and excellent long-term outcome, with >60% freedom from reoperation at 10 years.<sup>141</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>142</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.**

2022, United States: Underlying cause mortality—91. Any-mention mortality—395.

2021, United States: Hospital discharges—1195.

- From January 2006 to September 2015, tricuspid valve disease was present in 3235 292 or 1.7% of US hospitalized patients >50 years of age.<sup>143</sup>
  - The prevalence of tricuspid valve disease was higher in females than males and increased with increasing age.
  - From 2006 to 2015, the prevalence of tricuspid valve disease in all hospitalizations increased from 1.7% to 2.0%.
- The characteristics of patients with HF and MR with or without tricuspid regurgitation were examined in a prospective, multicenter observational study of 11 298 patients with HF from 133 participating centers across 21 European and European Society of Cardiology–affiliated countries in the ESC-HFA EORP HF Long-Term Registry.<sup>144</sup> Within this group, 7541 (67%) had no MR or tricuspid regurgitation, 1931 (17%) had isolated MR, 616 (5.5%) had isolated tricuspid regurgitation, and 1210 (11%) had combined mitral and tricuspid regurgitation. HFpEF was associated with an increased risk of isolated tricuspid regurgitation (OR, 1.94 [95% CI, 1.61–2.33]). Those with isolated tricuspid regurgitation had a higher risk of all-cause death or first HF hospitalization (aHR, 1.43 [95% CI, 1.18–1.73];  $P<0.001$ ), cardiovascular death or first HF hospitalization (aHR, 1.54 [95% CI, 1.25–1.89];  $P<0.001$ ), first HF hospitalization (aHR, 1.54 [95% CI, 1.23–1.93];  $P<0.001$ ), and cardiovascular death (aHR, 1.79 [95% CI, 1.25–2.58];  $P=0.002$ ).
- A meta-analysis of 29 RCTs and prospective and retrospective observational studies published from inception to January 2023 that reported the incidence of tricuspid regurgitation from echocardiography sought to identify the overall incidence of tricuspid regurgitation after pacemaker or ICD implantation.<sup>145</sup> Patients who underwent device implantation ( $n=1008$ ) were significantly more

likely to develop worsening tricuspid regurgitation than control subjects who did not undergo device implantation ( $n=58\,605$ ; OR, 3.18 [95% CI, 1.58–6.39];  $P<0.01$ ). Worsening tricuspid regurgitation after device implantation significantly increased mortality (HR, 1.42 [95% CI, 1.05–1.92];  $P=0.02$ ). Larger right atrial area was significantly associated with an increased risk of worsening tricuspid regurgitation after device implantation (OR, 1.11 [95% CI, 1.06–1.17];  $P<0.01$ ). There was no statistically significant difference in tricuspid regurgitation after either pacemaker or ICD implantation (OR, 1.12 [95% CI, 0.57–2.18];  $P=0.71$ ).

- In a meta-analysis of 52 studies (3 RCTs, 18 prospective, and 31 retrospective studies) published from inception to March 2023 including 130\,759 patients reporting the incidence or prognosis of cardiac implantable device-associated tricuspid regurgitation, the incidence of cardiac implantable device-associated tricuspid regurgitation was 24% (95% CI, 20%–28%; OR, 2.44 [95% CI, 1.58–3.77];  $P<0.001$ ).<sup>146</sup> Cardiac implantable device-associated tricuspid regurgitation was associated with an increased risk of all-cause mortality (aHR, 1.52 [95% CI, 1.36–1.69];  $P<0.001$ ), HF hospitalizations (aHR, 1.82 [95% CI, 1.19–2.78];  $P=0.006$ ), and the composite of mortality and HF hospitalizations (aHR, 1.96 [95% CI, 1.33–2.87];  $P=0.001$ ).
- Outcomes of transcatheter tricuspid valve interventions were analyzed in 317 high-risk patients with severe tricuspid regurgitation from the international Trivalve registry.<sup>147</sup> Such patients were treated either with transcatheter repair at the level of the leaflets (MitraClip, PASCAL), annulus (Cardioband, TriCinch, Trialign), or coaptation (FORMA) or with transcatheter replacement (Caval Implants). Procedural success, defined as successful device implantation with moderate or less tricuspid regurgitation, was 72.8%. Thirty-day mortality was significantly lower among patients with procedural success (1.9% versus 6.9%;  $P=0.04$ ). Actuarial survival at 1.5 years was  $82.8\pm4\%$  and was significantly higher among patients who had procedural success ( $70.3\pm8\%$  versus  $90.8\pm4\%$ ;  $P<0.0002$ ).
- Four hundred one patients from 39 clinical centers in the United States, Canada, and Germany undergoing mitral valve surgery for degenerative MR were randomly assigned to receive mitral valve surgery with or without tricuspid annuloplasty.<sup>148</sup> At 2 years, patients who underwent mitral valve surgery with tricuspid annuloplasty had fewer primary end-point events (death, reoperation for tricuspid regurgitation, progression of tricuspid regurgitation by 2 grades from baseline, or presence of severe

tricuspid regurgitation) than those who underwent mitral valve surgery alone (3.9% versus 10.2%; RR, 0.37 [95% CI, 0.16–0.86];  $P=0.02$ ).

- In TRILUMINATE Pivotal, patients with severe tricuspid regurgitation in 65 centers in the United States, Canada, and Europe were randomized to either transcatheter tricuspid valve repair ( $n=175$ ) or medical therapy ( $n=175$ ).<sup>149</sup> This was an unblinded trial without placebo. The primary end point was a hierarchical composite that included death resulting from any cause or tricuspid valve surgery, hospitalization for HF, and an improvement in health status measured by the Kansas City Cardiomyopathy Questionnaire. The results for the primary end point favored the TEER group (win ratio, 1.48 [95% CI, 1.06–2.13];  $P=0.02$ ), driven entirely by improvements in health status in this unblinded study. Transcatheter tricuspid valve repair significantly improved health status at 1 month (mean between-group difference in Kansas City Cardiomyopathy Questionnaire overall summary score, 9.4 points [95% CI, 5.3–13.4]), with a small additional improvement at 1 year (mean between-group difference, 10.4 points [95% CI, 6.3–14.6]).<sup>150</sup> Despite improvement in self-reported health status, there was no improvement in 6-minute walk distance with intervention (17.1; 95% CI, –12.0 to 46.1).

## Rheumatic Fever/Rheumatic HD

### **ICD-9 390 to 398; ICD-10 I00 to I09.**

2022, United States: Underlying cause mortality—4294. Any-mention mortality—9310.

2021, United States: Hospital discharges—25\,030.

#### **Prevalence**

- Rheumatic HD remains a leading cause of HF across the world.<sup>95</sup>
- A total of 1680 students between 6 and 18 years of age in eastern Egyptian Governorates were screened for rheumatic HD clinically or by echocardiography.<sup>151</sup> From the total screened students, 1560 studies (92.9%) were adequate and interpretable. Rheumatic HD prevalence was 2.3%. MR was the most prevalent lesion detected by echocardiography in students with rheumatic HD. Of students with rheumatic HD, mild MR was present in 29 students (90.6%), moderate MR was present in 2 patients (6.3%), and severe MR was present in 1 patient (3.1%).

#### **Subclinical Disease**

- 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>152</sup>

- Latent rheumatic HD appears to be half as common among youths 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 youths living with HIV.<sup>153</sup>

### Treatment

- A meta-analysis of 13 studies including 2410 mitral valve repairs and 3598 mitral replacements for rheumatic valve disease revealed that operative mortality of repair versus replacement was 3.2% versus 4.3% (OR, 0.68 [95% CI, 0.50–0.92];  $P=0.01$ ).<sup>154</sup> Mitral valve repair also conferred lower long-term mortality (OR, 0.41 [95% CI, 0.30–0.56];  $P<0.001$ ) and reoperation (OR, 3.02 [95% CI, 1.72–5.31];  $P<0.001$ ).
- There are limited data on TEER in patients with rheumatic HD. One study compiled all mitral valve TEER procedures<sup>155</sup> from the US Nationwide Readmissions Database for hospitalizations between 2016 and 2018. A total of 18240 procedures were included in the analysis, including 1779 in patients with rheumatic HD. Mitral TEER in patients with rheumatic HD was associated with in-hospital mortality similar to that in patients without rheumatic HD (OR, 1.47 [95% CI, 0.94–2.30];  $P=0.089$ ). However, rheumatic HD was associated with higher AMI (OR, 1.65 [95% CI, 1.07–2.56]), acute kidney injury (OR, 1.58 [95% CI, 1.30–1.94]), ventricular arrhythmia (OR, 1.50 [95% CI, 1.12–2.01]), high-degree heart block (OR, 1.67 [95% CI, 1.25–2.23]), and conversion to open surgical repair or replacement (OR, 2.53 [95% CI, 1.02–6.30]). Mitral TEER in rheumatic HD was also associated with higher 90-day all-cause readmission (HR, 1.19 [95% CI, 1.04–1.47];  $P=0.012$ ).

### Mortality

#### (See Table 23-3)

- In the United States in 2022, mortality attributable to rheumatic fever/rheumatic HD was 4294 for all ages (2772 females and 1522 males; Table 23-3).

### Complications

- 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>156</sup> The median age at first presentation was 13 years (interquartile range, 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% (17/94) underwent surgery.

### Global Burden of Rheumatic HD

#### (See Table 23-4 and Charts 23-6 and 23-7)

- Based on 204 countries and territories in 2021<sup>4</sup>:
  - There were 0.37 (95% UI, 0.32–0.44) million total deaths estimated for rheumatic HD, a decrease of 10.76% (95% UI, –25.98% to 7.00%) from 1990 to 2021 (Table 23-4).
  - Among regions, mortality estimated for rheumatic HD was substantially higher for South Asia and Oceania than any other region (Chart 23-6).
  - The number of prevalent cases of rheumatic HD was 54.79 (95% UI, 43.33–67.61) million cases, an increase of 69.43% (95% UI, 65.40%–73.38%) compared with 1990 (Table 23-4).
  - Rheumatic HD prevalence among regions was highest for sub-Saharan Africa, tropical and Andean Latin America, and the Caribbean (Chart 23-7).
- Among 56.2 million people living with HF across 204 countries and territories in the world in 2019, rheumatic HD was the third leading cause of HF.<sup>95</sup> The age-standardized prevalence of HF from rheumatic HD increased between 1990 and 2019; this was driven by increasing rates in males in low- (5% increase) and low-middle- (9.2% increase) SDI regions, most notably in Andean Latin America (16.7% increase). HF from rheumatic HD decreased in middle-, high-middle-, and high-income regions.

### Infective Endocarditis

#### ICD-9 421.0; ICD-10 I33.0.

2022, United States: Underlying cause mortality—1734. Any-mention mortality—3834.

2021, United States: Hospital discharges—11 620.

### Prevalence and Incidence

- 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>157</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).
- Data from the GBD Study show that the incidence of IE has continued to rise over the past 30 years globally.<sup>158</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.

**Secular Trends**

- Data from the North Carolina Hospital Discharge Database show 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>159</sup> In the final year (2016–2017), 42% of IE valve surgeries were for drug use–associated IE.

**Risk Factors**

- The 15-year cohort risk (through 2006) of IE after diagnosis of mitral valve prolapse (between 1989 and 1998) among Olmsted County, Minnesota, residents was  $1.1 \pm 0.4\%$  (incidence, 86.6 cases per 100 000 PY [95% CI, 43.3–173.2]).<sup>160</sup>
  - 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 ( $P < 0.001$ ).<sup>160</sup> 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 PY [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 PY [95% CI, 178.9–2861.0];  $P = 0.02$  compared with no flail mitral leaflet).<sup>160</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 PY, respectively.<sup>161</sup>
- Data from the IE After TAVI International Registry show stable rates for IE after TAVR when earlier (2005–2013) and later (2014–2020) study periods are compared, with an 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>162</sup> In-hospital mortality (36.4% versus 26.6%;  $P = 0.016$ ) and 1-year mortality (53.5% versus 37.8%;  $P < 0.001$ ) decreased over these 2 study periods. In the Swiss TAVI Registry, IE after TAVR occurred most frequently in the early period (<100 days; 2.59 events per 100 PY) and was most commonly caused by *Enterococcus* species (30.1% of cases).<sup>163</sup>

**Awareness, Treatment, and Control**

- 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>164</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>165</sup>

- A single-center retrospective observational study of 413 patients (25.4% female) who received surgery for IE showed that females had a higher 30-day mortality than males (26.7% versus 14.9%;  $P = 0.007$ ).<sup>166</sup> Female sex was predictive for 30-day mortality (OR, 2.090 [95% CI, 1.077–4.053];  $P = 0.029$ ).
- The ESC-HFA EORP European Infective Endocarditis is a prospective, multicenter registry of patients diagnosed with definite or possible IE from 2016 to 2018.<sup>167</sup> Of 2171 patients with left sided IE, 459 (21.1%) had a new embolic event or died within 30 days. The cutoff value of vegetation size for predicting embolic events or 30-day mortality was >10 mm (HR, 1.38 [95% CI, 1.13–1.69];  $P = 0.0015$ ). Other adjusted predictors of risk of embolic event or death were embolic event on admission (HR, 1.89 [95% CI, 1.54–2.33];  $P < 0.0001$ ), history of HF (HR, 1.53 [95% CI, 1.21–1.93];  $P = 0.0004$ ), creatinine >2 mg/dL (HR, 1.59 [95% CI, 1.25–2.03];  $P = 0.0002$ ), *Staphylococcus aureus* (HR, 1.36 [95% CI, 1.08–1.70];  $P = 0.008$ ), congestive HF (HR, 1.40 [95% CI, 1.12–1.75];  $P = 0.003$ ), presence of hemorrhagic stroke (HR, 4.57 [95% CI, 3.08–6.79];  $P < 0.0001$ ), alcohol abuse (HR, 1.45 [95% CI, 1.04–2.03];  $P = 0.03$ ), presence of cardiogenic shock (HR, 2.07 [95% CI, 1.29–3.34];  $P = 0.003$ ), and not performing left-sided surgery (HR, 1.30 [95% CI, 1.05–1.61];  $P = 0.016$ ).

**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).
- Between 1999 and 2019, there were a total of 279 154 reported deaths across the United States related to IE.<sup>168</sup>
  - The overall AAMR from IE in the United States declined from 54.2 per 1 million in 1999 to 51.4 per 1 million in 2019.

- AAMR from IE in the United States increased during this time period among males (2009–2019 annual percentage change, 0.4% [95% CI, 0.1%–0.6%]), NH White individuals (annual percentage change, 0.8% from 2009–2019 [95% CI, 0.5%–1.1%]), American Indian and Alaska Native individuals (annual percentage change, 1.4% from 2009–2019 [95% CI, 0.7%–2.0%]), and those in rural areas (annual percentage change, 1.0% from 2009–2019 [95% CI, 0.5%–1.5%]).

### Heart Valve Procedure Costs

- Among 190563 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>169</sup>

**Table 23-1. Global Mortality and Prevalence of Nonrheumatic Calcific Aortic Valve Disease, by Sex, 2021**

	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), 2021	0.14 (0.12 to 0.16)	13.32 (11.42 to 15.25)	0.06 (0.05 to 0.06)	7.30 (6.26 to 8.34)	0.08 (0.07 to 0.09)	6.02 (5.14 to 6.90)
Percent change (%) in total number, 1990–2021	145.47 (122.89 to 160.95)	184.21 (170.20 to 198.41)	135.81 (117.36 to 151.78)	192.90 (179.17 to 207.41)	152.95 (124.95 to 169.55)	174.35 (159.53 to 190.78)
Percent change (%) in total number, 2010–2021	36.06 (31.62 to 39.58)	35.87 (31.28 to 40.71)	39.76 (35.02 to 43.88)	37.90 (32.82 to 43.91)	33.51 (27.97 to 37.31)	33.49 (28.71 to 38.17)
Rate per 100 000, age standardized, 2021	1.83 (1.54 to 2.00)	158.35 (135.92 to 181.00)	1.89 (1.66 to 2.02)	193.24 (166.56 to 220.38)	1.73 (1.40 to 1.95)	128.88 (110.13 to 147.63)
Percent change (%) in rate, age standardized, 1990–2021	−5.03 (−12.20 to −0.20)	22.04 (16.30 to 28.85)	−2.68 (−9.33 to 2.58)	23.62 (17.67 to 29.94)	−5.98 (−14.07 to −0.84)	19.09 (13.09 to 26.84)
Percent change (%) in rate, age standardized, 2010–2021	−7.20 (−9.39 to −5.00)	−1.62 (−4.93 to 2.01)	−3.12 (−5.85 to −0.65)	−0.31 (−4.14 to 3.99)	−9.56 (−12.51 to −7.01)	−3.01 (−6.48 to 0.33)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>4</sup>

**Table 23-2. Global Prevalence and Mortality of Nonrheumatic Degenerative Mitral Valve Disease, 2021**

	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), 2021	0.04 (0.03 to 0.04)	15.49 (14.46 to 16.70)	0.01 (0.01 to 0.02)	9.83 (9.18 to 10.62)	0.02 (0.02 to 0.03)	5.67 (5.28 to 6.07)
Percent change (%) in total number, 1990–2021	53.81 (40.02 to 68.23)	117.87 (112.40 to 122.81)	65.55 (52.10 to 84.45)	127.29 (121.24 to 132.62)	47.28 (29.97 to 66.08)	103.26 (98.49 to 107.99)
Percent change (%) in total number, 2010–2021	27.15 (22.08 to 32.01)	31.57 (28.00 to 33.66)	33.61 (27.71 to 39.69)	33.72 (29.47 to 36.16)	23.43 (17.25 to 30.01)	28.00 (25.31 to 29.98)
Rate per 100 000, age standardized, 2021	0.46 (0.39 to 0.51)	182.13 (169.95 to 196.07)	0.41 (0.36 to 0.46)	257.92 (240.96 to 278.21)	0.49 (0.40 to 0.57)	121.11 (112.92 to 129.82)
Percent change (%) in rate, age standardized, 1990–2021	−36.05 (−40.73 to −30.59)	−5.65 (−7.74 to −3.71)	−30.37 (−35.19 to −23.57)	−5.30 (−7.51 to −3.21)	−38.59 (−44.64 to −31.28)	−9.97 (−11.98 to −7.93)
Percent change (%) in rate, age standardized, 2010–2021	−9.53 (−12.69 to −6.40)	−5.31 (−7.88 to −3.86)	−3.71 (−7.58 to 0.42)	−4.77 (−7.76 to −2.99)	−11.87 (−15.84 to −7.17)	−7.06 (−8.99 to −5.61)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

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**Table 23-3.** Rheumatic Fever/Rheumatic HD in the United States

Population group	Mortality, 2022: all ages*	Age-adjusted mortality rates per 100 000 (95% CI),* 2022
Both sexes	4294	1.0 (1.0–1.1)
Males	1522 (35.4%)†	0.8 (0.8–0.9)
Females	2772 (64.6%)†	1.2 (1.1–1.2)
NH White males	1196	0.9 (0.9–1.0)
NH White females	2227	1.3 (1.2–1.3)
NH Black males	125	0.7 (0.6–0.8)
NH Black females	240	1.0 (0.8–1.1)
Hispanic males	112	0.6 (0.4–0.7)
Hispanic females	167	0.7 (0.6–0.8)
NH Asian males	55‡	0.6 (0.4–0.8)‡
NH Asian females	92‡	0.7 (0.6–0.9)‡
NH American Indian or Alaska Native	31	1.2 (0.8–1.8)
NH Hawaiian or Pacific Islander	15	Unreliable (1.4–4.2)

Ellipses (...) indicate data not available; HD, heart disease; and NH, non-Hispanic.

\*Mortality for American Indian or Alaska Native people 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 decedents, Asian decedents, Pacific Islander decedents, 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 people, Filipino people, Japanese people, and other Asian people.

Sources: Mortality (for underlying cause of rheumatic fever/rheumatic HD): Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System<sup>1</sup> and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research<sup>2</sup>; data represent underlying cause of death only.

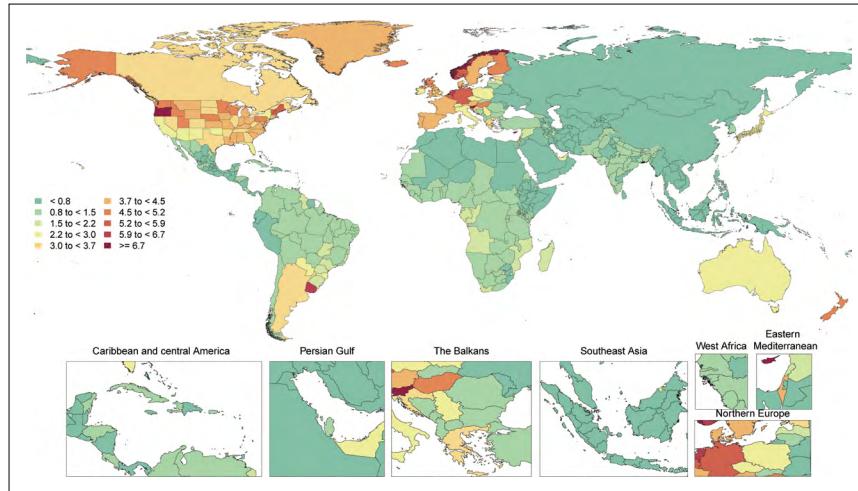
**Table 23-4.** Global Mortality and Prevalence of Rheumatic HD by Sex, 2021

	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), 2021	0.37 (0.32 to 0.44)	54.79 (43.33 to 67.61)	0.16 (0.13 to 0.24)	24.71 (19.41 to 30.54)	0.21 (0.18 to 0.26)	30.08 (24.11 to 37.04)
Percent change (%) in total number, 1990–2021	−10.76 (−25.98 to 7.00)	69.43 (65.40 to 73.38)	−11.86 (−25.67 to 10.18)	67.36 (63.40 to 71.38)	−9.91 (−32.39 to 24.40)	71.16 (66.76 to 75.45)
Percent change (%) in total number, 2010–2021	−2.86 (−17.09 to 12.18)	17.88 (16.66 to 19.30)	−9.19 (−23.45 to 7.61)	16.83 (15.63 to 18.29)	2.54 (−16.58 to 29.14)	18.76 (17.27 to 20.49)
Rate per 100 000, age standardized, 2021	4.47 (3.89 to 5.31)	684.20 (540.41 to 848.90)	4.22 (3.54 to 6.19)	614.20 (482.58 to 761.31)	4.72 (4.01 to 5.82)	754.77 (600.82 to 936.66)
Percent change (%) in rate, age standardized, 1990–2021	−56.22 (−63.78 to −47.51)	12.58 (10.34 to 14.39)	−56.53 (−63.31 to −45.71)	12.08 (10.42 to 13.66)	−56.21 (−67.27 to −40.07)	13.28 (10.51 to 15.63)
Percent change (%) in rate, age standardized, 2010–2021	−25.81 (−36.61 to −14.67)	5.26 (4.30 to 6.15)	−30.18 (−41.15 to −17.82)	4.39 (3.27 to 5.44)	−22.19 (−36.53 to −2.34)	6.11 (4.97 to 7.42)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; HD, heart disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>4</sup>

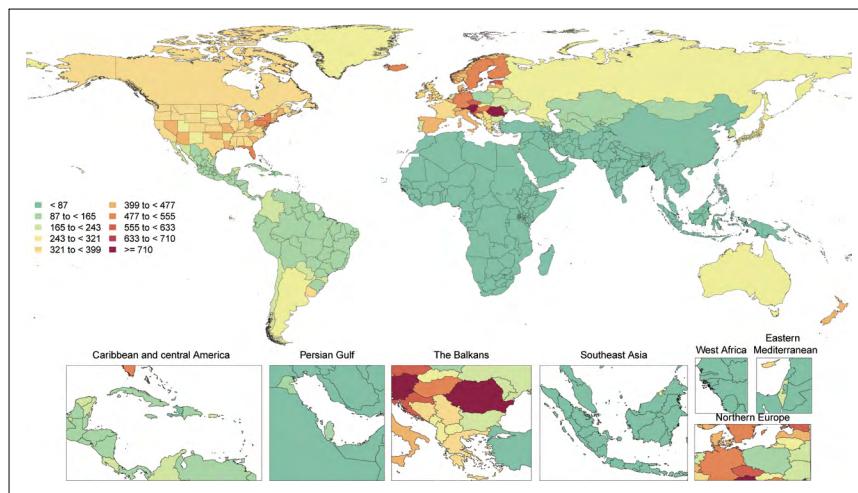


**Chart 23-1. Age-standardized mortality rates of nonrheumatic calcific aortic valve disease per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

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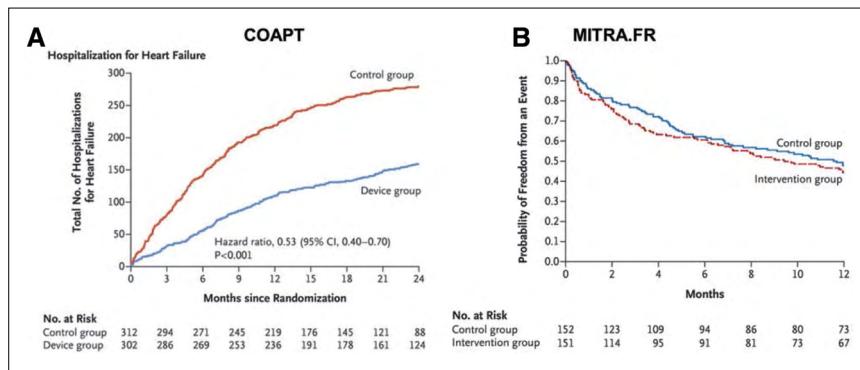


**Chart 23-2. Age-standardized prevalence rates of nonrheumatic calcific aortic valve disease per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

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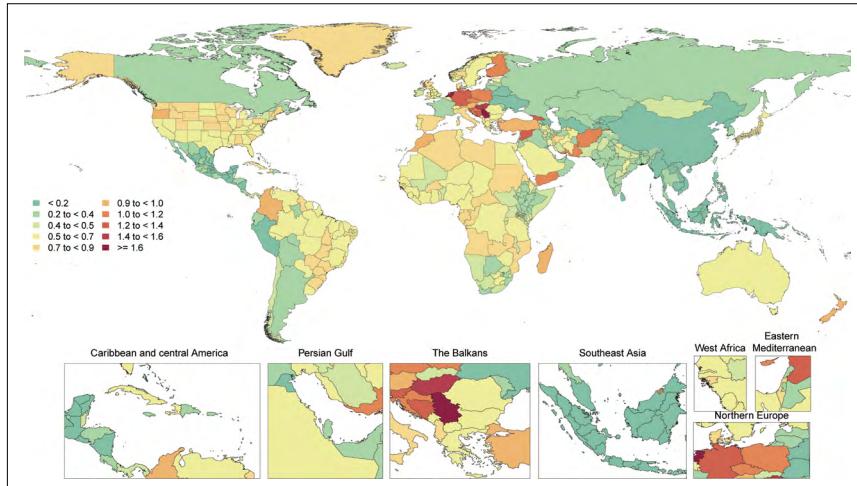
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>4</sup>



**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; 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>120</sup> Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. **B**, Reprinted from Obadia et al.<sup>121</sup> Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

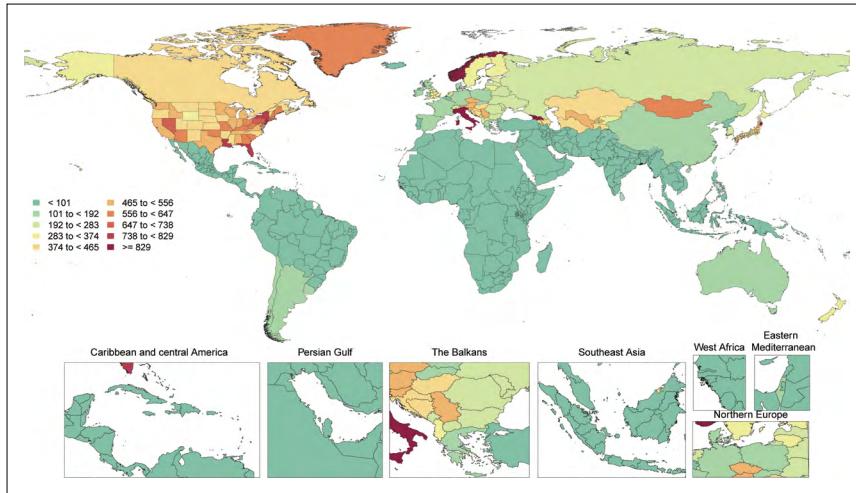


**Chart 23-4. Age-standardized mortality rates of nonrheumatic degenerative mitral valve disease per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

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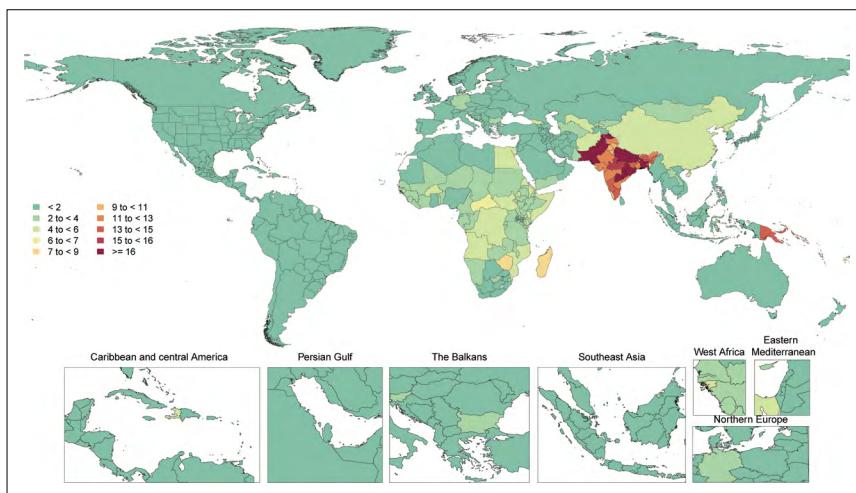
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>4</sup>


**Chart 23-5. Age-standardized prevalence rates of nonrheumatic degenerative mitral valve disease per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

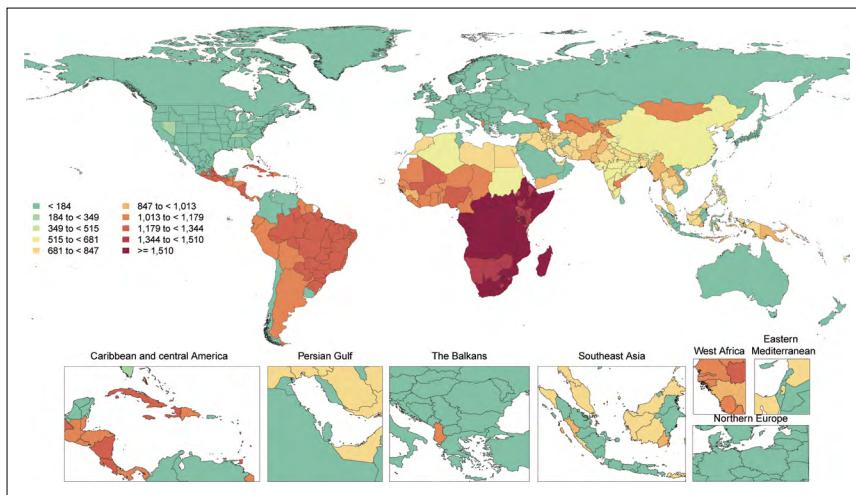
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>4</sup>


**Chart 23-6. Age-standardized global mortality rates of rheumatic HD per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and HD, heart disease.

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**Chart 23-7. Age-standardized global prevalence rates of rheumatic HD per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and HD, heart disease.

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## 24. VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM), CHRONIC VENOUS INSUFFICIENCY, PULMONARY HYPERTENSION

**See Table 24-1 and Charts 24-1 through 24-4**

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[Click here to return to the Abbreviations](#)

In this chapter, 2022 mortality data come from unpublished NHLBI tabulations using NVSS<sup>1</sup> and CDC WONDER.<sup>2</sup> Hospital discharge data, from 2021, come from unpublished NHLBI tabulations using HCUP.<sup>3</sup>

### Pulmonary Embolism

#### ***ICD-9 415.1; ICD-10 I26.***

2022, United States: Underlying cause mortality—9114. Any-mention mortality—50 620.

2021, United States: Hospital discharges—197 080 (principal diagnosis), 523 994 (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.***

2022, United States: Underlying cause mortality—3473. Any-mention mortality—23 731.

2021, United States: Hospital discharges—70 450 (principal diagnosis), 756 514 (all-listed diagnoses).

### Venous Thromboembolism

#### ***Incidence***

**(See Charts 24-1 and 24-2)**

- VTE includes both PE and DVT. In 2021, there were an estimated ≈523 994 cases of PE<sup>3</sup> (Chart 24-1), ≈756 514 cases of DVT<sup>3</sup> (Chart 24-2), and

The 2025 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 2025. 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.

≈1280 508 total VTE cases in the United States in inpatient settings. An analysis of health care claims data between 2011 and 2018 that included ≈200 000 individuals with VTE diagnosis observed that 37.6% of all patients were treated as outpatients. Moreover, a study with NHAMCS data from 2012 to 2020 revealed that 30.7% (95% CI, 22.3%–41.0%) of patients with PE were discharged from the ED.<sup>4</sup> The discharge rate from the ED remained stable over the study period.

- A study in individuals in Oklahoma (whose ethnic profile is similar to that of the US population) observed an age-standardized incidence of 2.47 (95% CI, 2.39–2.55), 1.47 (95% CI, 1.41–1.54), and 0.99 (95% CI, 0.93–1.04) per 1000 PY for VTE, DVT, and PE, respectively.<sup>5</sup>
  - In this analysis, the incidence in the Black population for VTE, DVT, and PE was 3.25 (95% CI, 3.02–3.49), 1.97 (95% CI, 1.80–2.16), and 1.27 (95% CI, 1.13–1.43) per 1000 PY, respectively, much higher than in NH White individuals (2.71 [95% CI, 2.61–2.63], 1.59 [95% CI, 1.50–1.67], and 1.12 [95% CI, 1.06–1.20] per 1000 PY), who have a higher incidence than Hispanic individuals (0.67 [95% CI, 0.54–0.82], 0.39 [95% CI, 0.30–0.51], and 0.27 [95% CI, 0.19–0.37] per 1000 PY) and Asian/Pacific Islander individuals (0.63 [95% CI, 0.43–0.91], 0.41 [95% CI, 0.26–0.65], and 0.22 [95% CI, 0.11–0.41] per 1000 PY).
- The MESA cohort yielded similar findings, with Black participants having an incidence rate of VTE of 4.02 per 1000 PY, which was higher compared with White participants (2.98 per 1000 PY) and Hispanic participants (2.08 per 1000 PY). These 3 ethnic groups had a higher incidence rate than Chinese participants (0.79 per 1000 PY).<sup>6</sup>
- Data from Medicare that involved ≈411 500 beneficiaries who underwent major surgeries revealed an overall 90-day rate of VTE of 2.8%.<sup>7</sup> Among the major procedures, the highest rate of VTE was found in patients who underwent pancreatectomy (VTE event rate, 4.68% [95% CI, 4.32%–5.04%]), whereas the lowest event rate was found in AAA repair (VTE event rate, 2.16% [95% CI, 2.03%–2.29%]). In patients who underwent orthopedic surgery, a study of a claims database with ≈132 000 individuals showed that the 30- and 90-day cumulative incidence of VTE was 1.19% (95% CI, 1.06%–1.32%) and 1.86% (95% CI, 1.70%–2.02%), respectively.<sup>8</sup>
- A study using data from 73 million childbirths in the United States found a VTE incidence of 6.6 per 10 000 deliveries.<sup>9</sup>
- Cancer-associated thrombosis is a prevalent condition among patients with active malignancy:

- A 16-year cohort study among ≈430 000 patients from the Veterans Affairs Health Care System in the treatment of cancer revealed a cumulative incidence of 4.5%.<sup>10</sup>
- The highest incidence of VTE at 1 year was noted in patients with acute lymphoblastic leukemia (18.6%), pancreatic cancer (12.1%), brain cancer (11.1%), aggressive non-Hodgkin lymphoma (11%), and gastric and esophageal cancer (10%). The lowest incidences were seen for thyroid cancer (1.5%), prostate cancer (1.6%), and melanoma (1.7%).
- VTE is a prevalent disease in the hospitalized patient setting:
  - 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>11</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 as NH White individuals (rate ratio, 1.9 [95% CI, 1.5–2.3]) after adjustment for age and sex.
  - A study with ≈5000 patients in a Level 1 trauma center found that those who underwent screening duplex ultrasonography of the legs had an early DVT incidence of 3.3%. Furthermore, during hospitalization, 3.9% of the total sample were diagnosed with VTE.<sup>12</sup>
  - An analysis of the National Surgical Quality Improvement Program observed a high incidence of VTE of 2.5% in 5003 patients undergoing colorectal surgery for inflammatory bowel disease.<sup>13</sup>
- Invasive devices, particularly the size of peripherally inserted central catheters, were the focus of a 2023 meta-analysis comprising >45 000 procedures involving mostly US patients. The analysis found a pooled incidence for symptomatic DVT of 0.89% (95% CI, 0.18%–4.31%) for 3F catheters, 3.26% (95% CI, 2.12%–4.98%) for 4F catheters, 5.46% (95% CI, 3.56%–8.29%) for 5F catheters, and 10.66% (95% CI, 4.69%–22.46%) for 6F catheters.<sup>14</sup>
- In patients with systemic lupus erythematosus, a 2023 meta-analysis observed a pooled incidence ratio of 8.04 per 1000 PY (95% CI, 4.58–11.08; 12 studies) for VTE, 3.11 per 1000 PY (95% CI, 1.73–4.86; 7 studies) for DVT, and 1.40 per 1000 PY (95% CI, 0.15–3.60; 7 studies) for PE.<sup>15</sup>
- Several studies since 2020 with data from the COVID-19 pandemic have addressed the incidence and prevalence of VTE in different settings:
  - Among ≈400 000 US outpatients with a COVID-19 diagnosis in Northern and Southern California, the overall incidence of VTE was 0.26 (95% CI, 0.24–0.30) per 100 PY.<sup>16</sup>
  - In an analysis of a health care database involving ≈546 000 hospitalized individuals in the United States with a COVID-19 diagnosis, thrombotic events were found in 10.0% of all hospitalized patients. The rate of DVT was 20.8% in those admitted to the ICU.<sup>17</sup>
  - It is important to note that 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 a routine screening approach (pooled incidence, 47.5% [95% CI, 25.3%–69.7%] versus 15.1% [95% CI, 8.35%–21.9%];  $P<0.001$ ).<sup>18</sup>
  - Data from the 2020 National Readmission Database revealed that VTE was the principal diagnosis in 22.5% among ≈645 000 readmissions of patients with COVID-19.<sup>19</sup>
  - An analysis involving ≈855 000 veterans >45 years of age observed a VTE rate in those vaccinated for COVID-19 of 1.3755 events per 1000 individuals (95% CI, 1.3752–1.3758) compared with 1.3741 per 1000 individuals (95% CI, 1.3738–1.3744) in nonvaccinated control subjects.<sup>20</sup> This translates to a marginal excess of 1.4 VTE events per 1 000 000 individuals, an incidence of significantly lower magnitude compared with the COVID-19-associated VTE data.
  - Furthermore, the incidence of VTE in the population with the COVID-19 vaccine did not differ from that in individuals who received the influenza vaccine before the SARS-CoV-2 pandemic ( $aHR$ , 0.95 [95% CI, 0.85–1.05]).<sup>21</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>22</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 2021, accompanied by a

progressive increase in the in-hospital death rate. Although the all-listed diagnoses (Chart 24-2) show that the number of hospitalized DVT cases also increased from 2005 to 2021, discharges with DVT as a principal diagnosis have fallen in the past 5 years.<sup>3</sup>

- An analysis of 20-year data from CDC WONDER found an increasing mortality rate in the young adult US population.<sup>23</sup> Among individuals 25 to 44 years of age, the AAMR per 100 000 population rose from 2.27 (95% CI, 2.17–2.37) in 1999 to 3.20 (95% CI, 3.13–3.31) in 2019, with an annual percentage change of 1.4% (95% CI, 1.1%–1.7%).
- From 1999 to 2017, NIS data showed a consistent trend of reduced mortality rates among patients with high-risk PE, whether treated with anticoagulants alone or with thrombolytic therapy. The mortality rate decreased from 72.7% in 1999 to 49.8% in 2017 ( $P<0.001$ ), despite a clear increase in both the absolute number (104 procedures in 1999 versus 955 in 2017;  $P<0.001$ ) and relative rate of high-risk patients treated (6.3% in 1999 versus 19.3% in 2017;  $P<0.001$ ) with thrombolytic therapy.<sup>24</sup>
- Another NIS analysis 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>9</sup>
- In the maternal PE setting, mortality has remained stable between 2003 and 2020 (overall incidence rate per 100 000 live births, 1.02 [95% CI, 0.95–1.10]).<sup>10,25</sup>
- Despite increasing trends in VTE diagnosis, an 18-year study of >6 million cardiac surgeries in the United States showed a consistent reduction in inpatient deaths after VTE complications (percentage change per year, –6.4%;  $P<0.001$ ).<sup>26</sup>
- In the orthopedic leg surgery setting, a study using Medicare data between 2010 and 2017 found a decrease in VTE incidence after total knee arthroplasty (in-hospital incidence rate, 0.3% in 2010 and 0.1% in 2017;  $P_{\text{trend}}=0.035$ ).<sup>27</sup>

### Risk Factors

- In a study involving 2 large databases, 32.4% of the ≈203 000 patients diagnosed with VTE among Medicare beneficiaries were considered provoked; this rate was 19.4% among ≈95 000 commercially insured individuals.<sup>28</sup> Provoked VTE was determined if patients had a major trauma, fracture, or major surgery; if they were hospitalized for ≥3 days in the 90 days preceding the index VTE admission; or if there was a presence of a cancer diagnosis code

on 2 distinct dates in the year before the index VTE admission.

- Hospitalized patients are at particularly high risk of VTE:
  - One study 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>29</sup>
  - A retrospective cohort with ≈1 110 000 admissions found the following risk factors for hospital-associated VTE, even after adjustment: active cancer (OR, 1.96 [95% CI, 1.85–2.08]), previous VTE (OR, 1.71 [95% CI, 1.63–1.79]), central line (OR, 1.63 [95% CI, 1.53–1.73]), recent surgery or trauma (OR, 1.50 [95% CI, 1.39–1.61]), known thrombophilia (OR, 1.22 [95% CI, 1.06–1.40]), obesity (OR, 1.12 [95% CI, 1.07–1.16] for BMI >30 kg/m<sup>2</sup>), infection as cause of admission (OR, 1.07 [95% CI, 1.04–1.11]), and male sex (OR, 1.07 [95% CI, 1.03–1.10]).<sup>30</sup>
- Independent VTE risk factors beyond the provoking factors noted previously:
  - An individual-level study by the Emerging Risk Factors Collaboration found an association between VTE incidence and age (HR per decade, 2.67 [95% CI, 2.45–2.91]), diabetes (HR, 1.69 [95% CI, 1.33–2.16]), WC (HR, 1.54 [95% CI, 1.37–1.73]), and smoking (HR, 1.38 [95% CI, 1.20–1.58]).<sup>31</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>32</sup>
  - Autoimmune diseases such as giant-cell arthritis and polymyalgia rheumatica are risk factors for DVT (IRR, 4.12 [95% CI, 3.13–5.35] and 1.44 [95% CI, 1.20–1.72], respectively) and PE (IRR, 3.99 [95% CI, 2.63–5.81] and 1.79 [95% CI, 1.39–2.28], respectively).<sup>33</sup> A 2023 meta-analysis found similar risk in patients with systemic lupus erythematosus for VTE (pooled RR, 4.38 [95% CI, 2.63–7.29]; 5 studies), DVT (pooled RR, 6.35 [95% CI, 2.70–14.94]), and PE (pooled RR, 4.94 [95% CI, 1.90–12.86]).<sup>15</sup>
  - An analysis of a 15-year US claims database identified an elevated risk of VTE in patients with amyotrophic lateral sclerosis (HR, 3.30 [95% CI, 2.60–4.00]) in the occurrence of both DVT (HR, 3.20 [95% CI, 2.50–4.10]) and PE (HR, 3.60 [95% CI, 2.50–5.10]).<sup>34</sup>
  - Use of testosterone therapy was also associated with doubling of VTE risk in males with and without evidence of hypogonadism (aOR for VTE after 6 months, 2.02 [95% CI, 1.47–2.77] in those without hypogonadism and 2.32 [95%

CI, 1.97–2.74] in patients with hypogonadism).<sup>35</sup> These 2019 findings applied a case-crossover design to a large administrative database.

- An updated 2020 US Preventive Services Task Force systematic review found, among other benefits and harms, an increased risk of both DVT and PE in postmenopausal females using hormone therapy during the estrogen plus progestin strategy (HR for DVT, 1.87 [95% CI, 1.37–2.54] and HR for PE, 1.98 [95% CI, 1.36–2.87] in a follow-up of 5.6 years), in addition to an increased risk in the postintervention period (HR for DVT, 1.24 [95% CI, 1.01–1.53] and HR for PE, 1.26 [95% CI, 1.00–1.59] in a cumulative follow-up of 13.2 years).<sup>36</sup> However, in females using an estrogen-only strategy, there was no difference in incidence rates of DVT or PE during the postintervention period (total cumulative follow-up, 13 years).
- For patients during cancer treatment and follow-up, the risk of overall cancer-associated thrombosis was higher in NH Black individuals (HR, 1.23 [95% CI, 1.19–1.27]) and lower in Asian/Pacific Islander individuals (HR, 0.84 [95% CI, 0.76–0.93]) compared with NH White individuals.<sup>10</sup>
- In the COVID-19 setting, several studies have shown a higher incidence of VTE in patients with COVID-19 compared with those with no SARS-CoV-2 infection:
  - Patients admitted with COVID-19 had a significantly higher risk of VTE compared with those hospitalized with a diagnosis of influenza before 2020 (HR, 1.89 [95% CI, 1.68–2.12]), regardless of whether they had a history of VTE (HR, 1.42 [95% CI, 1.16–1.74]) or no history (HR, 2.09 [95% CI, 1.82–2.40]).<sup>37</sup> Among these patients admitted with COVID-19, the risk factors for increased risk of VTE were age, male sex, prior VTE, obesity, cancer history, thrombocytosis, and primary thrombophilia.
  - Data from the AHA's COVID-19 CVD registry revealed a higher risk of VTE during the Delta wave compared to the Wild/Alpha wave (OR for PE or DVT in patients >40 years of age, 1.79 [95% CI, 1.53–2.11]).<sup>38</sup> In addition, patients >40 years of age also exhibited a higher risk of VTE compared with their younger counterparts (OR, 2.29 [95% CI, 1.91–2.74]).
  - Medicare data from ≈6300000 US adults >65 years of age revealed that the mRNA-1273 vaccine compared with the BNT162b2 vaccine showed a trend toward a lower risk of PE (RR, 0.96 [95% CI, 0.93–1.00]).<sup>39</sup>
  - A 2021 meta-analysis with 9180 transgender patients showed a higher risk of VTE in transfeminine people compared with transmasculine people

(assigned female at birth; OR, 5.29 [95% CI, 2.03–13.79]), with a high heterogeneity probably driven by duration of hormone replacement therapy.<sup>40</sup> To date, there are limited data on the risk of VTE in the transmasculine population compared with cisgender men.

- 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>41</sup>

### Social Determinants of Health/Health Equity

- In 2020, patients from rural areas accounted for 16.4% of all PE (95% CI, 15.7%–17.1%) and 13.7% of all DVT (95% CI, 13.0%–14.4%) hospital discharges.<sup>3</sup>
  - Although the rate of admissions for PE was higher in rural areas than in urban areas (discharges for 100 000 population, 65.6 [95% CI, 62.3–68.9] versus 47.0 [95% CI, 43.9–50.1] for patients living in large metro areas), the individual spendings were lower for rural inhabitants than for urban inhabitants who were admitted (average hospital charges per stay, \$43 153 [95% CI, \$41 152–\$45 154] versus \$68 782 [95% CI, \$65 521–\$72 043] for those living in large metro areas).
  - There is a similar scenario in those with DVT diagnosis (average hospital charges per stay, \$49 085 [95% CI, \$46 410–\$51 760] for patients living in rural areas versus \$68 175 [95% CI, \$64 692–\$71 658] for patients living in large metro areas).
- A 16-year cohort study involving ≈434 000 patients with cancer-associated thrombosis from the Veterans Affairs Health Care System observed that 35% of the individuals were from rural areas.<sup>10</sup>
  - In this same cohort, more than 289 000 individuals (61.9%) lived in areas of greater socioeconomic disadvantage. The prevalence of patients living in an Area Deprivation Index percentile of 51 to 75 and 76 to 100 was 29.6% and 32.3%, respectively. This was associated with a higher risk of mortality, with an HR of 1.06 (95% CI, 1.04–1.07) and 1.15 (95% CI, 1.13–1.16) for the respective percentiles.
- Data from ≈512 000 bariatric surgeries in the Metabolic and Bariatric Surgery Accreditation and Quality Improvement Project revealed that VTE-associated mortality was more prevalent in Black patients and Hispanic patients (27.8% and 25% of all deaths, respectively) compared with White patients (13.3%;  $P<0.001$ ).<sup>42</sup>
- In a US cohort of 14 140 patients with diagnosed VTE, Black individuals were less likely to

be prescribed DOACs than White individuals (OR, 0.86 [95% CI, 0.77–0.97]). However, Hispanic individuals and Asian individuals had no difference in DOAC prescription compared with White individuals ( $P=0.66$  and  $P=0.74$ , respectively).<sup>43</sup>

- In a 2021 analysis of 65 000 elderly Medicare patients, Black individuals who used both apixaban and warfarin had a higher risk of adverse events after experiencing a VTE compared with White individuals (incidence rates per 100 PY 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>44</sup> Patients with lower SES also had worse outcomes (incidence rates per 100 PY 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]).

### **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 populations (1.2%) and Asian populations (0.45%).<sup>46</sup> In ARIC, ≈5% of White people 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>22</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 disease (prevalence, 0.02%–0.2%) 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>
- GWASs have identified additional common genetic variants associated with VTE risk, including variants in *F5*, *F2*, *F11*, *FGG*, and *ZFPN2*.<sup>51</sup> These common variants individually increase the risk of VTE to a small extent, but a GRS composed of a combination of 5 common variants yielded an OR for VTE risk of 7.5.<sup>52</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 rare novel variants associated with VTE. Similarly, targeted sequencing efforts did not uncover rare novel variants for DVT. However, multiancestry genome-wide GWAS meta-analyses have established >30 novel VTE risk loci.<sup>53,54</sup>
- A GRS including 1 092 045 SNPs was associated with higher odds of incident VTE event (OR, 51% per 1-SD increase in GRS).<sup>54</sup> The risk of VTE in the higher tail end of this GRS was similar to that attributed to monogenic VTE variants. This GRS may guide decision-making on which individuals may benefit from anticoagulant therapy.

### **Prevention**

- Pharmacological prophylaxis has shown benefit with the use of low-molecular-weight heparin in critically ill patients (OR for DVT, 0.59 [95% CI, 0.33–0.90]).<sup>55</sup>
  - In an analysis involving ≈5000 high-risk patients for VTE who underwent general surgery, the correct prescription of chemoprophylaxis was associated with lower rates of VTE (OR, 0.58 [95% CI, 0.34–0.95]) and lower mortality (OR, 0.57 [95% CI, 0.34–0.93]).<sup>56</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>55</sup> and patients with trauma (OR for DVT, 0.67 [95% CI, 0.50–0.88]).<sup>57</sup>
  - In patients with cancer, thromboprophylaxis reduces both 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>58</sup>
  - In pregnant females with a history of VTE, there was no superiority of weight-adjusted over fixed-low-dose low-molecular-weight heparin (rate of VTE events up to 6 weeks postpartum, 2% versus 3%;  $P=0.33$ ).<sup>59</sup> For those with VTE risk in the prepartum, peripartum, or postpartum period, it is unclear whether pharmacological prophylaxis brings benefit to this population.<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 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>
  - In patients admitted with COVID-19, a 2022 Cochrane meta-analysis found that a higher dose of anticoagulants resulted in lower risk of PE

(pooled RR, 0.46 [95% CI, 0.31–0.70]; 4 studies) at the cost of increased risk of major bleeding (pooled RR, 1.78 [95% CI, 1.13–2.80]; 4 studies).<sup>63</sup>

- The use of antiplatelet therapy is not associated with the prevention of cancer-associated thrombosis ( $P=\text{not significant}$ )<sup>10</sup> or postoperative VTE in major orthopedic surgery (pooled RR of VTE compared with other anticoagulants, 1.45 [95% CI, 1.18–1.77]; 17 studies).<sup>64</sup>
- Furthermore, beyond the pharmacological prophylaxis:
  - 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>65</sup> In addition, after a VTE, elastic stockings may prevent PTS (pooled RR, 0.73 [95% CI, 0.53–1.00]), but there is no association with reduced risk of severe PTS, recurrent VTE, or mortality ( $P=\text{not significant}$ ).<sup>66</sup>
  - A 2022 Cochrane meta-analysis found that incorporating intermittent pneumatic leg compression into standard VTE drug prevention resulted in a reduction in the incidence of both PE (pooled OR, 0.46 [95% CI, 0.30–0.71]; 15 studies) and DVT (pooled OR, 0.38 [95% CI, 0.21–0.70]; 17 studies). There was no increased risk for orthopedic patients for PE and DVT incidence ( $P=0.82$  and  $P=0.69$ , respectively).<sup>67</sup>
- An early strategy of 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>56,68</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>69,70</sup>

### Awareness, Treatment, and Control

- Anticoagulation with oral or parenteral drugs is the mainstay of VTE treatment.
  - After DVT diagnosis, anticoagulants consistently reduced both VTE and DVT recurrence by 66% and 75%, respectively.<sup>71</sup>
  - An analysis of 2 large databases involving >203 000 Medicare beneficiaries and >95 000 commercially insured patients revealed that the initial prescription of DOAC after a VTE episode increased from 0% in 2010 to 86.8% in Medicare patients and 92.1% in commercially insured individuals in 2020.<sup>28</sup>
  - A study on anticoagulant strategy in ≈64 000 discharges showed an incidence of VTE recurrence with apixaban, rivaroxaban, and warfarin of 9.8 (95% CI, 6.8–13.6), 11.6 (95% CI, 8.5–15.4), and 13.6 (95% CI, 10.2–17.6) per 100 000

person-years.<sup>72</sup> The only statistically significant difference in VTE recurrence was observed in the analysis that compared patients using apixaban with those who were prescribed warfarin (HR, 0.69 [95% CI, 0.49–0.99]). Similar findings were reported in a cohort study from California involving ≈18 400 patients.<sup>73</sup> The rate of recurrent VTE with any DOAC and warfarin was 2.92 (95% CI, 2.29–3.54) and 4.14 (95% CI, 3.90–4.38) per 100 PY, respectively. The aHR for recurrent VTE in DOAC use was 0.66 (95% CI, 0.52–0.82) compared with warfarin use, with no difference in the risk of hospitalization for bleeding and mortality.

- An on-treatment analysis with GARFIELD-VTE data showed a lower all-cause mortality in the DOAC group (eg, rivaroxaban, apixaban, edoxaban, and dabigatran) compared with the vitamin K antagonists group (eg, warfarin; HR, 0.57 [95% CI, 0.42–0.79] in a mean follow-up of 12 months).<sup>74</sup>
- A retrospective analysis with Medicare patients who presented with cancer-associated thrombosis observed that the use of DOACs was associated with lower mortality (HR, 0.85 [95% CI, 0.78–0.91]).<sup>75</sup>
- Retrospective analyses of 5 US claims databases in a specific group of patients observed that the use of apixaban compared with warfarin was associated with the following:
  - Lower recurrent VTE (HR, 0.78 [95% CI, 0.70–0.87]), major bleeding (HR, 0.75 [95% CI, 0.67–0.83]), and intracranial bleeding (HR, 0.56 [95% CI, 0.42–0.76]) in those with high risk of bleeding;<sup>76</sup>
  - Lower VTE recurrence (HR, 0.78 [95% CI, 0.66–0.92]) and major bleeding (HR, 0.76 [95% CI, 0.65–0.88]) in patients with VTE diagnosis and prior CKD;<sup>77</sup> and
  - Lower VTE recurrence (HR, 0.58 [95% CI, 0.43–0.77]) and major bleeding (HR, 0.78 [95% CI, 0.62–0.98]) in patients on dialysis.<sup>78</sup>
- In a cohort of >220 000 veterans, the use of antivirals in the treatment of COVID-19, when indicated, was associated with a lower risk of VTE compared with no medication.<sup>79</sup> Among those who received nirmatrelvir, the HR was 0.72 (95% CI, 0.53–0.96) for DVT and 0.61 (95% CI, 0.51–0.74) for PE. Similar findings were issued among patients receiving molnupiravir (HR for DVT, 0.72 [95% CI, 0.53–0.99] and HR for PE, 0.65 [95% CI, 0.47–0.91]).<sup>80</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 ( $P=0.33$ ). Inferior vena cava filter did not provide a reduction in mortality ( $P=0.61$ ).<sup>81</sup>

- Data from the National Readmission Database, which involved >58 000 patients hospitalized with a proximal VTE, revealed that inferior vena cava filter was associated with a higher risk of 30-day unplanned rehospitalization (HR, 1.47 [95% CI, 1.38–1.56]).<sup>82</sup>
- In patients who had cancer-associated thrombosis, a US cohort analysis found a significant improvement in PE-free survival in those who underwent inferior vena cava filter placement (HR, 0.69 [95% CI, 0.64–0.75]) regardless of the underlying neoplasm.<sup>83</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>84</sup>
  - Moreover, percutaneous pharmacomechanical catheter-directed thrombolysis for DVT may reduce the risk of PTS (pooled RR, 0.84 [95% CI, 0.74–0.95]; 3 studies) but is associated with an increased risk of major bleeding (pooled RR, 2.03 [95% CI, 1.08–3.82]).<sup>85</sup>
  - A 2021 meta-analysis found no mortality benefit associated with systemic thrombolysis procedure ( $P=0.83$ ).<sup>86</sup>
- In patients with PE, ≈5000 patients were treated with percutaneous pulmonary artery thrombectomy in the United States from 2016 to 2018, which was 0.5% of all PE diagnoses.<sup>87</sup>
  - In this scenario, females exhibited a higher rate of bleeding during the procedure (16.9% versus 11.2%), received more red blood transfusions (11.9% versus 5.7%), experienced more vascular complications (5.0% versus 1.5%; all  $P<0.05$ ), and had higher in-hospital mortality (OR, 1.90 [95% CI, 1.20–3.00]) than males.
- An analysis using the Pulmonary Embolism Response Team Consortium Registry of patients admitted with a high-risk PE diagnosis found that 41.9% received advanced therapies such as systemic thrombolytics, catheter-directed thrombolysis, catheter-based embolectomy, surgical embolectomy, or mechanical circulatory support.<sup>88</sup>
- Although malignancy is a relevant risk factor with an incidence of 2.4% within 6 months after VTE diagnosis,<sup>89</sup> a Cochrane meta-analysis found no evidence for additional positron emission tomography/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>90</sup>

**Mortality**

- Data from Pulmonary Embolism Response Team Consortium Registry revealed a mortality of 20.6% in high-risk patients and 3.7% in intermediate-risk patients.<sup>88</sup> Among the high-risk individuals, in-hospital mortality was 42.1% for those admitted with a catastrophic PE; this rate was 17.1% in patients with a noncatastrophic high-risk PE.
- A study based on the analysis of data from CDC WONDER found a significant increase in mortality related to PE during the COVID-19 pandemic compared with the preceding years.<sup>91</sup> The AAMR per 100 000 people was 12.2 (95% CI, 12.1–12.3) in 2020 compared with 9.6 (95% CI, 9.5–9.7) in 2019 and 9.4 (95% CI, 9.3–9.5) in 2018.
- The GARFIELD-VTE study observed a 3-year mortality of 10.9% after a VTE. The incidence of death decreases gradually from the first month (incidence per 100 PY, 10.69 [95% CI, 8.72–13.11]) compared with months 2 to 12 (6.54 [95% CI, 6.05–7.07]), the second year (3.1 [95% CI, 2.75–3.50]), and the third year (2.0 [95% CI, 1.72–2.34]).<sup>92</sup>
- In patients with cancer diagnosis:
  - Compared with prostate malignancy, the cancer sites with the highest risk of death attributable to cancer-associated thrombosis were pancreas (HR, 10.05 [95% CI, 9.79–10.31]), brain (HR, 8.09 [95% CI, 7.73–8.48]), and liver (HR, 7.08 [95% CI, 6.92–7.23]), whereas the cancers with the lowest risk of cancer-associated thrombosis were chronic myeloid leukemia (HR, 0.50 [95% CI, 0.48–0.53]), chronic lymphoid leukemia (HR, 0.50 [95% CI, 0.48–0.52]), and thyroid cancer (HR, 0.87 [95% CI, 0.82–0.92]).<sup>10</sup>
  - Mortality caused by cancer-associated thrombosis increased with the stage of the disease. The HR for death was 1.58 for stage II (95% CI, 1.56–1.61), 2.18 for stage III (95% CI, 2.15–2.21), and 5.03 for stage IV (95% CI, 4.97–5.10) compared with stage I.
  - Despite high heterogeneity among cancer sites, age (HR per 10-year increase, 1.47 [95% CI, 1.47–1.48]), hospitalization in the past 90 days (HR, 1.45 [95% CI, 1.43–1.46]), anemia (HR for hemoglobin <10 g/dL, 1.37 [95% CI, 1.35–1.39]), platelet count >350×10<sup>9</sup>/L (HR, 1.29 [95% CI, 1.27–1.31]), white blood cell count >10×10<sup>9</sup>/L (HR, 1.28 [95% CI, 1.27–1.30]), male sex (HR, 1.24 [95% CI, 1.21–1.28]), prior VTE (HR, 1.11 [95% CI, 1.09–1.13]), and immobility (HR, 1.09 [95% CI, 1.05–1.14]) emerged as additional epidemiological and laboratory risk factors for cancer-associated thrombosis mortality.
- In the hospitalized population with VTE diagnosis, patients with COVID-19 had at least a 3-fold risk of death compared with those admitted for influenza

infection (HR for 30-day all-cause mortality, 2.96 [95% CI, 1.84–4.76] in the prevaccination period and 3.80 [95% CI, 2.41–6.00] at the beginning of vaccine availability).<sup>37</sup> When stratified by disease severity, the OR for mortality in the ICU was 2.63 (95% CI, 1.49–4.67) and for patients on mechanical ventilation was 3.14 (95% CI, 1.97–5.02).<sup>93</sup>

### **Complications**

- VTE is a chronic disease with episodic recurrence.
  - An analysis of a US health claims database between January 2010 and December 2019 (with ≈14 000 patients with a prior diagnosed VTE) observed a 6-month VTE recurrence rate of 6.1%, with higher recurrence in patients with arrhythmia (HR, 1.46 [95% CI, 1.07–1.99]), congestive HF (HR, 1.33 [95% CI, 1.07–1.66]), and CKD (HR, 1.24 [95% CI, 1.02–1.50]).<sup>94</sup>
  - Data from GARFIELD-VTE showed a 3-year incidence of recurrent VTE of 3.47 (incidence per 100 PY [95% CI, 3.24–3.70]) and in the first year of follow-up (incidence per 100 PY, 5.34 [95% CI, 4.89–5.82]).<sup>92</sup>
  - Although studies have shown an increased risk of VTE in females using estrogen-containing contraceptives, a 2022 Cochrane metaanalysis found no association with recurrent events, whether in a follow-up of ≤1, 1 to 5, or >5 years. The meta-analysis reported a low VTE recurrence (incidence per 100 patient-years, 1.57 [95% CI, 1.10–2.23]).<sup>95</sup>
- Major bleeding is a potentially life-threatening adverse event that can occur during VTE treatment:
  - According to the GARFIELD-VTE data, the main site of major bleeding is the gastrointestinal tract (31.6% of all events) followed by the uterus (13%). Hemorrhagic stroke accounted for 5.5% of the total major bleeding episodes.<sup>92</sup>
  - Data from NIS with >138 000 Americans with proximal DVT indicated an intracranial bleeding rate of 0.2% in patients using anticoagulants and 0.7% in those receiving catheter-directed thrombolysis.<sup>96</sup> In this population, the main predictors of bleeding risk were a history of stroke (OR, 19.4 [95% CI, 8.76–42.77]), age >74 years (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]).
  - Patients from the Pulmonary Embolism Response Team Consortium Registry with high- and intermediate-risk PE had a major bleeding rate of 10.5% and 3.5%, respectively.<sup>88</sup>
  - A study of ≈64 000 US patients followed up for 90 days after a VTE hospitalization showed no difference in major bleeding among apixaban, rivaroxaban, and warfarin prescriptions.<sup>72</sup>

- Heparin-induced thrombocytopenia was observed as a complication in 0.6% of patients admitted with VTE in an analysis of the NIS database, which involved ≈790 000 individuals.<sup>97</sup>
- Superior vena cava syndrome is a complication of thoracic vein thrombosis. Data from ≈1 000 000 visits to 950 US EDs between 2010 and 2018 showed a superior vena cava syndrome incidence of 3.5 per 100 000 emergency admissions.<sup>98</sup> The most common causes were cancer (10.6%), cardiac implantable electronic devices (7.5%), and intravascular catheters (4.5%).
- 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 for PTS of 23.3% (95% CI, 16.6%–31.7%;<sup>99</sup> 17 studies) in the short term (median follow-up, 21 months) and up to 70% in the long term (follow-up >5 years).<sup>84</sup> In this context, the PTS incidence was lower in those treated with DOAC drugs (11.8% [95% CI, 6.5%–20.6%]) than low-molecular-weight heparin (27.9% [20.9%–36.2%]) and vitamin K antagonists (24.5% [95% CI, 17.6%–33.1%]).<sup>99</sup>

### **Health Care Use: Hospital Discharges/Ambulatory Care Visits**

- In 2019, data from the NAMCS, which tracks medical care provided by office-based physicians in the United States, indicated that there were ≈1 593 000 physician office visits for DVT (unpublished NHLBI tabulation using NAMCS<sup>100</sup>).
- In 2021, there were 210 712 ED discharges with a DVT primary diagnosis (HCUP<sup>3</sup> unpublished NHLBI tabulation).
- According to an analysis of ≈1 635 300 patients with PE in the ED, even after being classified as low-risk PE according to the Pulmonary Embolism Severity Index, almost two-thirds of these patients were not discharged from the ED (discharge rate of low-risk PE, 33.1% [95% CI, 21.6%–47%]).<sup>4</sup>
- A study that examined 133 414 US patients with a DVT diagnosis 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>101</sup>

### **Costs**

- In 2020, the aggregate charges in hospitalized patients amounted to ≈\$15.5 billion compared with ≈\$10 billion in 2018. Medicare and Medicaid covered two-thirds of the total charge, whereas private insurance accounted for more than one-quarter of all payments.<sup>3</sup>

- The incidence of VTE causes a 2-fold increase in annual costs in rheumatoid arthritis (adjusted annual total health care cost ratio for DVT and PE in the disease-modifying antirheumatic drug-naïve population, 2.04 [95% CI, 1.77–2.35] and 2.58 [95% CI, 2.06–3.24], respectively).<sup>102</sup> In those with inflammatory bowel disease, VTE increases 1-year costs 3-fold (cost after VTE, \$67 054 versus \$22 424;  $P<0.01$ ).<sup>103</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>104</sup>

### Global Burden

- The Computerized Registry of Patients With Venous Thromboembolism registry, a database from 26 countries (including 6 US centers) that includes ~121 000 patients, found a 30-day mortality of 1.95% for lower-limb DVT, 2.7% for upper-limb DVT, and 5.05% for PE.<sup>105</sup> The risk of death was lower for distal DVT compared with proximal DVT at the 1-year follow-up (HR, 0.72 [95% CI, 0.64–0.82]).<sup>103</sup>
- In hospitalized patients with COVID-19, the incidence of DVT was higher in Asia (unadjusted pooled incidence, 40.8% [interquartile range, 24.6%–54.5%]) compared with the Middle East (15.6% [interquartile range, 8.6%–16.4%]), North America (12.8% [interquartile range, 3.8%–24.2%]), and Europe (8.0% [interquartile range, 3.9%–14.9%]).<sup>106</sup>
  - However, the incidence of PE was higher in the Middle East (unadjusted pooled incidence, 16.2% [interquartile range, 8.1%–24.4%]) and Europe (14.6% [interquartile range, 6.4%–26.3%]) than in North America (5.0% [interquartile range, 3.0%–11.8%]) and Asia (3.2% [interquartile range, 1.9%–3.5%]).
  - In a Swedish cohort comprising >950 000 patients with COVID-19, those who were hospitalized retained a higher risk of both PE (HR, 2.01 [95% CI, 1.51–2.68]) and DVT (HR, 1.46 [95% CI, 1.05–2.01]) even after 180 days compared with those without COVID-19.<sup>107</sup>

### Chronic Venous Insufficiency

#### ICD-10 I87.2.

2022, United States: Underlying cause mortality—62. Any-mention mortality—977.

2021, United States: Hospital discharges—5805 (principal diagnosis), 234 655 (all-listed diagnoses).

#### Prevalence

- No updated data are currently available on the prevalence of CVI in the United States. Practically all studies rely on a US prevalence of CVI of 28%

based on studies from >20 years ago.<sup>108</sup> Meta-analyses with global data continue to use this figure to define the prevalence in North America.

- 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>109</sup>

#### Incidence

- Data from the Mass General Brigham health care system of >156 000 females after pregnancy showed an incidence of 3% in 10 years of follow-up (incidence of varicose veins, 3.0% [95% CI, 2.9%–3.2%]) and 7% in 20 years of follow-up (incidence of varicose veins, 7.3% [95% CI, 7.0%–7.6%]).<sup>110</sup>

#### Risk Factors

- This study identified risk factors for varicose veins, including age (HR: 35–40 years of age, 1.61 [95% CI, 1.48–1.77]; 40–50 years of age, 1.66 [95% CI, 1.51–1.84]; and >50 years of age, 1.91 [95% CI, 1.63–2.23] compared with individuals <35 years of age), number of births (HR: 1 delivery, 1.78 [95% CI, 1.55–1.99]; ≥6 deliveries, 4.83 [95% CI, 2.15–10.90]), excessive weight gain during pregnancy (HR, 1.44 [95% CI, 1.09–1.91]), and postterm pregnancy (HR, 1.12 [95% CI, 1.02–1.21]).<sup>110</sup>
- The ARIC researchers found an association between low physical function (evaluated by a score that analyzes components such as chair stands, standing balance, and gait speed) and incidence of varicose veins (HR, 1.77 [95% CI, 1.04–3.00] between those with scores ≤6 and >6).<sup>111</sup>
- PTS, a subset of CVI, has specific risk factors that can be identified at the time of or after DVT:
  - Using data from the GARFIELD-VTE registry, the predictors for severe PTS (assessed by the Villalta score) were chronic HF (OR, 3.3 [95% CI, 1.46–7.49]), prior VTE episode (OR, 1.82 [95% CI, 1.32–2.51]), and chronic immobilization (OR, 1.78 [95% CI, 1.03–3.08]).<sup>112</sup>

#### Social Determinants of Health/Health Equity

- A prospective study involving 449 US patients observed a linear association between CVI severity, measured by clinical-etiology-anatomy-pathophysiology classes and lower SES ( $P<0.003$ ).<sup>113</sup> Patients classified with the 2 most severe categories based on clinical-etiology-anatomy-pathophysiology classification system for chronic venous disorders had a median annual household income of <\$40 000.

#### 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>114</sup>

- Although a number of genes have been implicated,<sup>115</sup> to date, no causal association has been proven.<sup>116</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>117</sup>

### **Prevention**

- In a meta-analysis of ≈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>118</sup>

### **Awareness, Treatment, and Control**

- In Medicare, the endovascular treatment of CVI increased by 66% from 2010 to 2018 (6466 to 10 860 per 1 000 000 beneficiaries), driven by an increase in traditional sclerotherapy (2883 to 3969 per 1 000 000 beneficiaries; 38% increase) and radiofrequency ablation (1385 to 3270 per 1 000 000 beneficiaries; 136% increase).<sup>119</sup> On the other hand, the study observed a 66% decrease in surgical approach (181 to 61 per 1 000 000 beneficiaries).
- Several treatment options are available for patients with severe varicose veins, but evidence for the best approach is scarce. A 2021 Cochrane metaanalysis 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]; 3 studies) and surgery (pooled OR, 2.31 [95% CI, 1.27–4.23]; 6 studies), in addition to the benefit of the surgery over ultrasound-guided foam sclerotherapy (pooled OR, 0.09 [95% CI, 0.03–0.30]; 3 studies). None of the procedures showed a solid benefit over the others when the recurrence rate was analyzed.<sup>120</sup> The success of these procedures is critically compromised according to the progressive increase in weight, especially in those with a BMI ≥35 kg/m<sup>2</sup>.<sup>121</sup> Compiled data from the Vascular Quality Initiative Varicose Vein Registry and the American Vein & Lymphatic Society PRO Venous Registry showed that patients undergoing these procedures in accredited centers experience greater benefit than those in nonaccredited centers. There was an absolute reduction in Venous Clinical Severity Score (5.61±3.6 versus 4.98±4.0;  $P<0.001$ ), in addition to a lower incidence of complications (absolute incidence, 0.1% versus 0.4%;  $P<0.001$ ).<sup>122</sup>
- Among those treated with endovenous ablation, data for ≈10 000 patients from the Vascular Quality Initiative's Varicose Vein Registry found sex-related differences in outcomes: Females have fewer local

complications (incidence rate compared with males, 6.1% versus 8.6%;  $P=0.001$ ), site infections (incidence rate, 0.4% versus 0.7%;  $P=0.001$ ), and procedure-induced venous thromboses (incidence rate, 1.1% versus 2.2%;  $P=0.002$ ).<sup>123</sup>

- Oral phlebotonics (eg, benzopyrones, saponins, synthetic products, and other plant extracts) 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>124</sup>
- Balneotherapy compared with no treatment demonstrated marginal improvement in symptoms (pooled mean difference of the Venous Clinical Severity Score, −1.75 [95% CI, −3.02 to −0.49]; 3 studies) and pain (mean difference of Visual Analog Scale, −1.12 [95% CI, −1.35 to −0.88]; 2 studies) but with no evidence of benefit in edema, incidence of leg ulcers, thromboembolic events, and erysipelas ( $P=\text{not significant}$ ).<sup>125</sup>

### **Complications**

- The presence of varicose veins was associated a higher risk of VTE in patients undergoing lower-limb arthroplasty (OR, 2.37 [95% CI, 1.54–3.63]).<sup>126</sup>
- Leg wound is one of the most critical complications of CVI:
  - A study of the American Vein & Lymphatic Society PRO Venous Registry involving ≈270 000 patients found a leg wound prevalence of 1.1%.<sup>127</sup>
  - In a retrospective analysis of the Medicare Limited Data Set spanning from 2015 to 2019, among ≈1 225 000 beneficiaries with a claim diagnosis of CVI, 42% developed a confirmed diagnosis of venous leg ulcer during the follow-up period.<sup>128</sup>
  - Compression bandages or stockings are associated with improved wound healing time (pooled HR, 2.17 [95% CI, 1.52–3.10]), a higher rate of fully healed wounds (pooled RR, 1.77 [95% CI, 1.41–2.21]), and reduced 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>129</sup>

### **Costs**

- Annual US spending on venous leg ulcers, a common complication of CVI, is estimated at ≈\$5 billion, most of which is for practitioner and hospital expenses.<sup>130</sup>
- A cost-effectiveness analysis found a dominance of compression therapy with early endovenous ablation over deferred ablation (per-patient cost, \$12 527 versus \$15 208; QALY, 2.011 versus 1.985 in a 3-year scenario).<sup>131</sup>

## Health Care Use: Hospital Discharges/Ambulatory Care Visits

- In 2020, varicose veins and CVI/PTS were the main diagnosis in >66 000 ED visits. Furthermore, ≈11 600 discharges were attributed to CVI/PTS and varicose veins.<sup>3</sup>

## Global Burden

- A nationwide analysis in Korea revealed that ≈220 000 patients were undergoing treatment for CVI in 2020, which represents a 1.5-fold increase compared with 2010.<sup>132</sup> However, the rate of venous leg ulcer decreased from 3.1% in 2010 to 1.7% in 2020.
- In a Spanish registry covering 5.8 million people, CVI incidence was 3.37 per 1000 PY (95% CI, 3.31–3.43), increasing with age: 0.61 per 1000 PY in those <30 years of age and up to 10.95 per 1000 PY in those ≥80 years of age. Females presented ≈2.5-fold more CVI incidence than males (4.77 and 1.95 per 1000 PY, respectively). Venous stasis ulcer incidence was 0.23 per 1000 PY (95% CI, 0.21–0.24).<sup>133</sup>
- A Brazilian study with ≈870 000 public health care surgeries between 2009 and 2018 observed a rate of 4.52 CVI procedures per 10 000 PY at a cost of US \$230 million.<sup>134</sup> The in-hospital mortality rate was 0.0056%.
- An online-based survey of 16 015 individuals from different nations showed a 22% prevalence of CVI, from 14% in French respondents to 37% in Russian respondents, and fewer than half of those with CVI sought medical attention.<sup>135</sup> Among 19 104 workers in Germany in a population-based study, the prevalence of CVI was similar (22.3%).<sup>136</sup>

## Pulmonary Hypertension

### ICD-10 I27.0, I27.2.

2022, United States: Underlying cause mortality—9635. Any-mention mortality—33 796.

2021, United States: Hospital discharges—12 855 (principal diagnosis), 1 131 494 (all-listed diagnoses).

#### Incidence

- A 2023 analysis of a US claims database with ≈61 000 000 patients found a PH diagnosis in 5.2% of ≈855 000 of those who had chronic unexplained dyspnea. Furthermore, 0.1% had a diagnosis of PAH.<sup>137</sup>
- 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>138</sup>
- PH incidence is somewhat higher in females than males,<sup>137,139</sup> and females have at least a 3-fold

higher prevalence of PAH both in hospitalized patients<sup>140</sup> and in the outpatient setting.<sup>141</sup>

- Data from the US kidney transplantation registry observed a PH prevalence of 8.2% before the transplantation.<sup>142</sup> The cumulative incidence after 3 years after transplantation was 10.6% (95% CI, 10.3%–11.0%).
- Among ≈600 000 Medicare patients admitted with acute exacerbated chronic obstructive pulmonary disease, secondary PH diagnosis was present in 10.9%.<sup>143</sup>

#### Lifetime Risk and Cumulative Incidence

- In a US health care claim database study involving ≈170 000 patients after a VTE between 2011 and 2018<sup>139</sup>:
  - The 1-, 2-, and 5-year cumulative incidence of CTEPH was 2.09% (95% CI, 2.01%–2.17%), 3.54% (95% CI, 3.43%–3.65%), and 7.24% (95% CI, 7.01%–7.48%), respectively.
  - In individuals with a PE diagnosis, the 1-, 2-, and 5-year cumulative incidence of CTEPH was 3.82% (95% CI, 3.68%–3.97%), 6.24% (95% CI, 6.03%–6.45%), and 12.12% (95% CI, 11.69%–12.56%), respectively.

#### Secular Trends

- In the United States, data from HCUP NIS show an upward trend in hospitalizations for PH between 2000 and 2014 in both principal and all-listed diagnoses. However, since 2016, a plateau in PH admissions has been observed.<sup>3</sup>

#### Risk Factors

- PH incidence is somewhat higher in females than males (PH incidence rate per 1000 PY after a VTE, 20.1 [95% CI, 19.4–20.8] in females versus 15.9 [95% CI, 15.3–16.6] in males),<sup>137,139</sup> and females have at least 3-fold higher prevalence of PAH in a study of US hospitalized patients.<sup>140</sup>
- Risk factors are implicit in the WHO disease classification of the 5 mechanistic subtypes of PH. The most common risk factors are left-sided HD and lung disease.
  - In patients with WHO group I PH, a 10-year analysis from HCUP data found a high prevalence of CHF (32.0%), hypertension (19.7%), chronic pulmonary disease (17.7%), valvular HD (12.5%), congenital HD (13.5%), and hypothyroidism (12%).<sup>140</sup> A study of the REVEAL registry showed that males with newly diagnosed PAH with a smoking history had worse outcomes (HR for mortality, 1.80 [95% CI, 1.10–3.00]; HR for composite of transplantation or death, 2.23 [95% CI, 1.39–3.56]; and HR for time to first hospitalization, 1.77 [95% CI, 1.18–2.68]).<sup>144</sup>

- The Pulmonary Hypertension Association Registry researchers found that 21.8% of the 541 patients in the registry had methamphetamine use as the underlying cause of PAH in the United States in 2015 to 2020.<sup>145</sup>
- A US health care data analysis found higher risk of CTEPH after a VTE in initial presentation as a PE (HR, 5.04 [95% CI, 4.72–5.38]), HF (HR, 2.17 [95% CI, 2.04–2.31]), chronic pulmonary disease (HR, 2.01 [95% CI, 1.90–2.14]), alcohol abuse (HR, 1.66 [95% CI, 1.29–2.13]), AF (HR, 1.55 [95% CI, 1.43–1.68]), MI (HR, 1.53 [95% CI, 1.40–1.67]), hypertension (HR, 1.52 [95% CI, 1.43–1.61]), CKD (HR, 1.46 [95% CI, 1.36–1.58]), diabetes (HR, 1.42 [95% CI, 1.34–1.50]), liver disease (HR, 1.33 [95% CI, 1.23–1.45]), hematological disorders (HR, 1.32 [95% CI, 1.24–1.41]), older age (HR per decade, 1.26 [95% CI, 1.24–1.28]), female sex (HR, 1.24 [95% CI, 1.17–1.31]), autoimmune disease (HR, 1.23 [95% CI, 1.15–1.31]), and metastatic cancer (HR, 1.17 [95% CI, 1.06–1.30]).<sup>139</sup>
- In patients undergoing kidney transplantation, newly diagnosed PH was associated with older age (HR: >60 years of age, 2.88 [95% CI, 2.15–3.86]; 45–59 years of age, 2.18 [95% CI, 1.63–2.91]; and 31–44 years of age, 1.55 [95% CI, 1.15–2.10], all compared with individuals between 18 and 30 years of age), valvular HD (HR, 1.51 [95% CI, 1.37–1.67]), chronic obstructive pulmonary disease (HR, 1.44 [95% CI, 1.28–1.61]), smoking history (HR, 1.32 [95% CI, 1.03–1.70]), female sex (HR, 1.29 [95% CI, 1.15–2.10]), OSA (HR, 1.28 [95% CI, 1.11–1.49]), >5 years of hemodialysis (HR, 1.26 [95% CI, 1.07–1.47]), diabetes (HR, 1.23 [95% CI, 1.07–1.42]), obesity (HR, 1.18 [95% CI, 1.05–1.33]), and CAD (HR, 1.15 [95% CI, 1.02–1.30]).<sup>142</sup>

### Social Determinants of Health/Health Equity

- An analysis of patients in the Pulmonary Hypertension Association Registry showed an important impact of annual income, education level, and health insurance on death/lung transplantation in the Hispanic population with PAH. After adjustment for these social factors, the difference in transplantation-free survival between the Hispanic and NH population was attenuated, and there was no significant difference (HR for transplantation-free survival, 0.70 [95% CI, 0.35–1.62] after social determinants of health adjustment;  $P=0.474$ ).<sup>146</sup>
- Among the patients with WHO group I PH:
  - Those with methamphetamine-related PAH had a clearly lower SES compared with the other patients in this group (prevalence of patients with college education, 17% versus 34%;

prevalence of patients with a taxable income per year <\$50 000, 84% versus 50%, respectively;  $P<0.001$ ).<sup>145</sup>

- Veterans in the highest annual income strata (>\$100 000) had shorter time to diagnosis than those with household income <\$20 000 (HR, 0.74 [95% CI, 0.60–0.91]).<sup>147</sup>
- The risk of CTEPH in the United States is lower among those with a high-deductible health plan compared with those with other health insurance plans (HR, 0.83 [95% CI, 0.72–0.96]).<sup>139,145,147</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>148</sup>
- A Japanese family study identified *BMPR2* (bone morphogenetic protein receptor type 2) as a risk factor for PAH.<sup>149</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>150</sup>
- GWASs in >11 000 individuals have identified risk loci for PAH, including *SOX17* and *HLA-DPA1/DPB1*.<sup>151</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>152</sup>

### Awareness, Treatment, and Control

- There is a meaningful delay between the beginning of the symptoms and PAH diagnosis (median interval time, 2.26 years [interquartile range, 0.73–4.22 years]), requiring a median of 3 (interquartile range, 2–4) echocardiograms, 6 (interquartile range, 3–12) specialist visits, and 2 (interquartile range, 1–4) hospitalizations until a definitive diagnosis is made.<sup>137</sup> This late diagnosis affects several outcomes, including length of hospital stay (IRR for >24 months' delay, 1.71 [95% CI, 1.29–2.12] compared to ≤12 months' delay), 30-day readmission (IRR, 2.22 [95% CI, 1.16–3.73]), ICU length of stay (IRR, 2.15 [95% CI, 1.45–2.88]), and outpatient visits (IRR, 1.26 [95% CI, 1.08–1.41]).<sup>153</sup>
- As nonpharmacological therapy, exercise-based rehabilitation programs have shown improvements in cardiovascular fitness, including 6-minute walk distance (+47.7 m [95% CI, 33.9–61.7]) and  $\text{Vo}_2\text{peak}$  (+2.96  $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  [95% CI, 2.49–3.43]).<sup>154</sup>
- In the WHO group 1 PH:
  - Data from the TRIO comprehensive and integrated patient data repository showed that 40%

- were on monotherapy, 43% were on dual therapy, and 17% were on triple therapy.<sup>141</sup> Among all patients in the registry, 61% were using phosphodiesterase 5 inhibitors, 55% were receiving some endothelin receptor antagonist, and 51% were prescribed prostacyclin.
- Phosphodiesterase 5 inhibitors showed a clear benefit in 6-minute walk distance (+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>155</sup> Endothelin receptor antagonists improve 6-minute walk distance (+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>156</sup>
  - In symptomatic patients with intermediate risk of 1-year mortality, the REPLACE investigators found benefit of switching from other phosphodiesterase 5 inhibitors to riociguat for improvement of 2- or 6-minute walk distance, 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>157</sup>
  - Intravenous prostacyclin exhibited improvements in WHO functional class (OR, 14.96 [95% CI, 4.76–47.04]), 6-minute walk distance (+91 m [95% CI, 59–124]), and mortality (OR, 0.29 [95% CI, 0.12–0.69]).<sup>158</sup> However, serious adverse events may occur in 12% to 25% of cases, including sepsis, hemorrhage, pneumothorax, and PE.
  - Anticoagulation therapy showed no benefit in mortality regardless of the underlying cause of PH ( $P=0.11$ ), in addition to worsening of quality of life (adjusted mean difference of emPHasis-10 score, 1.74 [95% CI, 0.40–3.09]), more ED visits (aIRR, 1.41 [95% CI, 1.28–1.56]), hospitalization (aIRR, 1.33 [95% CI, 1.14–1.55]), and days in the hospital (aIRR, 1.30 [95% CI, 1.23–1.37]).<sup>159</sup>
  - 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 PH ( $P<0.001$  versus operable but not operated and inoperable).<sup>160</sup>
  - A comprehensive study of data from 132 552 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>161</sup>

## Mortality

- An analysis of CDC WONDER data revealed a progressive increase in PH-related mortality from 2003 to 2020.<sup>153</sup> The age-standardized mortality rate per 1 000 000 PY rose from 17.81 in 2003 to 23.89 in 2020 (annual percentage change, 2.3% [95% CI, 2.0%–2.6%]), driven by a pronounced increase in deaths in PH groups 2 through 5 (annual percentage change, 2.7% [95% CI, 2.5%–2.9%]) despite a decrease in mortality in the PH group 1 (annual percentage change, −5.8% [95% CI, −8.7% to −2.7%]).
- Data from HCUP show that the in-hospital PH mortality rate rose from 3.9% in 2016 to 5.9% in 2020.<sup>3</sup>
- 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>162</sup>
- The Pulmonary Hypertension Association Registry, a US multicenter cohort of ≈1000 patients with group I PH, observed a 1-, 2-, and 3-year composite of death/lung transplantation of 8.6% (95% CI, 6.8%–10.7%), 16.9% (95% CI, 14.1%–20.2%), and 23.1% (95% CI, 19.4%–27.7%), respectively.<sup>163</sup> In high-risk strata, the 3-year mortality rate was from 28% to 56% according to risk tool used.
- 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 ≥80 years of age.<sup>138</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>143</sup>
- Data from the US CTEPH Registry showed an overall 1-, 2- and 3- year survival rate of 93%, 91%, and 87%, respectively.<sup>164</sup> When stratified by pulmonary thromboendarterectomy status, the 1-, 2- and 3-year survival was 95%, 93%, and 90%, respectively, for operated patients; 91%, 85%, and 74% for those in whom surgery was feasible but who decided not to have the procedure; and 88%, 84%, and 80% in inoperable patients ( $P=0.001$ ).
- Mortality rates also vary according to WHO functional class. A meta-analysis including 10 studies found a 1-, 2-, and 3-year survival rate 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>165</sup>

- In an analysis using NIS data between 2005 and 2014, which involved > 5 million PH hospitalizations, patients presenting with AF (46.6% of total sample) had a higher risk of death (HR, 1.35 [95% CI, 1.15–1.55]).<sup>166</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 6-minute walk distance  $\geq 440$  m had a better prognosis (HR, 0.225 [95% CI, 0.098–0.519]).<sup>167</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>168</sup>
- In noncardiac surgery setting, in a 2023 meta-analysis with >18 million patients (predominantly US individuals), the presence of PH was associated with higher risk of mortality compared with no PH (pooled aOR, 2.09 [95% CI, 1.51–2.90]; 8 studies).<sup>169</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>170</sup> In addition, 58% of births were PTBs.
- Despite the mortality rate noted previously, only 5.8% of patients enrolled in the Pulmonary Hypertension Association Registry were referred for palliative care. Among them, 43% were referred in the last appointment before death.<sup>171</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 individuals in metropolitan counties.<sup>172</sup>

### Health Care Use: Hospital Discharges/Ambulatory Care Visits

- In 2021, there were 12855 hospital discharges with PH as the principal diagnosis (HCUP,<sup>3</sup> unpublished NHLBI tabulation).
- In 2019, PH was the principal diagnosis for 278000 physician office visits (NAMCS,<sup>100</sup> unpublished NHLBI tabulation).

### Costs

- Health care costs associated with PH are substantial. In inpatient scenarios, the mean charge increased progressively from \$82000 in 2016 to \$125000 in 2020.<sup>3</sup>
  - In patients with acute exacerbated chronic obstructive pulmonary disease, an additional diagnosis of WHO group 3 PH results in an increase in hospitalization costs of \$2785 (mean difference [95% CI, \$2602–\$2967]).<sup>143</sup>

- Delayed PH diagnosis of >24 months results in higher total costs (mean cost overrun, \$5366 [95% CI, \$2107–\$8524]), whether ICU costs (mean cost overrun, \$4266 [95% CI, \$1593–\$6477]), medical expenses (mean cost overrun, \$4237 [95% CI, \$907–\$7031]), or hospitalization costs (mean cost overrun, \$4048 [95% CI, \$1401–\$6342]), compared with those with  $\leq 12$  months' delay in the diagnosis.<sup>173</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>174</sup>
- Among patients diagnosed with PH referred to the Mayo Clinic specialty center, half had their previously prescribed medications discontinued (eg, sildenafil, tadalafil, riociguat, ambrisentan, treprostinil, macitentan, and selexipag), resulting in a monthly savings of  $\approx \$7000$  per patient with an inappropriate diagnosis.<sup>175</sup>

### Global Burden

(See Table 24-1 and Chart 24-3 and Chart 24-4)

- Based on 204 countries and territories in 2021<sup>176</sup>:
  - The number of prevalent cases of PAH was 0.19 (95% UI, 0.16–0.24) million, with an age-standardized rate of 2.28 (95% UI, 1.85–2.80) per 100 000. There were 0.02 (95% UI, 0.02–0.03) million total deaths estimated for PAH, with an age-standardized rate of 0.27 (95% UI, 0.23–0.32) per 100 000 (Table 24-1).
  - Among regions, PAH prevalence was highest for Western Europe and central Latin America (Chart 24-3).
  - Mortality estimated for PAH among regions was highest for North Africa and the Middle East and Central and east Asia and lowest for central Latin America and Eastern Europe (Chart 24-4).
- A systematic review from the GBD Study 2020 showed a wide range of prevalence of PAH (WHO group 1 PH) worldwide, ranging from 0.7 to 15 per 100 000 inhabitants in France and Australia, respectively.<sup>177</sup> When stratified by diagnosis through right-sided heart catheterization, the mean PAH prevalence across 37 low-, middle-, and high-income countries was 3.7 per 100 000 people.
- A meta-analysis with 5834 patients observed an overall CTEPH incidence after acute PE of 2.82% (95% CI, 2.11%–3.53%).<sup>178</sup> In this scenario, Asian individuals showed a higher risk of CTEPH compared with European individuals (pooled incidence, 5.08% [95% CI, 2.67%–7.49%] versus 1.96% [95% CI, 1.29%–2.63%], respectively).

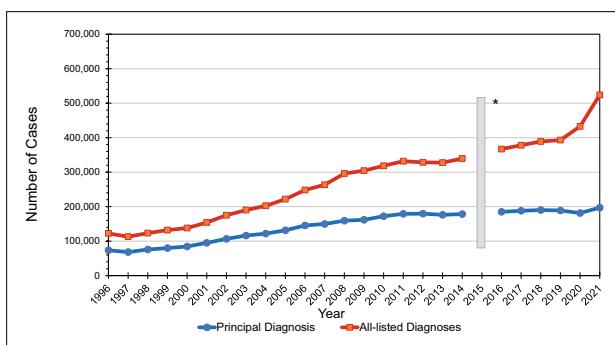
**Table 24-1. Global Mortality and Prevalence of PAH, by Sex, 2021**

	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), 2021	0.02 (0.02 to 0.03)	0.19 (0.16 to 0.24)	0.01 (0.01 to 0.01)	0.07 (0.06 to 0.09)	0.01 (0.01 to 0.02)	0.12 (0.10 to 0.15)
Percent change (%) in total number, 1990–2021	48.36 (20.97 to 78.48)	81.46 (73.47 to 89.06)	30.74 (7.31 to 64.57)	85.50 (76.33 to 94.03)	65.53 (27.24 to 135.23)	79.06 (71.54 to 86.05)
Percent change (%) in total number, 2010–2021	4.34 (−5.12 to 16.68)	21.32 (18.30 to 24.07)	−1.02 (−14.42 to 13.13)	21.76 (18.81 to 24.66)	8.88 (−3.28 to 27.03)	21.04 (18.05 to 23.87)
Rate per 100 000, age standardized, 2021	0.27 (0.23 to 0.32)	2.28 (1.85 to 2.80)	0.27 (0.21 to 0.33)	1.78 (1.44 to 2.17)	0.28 (0.22 to 0.34)	2.75 (2.24 to 3.39)
Percent change (%) in rate, age standardized, 1990–2021	−22.08 (−34.52 to −7.57)	−0.92 (−1.64 to −0.30)	−27.55 (−42.72 to −6.33)	1.86 (1.03 to 2.67)	−17.12 (−34.21 to 11.89)	−2.20 (−3.03 to −1.44)
Percent change (%) in rate, age standardized, 2010–2021	−20.29 (−27.32 to −11.71)	−1.63 (−2.11 to −1.20)	−23.36 (−33.69 to −12.60)	−0.98 (−1.63 to −0.35)	−17.64 (−26.93 to −4.78)	−1.92 (−2.52 to −1.29)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; PAH, pulmonary arterial hypertension; and UI, uncertainty interval.

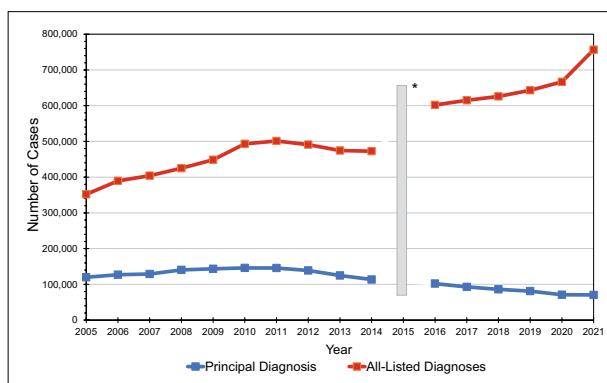
Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>176</sup>

**Chart 24-1. Trends in hospitalized PE, United States, 1996 to 2021.**

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.

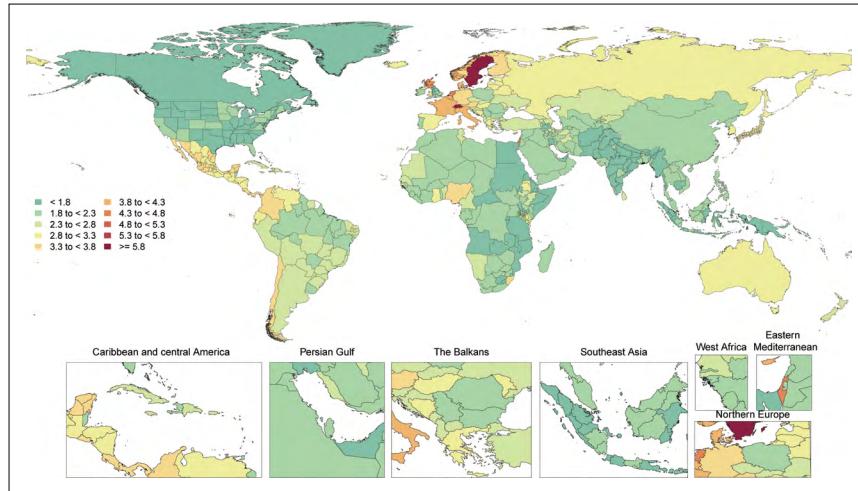
Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>3</sup>

**Chart 24-2. Trends in hospitalized DVT, United States, 2005 to 2021.**

DVT indicates deep vein thrombosis.

\*Data not available for 2015. Readers comparing data across years should note that beginning October 1, 2015, a transition was made from the 9th revision to the 10th revision of the *International Classification of Diseases*. This should be kept in consideration because coding changes could affect some statistics, especially when comparisons are made across these years.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>3</sup>

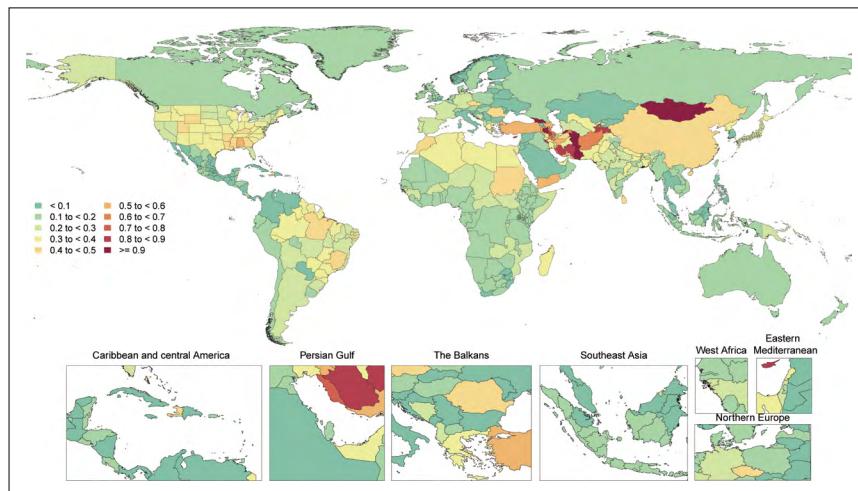


**Chart 24-3. Age-standardized prevalence rates of PAH per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and PAH, pulmonary arterial hypertension.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>176</sup>



**Chart 24-4. Age-standardized mortality rates of PAH per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and PAH, pulmonary arterial hypertension.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>176</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 25-5

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### Peripheral Artery Disease

#### Prevalence

(See Charts 25-1 and 25-2)

- Data from the GBD Study 2019 estimate that the US prevalence of PAD among those  $\geq 40$  years of age was 12 461 375 individuals (95% UI, 11 235 661–13 740 797).<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>2,3</sup>
  - PAD prevalence in males and females varies by age, race, and ethnicity.<sup>1,2</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>2,3</sup>

#### Incidence

- In the GBD Study 2019, the age-standardized incidence rate of PAD in the United States was 193.5 per 100 000 (95% UI, 173.7–215.6 per 100 000).<sup>1</sup>
- Among 77 041 individuals in the Veterans Affairs birth cohort born between 1945 and 1965 with normal baseline ABIs, risk of incident PAD, defined as subsequent ABI  $<0.90$ , surgical or percutaneous revascularization, or nontraumatic amputation, varied by sex and race.<sup>4</sup>
  - Females were at lower risk of incident PAD compared with males (multivariable-adjusted HR, 0.49 [95% CI, 0.41–0.59]).

The 2025 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 2025. 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.

- Black participants had an increased risk of incident PAD compared with White participants (multivariable-adjusted HR, 1.09 [95% CI, 1.02–1.16]). This increased overall risk was attributed to a greater risk of amputation (multivariable-adjusted HR, 1.20 [95% CI, 1.06–1.36]) without an increased risk of revascularization (multivariable-adjusted HR, 1.10 [95% CI, 0.98–1.23]) or subsequent ABI  $<0.90$  (multivariable-adjusted HR, 1.04 [95% CI, 0.95–1.13]).

#### 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 individuals, Hispanic individuals, and Black individuals, respectively, from pooled data from 6 US community-based cohorts.<sup>5</sup>

#### Secular Trends

- Based on the GBD, the US prevalence of PAD among those  $\geq 40$  years of age increased from 99 039 35 (95% UI, 84 900 068–113 319 86) in 1990 to 12 461 375 (95% UI, 11 235 661–13 740 797) in 2019.<sup>1</sup>
  - Despite an increase in the number of individuals with PAD, the age-standardized rate decreased by 27.7 (95% UI, 32.7–21.4) per 100 000.
- From 2011 to 2017, the proportion of hospitalizations for PAD increased from 4.5% to 8.9% ( $P_{trend} < 0.0001$ ) according to NIS data.<sup>6</sup>
- Similarly, from 2011 to 2017, the proportion of hospitalizations for CLTI increased from 0.9% to 1.4% ( $P_{trend} < 0.0001$ ) in the NIS.<sup>6</sup>
- From 2011 to 2021, principal discharge diagnosis for PAD decreased from 135 969 to 74 105 (HCUP, unpublished NHLBI tabulation).
- Between 2011 and 2017, the annual rate of endovascular lower-extremity peripheral artery interventions increased from 464.47 to 509.99 per 100 000 individuals among Medicare beneficiaries.<sup>7</sup>
- Rates of lower-extremity amputation are also increasing.
  - 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>8</sup>
  - Among patients in the Veterans Affairs health care system, rates of lower-extremity amputation increased from 12.89 (95% CI, 12.53–13.25) per 10 000 individuals to 18.12 (95% CI, 17.70–18.54) per 10 000 individuals from 2008 to 2018.<sup>9</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>3,5,10,11</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>3,5</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>12</sup>
- Diabetes is associated with increased risk for PAD with ORs ranging from 1.38 to 1.89.<sup>5,10</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>10</sup>
  - Each 20-mmHg increase in SBP was associated with an OR of 1.27 (95% CI, 1.22–1.32) for PAD.<sup>5</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>13</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>14,15</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>14,15</sup>
  - Further lipid subfraction analyses suggest that markers of atherogenic dyslipidemia, including elevated concentrations of triglyceride-rich lipoproteins such as small LDL particles (HR, 2.17 [95% CI, 1.10–4.27]) and total HDL particles (HR, 0.29 [95% CI, 0.16–0.52]), are independently associated with PAD.<sup>14–17</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>18</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>19</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>20</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>21,22</sup>

## Social Determinants of Health/Health Equity

- Lower SES (defined as living in a zip code with a median household income  $<\$40\,000$ ) was associated with greater risk for amputation (HR, 1.12 [95% CI, 1.06–1.17]).<sup>23</sup>
- Among patients with PAD requiring revascularization or amputation in the Vascular Quality Initiative, neighborhood social disadvantage, measured with the Area Deprivation Index, was associated with later presentation and a lower likelihood of limb salvage.<sup>24</sup>
  - Compared with those in the lowest quintile of the Area Deprivation Index, those in the highest quintile were more likely to present with rest pain compared with claudication (RR, 2.0 [95% CI, 1.8–2.2];  $P<0.001$ ) or tissue loss compared with claudication (RR, 1.4 [95% CI, 1.3–1.6];  $P<0.001$ ).
  - Compared with those in the lowest quintile of the Area Deprivation Index, those in the highest quintile were also less likely to undergo attempts at revascularization (RR, 0.59 [95% CI, 0.51–0.70];  $P<0.001$ ).
- The rate of lower-extremity amputation varies geographically within the United States and may be influenced by patient rurality and race.<sup>25</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>25</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>26</sup>

## Risk Prediction

- Models for predicting the probability of an ABI  $<0.9$  have been developed from NHANES data.<sup>5,27</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>27</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>5,28</sup>
- In a study using electronic medical record data to identify patients at high risk of an abnormal ABI, a machine-learning method had a C statistic of 0.68 in 2 validation cohorts derived from separate academic health care systems.<sup>29</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>30</sup> Chip-based genetic analyses similarly suggest that the heritability of PAD is 55%.<sup>31</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>32</sup>
  - Other common PAD-associated genetic loci include SNPs on chromosome 9 near the *CDKN2B*, *DAB21P*, and *CYBA* genes.<sup>33</sup>
  - A large-scale GWAS in >31 000 cases with PAD and >211 000 controls from the MVP 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>34</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>35</sup> In another study, targeted sequencing of 41 genome regions associated with CAD performed in 1749 cases with PAD and 1855 controls found overlap of several genes between CAD and PAD.<sup>36</sup>
- Mendelian randomization, primarily in populations of European descent, 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 factor VIII, von Willebrand factor, apolipoprotein B, very-low-density lipoprotein, smoking, BP, and gut microbiota taxa affect PAD.<sup>18,37–40</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>31</sup> The authors reported a lead variant near *CCSER1* that showed genome-wide significant evidence of association with PAD only in those with diabetes ( $P=2.5\times10^{-9}$ ;  $P_{\text{interaction}}=5.3\times10^{-7}$ ). This potentially suggests unique pathways of PAD development in those with diabetes.
- 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>31</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 are extrapolated 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.<sup>41</sup>

### **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, only 25% of individuals expressed familiarity with PAD compared with 67% for CAD and 74% for stroke.<sup>42</sup> Income and education levels were positively associated with all knowledge domains.
- Physicians may underappreciate and undertreat PAD.
  - Patients with PAD receive optimal medical therapy less frequently than patients with CAD. Data from the MarketScan and Medicare databases showed that only 34% of patients with PAD were prescribed guideline-recommended statins compared with 52% of patients with CAD.<sup>43</sup>
  - Similarly, only 24.5% of patients with PAD in the MarketScan database achieved a target LDL-C  $<70$  mg/dL.<sup>44</sup>
  - In the BEST-CLI trial, an RCT comparing revascularization strategies for patients undergoing treatment of CLTI, only 25% of participants were receiving optimal medical treatment defined as smoking abstinence, controlled BP, use of an antiplatelet agent, and use of at least 1 lipid-lowering agent.<sup>45</sup>

#### **Treatment**

- Treatment of patients with lower-extremity PAD is summarized in the 2024 AHA/ACC guideline and includes addressing modifiable risk factors such as PA, smoking cessation, dyslipidemia, BP and glycemic control, and revascularization approaches.<sup>41</sup>
- Optimal exercise programs for patients with PAD are summarized in a 2019 AHA scientific statement.<sup>46</sup>
  - In a randomized trial of optimal medical care versus supervised exercise training versus iliac artery stent placement, supervised exercise resulted in superior treadmill walking time at 6 months compared with stenting (mean increase from baseline,  $5.8\pm4.6$  minutes versus  $3.7\pm4.9$  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>47</sup>
- Smoking cessation compared with continued smoking is associated with lower risks of death (14% versus 31%; HR, 0.40 [95% CI, 0.18–0.90]) and amputation (19% versus 40%; HR, 0.43 [95% CI, 0.22–0.86]) over a follow-up of up to 5 years.<sup>48</sup>
  - In a retrospective analysis of patients with PAD and intermittent claudication undergoing revascularization in the Veterans Affairs health care system, smokers were more likely to experience wound complications (absolute risk difference, 4.05% [95% CI, 2.12%–5.99%];  $P < 0.001$ ) or graft failure (absolute risk difference, 1.50% [95% CI, 0.63%–2.37%];  $P = 0.001$ ) compared with nonsmokers.<sup>49</sup>
- Lipid-lowering therapy with a high-intensity statin and, in some cases, a PCSK9 inhibitor is recommended for the treatment of PAD.<sup>41,49,50</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>51</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>52</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 CLTI, limb revascularization, or amputation (HR, 0.69 [95% CI, 0.54–0.80]).<sup>53</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>54</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>54</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>55</sup>
- Glycemic control may be associated with better limb outcomes among patients with PAD according to observational studies<sup>56,57</sup>.
  - In 149 patients with diabetes, 1-year patency after infrapopliteal percutaneous intervention was greater among patients with below-median compared with above-median FPG (HR, 1.8 [95% CI, 1.2–2.8]).<sup>56</sup>
  - Among 197 Japanese individuals with diabetes who underwent percutaneous transluminal angioplasty for CLTI, 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>57</sup>
- Surgical revascularization may be superior to endovascular therapy in select patients with CLTI.<sup>58</sup>
  - In the BEST-CLI trial, 1 cohort of 1434 patients with CLTI and an adequate great saphenous vein for grafting underwent randomization to either initial surgical or endovascular revascularization. Initial surgical revascularization was associated with a reduction in the primary outcome of major adverse limb events or death resulting from any cause compared with initial endovascular revascularization (HR, 0.68 [95% CI, 0.59–0.79];  $P < 0.001$ ).<sup>58</sup>
  - In a second cohort of 396 patients with CLTI but without an adequate great saphenous vein, initial surgical revascularization did not reduce major adverse limb events or death resulting from any cause compared with initial endovascular revascularization (HR, 0.79 [95% CI, 0.58–1.06];  $P = 0.12$ ).<sup>58</sup>
- Revascularization for patients with claudication or CLTI 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>59</sup>
  - Similarly, in a propensity-matched sample from the PORTRAIT registry, those who underwent early invasive management for claudication had a greater improvement in health status at 1 year compared with those treated noninvasively according to the Peripheral Artery Questionnaire ( $P < 0.001$  for all questionnaire domains).<sup>60</sup>

### Mortality (See Table 25-1)

- In 2022, PAD was the underlying cause in 11 596 deaths. The number of any-mention deaths attributable to PAD was 60 000 (Table 25-1; unpublished NHLBI tabulation using NVSS<sup>61</sup> and CDC WONDER).<sup>62</sup>

- In 2022, the overall underlying cause age-adjusted death rate for PAD was 2.7 per 100 000 (unpublished NHLBI tabulation using CDC WONDER).<sup>62</sup> Age-adjusted death rates for PAD by race, ethnicity, and sex are listed in Table 15-1.
- 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 ABI  $\leq 1.1$ , whereas individuals with ABI between 1.11 and 1.40 had the lowest risk.<sup>63</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>63</sup>
- 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>64</sup>
  - In contrast, based on data from 2011 to 2017 in the NIS, in-hospital mortality for patients with CLTI was higher for females compared with males (OR, 1.13 [95% CI, 1.11–1.14]).<sup>6</sup>
  - Among participants with type 2 diabetes or prediabetes plus additional cardiovascular risk factors in 3 randomized trials, ABI  $< 1$  was associated with an increased risk of all-cause mortality compared to those with ABI  $\geq 1.2$  (HR, 1.68 [95% CI, 1.56–1.82];  $P < 0.0001$ ).<sup>65</sup>

### Complications

#### Cardiovascular Disease

- Individuals with PAD are at heightened risk for other types of CVD.
  - In EUCLID, participants with PAD had a cumulative incidence of stroke and TIA of 0.87 per 100 patient-years and 0.27 per 100 patient-years, respectively.<sup>66</sup>
  - Similarly, the incidence of type 1 MI in EUCLID was 2.4 events per 100 patient-years.<sup>67</sup>

#### Tissue (Limb) Loss

- Among 6 493 141 veterans followed up from 2008 to 2018, PAD was independently associated with an increased risk of lower-limb amputation (HR, 3.04 [95% CI, 2.95–3.13]).<sup>9</sup>
- 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>68</sup>
- Among Medicare beneficiaries who underwent peripheral vascular interventions from 2016 to 2018, the age- and sex-adjusted incidence of death or major amputation was greater among

Black individuals compared with White individuals (25.03% [95% CI, 24.45%–25.61%] versus 18.62% [95% CI, 18.39%–18.85%]).<sup>69</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>70</sup>
- Mortality by 1 year after major lower-extremity amputation was estimated at 48.3% among 186 338 Medicare patients  $\geq 65$  years of age with PAD.<sup>71</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>72</sup>
- Among patients with PAD, lower PA levels are associated with faster rates of functional decline measured by 6-minute walk distance performance, 4-m walking velocity, and the Short Performance Physical Battery (all  $P < 0.05$ ).<sup>73</sup>
- In the GBD Study 2019, the age-standardized rate of DALYs attributable to PAD was 40.0 per 100 000 (95% UI, 22.3–69.5) compared with 1629.4 per 100 000 (95% UI, 1539.9–1712.3) for IHD.<sup>74</sup>

#### Health Care Use: Hospital Discharges and Ambulatory Care Visits

- In 2019, primary diagnosis of PAD accounted for 1 377 000 physician office visits (NAMCS,<sup>75</sup> unpublished NHLBI tabulation) and, in 2021, 74 105 primary diagnoses hospital discharges (HCUP,<sup>76</sup> unpublished NHLBI tabulation) and 58 981 ED visits (HCUP,<sup>76</sup> unpublished NHLBI tabulation).

#### Cost

- Among patients with PAD hospitalized in 2014, median hospitalization costs were \$15 755 (95% CI, \$8972–\$27 800) in 2017 US dollars.<sup>77</sup> This corresponded to an annual cost of hospitalization for PAD of approximately \$6.31 billion dollars.
- 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) compared with patients without these events.<sup>78</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 (\$64 041 versus \$45 918) over 1 year.<sup>79</sup>

## Global Burden

### Prevalence

(See Table 25-2 and Charts 25-3)

- Based on 204 countries and territories in the GBD Study 2021<sup>80</sup>:
  - PAD was prevalent among 113.71 (95% UI, 98.50–131.22) million individuals (Table 25-2).
  - PAD prevalence was highest for high-income North America, followed by Western Europe and southern Latin America (Chart 25-3).
- 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>81</sup>
- PAD estimates in sub-Saharan Africa range from 3.1% to 24% in adults ≥50 years of age, with the variability possibly caused by differences in the prevalence of cardiovascular risk factors in the communities surveyed.<sup>82</sup>
- In a cross-sectional analysis of individuals living in rural South Africa, 6.6% of adults 40 to 69 years of age had ABI ≤0.90.<sup>83</sup>

### Mortality

(See Table 25-2 and Chart 25-4)

- In the GBD Study 2021<sup>80</sup>:
  - The age-standardized mortality estimated for PAD was 0.85 (95% UI, 0.75–0.93) per 100 000 individuals (Table 25-2).
  - PAD age-standardized mortality among regions was highest for Eastern and Central Europe and lowest for East and Southeast Asia, Oceania, and Andean Latin America (Chart 25-4).

## 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.
  - Among 5662 patients who underwent chest CT imaging for any reason in 2016, 121 (2.14%) were incidentally found to have an ascending aorta measuring at least 4.0 cm.<sup>84</sup>
- AAA is more common in males than females, and its prevalence increases with age.<sup>85,86</sup>
- AAA is ≈4 times more common in males than females according to data from an ultrasound screening study of 125 722 veterans 50 to 79 years of age conducted between 1992 and 1997.<sup>87,88</sup>

- Approximately 1% of males between 55 and 64 years of age have an AAA ≥4.0 cm, and every decade thereafter, the absolute prevalence increases by 2% to 4%.<sup>89,90</sup> At 65 to 74 years of age, the prevalence of AAA ≥4.0 cm in the Tromsø study was 4.1%.<sup>89</sup>

### Incidence

- 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>91</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>92</sup>

### Secular Trends

- Between 1995 and 2015, the incidence of aortic dissection, intramural hematoma, or penetrating aortic ulcer remained stable at 10.2 (males) and 5.7 (females) per 100 000 PY according to data from the Rochester Epidemiology Project.<sup>93</sup>

### Risk Factors

- TAAs in younger individuals are more likely caused by heritable thoracic aortic disease or congenital conditions, the prototype examples being Marfan syndrome and bicuspid aortic valve disease. 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>94</sup>
- In a mendelian randomization analysis from the UK Biobank and MVP, genetically predicted SBP, DBP, and mean arterial pressure were all associated with increased ascending thoracic aortic diameter (all  $P<0.05$ ).<sup>95</sup>
- In a meta-analysis of 4 563 501 patients, patients with a history of hypertension were more likely to have aortic dissection than those without hypertension (RR, 3.07 [95% CI, 2.15–4.38]).<sup>96</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>97</sup>
- Risk factors for AAA were assessed in a retrospective analysis of 3.1 million patients between

2003 and 2008.<sup>98</sup> Male sex (OR, 5.71 [95% CI, 5.57–5.85]), family history (OR, 3.80 [95% CI, 3.66–3.95]), and hypertension (OR, 1.25 [95% CI, 1.21–1.28]) 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  $P < 0.0001$ ).

- Mendelian randomization suggests that genetically predicted greater height and higher pulse pressure are associated with larger infrarenal aortic diameter (all  $P < 0.05$ ).<sup>99</sup>
- 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>100</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>19</sup>
- In the Veterans Aging Cohort Study, people with HIV and time-updated CD4+ T-cell counts  $< 200$  cells/mm<sup>3</sup> (HR, 1.29 [95% CI, 1.02–1.65]) or HIV viral load  $\geq 500$  copies/mL (HR, 1.29 [95% CI, 1.09–1.52]) were at greater risk of incident AAA than those without HIV.<sup>101</sup>
- Diabetes may be associated with lower risk of aortic aneurysmal disease.<sup>94,102,103</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>102</sup>
- Evidence suggests that 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 those prescribed other antibiotics (HR, 1.31 [95% CI, 1.25–1.37]).<sup>104</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>105</sup>
  - In a case-crossover analysis of patients in the United Kingdom, fluoroquinolone use was associated with an increased odds of aortic aneurysm or dissection hospitalization compared with nonuse (OR, 1.58 [95% CI, 1.37–1.83]).<sup>106</sup> However, there was no increased risk for fluoroquinolone use compared with use of other antibiotic classes.

### Social Determinants of Health/Health Equity

- 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 Black individuals (OR, 1.71 [95% CI, 1.37–2.13]), Hispanic individuals (OR, 1.70 [95% CI, 1.22–2.37]), and Native American individuals (OR, 2.37 [95% CI, 1.44–3.91]) compared with White individuals. Those with a mean annual income below \$25 000 were also more likely to undergo endovascular rather than open surgical repair than those with a mean annual income exceeding \$35 000 (OR, 1.24 [95% CI, 1.03–1.62]).<sup>107</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>108</sup>

### Subclinical/Unrecognized Disease

- 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>109,110</sup> TAAs with familial and genetic causes may display faster rates of expansion ( $P < 0.0001$ ).<sup>111</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.<sup>112</sup> In a nationwide Swedish program targeting males  $\geq 65$  years of age, the initiation of an AAA screening program found a number needed to screen of 667 to prevent a single premature death.<sup>113</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>114</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>114</sup>

### 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%.<sup>115</sup>
- In a study of UK Biobank participants, a PRS for aortic diameter was associated with an increased risk of TAA (HR, 1.42 per SD [95% CI, 1.34–1.50]).<sup>116</sup>

- There are syndromic thoracic aortic diseases caused by rare genetic variants, including Marfan syndrome (caused primarily by variants in the *FBN1* gene), Loeys-Dietz syndrome (TGF- $\beta$  pathway-related genes, including *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>117,118</sup>
- AAA is heritable, and twin studies suggest that the degree of heritability ranges from 70% to 77%.<sup>119,120</sup>
- A GWAS of individuals in the MVP identified 24 common genetic variants associated with AAA, including a locus on chromosome 9p21, as well as SNPs in *LPA*, *IL6R*, *LDLR*, and *APOE* (all  $P < 5 \times 10^{-8}$ ).<sup>121</sup>
- A GWAS of TAAs/dissections was also conducted in the MVP (n=8626 cases).<sup>122</sup> The authors identified 21 loci, 17 of which were novel and highlighted the role of extracellular matrix integrity. Unlike other CVDs, lipoprotein loci did not appear to be associated with TAAs/dissections. These results suggested that genetic pathways for TAA/dissections may be distinct from those for other CVDs, including AAAs.
- Genetic variants associated with intracranial aneurysms have been found in several genes, including *RBBP8*, *STRAD13/KL*, *SOX17*, and *CDKN2A/B* (all  $P < 5 \times 10^{-8}$ ).<sup>123</sup> Rare variants in *ANGPTL6* are associated with familial cases of intracranial aneurysms ( $P < 0.05$ ).<sup>124</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>121</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>125</sup> and functional analyses have demonstrated that this locus regulates endothelin-1 expression.<sup>126</sup>
  - In the UK Biobank, a PRS for AAA was also associated with an increased risk of fibromuscular dysplasia (OR, 1.03 [95% CI, 1.01–1.05];  $P = 2.6 \times 10^{-3}$ ).<sup>127</sup>
  - A variant at chromosome 1q21.2 that affects *ADAMTSL4* expression and variants in *PHACTR1*, *LRP1*, and *LINC00310* are associated

with spontaneous coronary artery dissection (all  $P < 5 \times 10^{-8}$ ).<sup>128</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>129</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.<sup>130</sup> 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 Services data.<sup>131</sup>
- Treatment of TAA and AAA is aimed at slowing progression and preventing complications, namely rupture and dissection.
  - Thresholds for surgical repair of TAAs are based on size, rate of growth, presence of syndromic or nonsyndromic heritable thoracic aortic disease, specific genetic variants, and concomitant valve disease and are outlined in the “2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease.”<sup>132</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>133</sup>
  - Racial disparities in perioperative 30-day mortality after TAA repair are 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>133</sup>
  - Elective AAA repair is typically not recommended among asymptomatic individuals until the diameter exceeds 5.5 cm or if the 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>132,134</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>135</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>136</sup>
- After elective AAA repair, survival after endovascular versus open surgical repair varies on the basis of timing since the 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>137</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>138</sup>
  - Similarly, in the OVER Veterans Affairs Cooperative Study 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>139</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/y versus 1.4% in those with 49–198 cases/y;  $P<0.01$ ). 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>140</sup>
  - Of all AAA repairs, endovascular AAA repair increased from 5% to 74% between 2000 and 2010 despite a 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>141</sup>

### Mortality

2022, United States: Underlying cause mortality—9999. Any-mention mortality—19 422.

- TAA

- Between 1999 and 2016, deaths attributable to ruptured TAA declined significantly from 5.5 to 1.8 per million according to US NVSS data.<sup>142</sup>
- From 1996 to 2018, the mortality rate in IRAD for type A thoracic aortic dissection over the first 48 hours was 5.8%. This rose to 23.7% for those treated medically. The mortality rate for those planned for surgical repair was 4.4%.<sup>143</sup>
- Type B thoracic aortic dissections were more likely to be treated with endovascular therapies, but mortality rates remained similar between 1996 and 2013.<sup>144</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>145</sup>
- Among Medicare beneficiaries hospitalized with acute type B aortic dissections from 2011 to 2018, initial thoracic endovascular aortic repair within 30 days was not associated with a decrease in mortality (HR, 0.95 [95% CI, 0.85–1.06]) or aorta-related hospitalizations (HR, 1.12 [95% CI, 0.99–1.27]) compared with initial medical therapy.<sup>146</sup>
- AAA
  - From 1999 to 2016, the death rate attributable to ruptured AAA declined from 26.3 to 7.9 per million according to US NVSS data.<sup>142</sup>
  - 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>147</sup>
  - A meta-analysis of 619 068 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>148</sup>
  - Similarly, in the Vascular Quality Initiative, females undergoing repair of ruptured AAAs had a greater likelihood of in-hospital mortality (OR, 1.36 [95%

CI, 1.12–1.66];  $P=0.002$ ) and mortality at 8 years (HR, 1.25 [95% CI, 1.04–1.50];  $P=0.02$ ) compared with males.<sup>149</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>150</sup>

### Complications

Dissection and rupture are the predominant complications of aortic aneurysmal disease, and their risks are proportional to aortic diameter and expansion rate, as well as familial or genetic causes.

TAA:

- At a diameter of 4.0 to 4.9 and  $>6.0$  cm, the annual rate of TAA dissection or rupture is estimated at  $\approx 2\%$  and  $\approx 7\%$ , respectively.<sup>151</sup>
- Most TAA dissections in absolute numbers, however, occur at relatively smaller diameters. In IRAD, 59.1% and 40.9% of dissections occurred at diameters  $<5.5$  and  $<5.0$  cm, respectively.<sup>152</sup>
- Annual age- and sex-adjusted incidences per 100 000 people were estimated at 3.5 (95% CI, 2.2–4.9) for TAA rupture and 3.5 (95% CI, 2.4–4.6) for acute aortic dissection according to data from Olmsted County, Minnesota.<sup>153</sup>

AAA:

- The risk of AAA rupture is also proportionately related to diameter.
  - Rates of rupture of small AAAs (3.0–5.4 cm in diameter) range from 0.71 to 11.03 per 1000 PY 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>114</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>154</sup>

### Health Care Use: Hospital Discharges and Ambulatory Care Visits

- In 2021, hospital discharges with aortic aneurysm as principal diagnoses totaled 65 260 (HCUP<sup>76</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>155</sup>

### Global Burden

#### (See Table 25-3 and Chart 25-5)

- Based on a meta-analysis of data from 19 countries, the 2019 global prevalence of AAA measuring at least 3.0 cm in people 30 to 79 years of age was 0.92% (95% CI, 0.65%–1.30%), which corresponded to 35.12 (95% CI, 24.94–49.80) million individuals.<sup>156</sup>
- Global mortality attributable to aortic aneurysm by sex according to the GBD Study 2021 of 204 countries and territories is shown in Table 25-3.
  - There were 0.15 (95% UI, 0.14–0.17) million total deaths attributable to aortic aneurysm, an increase of 74.22% (95% UI, 62.98%–83.64%) from 1990.
  - The highest age-standardized mortality rates estimated for aortic aneurysm among regions were for high-income Asia Pacific, tropical Latin America, and Eastern Europe. Rates were lowest for East Asia (Chart 25-5).
- In New Zealand, the age-standardized rate of AAA-related hospitalizations decreased from 43.7 per 100 000 in 2001 to 15.4 per 100 000 in 2018.<sup>157</sup>
- Geographic variation in the management of 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>158</sup>

### Atherosclerotic Renal Artery Stenosis

#### ICD-9 440.1; ICD-10 I70.1

##### Prevalence

- The prevalence of renal artery disease by renal duplex ultrasonography was 6.8% in the North Carolina subcohort of the CHS between 1997 and 1998.<sup>159</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 16.6% among patients undergoing coronary angiography on the basis of data ascertained from 2007 to 2008 in Italy (n=1298) and from 2014 to 2015 in Romania (n=181), respectively.<sup>160,161</sup>
- In a French study of patients undergoing peripheral angiography for PAD, the prevalence of renal artery stenosis was 14%.<sup>162</sup>

##### Incidence

- The incidence rate of renal artery stenosis was estimated at 3.09 per 1000 patient-years from Medicare claims data between 1992 and 2004.<sup>163</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>163</sup>

**Risk Factors**

- In a multiple logistic regression analysis of 1298 patients undergoing both coronary and renal artery angiography, PAD (OR, 2.98 [95% CI, 1.76–5.03]), dyslipidemia (OR, 2.82 [95% CI, 1.15–6.88]), eGFR <67 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> (OR, 2.63 [95% CI, 1.54–4.47]), age >66 years (OR, 2.20 [95% CI, 1.26–3.85]), and multivessel CAD (OR, 1.82 [95% CI, 1.06–3.13]) were all associated with ≥50% renal artery stenosis (all  $P < 0.05$ ).<sup>164</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>165</sup>

**Awareness, Treatment, and Control**

- Optimal medical therapy is the first-line treatment in the management of renal artery stenosis.<sup>166</sup> In CORAL, a randomized clinical trial of 943 patients with renal artery stenosis and either hypertension requiring ≥2 medications or CKD recruited between 2005 and 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>167</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>168</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>169</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>163</sup>

**Table 25-1. PAD in the United States**

Population group	Mortality, 2022, all ages*	Age-adjusted mortality rates per 100 000 (95% CI)* 2022
Both sexes	11 596	2.7 (2.7–2.8)
Males	5708 (49.2%)†	3.1 (3.1–3.2)
Females	5888 (50.8%)†	2.4 (2.3–2.4)
NH White males	4347	3.2 (3.1–3.2)
NH White females	4479	2.4 (2.3–2.5)
NH Black males	770	4.8 (4.5–5.2)
NH Black females	805	3.4 (3.1–3.6)
Hispanic males	401	2.3 (2.1–2.6)
Hispanic females	398	1.7 (1.6–1.9)
NH Asian males	111‡	1.2 (1.0–1.5)‡
NH Asian females	133‡	1.0 (0.8–1.2)‡
NH American Indian/Alaska Native	55	2.2 (1.7–2.9)
NH Native Hawaiian or Pacific Islander	18	Unreliable (1.7–4.7)

Ellipses (...) indicate data not available; NH, non-Hispanic; and PAD, peripheral artery disease.

\*Mortality for Hispanic people, American Indian or Alaska Native people, Asian people, and Native Hawaiian or Other 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 decedents, Asian decedents, Pacific Islander decedents, 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 people, Filipino people, Japanese people, and other Asian people.

Sources: Mortality (for underlying cause of PAD): Unpublished National Heart, Lung, and Blood Institute tabulation using National Vital Statistics System<sup>61</sup> and Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research.<sup>62</sup>

**Table 25-2. Global Mortality and Prevalence of Lower-Extremity PAD, by Sex, 2021**

	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), 2021	0.07 (0.06 to 0.07)	113.71 (98.50 to 131.22)	0.03 (0.03 to 0.04)	37.54 (32.49 to 43.50)	0.03 (0.03 to 0.04)	76.17 (66.06 to 87.74)
Percent change (%) in total number, 1990–2021	72.79 (61.84 to 81.43)	102.01 (99.93 to 104.37)	72.52 (59.75 to 84.30)	112.43 (109.39 to 115.68)	73.06 (58.62 to 83.78)	97.23 (94.90 to 99.60)
Percent change (%) in total number, 2010–2021	14.94 (10.48 to 19.44)	33.99 (32.80 to 35.23)	16.56 (11.05 to 24.75)	36.05 (34.34 to 37.99)	13.41 (7.29 to 19.26)	32.99 (31.88 to 34.15)
Rate per 100 000, age standardized, 2021	0.85 (0.75 to 0.93)	1,326.45 (1,153.78 to 1,526.53)	0.98 (0.90 to 1.11)	953.49 (830.78 to 1,098.16)	0.73 (0.61 to 0.81)	1,643.00 (1,425.90 to 1,893.27)
Percent change (%) in rate, age standardized, 1990–2021	-35.89 (-38.99 to -33.12)	-12.33 (-13.40 to -11.29)	-35.82 (-40.09 to -31.82)	-10.28 (-11.55 to -9.05)	-36.61 (-40.95 to -32.99)	-11.98 (-13.12 to -10.83)
Percent change (%) in rate, age standardized, 2010–2021	-20.96 (-23.88 to -17.85)	-2.23 (-2.88 to -1.55)	-19.13 (-22.72 to -14.02)	-1.22 (-2.23 to -0.16)	-22.11 (-26.39 to -18.06)	-2.36 (-3.04 to -1.75)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; PAD, peripheral artery disease; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>80</sup>

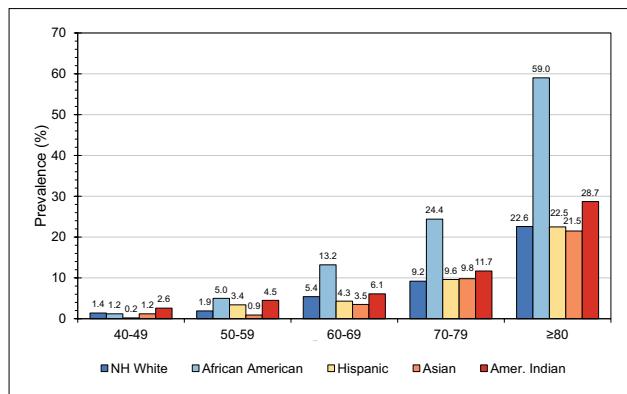
**Table 25-3. Global Mortality of Aortic Aneurysm, by Sex, 2021**

	Both sexes (95% UI)	Males (95% UI)	Females (95% UI)
Total number (millions), 2021	0.15 (0.14 to 0.17)	0.09 (0.09 to 0.10)	0.06 (0.05 to 0.07)
Percent change (%) in total number, 1990–2021	74.22 (62.98 to 83.64)	63.08 (53.44 to 73.74)	95.04 (75.25 to 110.89)
Percent change (%) in total number, 2010–2021	25.18 (20.35 to 29.65)	22.01 (16.75 to 27.35)	30.47 (23.53 to 36.47)
Rate per 100 000, age standardized, 2021	1.86 (1.67 to 2.00)	2.57 (2.36 to 2.79)	1.28 (1.10 to 1.42)
Percent change (%) in rate, age standardized, 1990–2021	-26.69 (-31.06 to -23.13)	-33.58 (-37.06 to -29.76)	-18.79 (-26.03 to -12.76)
Percent change (%) in rate, age standardized, 2010–2021	-9.98 (-13.31 to -6.92)	-12.96 (-16.37 to -9.41)	-6.64 (-11.47 to -2.47)

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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.

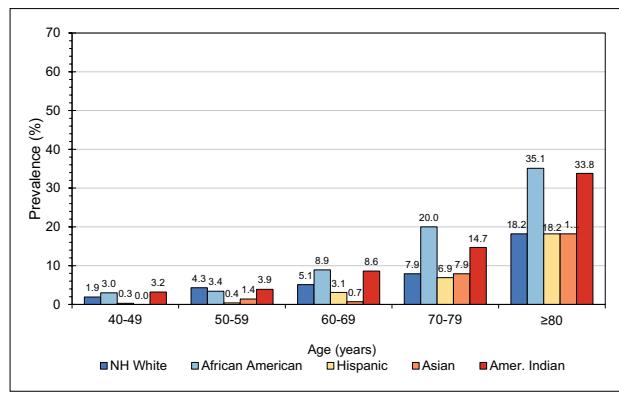
GBD indicates Global Burden of Diseases, Injuries, and Risk Factors; and UI, uncertainty interval.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>80</sup>

**Chart 25-1. Estimates of prevalence of PAD in males, by age and ethnicity, United States, 2000.**

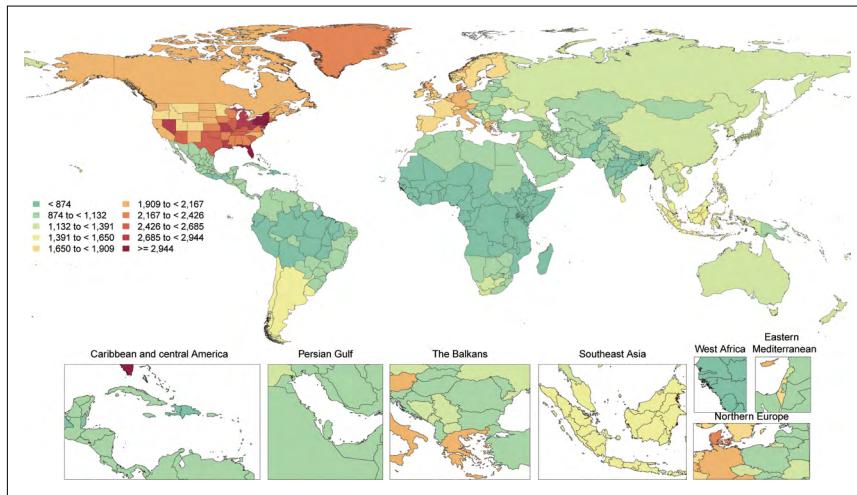
Amer. indicates American; NH, non-Hispanic; and PAD, peripheral artery disease.

Source: Data derived from Allison et al.<sup>2</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>2</sup>

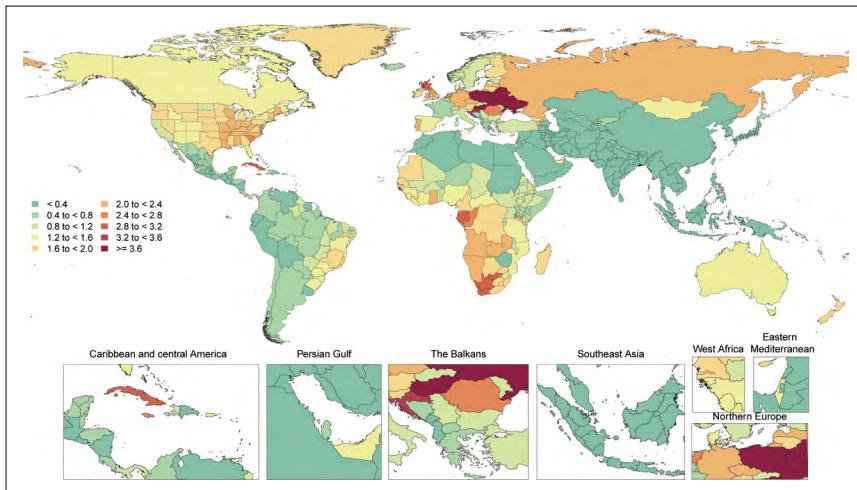


**Chart 25-3. Age-standardized global prevalence of lower-extremity PAD per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and PAD, peripheral artery disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>80</sup>

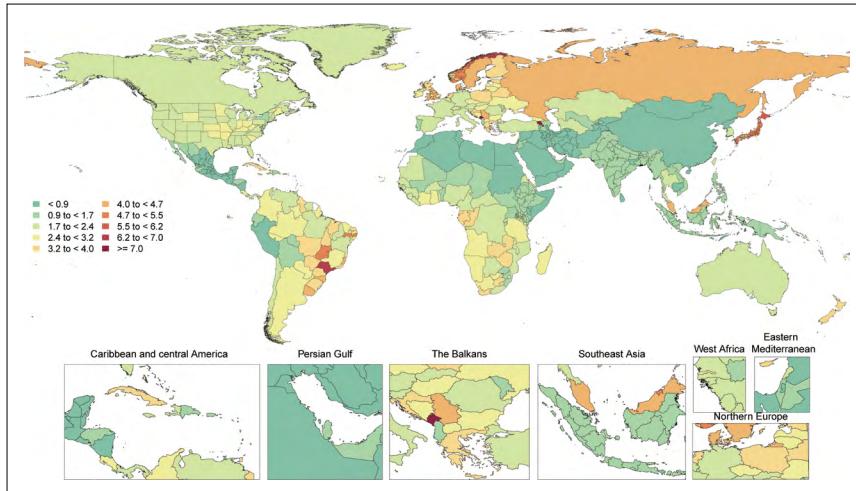


**Chart 25-4. Age-standardized global mortality rates of lower-extremity PAD per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors; and PAD, peripheral artery disease.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>80</sup>



**Chart 25-5. Age-standardized global mortality rates of aortic aneurysm per 100 000, both sexes, 2021.**

These estimates reflect improvements in demography and population estimation, statistical and geospatial modeling methods, and the addition of nearly 3000 new data sources since the 2024 AHA Statistical Update. 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 Diseases, Injuries, and Risk Factors.

Source: Data courtesy of the GBD Study. Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.<sup>80</sup>

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## 26. QUALITY OF CARE

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Quality-of-care assessment uses performance measures as explicit standards against which care delivery can be evaluated.<sup>1</sup> This differs from guidelines, which provide clinical recommendations to inform usual clinical scenarios but ultimately leave decisions to reasonable clinician discretion. Measuring performance necessitates robust data collection across various care settings, rigorous analytics, and the timely dissemination of information. Broadly, there are 2 types of measures: process measures, which focus on tasks that are directly under the control of the clinician (Did patients receive a prescription for a statin after an MI?), and outcomes measures, which focus on end points that are meaningful to patients (What proportion of individuals are alive at 30 days after a hospitalization for an MI?).

Decades of outcomes research have contributed iteratively to measuring and enhancing the quality of delivered care, thereby improving CVH outcomes. In the United States, much of this body of work has relied on cardiovascular registries, many of which are administered by the AHA's GWTG program<sup>2</sup> and the ACC's NCDR program.<sup>3</sup> Health care claims data from payers (Medicare, commercial claims) or integrated health care systems (Veterans Affairs, Kaiser Permanente) have also been used to examine quality. Although claims data typically lack the granular phenotyping available in registries, their scale and ability to capture long-term follow-up make them powerful for examining quality of care and outcomes. Increasingly, linked datasets that combine registries, claims, and other hospital- or community-level data are being used to evaluate outcomes and quality of care. For instance, the AHA's COVID-19 registry has been linked with Medicare claims to evaluate long-term outcomes after a COVID-19 hospitalization.<sup>4</sup> Simulation modeling approaches that systematically integrate data from numerous disparate sources have been used to evaluate the cost-effectiveness of diagnostic tests,

The 2025 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 2025. 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.

drugs, devices, and programs as a measure of the efficiency of health care.<sup>5,6</sup>

The following sections present illustrative examples of how quality of care is measured in the United States and overseas. They are not meant to be comprehensive given the sheer volume of quality data reported annually. When possible, we report standardized quality indicators drawn from quality-improvement registries using methods that are consistent with performance measures endorsed by the ACC and the AHA.<sup>1</sup> We also provide a few examples of how social determinants of health affect cardiovascular care and outcomes; a more extensive discussion related to health equity is included in individual condition-specific chapters. Of note, the first year of the COVID-19 pandemic saw marked worsening in quality of cardiovascular care and outcomes<sup>7</sup>; although quality of care has recovered in recent years, the recovery has, in some settings, been incomplete and inequitable.<sup>8,9</sup> The projected increase in the prevalence of cardiovascular risk factors and conditions and CVD-related health care spending in the coming decades calls for concerted efforts to improve the quality of care in cardiovascular prevention and treatment.<sup>10,11</sup>

### Prevention and Risk Factor Modification

(See Table 26-1)

- Recent data suggest that patients using a Medicaid health maintenance organization have better performance on several key preventive measures related to CVD and diabetes than patients using a commercial preferred provider organization (Table 26-1).
- 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 26-1).<sup>12</sup>
- In a cross-sectional study of 12924 adults 20 to 44 years of age from 2009 to 2020, there were increases in the prevalence of diabetes and obesity and no improvement in the prevalence of hypertension. Black young adults had the highest rates of hypertension over the study period, whereas increases in hypertension and diabetes were observed among Hispanic adults.<sup>13</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>14</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>15</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 ( $P_{\text{trend}} = 0.003$ ).

**Cost-Effectiveness of Intensive BP control**

- In SPRINT, individuals at high risk for CVD who received intensive SBP control (targeting SBP  $<120$  mmHg) had significantly lower rates of death and MACEs compared with individuals who received standard BP control (targeted SBP  $<140$  mmHg).<sup>16</sup> A validated microsimulation model used patient-level data from the trial to evaluate the lifetime cost-effectiveness of intensive BP control from a US health care sector perspective.<sup>17</sup> If the treatment effect is assumed to persist over the patient's lifetime, the intensive BP control group would achieve 0.43 QALYs (95% CI, 0.04–0.84) more than individuals in the standard control group at an incremental cost of \$28 000 more per QALY gained. The findings were robust to changes in input parameters in sensitivity analyses. Thus, intensive BP control in SPRINT-eligible patients is an effective and high-value intervention.

**Social Determinants of Health/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 16 531 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>18</sup>
  - Compared with White adults, Black adults had a higher prevalence rate (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>19</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.

**Hyperlipidemia**

- In a PINNACLE Registry study of 1 655 723 patients, 57% to 62% of patients were treated with appropriate statin therapy under the ACC/AHA guidelines.<sup>20</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, only 3994 of 7550 patients (52.9%) who were eligible for statin therapy were prescribed a statin.<sup>21</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 24 651 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>22</sup> However, fewer than half of patients (45%) received guideline-recommended 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 patients with underweight (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>23</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.
- An emphasis on short-term risk vastly misses younger individuals at elevated lifetime risk. Recent findings<sup>13</sup> showed a rising prevalence of diabetes, hypertension, and hypercholesterolemia among young individuals 20 to 44 years of age from 2009 to 2020, particularly among Black adults and Hispanic adults.

## Acute MI

### (See Tables 26-2 through 26-5)

- Tables 26-2 through 26-5 show the latest metrics of STEMI and NSTEMI quality of care at US hospitals participating in the GWTG-CAD program.

### Quality and Outcomes Across Hospitals

- The Centers for Medicare & Medicaid Services 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 2020 through June 2021, the median hospital risk-standardized mortality rate for MI was 12.9% (interquartile range, 12.6%–13.3%).<sup>24</sup>
- An analysis spanning from April 2011 through December 2017 of patients with AMI from 625 sites using both 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>25</sup>

There was a 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. This suggests that procedural metrics alone might not fully reflect the quality of AMI care (because providers may avoid performing high-risk PCIs to maintain better procedural statistics, which could result in higher disease-based mortality rates).<sup>25</sup> Thus, disease-based metrics could provide a more comprehensive assessment of hospital performance.

### Measuring Quality and Outcomes in Medicare Beneficiaries

- In a cohort analysis of 4070 US acute care hospitals, 2820 hospitals had >25 admissions for AMI, CHF, or pneumonia. There was modest but significant correlation in the 30-day risk-standardized readmission rates for patients with traditional Medicare versus Medicare Advantage (correlation coefficients, 0.31 for AMI, 0.40 for HF, and 0.41 for pneumonia).<sup>26</sup> The traditional Medicare risk-standardized readmission rate showed a systematic underestimation of risk for AMI and other conditions. Because enrollees in Medicare Advantage now represent the majority of Medicare beneficiaries,<sup>27</sup> it is critical to ensure that quality metrics are robust to differential coding practices and provide an unbiased assessment of quality in the 2 groups.

### Effect of Health Policy on Quality of AMI Care

- The HRRP announcement in March 2010 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,  $-0.26\%$ ;  $P=0.01$ ) that did not change significantly after HRRP implementation.<sup>28</sup>
- The association of state Medicaid expansion with quality of AMI care and outcomes was investigated in 55 737 patients with low income who were <65 years of age across 765 sites using NCDR data from January 1, 2012, to December 31, 2016.<sup>29</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 summary, Medicaid expansion did not lead to detectable improvements in AMI care quality or outcomes.

### Social Determinants of Health/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 ( $P_{\text{trend}}=0.002$ ). Of note, this 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 GDMTs (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>30</sup>
- Among 237 549 AMI survivors in the US Nationwide Readmissions Database, sex differences in HF hospitalization risk were explored.<sup>31</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 the Veterans Affairs health care system including 147 600 veteran primary care patients identified sex-related disparities in secondary prevention for IHD.<sup>32</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  $-0.01$ ]).
- 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>33</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 25% (HR, 1.25 [95% CI, 1.08–1.44]) greater 1-year mortality.

- 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>34</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, suggesting that sociodemographic factors other than guideline-concordant care may influence AMI outcomes.

### Heart Failure

#### (See Tables 26-6 and 26-7)

- Current US HF quality data are captured by the widespread but voluntary GWTG-HF program (Tables 26-6 and 26-7) and analyses of health care claims data.

### Hospitalizations for HF

- In a cohort study using data from 8 272 270 adult hospitalizations of 5 092 626 unique patients (mean, 72.1 years of age; 48.9% females) in the Nationwide Readmission Database through 2017, primary HF hospitalization rates per 1000 US adults increased from 4.1 in 2013 to 4.9 in 2017.<sup>35</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, increased detection attributable to rising use of HF biomarkers, the use of more sensitive definitions of HFpEF, or changes in coding practices.
- A majority of Medicare beneficiaries are now enrolled in Medicare Advantage plans compared with fee-for-service Medicare (52% versus 48% in 2023).<sup>36</sup> Thus, it is increasingly important to examine outcomes among beneficiaries enrolled in Medicare Advantage plans in addition to those in traditional fee-for-service Medicare. 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 (rather than a post-acute care facility) compared with patients enrolled in traditional

fee-for-service Medicare ( $aOR, 1.16 [95\% CI, 1.13–1.19]; P<0.001$ ) and slightly less likely to be discharged within 4 days ( $aOR, 0.97 [95\% CI, 0.93–1.00]; P=0.04$ ).<sup>37</sup> No significant differences were noted in the quality of care received or in-hospital mortality between those enrolled in Medicare Advantage and those in fee-for-service Medicare.

### Effect of Health Policy on HF Hospitalizations

A number of studies noted a decline in HF readmissions after the implementation of the HRRP. However, there is evidence of a potential unintended negative effect of HRRP, with increased mortality among patients with HF who were not readmitted.

- 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 (absolute difference,  $-1.25 [95\% CI, -1.64 to -0.86]$  percentage point reduction in penalized compared with nonpenalized hospitals).<sup>38</sup>
- Reductions in readmission rates were greater for target than for nontarget conditions for patients at the penalized hospitals but not at nonpenalized hospitals.<sup>39</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 worseperforming 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>39</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 the HRRP were associated with an increase in death within 30 days of hospitalization.<sup>28</sup> Compared with this baseline trend, post-discharge mortality increased by 0.49% after the announcement of the HRRP ( $P=0.01$ ) and 0.52% after implementation of the 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.

### Alternative Metrics of Care Quality for HF

- As noted, the increasing enrollment in Medicare Advantage plans necessitates that any quality evaluation includes both fee-for-service and Medicare Advantage patients. A recent study showed that  $\approx 1$  in 4 “top-performing” hospitals (based on outcomes among fee-for-service patients) would be reclassified to a lower performance group when Medicare Advantage beneficiaries are included in the evaluation of hospital readmissions and mortality.<sup>40</sup> Between 21.6% and 30.2% were reclassified

to a lower-performing quintile, and similar proportions of hospitals were reclassified from the bottom performance quintile to a higher one. Future studies evaluating Medicare programs should include both fee-for-service and Medicare Advantage patients to provide a more complete picture of hospital performance.

- 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>
- 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>42</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.

### 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 (compared with prior score or change in score) of the Kansas City Cardiomyopathy Questionnaire scores was associated 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>43</sup>

### Cost-Effectiveness and Affordability of HF Therapies

- Simulation modeling studies have examined the cost-effectiveness of sacubitril-valsartan in patients with HFrEF.<sup>44</sup> Among patients with New York Heart Association class II to IV HF and LVEF of  $\le 40\%$ , the sacubitril-valsartan group gained 0.69 additional life-year and 0.62 additional QALY over a lifetime.

Assuming a monthly cost of sacubitril-valsartan to be \$380 produced an incremental cost per QALY gained of \$47 000. However, sacubitril-valsartan prices are higher now than when the drug first entered the market.<sup>45</sup> According to the sensitivity analyses reported in the aforementioned study, the use of sacubitril-valsartan is likely intermediate value per the ACC/AHA value framework (ie, \$50 000 to <\$150 000 per QALY gained).<sup>46</sup>

- Similarly, simulation modeling studies have found that the use of an SGLT-2 inhibitor as a part of GDMT for HFrEF is of intermediate economic value (ie, \$50 000 to <150 000 per QALY gained), regardless of the diabetes status of the patient.<sup>47,48</sup> In 1 study,<sup>47</sup> dapagliflozin, at an annual cost of \$4192, was projected to add 0.63 QALY at an incremental lifetime cost of \$42 800, for an incremental cost-effectiveness ratio of \$68 300 per QALY gained (95% UI, \$54 600–\$117 600 per QALY gained; cost-effective in 94% of probabilistic simulations at a threshold of \$100 000 per QALY gained). Findings were similar in individuals with and those without diabetes but were sensitive to drug cost.
- In contrast, the use of an SGLT-2 inhibitor for HFpEF was estimated to be of low economic value in 1 study<sup>49</sup> and low to intermediate value in another study,<sup>50</sup> largely because of the lack of benefit on mortality and small benefit on quality of life.
- A major barrier to accessing novel but effective GDMTs for HF has been the high out-of-pocket costs faced by patients, including Medicare beneficiaries. Two studies suggest that the Inflation Reduction Act of 2022 will lower out-of-pocket costs by 29% to 40% for patients with HFrEF by capping out-of-pocket costs to \$2000 starting in 2025.<sup>51</sup> One study evaluated 4137 Medicare Part D plans for out-of-pocket costs associated with comprehensive guideline-directed HFrEF therapy and found that patient costs were projected to decline from \$2758 in 2022 to \$1954 in 2025 (a 29% reduction).<sup>52</sup> Patients on concurrent DOAC therapy for AF are projected to see an even larger reduction in out-of-pocket costs (from \$3259 in 2022 to \$2000 in 2025, a 39% reduction).

## 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>53</sup> When analyzed by zip code, receipt of TAVR was directly related to median household income but inversely related to the proportion of beneficiaries also enrolled in Medicaid and community-level social deprivation. For every \$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%). For each 1% increase in the proportion of patients who were dually enrolled in Medicaid and Medicare services, the number of TAVR procedures per 100 000 Medicare beneficiaries declined by 2.1% (95% CI, 1.3%–2.9%). Every 1-unit increase in the Distressed Communities Index score was associated with 0.4% (95% CI, 0.2%–0.5%) fewer TAVR procedures performed per 100 000 Medicare beneficiaries. 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 factors, age, and clinical comorbidities. Disparities in access and outcome were also noted for patients residing in low-population-density areas.<sup>54</sup> In a geo-spatial study of 6531 patients undergoing TAVR in Florida between 2011 and 2016, those residing in the lowest density category (<50 people per square mile) faced longer unadjusted driving distances and times to their TAVR center (mean extra distance, 43.5 miles [95% CI, 35.6–51.4]; mean extra time, 45.6 minutes [95% CI, 38.3–52.9]). Compared with the highest-population-density regions, the lowest-population-density regions had a 7-fold lower TAVR use rate (7 versus 45 per 100 000;  $P<0.001$ ) and increased in-hospital mortality after TAVR (aOR, 6.13 [95% CI, 1.97–19.1]).

### Clinical Outcomes

- A retrospective cohort study using data from the STS/ACC TVT 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>55</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

### In-Hospital Cardiac Arrests (See Table 26-8)

Quality measures in resuscitation have targeted inpatient care settings. Started in 1999, the AHA GWTG-R Registry remains the dominant source of US quality-improvement data (Table 26-8). GWTG-R 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 192 adult hospitals in the GWTG-R 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>56</sup> Compared with sites without a very active resuscitation champion, hospitals with a very active physician champion were more likely to be in a higher survival quintile (aOR, 3.90 [95% CI, 1.39–10.95]). There was no difference in survival between sites without a very active champion and those with a very active nonphysician champion (aOR, 1.28 [95% CI, 0.62–2.65]).
- In a temporal trend evaluation of survival to discharge after IHCA, there was a significant increase in survival in Black individuals (11.3% in 2000 versus 21.4% in 2014) and White individuals (15.8% versus 23.2%), and a reduction in the disparity between races was noted ( $P_{\text{interaction}} < 0.001$ ).<sup>57</sup>

### Out-of-Hospital Cardiac Arrests

- Recent work within a large US registry demonstrated that Black individuals and Hispanic individuals were 26% less likely to receive bystander CPR at home (38.5%) than White individuals (47.4%; aOR, 0.74 [95% CI, 0.72–0.76]) and 37% less likely to receive bystander CPR in public locations (45.6% versus 60.0%; aOR, 0.63 [95% CI, 0.60–0.66]) than White individuals.<sup>58</sup> Significant disparities in bystander CPR exist after controlling for income variables, regardless of the racial and ethnic composition of the location of the arrest.
- In a study using a large US registry of OHCA to compare outcomes during the pandemic period of March 16 through April 30, 2020,<sup>59</sup> incidence of OHCA was significantly higher in 2020 compared with 2019, largely in communities with high COVID-19 mortality (adjusted mean difference, 38.6 [95% CI, 37.1–40.1] per 1 million residents) and very high COVID-19 mortality (adjusted mean difference, 28.7 [95% CI, 26.7–30.6] per 1 million residents). However, there was no difference in rates of sustained return of spontaneous circulation or survival to discharge during the prepandemic and peripandemic periods in 2020 versus 2019.

- 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>60</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%;  $P=0.02$ ).

## Implantable Defibrillators and Cardiac Resynchronization Therapy

- In an observational analysis of patients hospitalized with HF and an EF ≤35% without an ICD in the GWTG-HF program (2011–2014), the overall rate of predischarge ICD counseling was low at 22.6%. Females were less likely than males to receive predischarge ICD 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 groups, 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>61</sup> Among patients who were counseled, females and males were similarly likely to receive an ICD (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 ICD.
- In a multicenter retrospective analysis of 106 individuals ≤21 years or age without prior cardiac disease who received an ICD after SCA, 20 individuals (19%) received appropriate shocks, 16 individuals (15%) received inappropriate shocks (including 3 individuals who had both appropriate and inappropriate shocks), and 73 individuals (69%) received no shocks over a median follow-up of 3 years.<sup>62</sup> Guideline-concordant use of ICD was high, regardless of underlying disease.
- Using an antibiotic-eluting envelope during cardiac implantable electronic device procedures reduces the risk of device infection but increases procedural costs. A simulation modeling study examined the cost-effectiveness of using an antibiotic-eluting envelope during cardiac implantable electronic device procedures among patients with HF.<sup>63</sup> Effectiveness was estimated from the Worldwide Randomized Antibiotic Envelope Infection Prevention Trial. Compared with usual care, using an antibiotic-eluting envelope at a cost of \$953

per unit during initial implantations produced an incremental cost-effectiveness ratio of \$112 000 per QALY gained (39% probability of being cost-effective). In contrast, using an antibiotic-eluting envelope during generator replacement procedures produced an incremental cost-effectiveness ratio of \$54 000 per QALY gained (84% probability of being cost-effective). Sensitivity analyses showed that results were sensitive to the underlying rate of infection, cost of the envelope, and durability of effectiveness to prevent infections.

## Atrial Fibrillation

### (See Tables 26-9 and 26-10)

- Current US AF quality data are captured by the widespread but voluntary GWTG-AFIB program (Tables 26-9 and 26-10) and analyses of health care claims data.

### **Prescription of Oral Anticoagulants and Outcomes**

- An analysis of data from the AHA GWTG-AFIB 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, with 93.5% of eligible patients without contraindications being prescribed oral anticoagulation therapy for stroke prevention in AF.<sup>64</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-AFIB registry, overall discharge prescription of anticoagulation was 85.6%.<sup>65</sup> 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%).
- In an analysis claims of Medicare Advantage beneficiaries with newly diagnosed AF from 2010 to 2020, among patients who were prescribed any oral anticoagulant, apixaban was the most commonly prescribed oral anticoagulant followed by rivaroxaban (77.7% and 16.0% of patients receiving DOACs respectively).<sup>66</sup>
- Aspirin alone as an alternative to oral anticoagulant in patients with AF was common in 2008 to 2012. According to the data from ACC NCDR PINNACLE Registry, among patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC score ≥2 who were prescribed either aspirin or oral anticoagulant, 38.2% were prescribed aspirin alone.<sup>67</sup> Whether the prevalence of aspirin-alone therapy

has decreased with increased use of DOACs is unknown.

- An AHA GWTG-Stroke study compared outcomes with DOAC therapy (dabigatran, rivaroxaban, or apixaban) with outcomes with warfarin in 11 662 patients ≥65 years of age with AF who were anti-coagulation 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>68</sup>
- Although there are no trial data comparing the DOACs with each other, high-quality observational studies<sup>69–72</sup> have compared major ischemic and hemorrhagic outcomes in patients with AF treated with rivaroxaban or apixaban. A retrospective cohort study using Medicare fee-for-service claims identified 581 451 patients with AF who began rivaroxaban (n=227 572) or apixaban (n=353 879).<sup>69</sup> Among patients receiving rivaroxaban, the rate of a composite outcome of major ischemic (stroke/systemic embolism) and hemorrhagic (ICH/other intracranial bleeding/fatal extracranial bleeding) events was 16.1 per 1000 PY versus 13.4 per 1000 PY for apixaban (HR, 1.18 [95% CI, 1.12–1.24]). The rivaroxaban group had increased risk for both major ischemic events (8.6 versus 7.6 per 1000 PY; HR, 1.12 [95% CI, 1.04–1.20]) and hemorrhagic events (7.5 versus 5.9 per 1000 PY; HR, 1.26 [95% CI, 1.16–1.36]). The authors concluded that among Medicare beneficiaries ≥65 years of age with AF, treatment with rivaroxaban compared with apixaban was associated with a significantly increased risk of major ischemic or hemorrhagic events.

### **Adherence to Anticoagulation**

- A systematic review and meta-analysis demonstrated suboptimal adherence and persistence to DOACs in patients with AF.<sup>73</sup> Among 48 observational studies with a combined 594 784 patients with AF (59% male; mean, 71 years of age), 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 19749 patients with AF (mean, 70.6 years of age; 56% male; mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score, 2.8).<sup>74</sup> Group-based trajectory modeling identified 74% of patients as having “consistent adherence,” defined as a high and steady proportion of days covered by the prescription medication, typically ~80%, 12% as having “rapid decline and discontinuation,” 10% as having “rapid decline and partial recovery,” and 4% as having “slow decline and discontinuation.”<sup>74</sup> Clinical and demographic characteristics were not able to provide strong performance in predicting these adherence trajectories.

### **Other AF Therapies**

- In a NCDR PINNACLE Registry study, 107 759 of 658 250 patients (16.4%) with AF without CVD were inappropriately prescribed combination antiplatelet and anticoagulant therapy, and 5731 of 150 079 patients (3.8%) with AF with reduced LVEF received an inappropriate prescription for a nondihydropyridine calcium channel blocker.<sup>75</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 Left Atrial Appendage Occlusion Registry, 49 357 patients (mean, 76.1 years of age; 41.3% females) with AF undergoing LAAO with the Watchman device from January 1, 2016, to June 30, 2019, were analyzed.<sup>76</sup> After multivariable adjustment, females had a higher risk of in-hospital adverse events after LAAO than males (1284 [6.3%] versus 1144 [3.9%];  $P<0.001$ ; OR, 1.63 [95% CI, 1.49–1.77];  $P<0.001$ ).
- An economic evaluation of the CABANA trial examined medical resource use data for all trial participants (N=2204), US unit costs of care, and quality-of-life adjustments based on EQ-5D-based utilities measured during the trial.<sup>77</sup> Catheter ablation was associated with an increased lifetime mean cost of \$15 516 (95% CI, -\$2963 to \$35 512) compared with drug therapy with an incremental cost-effectiveness ratio of \$57 893 per QALY gained (<\$100 000 per QALY in 75% of bootstrap replications). However, the incremental cost-effectiveness ratio rose to \$183 318 per life-year gained if one were to assume no quality-of-life gains. The authors concluded that catheter ablation of AF was economically attractive compared with drug therapy on the basis of projected incremental quality-adjusted survival but not survival alone.

### **Social Determinants of Health/Health Equity in AF Care**

- Health care insurance coverage may influence oral anticoagulant and DOAC 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>78</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 DOAC use (military, 24%; private, 19%; Medicare, 17%; other, 17%; Medicaid, 8%;  $P<0.001$ ). In addition, access to cardiologists may influence the likelihood of being prescribed a DOAC. An analysis of 2013 to 2018 Medicare Provider Utilization and Payment Data reported a rapid uptake of DOACs among cardiologists compared with internists, family medicine physicians, and advanced practice clinicians.<sup>79</sup> For example, in 2013, 18.7% of cardiologists prescribed only warfarin, whereas 83.0% of internists, 77.7% of family medicine physicians, and 83.0% of advanced practice clinicians prescribed only warfarin. The corresponding numbers in 2018 were 1.6% for cardiologists, 12.6% for internists, 20.0% for family medicine physicians, and 28.2% for advanced practice clinicians.

- In an analysis of Medicare Advantage claims data from 2016 to 2019, Black race was associated with lower odds of receiving either antiarrhythmic drug or catheter ablation (aOR, 0.89 [95% CI, 0.83–0.94];  $P<0.001$ ), and Hispanic ethnicity was associated with lower odds of receiving catheter ablation (aOR, 0.73 [95% CI, 0.60–0.89];  $P=0.002$ ).<sup>80</sup> Lower median household income was associated with lower odds of receiving either antiarrhythmic drug or catheter ablation (aOR for <\$50 000, 0.83 [95% CI, 0.79–0.87];  $P<0.001$ ; aOR for \$50 000–\$99 999, 0.92 [95% CI, 0.88–0.96];  $P\leq0.001$ ) and catheter ablation (aOR for <\$50 000, 0.61 [95% CI, 0.54–0.69];  $P<0.001$ ; aOR for \$50 000–\$99 999, 0.81 [95% CI, 0.72–0.90];  $P<0.001$ ).

## **Stroke**

### **Prehospital Care**

- A retrospective pre-post study examined the effect of a regional prehospital EMS transport policy to triage patients with suspected large-vessel occlusion stroke to comprehensive stroke centers.<sup>81</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 comprehensive stroke centers 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%];  $P<0.001$ ). 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>81</sup>

### Acute Stroke Care

#### (See Tables 26-11 and 26-12)

- The AHA GWTG-Stroke program (Table 26-11 and 26-12) 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 with 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>82</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>83</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.
- 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 individuals 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>84</sup>
- A systematic review examined the cost-effectiveness of several strategies to reduce delays in the management of AIS.<sup>85</sup> Twenty studies performed in

12 countries evaluated 4 main strategies: educational interventions, organizational models, health care delivery infrastructure, and workflow improvements. Sixteen studies showed that a wide range of strategies aimed at reducing delays in treatment—including educational interventions, telemedicine between hospitals, mobile stroke units, and workflow improvements—were considered cost-effective in their local settings.

### 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 36.5% of patients with acute stroke were functionally dependent or dead at 3 months after stroke in 2006 through 2008. Rates of dependence or death varied considerably across hospitals (0%–67%; adjusted interquartile range, 32%–41%), which indicates the need to understand which process measures could be targeted to minimize hospital variation and to improve poststroke functional outcomes.<sup>86</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>87</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 Medicaid expansion 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. A study using GWTG-Stroke data 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 inpatient comfort 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>88</sup>

## Global Efforts in Quality Measurement

The AHA's quality measurement and improvement efforts, including the GWTG registries, have now expanded globally. The first international adoption was in China, where the registries were adapted for MI, stroke, and cardiometabolic conditions. These China-based registries have captured data on >175 000 encounters/patients and published >40 scientific publications. As of 2023, the AHA has partnered with private and public stakeholders to implement the GWTG portfolio and Hospital Certification programs in multiple countries, including the United Arab Emirates, Kingdom of Saudi

Arabia, Canada, Mexico, Vietnam, Taiwan, Thailand, Indonesia, and Malaysia. There is evidence that implementation of these programs is associated with improvement in quality in these settings. For instance, implementing a quality improvement program adapted from the AHA's GWTG initiative resulted in an overall sustained improvement in AF, HF, and ACS management in Brazil.<sup>89</sup> Among 12 167 patients enrolled in 19 hospitals in Brazil between 2016 and 2022, adoption of the Best Practice in Cardiology program was associated with an increase in the composite score (a combination of primary ACC/AHA performance measures for each condition, adapted to the local context) from baseline to the last quarter of follow-up: 65.8±36.2% to 73±31.2% for AF ( $P=0.024$ ), 81.0±23.6% to 89.9±19.3% for HF ( $P<0.001$ ), and 88.0±19.1% to 91.2±14.9% for ACS ( $P<0.001$ ).

**Table 26-1. National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set on CVD, Diabetes, Tobacco, Nutrition, and Lifestyle, United States, 2022**

	Commercial*		Medicare*		Medicaid*
	HMO	PPO	HMO	PPO	HMO
<b>CVD</b>					
β-Blocker persistence after MI†	85.1	85.9	89.1	88.8	79.9
BP control‡	63.8	54.9	72.9	70.2	60.9
Statin therapy for patients with CVD	81.9	81.8	85.4	84.2	78.7
<b>Diabetes</b>					
HbA1c testing	91.1	89.4	93.9	94.2	85.3
HbA1c >9.0%	28.5	36.6	21.9	21.8	40.3
Eye examination performed	51.6	49	71.8	69.2	51.5
Monitoring nephropathy	NA	NA	94.9	94.9	NA
BP <140/90 mm Hg	64.4	55.8	70.4	66	63.6
Statin therapy for patients with diabetes	65.4	63.3	79.2	77	63.8
<b>Tobacco, nutrition, and lifestyle</b>					
Advising smokers and tobacco users to quit	NA	NA	NA	NA	72.8
BMI percentile assessment in children and adolescents (3–17 y of age)	74.4	62.1	NA	NA	76.8
Nutrition counseling (children and adolescents [3–17 y of age])	64.3	53.9	NA	NA	68.1
Counseling for PA (children and adolescents [3–17 y of age])	61.5	NA	NA	NA	64.8
BMI assessment for adults (18–74 y of age; 2019 data)	84.9	69.7	NA	NA	88.4
PA discussion in older adults (≥65 y of age; 2018 data)	NA	NA	NA	57.5	55.3
PA advice in older adults (≥65 y of age; 2018 data)	NA	NA	NA	51.1	52.3

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; PA, physical activity; and PPO, preferred provider organization.

\*Data presented are from 2022 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 <140/90 mm Hg, adults 60 to 85 years of age with a diagnosis of diabetes and BP <140/90 mm Hg, and adults 60 to 85 years of age without a diagnosis of diabetes and BP <150/90 mm Hg.

Source: Healthcare Effectiveness Data and Information Set.<sup>12</sup>

**Table 26-2. Quality-of-Care Measures in the GWTG-CAD Program: STEMI, United States, 2021 to 2023**

Quality-of-care measure	2021	2022	2023
ACE inhibitor or ARB at discharge when LVEF <40%	91.4	93.2	93.0
Aspirin at discharge	99.3	99.2	99.3
β-Blocker at discharge	97.3	97.6	98.0
Cardiac rehabilitation referral	89.4	89.7	91.6
ECG within 10 min of arrival	72.5	75.0	77.6
High-intensity statin at discharge	96.0	96.7	97.7
Smoking cessation counseling	91.0	92.6	92.0
Aspirin at arrival	98.6	98.9	97.0
Receiving-only time metrics			
Arrival at first facility to PCI within 120 min	73.0	72.6	73.8
EMS FMC to PCI within 90 min OR within 120 min when transport time is prolonged	76.8	77.6	78.2
PCI within 90 min	94.4	95.0	95.3
FMC to PCI within 120 min among transferred patients	71.7	69.7	70.7
Referring-only time metrics			
Arrival to thrombolytics within 30 min	55.4	52.3	53.4
Arrival to transfer to PCI center within 45 min	39.1	40.0	44.6
Arrival to transfer to PCI center within 30 min	15.8	15.4	17.5

Values are percentages.

GWTG-CAD is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ECG, electrocardiogram; EMS, emergency medical service; FMC, first medical contact; GWTG-CAD, Get With The Guidelines—Coronary Artery Disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Source: Unpublished American Heart Association tabulation, GWTG-CAD.

**Table 26-3. Quality-of-Care by Race and Ethnicity and Sex in the GWTG-CAD Program: STEMI, United States, 2023**

Quality-of-care measure	Race and ethnicity				Sex	
	White	Black	Hispanic	Asian	Male	Female
ACE inhibitor or ARB at discharge when LVEF <40%	93.1	93.4	94.0	92.5	93.8	90.4
Aspirin at discharge	99.3	99.1	99.3	99.1	99.4	98.9
β-Blocker at discharge	97.9	98.3	97.6	97.7	98.2	97.6
Cardiac rehabilitation referral	92.1	90.7	88.8	89.8	91.5	91.9
ECG within 10 min of arrival	78.7	71.3	76.9	76.5	79.9	71.3
High-intensity statin at discharge	97.8	97.1	97.4	97.9	97.9	97.2
Smoking cessation counseling	91.6	93.7	92.4	92.1	91.9	92.2
Aspirin at arrival	96.9	98.6	98.3	96.8	94.6	94.9
Receiving-only time metrics						
Arrival at first facility to PCI within 120 min	73.6	65.7	74.7	87.4	75.3	69.2
EMS FMC to PCI within 90 min OR within 120 min when transport time is prolonged	78.7	72.7	78.9	79.7	80.1	73.5
PCI within 90 min	95.5	93.2	95.1	95.3	95.6	94.5
FMC to PCI within 120 min among transferred patients	71.1	59.1	71.6	82.7	73.1	62.9
Referring-only time metrics						
Arrival to thrombolytics within 30 min	53.1	60.3	29.6	25.0	54.7	49.7
Arrival to transfer to PCI center within 45 min	45.6	34.6	52.9	39.1	46.8	38.9
Arrival to transfer to PCI center within 30 min	17.1	12.1	32.4	17.4	18.3	15.6

Values are percentages.

GWTG-CAD is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ECG, electrocardiogram; EMS, emergency medical service; FMC, first medical contact; GWTG-CAD, Get With The Guidelines—Coronary Artery Disease; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Source: Unpublished American Heart Association tabulation, GWTG-CAD.

**Table 26-4. Quality-of-Care Measures in the GWTG-CAD Program: NSTEMI, United States, 2021 to 2023**

Quality-of-care measure	2021	2022	2023
ACE inhibitor or ARB at discharge	86.7	88.3	90.4
Smoking cessation counseling	92.6	94.5	96.4
Cardiac rehabilitation referral	83.8	82.9	83.8
Dual antiplatelet therapy at discharge	71.2	72.3	72.5
LV systolic function evaluated during admission or planned after discharge	94.9	95.8	95.5

Values are percentages.

GWTG-CAD is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GWTG-CAD, Get With The Guidelines—Coronary Artery Disease; LV, left ventricular; and NSTEMI, non-ST-segment-elevation myocardial infarction.

Source: Unpublished American Heart Association tabulation, GWTG-CAD.

**Table 26-5. Quality-of-Care Measures by Race and Ethnicity and Sex in the GWTG-CAD Program: NSTEMI, United States, 2023**

Quality-of-care measure	Race and ethnicity				Sex	
	White	Black	Hispanic	Asian	Male	Female
ACE inhibitor or ARB at discharge	89.6	92.6	89.5	87.9	90.6	89.5
Smoking cessation counseling	96.3	96.5	97.6	96.7	96.7	95.7
Cardiac rehabilitation referral	84.3	83.6	80.4	81.0	85.2	80.6
Dual antiplatelet therapy at discharge	72.6	75.3	68.1	67.8	76.3	67.3
LV systolic function evaluated during admission or planned after discharge	95.5	95.1	95.6	95.6	95.7	95.1

Values are percentages.

GWTG-CAD is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; GWTG-CAD, Get With The Guidelines—Coronary Artery Disease; LV, left ventricular; and NSTEMI, non-ST-segment-elevation myocardial infarction.

Source: Unpublished American Heart Association tabulation, GWTG-CAD.

**Table 26-6. Quality-of-Care Measures in the GWTG-HF Program, United States, 2021 to 2023**

Quality-of-care measure	2021	2022	2023
Evidence-based specific β-blockers at discharge for patients with HFrEF	93.4	94.3	94.6
Measure LV function	99.2	99.3	99.1
Postdischarge appointment for HF patients	85.6	86.2	87.4
ARNI at discharge for patients with HFrEF	49.3	57.0	61.1
SGLT-2 inhibitor at discharge for patients with HFrEF	10.8	37.5	60.6
MRA at discharge for patients with HFrEF	57.1	61.3	68.1
ACE inhibitor/ARB or ARNI at discharge for patients with HFrEF	91.8	92.6	92.6
Anticoagulation for AF or atrial flutter	91.9	92.8	93.1
CRT-D or CRT-P placed or prescribed at discharge for eligible patients	39.4	35.4	36.7
DVT prophylaxis	93.8	92.6	92.2
Follow-up visit within 7 d or less	65.4	64.0	65.3
Hydralazine nitrate at discharge in self-identified Black patients with HFrEF	28.1	25.9	23.1
ICD counseling or ICD placed or prescribed at discharge for eligible patients	70.6	56.2	56.9
Influenza vaccination during flu season	73.1	70.6	70.0
Pneumococcal vaccination	64.2	63.7	65.2
Laboratory monitoring follow-up within 7 d of MRA prescription or dose change	NA	NA	70.9
Defect-free care for quadruple therapy medication for patients with HFrEF	18.4	61.2	69.7
DOAC at discharge for HF with nonvalvular AF or atrial flutter patients	43.4	45.1	67.6
SGLT-2 inhibitor at discharge for patients with HFpEF/HFmrEF	NA	NA	22.6

Values are percentages.

GWTG-HF is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor/neprilysin inhibitor; CRT-D, cardiac resynchronization therapy pacemaker defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DOAC, direct-acting oral anticoagulant; DVT, deep vein thrombosis; GWTG, Get With The Guidelines; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NA, not available; and SGLT-2, sodium-glucose cotransporter-2.

Source: Unpublished American Heart Association tabulation, GWTG-HF.

**Table 26-7. Quality-of-Care by Race and Ethnicity and Sex in the GWTG-HF Program, United States, 2023**

Quality-of-care measure	Race and ethnicity*				Sex	
	White	Black	Hispanic	Asian	Males	Females
Evidence-based specific β-blockers at discharge for patients with HFrEF	93.9	96.0	95.2	94.3	95.0	93.9
Measure LV function	99.2	99.1	99.2	97.3	99.3	99.1
Postdischarge appointment for HF patients	88.2	85.9	87.7	86.2	87.4	87.7
ARNI at discharge for patients with HFrEF	58.2	66.5	61.1	55.9	61.5	59.8
SGLT-2 inhibitor at discharge for patients with HFrEF	56.6	67.1	62.9	65.0	61.9	57.4
MRA at discharge for patients with HFrEF	65.5	72.9	68.8	68.5	68.8	66.4
ACE inhibitor/ARB or ARNI at discharge for patients with HFrEF	91.6	94.4	94.2	93.1	92.9	92.2
Anticoagulation for AF or atrial flutter	93.3	93.1	92.7	90.1	93.2	93.2
CRT-D or CRT-P placed or prescribed at discharge for eligible patients	37.0	37.4	41.2	34.6	39.2	31.9
DVT prophylaxis	91.9	94.3	93.7	87.2	92.6	93.4
Follow-up visit within 7 d or less	67.1	61.6	63.2	67.3	64.6	66.3
Hydralazine nitrate at discharge in self-identified Black patients with HFrEF	NA	23.1	NA	33.3	24.7	20.4
ICD counseling or ICD placed or prescribed at discharge for eligible patients	68.9	68.7	69.2	50.3	70.4	64.3
Influenza vaccination during flu season	72.3	63.5	71.2	70.1	69.1	72.1
Pneumococcal vaccination	68.5	57.1	62.7	67.4	62.7	68.8
Laboratory monitoring follow-up within 7 d of MRA prescription or dose change	50.7	42.9	45.8	44.3	47.9	48.8
Defect-free care for quadruple therapy medication for patients with HFrEF	52.7	59.5	54.8	58.7	55.8	53.4
DOAC at discharge for HF with nonvalvular AF or atrial flutter patients	66.9	70.5	69.5	64.5	68.2	67.6
SGLT-2 inhibitor at discharge for patients with HFpEF/HFmrEF	20.8	29.6	25.9	22.2	25.7	20.2

Values are percentages.

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ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin-receptor/neprilysin inhibitor; CRT-D, cardiac resynchronization therapy pacemaker defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DOAC, direct-acting oral anticoagulant; DVT, deep vein thrombosis; GWTG, Get With The Guidelines; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NA, not available; and SGLT-2, sodium-glucose cotransporter-2.

\*Race and ethnicity are assessed by the patient or, if that is not available, by the physician or institution.

Source: Unpublished American Heart Association tabulation, GWTG-HF.

**Table 26-8. Quality-of-Care of Patients Among GWTG-R Hospitals, United States, 2021 to 2023**

Population	Quality-of-care measure	2021	2022	2023
Adult	Confirmation of airway device placement in trachea	83.8	85.4	86.0
	Percent pulseless cardiac events monitored or witnessed	96.3	96.4	96.6
	Time to first shock ≤2 min for VF/pulseless VT first documented rhythm	73.0	74.7	76.9
	Time to IV/IO epinephrine ≤5 min for asystole or pulseless electrical activity	94.1	94.0	94.5
Pediatric	Confirmation of airway device placement in trachea	87.1	90.3	89.8
	Percent pulseless cardiac events occurring in an ICU setting vs a ward setting	91.6	92.1	93.6
	Time to IV/IO epinephrine ≤5 min for asystole or pulseless electrical activity	94.0	93.4	94.5
	Time to first chest compressions ≤1 min in pediatric patients	99.4	98.1	97.8
Infant/neonate	Confirmation of airway device placement in trachea	85.2	88.5	88.3
	Percent pulseless cardiac events occurring in an ICU setting vs a ward setting	96.0	96.0	94.8
	Time to IV/IO epinephrine ≤5 min for asystole or pulseless electrical activity	94.6	92.0	94.9
	Time to first chest compressions ≤1 min in neonates	96.9	97.7	97.8
Newly born	Advanced airway placed before initiation of chest compressions	63.5	69.0	66.3
	Confirmation of airway device placement in trachea	81.7	79.6	85.7
	Pulse oximetry in place before initiation of chest compressions	69.0	76.6	80.1
	Time to positive pressure ventilation <1 min from CPA recognition	91.0	88.6	87.8

Values are mean percentages.

GWTG-R is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

CPA indicates cardiopulmonary arrest; GWTG-R, Get With The Guidelines—Resuscitation; ICU, intensive care unit; IHCA, in-hospital cardiac arrest; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Source: Unpublished American Heart Association tabulation, GWTG-R.

**Table 26-9. Quality-of-Care Measures in the GWTG-AFIB Program, United States, 2021 to 2023**

Quality-of-care measure	2021	2022	2023
ACE inhibitor/ARB or ARNI at discharge when LVEF ≤40%	84.5	84.3	82.7
β-Blocker at discharge when LVEF ≤40%	95.3	94.6	95.2
CHADS <sub>2</sub> -VASc score documented before discharge	83.9	79.0	76.6
FDA-approved anticoagulation at discharge	98.8	98.7	99.2
PT/INR planned follow-up documented before discharge for warfarin treatment	88.2	83.1	77.6
Statin at discharge in patients with AF with CAD, CVA/TIA, PVD, or diabetes	86.8	85.4	85.3
Aldosterone antagonist at discharge	34.1	39.2	42.3
Anticoagulation therapy education	73.8	61.5	54.1
DOAC at discharge for patients with nonvalvular AF or atrial flutter	88.6	90.8	91.6
Discharge HR ≤110 bpm	94.1	95.1	94.3
Inappropriate use of antiarrhythmics in patients with permanent AF	9.1	9.6	11.6
Inappropriate use of antiplatelets and anticoagulation in patients without CAD or vascular disease	13.4	13.6	12.4
Inappropriate use of DOAC in patients with AF and a mechanical heart valve	9.3	14.9	17.0
Inappropriate use of dofetilide or sotalol in patients with AF and end-stage kidney disease or on dialysis	1.8	1.8	0.3
Inappropriate use of calcium channel blocker when LVEF <40%	3.6	3.1	2.5
Smoking cessation counseling	80.3	71.9	67.4
Warfarin at discharge for patients with valvular AF or atrial flutter	71.5	62.3	54.2

Values are percentages.

GWTG-AFIB is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CAD, coronary artery disease; CVA, cerebral vascular accident; DOAC, direct oral anticoagulant; FDA, US Food and Drug Administration; GWTG-AFib, Get With The Guidelines—Atrial Fibrillation; HR, heart rate; INR, international normalized ratio; LVEF, left ventricular ejection fraction; PT, prothrombin time; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

Source: Unpublished American Heart Association tabulation, GWTG-AFib.

**Table 26-10. Quality-of-Care Measures by Race and Ethnicity and Sex in the GWTG-AFib Program, United States, 2023**

Quality-of-care measure	Race and ethnicity*				Sex	
	White	Black	Hispanic	Asian	Males	Females
ACE inhibitor/ARB or ARNI at discharge when LVEF ≤40%	82.1	84.6	89.6	73.3	83.2	81.4
β-Blocker at discharge when LVEF ≤40%	95.2	95.4	96.2	90.9	95.4	94.4
CHADS <sub>2</sub> -VASc score documented before discharge	77.7	77.2	66.7	65.3	76.2	77.4
FDA-approved anticoagulation at discharge	99.3	98.0	97.9	98.8	99.2	99.1
PT/INR planned follow-up documented before discharge for warfarin treatment	77.1	86.9	78.9	88.0	77.6	77.7
Statin at discharge in patients with AF with CAD, CVA/TIA, PVD, or diabetes	85.3	84.9	84.3	86.3	86.9	82.3
Aldosterone antagonist at discharge	41.6	44.6	42.7	56.3	41.5	44.8
Anticoagulation therapy education	53.7	60.0	55.4	65.9	52.2	57.1
DOAC at discharge for patients with nonvalvular AF or atrial flutter	91.7	91.1	92.1	95.4	91.9	91.3
Discharge HR ≤110 bpm	94.4	93.8	92.9	87.0	94.4	94.2
Inappropriate use of antiarrhythmics in patients with permanent AF	11.3	22.6	0.0	0.0	12.8	9.2
Inappropriate use of antiplatelets and anticoagulation in patients without CAD or vascular disease	12.2	12.9	11.1	11.2	13.3	11.1
Inappropriate use of DOAC in patients with AF and a mechanical heart valve	17.1	6.7	5.3	0.0	19.1	14.1
Inappropriate use of dofetilide or sotalol in patients with AF and end-stage kidney disease or on dialysis	0.2	0.0	1.9	0.0	0.5	0.0
Inappropriate use of calcium channel blocker when LVEF <40%	2.5	3.2	1.5	0.0	2.8	1.6
Smoking cessation counseling	67.6	69.5	65.0	70.0	65.5	71.6
Warfarin at discharge for patients with valvular AF or atrial flutter	53.5	58.8	66.7	62.5	52.2	56.4

Values are percentages.

GWTG-AFIB is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CAD, coronary artery disease; CVA, cerebral vascular accident; DOAC, direct oral anticoagulant; FDA, Food and Drug Administration; GWTG-AFib, Get With The Guidelines—Atrial Fibrillation; HR, heart rate; INR, international normalized ratio; LVEF, left ventricular ejection fraction; PT, prothrombin time; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

\*Race and ethnicity are assessed by the patient or, if that is not available, by the physician or institution.

Source: Unpublished American Heart Association tabulation, GWTG-AFIB.

**Table 26-11. Adherence to Quality-of-Care Measures in the GWTG-Stroke Program, United States, 2021 to 2023**

Quality-of-care measure	2021	2022	2023
Anticoagulation at discharge for AF/atrial flutter	97.0	97.0	96.7
Antithrombotics at discharge	96.5	97.4	97.3
Antithrombotics by end of hospital day 2	96.6	96.4	95.6
Statin at discharge: high intensity for ≤75 y of age or at least moderate intensity for >75 y of age	93.8	94.5	93.7
IV thrombolytic arrive by 3.5 h, treat by 4.5 h	92.2	93.0	91.4
Smoking cessation counseling	97.6	97.5	97.4
VTE prophylaxis day of or day after admission	99.0	99.0	99.0
Dysphagia screen before any oral intake	83.5	82.8	82.3
Stroke education	94.0	93.6	93.6
Rehabilitation assessed or received	99.0	98.9	98.4
LDL documented	93.7	93.7	93.1
Initial NIHSS score reported	93.9	94.1	92.1
Door to IV thrombolytic therapy within 60 min	86.3	86.4	87.5
Door to IV thrombolytic therapy within 45 min	64.6	65.0	70.3
Door to IV thrombolytic therapy within 30 min	30.6	31.5	36.3
Door to EVT device within 60 min for patients transferred or 90 min for patients presenting directly (24-h treatment window)	41.0	42.8	46.9
Door to EVT device within 60 min for patients transferred or 90 min for patients presenting directly (6-h treatment window)	39.5	40.8	43.0

Values are percentages.

GWTG-Stroke is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

AF indicates atrial fibrillation; EVT, endovascular therapy; GWTG, Get With The Guidelines; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and VTE, venous thromboembolism.

Source: Unpublished American Heart Association tabulation, GWTG-Stroke.

**Table 26-12. Adherence to Quality-of-Care Measures by Race and Ethnicity and Sex in the GWTG-Stroke Program, United States, 2023**

Quality-of-care measure	Race and ethnicity*				Sex	
	White	Black	Hispanic	Asian	Males	Females
Anticoagulation at discharge for AF/atrial flutter	96.7	96.4	96.5	98.0	96.7	96.7
Antithrombotics at discharge	97.3	97.7	97.0	97.2	97.7	97.4
Antithrombotics by end of hospital day 2	95.6	95.6	95.3	96.5	96.1	95.5
Statin at discharge: high intensity for ≤75 y of age or at least moderate intensity for >75 y of age	93.5	94.2	93.6	94.3	94.4	93.4
IV thrombolytic arrive by 3.5 h, treat by 4.5 h	91.3	91.4	92.8	92.1	91.8	91.6
Smoking cessation counseling	97.4	97.4	96.8	98.0	97.5	97.4
VTE prophylaxis day of or day after admission	99.0	99.1	98.8	99.1	99.0	99.0
Dysphagia screen before any oral intake	82.3	81.4	83.8	84.3	82.8	82.2
Stroke education	93.5	93.8	95.0	94.3	93.9	93.3
Rehabilitation assessed or received	98.4	98.4	98.3	98.4	98.4	98.4
LDL documented	92.9	93.2	93.9	94.6	93.5	93.2
Initial NIHSS score reported	92.2	91.5	92.9	92.6	92.5	92.0
Door to IV thrombolytic therapy within 60 min	87.3	87.3	88.1	91.6	87.9	87.1
Door to IV thrombolytic therapy within 45 min	69.5	70.9	72.5	78.0	71.0	69.6
Door to IV thrombolytic therapy within 30 min	35.5	35.7	38.7	45.3	37.8	34.6
Door to EVT device within 60 min for patients transferred or 90 min for patients presenting directly (24-h treatment window)	48.6	40.5	46.4	44.4	47.1	46.7
Door to EVT device within 60 min for patients transferred or 90 mins for patients presenting directly (6-h treatment window)	44.9	37.0	42.8	37.9	42.8	43.2

Values are percentages.

GWTG-Stroke is an in-hospital program for improving care by promoting consistent adherence to the latest scientific treatment guidelines.

AF indicates atrial fibrillation; EVT, endovascular therapy; GWTG, Get With The Guidelines; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and VTE, venous thromboembolism.

\*Race and ethnicity are assessed by the patient or, if that is not available, by the physician or institution.

Source: Unpublished American Heart Association tabulation, GWTG-Stroke.

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## 27. MEDICAL PROCEDURES

**See Table 27-1 and Charts 27-1 through 27-3**

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### Trends in Operations and Procedures

(See Table 27-1 and Chart 27-1)

According to HCUP data from the Agency for Healthcare Research and Quality for the year 2021<sup>1</sup> (Table 27-1):

- There were 444 730 PCIs performed on an inpatient basis in the United States.
- A total of 110 245 inpatient procedures involving carotid endarterectomy or stenting were performed.
- A total of 51 695 LA appendage-related procedures were performed.
- A total of 56 705 inpatient peripheral arterial bypass procedures were performed.
- Trends in the numbers of 5 common cardiovascular procedures in the United States from 2016 to 2021 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

- The STS Adult Cardiac Surgery Database collects data from participating groups, and as of December 31, 2021, the database included data from 1010 sites in United States, 5 sites from Canada, and 6 other international sites.<sup>2</sup> Data from the STS Adult Cardiac Surgery Database indicate that a total of 153 209 procedures involved isolated CABG in 2021. Isolated CABG made up 71.6% of the 8 major surgeries performed (N=213 996).
- Among other major procedures in 2021, there were 17 867 isolated aortic valve replacements, 10 449 isolated mitral valve replacements, 11 601 isolated mitral valve repairs, 12 543 procedures involving both aortic valve replacement and CABG, 3 416 procedures involving both mitral valve replacement and CABG, 3 443 procedures involving both

The 2025 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 2025. 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.

mitral valve repair and CABG, and 2 463 procedures involving both mitral valve replacement and aortic valve replacement.<sup>2</sup>

- Operative mortality for the major procedures in 2021 was as follows: isolated CABG, 2.5%; isolated aortic valve replacement, 2.3%; isolated mitral valve replacement, 5.5%; aortic valve replacement plus CABG, 4.4%; mitral valve replacement plus CABG, 11%; mitral valve repair, 1.1%; mitral valve repair plus CABG, 4.8%; and aortic valve replacement plus mitral valve replacement, 10%.<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 (interquartile range, 4–7 days) for isolated CABG. It was longest for mitral valve replacement plus CABG and aortic valve replacement plus mitral valve replacement (9 days [interquartile range, 7–14 days] for both).<sup>2</sup>

### Transcatheter Aortic Valve Replacement

- The STS-ACC TVT Registry collects data on TAVR procedures performed in the United States.<sup>3</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 4 508 in 2019. The number of sites in the United States performing TAVR was 715 by the end of August 2020.<sup>3</sup> The median age of patients undergoing TAVR in 2019 was 80 years of age (interquartile range, 73–85 years of age) compared with 84 years of age (interquartile range, 78–88 years of age) in the initial years after FDA approval of TAVR.
- In-hospital and 30-day mortality rates of TAVR have improved over time. In-hospital and 30-day mortality rates were 5.4% and 7.2%, 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 and 10.8% in 2019). Median length of stay was 2 days in 2019 (interquartile range, 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).

## Percutaneous LAAO

- The NCDR Left Atrial Appendage Occlusion Registry is an FDA-mandated postmarket surveillance registry. Hospitals are required by Centers for Medicare & Medicaid Services to submit data to this registry for Medicare reimbursement.<sup>4</sup> Between January 1, 2016, and December 31, 2018, it collected data on 38 158 percutaneous LAAO procedures in the United States. According to data from the registry:
  - The mean $\pm$ SD age of the patients was 76.1 $\pm$ 8.1 years of age, and 92.7% were  $\geq$ 65 years of age. Of the patients, 58.9% were male, 92.6% were White, and 4.6% were Black.
  - Of the hospitals that performed percutaneous LAAO, 37.6% were in the South, 22.7% were in the West, 22.2% were in the Midwest, and 17.4% were in the Northeast. Private/community hospitals and university hospitals performed 77.4% and 21.5% of the procedures, respectively.
  - In-hospital and 45-day mortality rates after discharge were 0.19% and 0.80%, respectively. Risk of any in-hospital major adverse event was 2.16%.<sup>5</sup>

## Congenital Heart Surgery

According to data from the STS Congenital Heart Surgery Database<sup>6</sup>:

- The database includes 143 910 congenital heart surgeries performed from July 2017 to June 2021 in 114 North American sites. After the exclusion of patients with a surgery date between April 1, 2020, and June 30, 2021, and who were diagnosed with SARS-CoV-2 before procedure or within 30 days after surgery, the unadjusted operative mortality was 2.7% (95% CI, 2.6%–2.8%) during that time period. The operative mortality stratified by age was as follows: 7.5% (95% CI, 7.1%–7.9%) in neonates, 2.4% (95% CI, 2.3%–2.6%) in infants, 1% (95% CI, 0.9%–1.2%) in children, and 1.5% (95% CI, 1.3%–1.8%) in adults.
- The frequencies of the 10 benchmark operations, selected by the STS Congenital Heart Surgery

Database Task Force using the most frequent procedures across all participating sites, were as follows: VSD, n=6788; TOF, n=4244; Glenn/hemi-Fontan, n=3729; Fontan, n=3608; off-bypass coarctation, n=3169; atrioventricular canal, n=2972; Norwood, n=2477; arterial switch operation, n=1809; arterial switch operation plus VSD, n=816; and truncus, n=509.

## Heart Transplantations

(See Charts 27-2 and 27-3)

According to data from the Organ Procurement and Transplantation Network<sup>7</sup>:

- In 2023, 4545 heart transplantations were performed in the United States, the most ever (Chart 27-2). A total of 54 combined heart-lung transplantations were performed in 2022 (up from 51 in 2022).
- The highest numbers of heart transplantations were performed in California (621), Texas (412), New York (361), and Florida (308).
- Of the recipients in 2023, 70.6% were males, 56.6% were NH White people, 24.8% were NH Black people, 12.8% were Hispanic people, 3.7% were Asian people, 0.8% were American Indian/Alaska Native people, 0.4% were Pacific Islander people, and 0.7% were multiracial people. Heart transplantations by recipient age are shown in Chart 27-3. The largest proportion of these patients (42.1%) were between 50 and 64 years of age.
- For transplantations that occurred between 2008 and 2015, the 1-year survival rate was 90.6% for males and 91.1% for females; the 3-year survival rate was 85.2% for males and 85.3% for females. The 5-year survival rates based on 2008 to 2015 transplantations were 78.4% for males and 77.7% for females. The 1- and 5-year survival rates for White individuals undergoing cardiac transplantation were 90.7% and 79.1%, respectively. For Black people, they were 90.7% and 74.1%, respectively. For Hispanic people, they were 90.1% and 79.9%, respectively. For Asian individuals, they were 91.4% and 80.2%, 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 May 21, 2024, 3468 individuals were on the waiting list for a heart transplantation, and 43 people were on the list for a heart-lung transplantation.

**Table 27-1. Estimated Inpatient Cardiovascular Operations, Procedures, and Patient Data, by Sex and Age (in Thousands), United States, 2021**

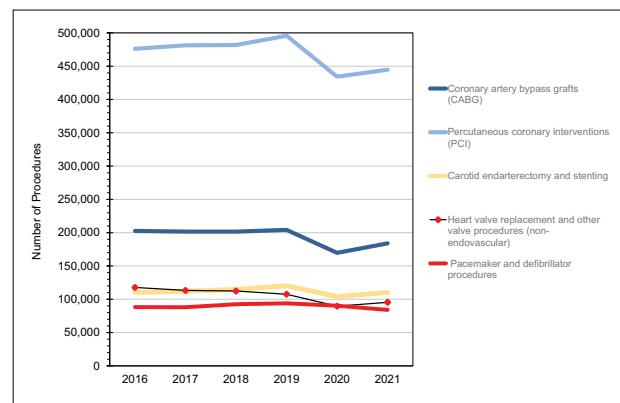
Operation/procedure	CCSR code	All	Sex		Age, y			
			Male	Female	18–44	45–64	65–84	≥85
Heart conduction mechanism procedures	CAR002	65 915	41 455	24 455	3255	19 160	39 120	3855
CABG	CAR003	184 000	140 630	43 350	4015	68 925	108 630	2405
PCI	CAR004	444 730	301 385	143 240	20 455	176 790	218 395	28 915
Other coronary artery procedures (excluding CABG and PCI)	CAR005	7110	5120	1985	615	2540	2730	130
CEA and stenting	CAR006	110 245	64 835	45 385	2790	26 630	72 980	7415
Embolectomy, endarterectomy, and related vessel procedures (nonendovascular; excluding carotid)	CAR007	75 710	45 310	30 380	5360	25 200	39 640	4750
Angioplasty and related vessel procedures (endovascular; excluding carotid)	CAR008	226 055	125 290	100 680	19 120	75 800	109 535	18 185
LA appendage procedures	CAR009	51 695	36 545	15 140	1495	16 565	32 765	850
Ligation and embolization of vessels	CAR010	97 020	54 530	42 475	20 710	29 790	32 965	5300
Aneurysm repair procedures	CAR011	82 965	50 710	32 245	7395	23 340	45 280	5530
Vessel repair and replacement	CAR012	102 415	65 425	36 955	13 330	31 650	46 210	3790
Heart and great-vessel bypass procedures	CAR013	7930	4630	3290	495	715	775	*
Peripheral arterial bypass procedures	CAR014	56 705	36 715	19 975	3250	20 675	30 450	2070
Peripheral arteriovenous fistula and shunt procedures	CAR015	17 880	10 520	7355	2645	7060	7395	710
Portal and other venous bypass procedures	CAR016	8090	5010	3075	1520	4140	2265	*
Pericardial procedures	CAR017	24 360	14 135	10 210	3910	8185	10 240	910
Heart transplantation	CAR018	3615	2545	1070	640	1825	620	0
Septal repair and other therapeutic heart procedures	CAR019	36 730	20 205	16 510	4655	9360	10 945	655
Saphenous vein harvest and other therapeutic vessel removal	CAR020	200 740	148 845	51 875	10 155	73 395	111 800	3270
Artery, vein, and great-vessel procedures, NEC	CAR021	13 150	6330	6815	1975	4165	5590	675
Heart valve replacement and other valve procedures (nonendovascular)	CAR022	95 410	60 200	35 200	9170	33 670	46 585	1135
Heart valve replacement and other valve procedures (endovascular)	CAR023	111 425	63 375	48 035	1680	8600	74 385	25 720
Pacemaker and defibrillator procedures	CAR026	84 020	55 120	28 885	5405	22 635	45 200	9720
Heart assist device procedures	CAR027	27 955	20 345	7605	2100	9805	14 005	1745

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 to AHRQ by the states. Total number of weighted discharges in the United States is based on HCUP NIS=33 334 053.

AHRQ indicates Agency for Healthcare Research and Quality; CABG, coronary artery bypass graft; CCSR, Clinical Classifications Software Refined; CEA, carotid endarterectomy; HCUP, Healthcare Cost and Utilization Project; LA, left atrial; NEC, not elsewhere classified; NIS, National/Nationwide Inpatient Sample; and PCI, percutaneous coronary intervention.

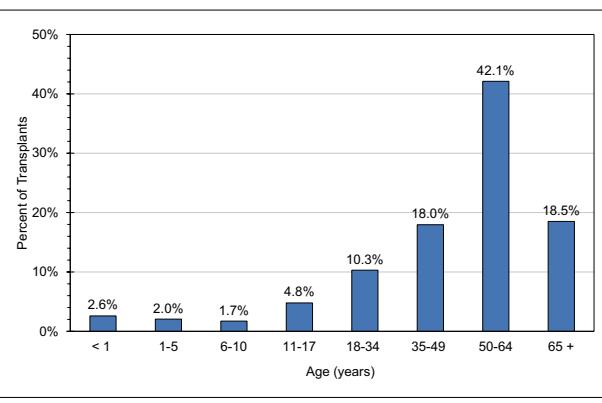
\*These statistics are suppressed.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using HCUP.<sup>1</sup>



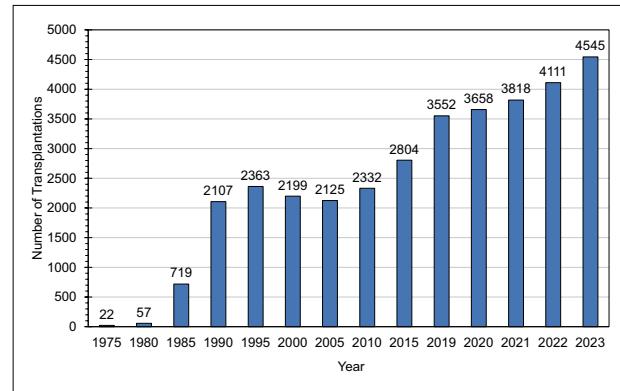
**Chart 27-1. Estimated inpatient cardiovascular operations and procedures, United States, 2016 to 2021.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Healthcare Cost and Utilization Project.<sup>1</sup>



**Chart 27-3. Heart transplantations by recipient age, United States, 2023.**

Source: Data derived from the Organ Procurement and Transplantation Network.<sup>7</sup>



**Chart 27-2. Trends in heart transplantations, United States, 1975 to 2023.**

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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In 2020 to 2021 (annual average) the annual direct and indirect costs of CVD in the United States were an estimated \$417.9 billion (Table 28-1). This figure includes \$233.3 billion in expenditures (direct costs, which include the costs of physicians and other professionals, hospital services, prescribed medications, and home health care but not the cost of nursing home care) and \$184.6 billion in lost future productivity (indirect mortality costs) attributed to premature CVD mortality in 2020 to 2021.

The direct costs for CVD for 2020 to 2021 (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." Indirect mortality costs are estimated for 2020 to 2021 (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 2020 to 2021.<sup>2</sup> 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 removes the effect of inflation in income over the lifetime of earnings.<sup>4</sup> The estimate is for 2014, inflated to 2021 to account for the 2014 to 2021 change in hourly worker compensation in the business sector reported by the US Bureau of Labor Statistics.<sup>5</sup> These estimates of

indirect costs do not include lost productivity attributable to cardiovascular morbidity from chronic, prevalent non-fatal CVD illness during 2020 to 2021 among workers, people keeping house, people in institutions, and people unable to work. Those morbidity costs were substantial in previous estimates, but because of the lack of contemporary data, an adequate comparable update could not be made.

### Costliest Diseases

**(See Tables 28-1 and 28-2 and Charts 28-1 through 28-3)**

Directs costs for CVD (diseases of the circulatory system) accounted for 11% of total US health expenditures in 2020 to 2021, more than any major diagnostic group except diseases of the musculoskeletal system.<sup>1</sup> By way of comparison, CVD direct costs shown in Table 28-1 were higher than the 2020 to 2021 Agency for Healthcare Research and Quality direct costs for neoplasms, which were \$173.3 billion.<sup>1</sup>

Table 28-1 shows direct and indirect costs for CVD by sex and by 2 broad age groups. During 2020 to 2021, 47% of the direct costs were in females and 39% of the direct costs were in individuals <65 years of age. CHD had the highest direct costs of the CVD conditions (Table 28-2). Chart 28-1 shows the direct costs of hypertension by the percentage of event type; the largest direct costs were for prescription medicines (30%) and office-based events (30%). Chart 28-2 shows direct costs for the 5 leading body systems on the MEPS list.

The estimated direct costs of CVD in the United States increased from \$189.7 billion in 2012 to 2013 to \$233.3 billion in 2020 to 2021 (Chart 28-3). The estimated direct costs in 2020 to 2021 were lower than in 2018 to 2019, likely because of COVID-19 shelter-in-place restrictions. In 2020 to 2021, CHD, ischemic stroke/TIA, and hypertension represented 23%, 11%, and 18%, respectively, of direct CVD costs.

The 2025 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 2025. 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. Costs of CVD (in Billions of Dollars), by Sex and Age, United States, Average Annual, 2020 to 2021**

	Total	Males	Females	<65 y of age	≥65 y of age
Direct costs*	233.3	124.0	109.3	91.8	141.5
Indirect costs, mortality only†	184.6	138.3	46.3	151.7	32.9
Total	417.9	262.3	155.6	243.5	174.4

Numbers do not add to total because of rounding.

CVD indicates cardiovascular disease.

\*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 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 are for people who died in 2020 to 2021, discounted at 3%.

Sources: Unpublished National Heart, Lung, and Blood Institute tabulation using the Household Component of the MEPS for direct costs (average annual 2020–2021).<sup>1</sup> Indirect mortality costs are based on 2020 to 2021 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 2021 from change in worker compensation reported by the US Bureau of Labor Statistics.<sup>5</sup>

**Table 28-2. Direct Costs (in Billions of Dollars) of CVD by Age Group, United States, Average Annual, 2020 to 2021**

	≥18 y of age	18–64 y of age	≥65 y of age
CHD	52.8	21.5	31.3
Heart attack/MI	22.1	10.2	11.8
Other CHD/angina	30.8	11.3	19.5
Cardiac dysrhythmias (including AF)	31.4	10.4	21.0
Hypertension*	41.4	17.9	23.4
Ischemic stroke/TIA	25.0	9.1	15.9
Diseases of arteries, veins, and lymphatics	40.0	18.7	21.3
Other HD and other stroke†	40.1	11.6	28.5
Total	230.8	89.3	141.5

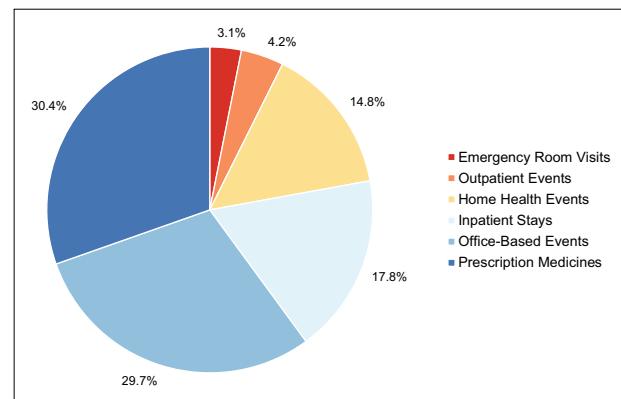
Numbers do not add to total because of rounding. Direct costs of \$2.5 billion for <18 years of age not shown.

AF indicates atrial fibrillation; CHD, coronary heart disease; CVD, cardiovascular disease; HD, heart disease; MI, myocardial infarction; and TIA, transient ischemic attack.

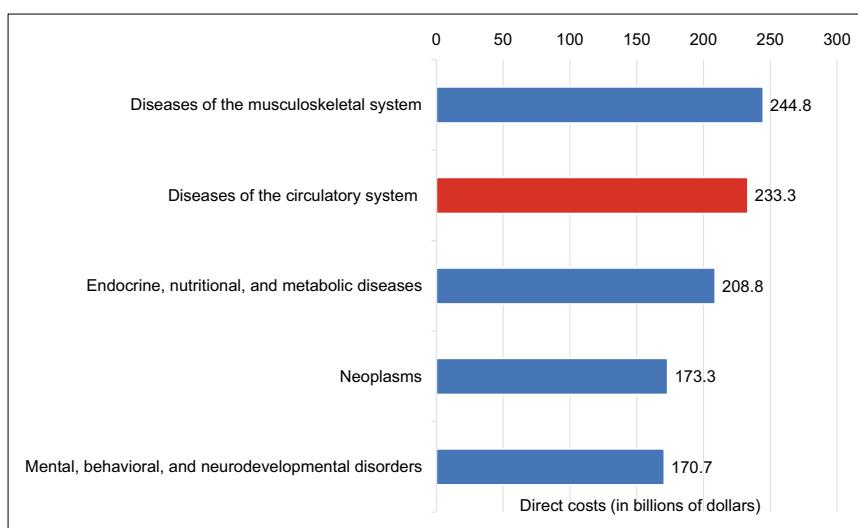
\*Costs attributable to hypertensive disease are limited to hypertension without HD.

†This category includes other types of HD, hemorrhagic stroke, and unspecified stroke.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey, average annual 2020 to 2021.<sup>1</sup>

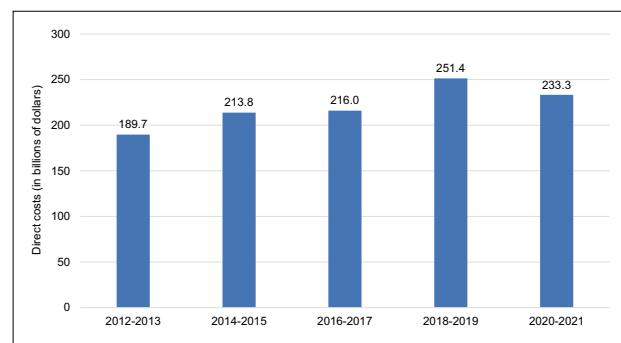
**Chart 28-1. Direct costs of hypertension by event type (percent), United States, average annual 2020 to 2021.**

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey data and excluding nursing home costs.<sup>1</sup>



**Chart 28-2. Direct costs by body system, United States, average annual 2020 to 2021 (in billions of dollars).**

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. Direct costs (in billions of dollars) of CVD, United States, average annual (2012–2013 to 2020–2021).**

CVD indicates cardiovascular disease.

*International Classification of Diseases, 9th Revision* coding for 2012 to 2015; *International Classification of Diseases, 10th Revision* coding for 2016 to 2021.

Source: Unpublished National Heart, Lung, and Blood Institute tabulation using Medical Expenditure Panel Survey for direct costs (average annual 2012–2013 to 2020–2021).<sup>1</sup>

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## 29. AT-A-GLANCE SUMMARY TABLES

See Tables 29-1 through 29-3

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

[Click here to return to the Abbreviations](#)

Sources: See the following summary tables for complete details:

- Obesity in Youth and Adults in the United States—Tables 6-1 and 6-2
- 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
- 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 2025 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 2025. 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* (both sexes)	NH Native Hawaiian or Pacific Islander* (both sexes)
Overweight and obesity								
Prevalence, 2017–2020								
Obesity, BMI $\geq 30.0 \text{ kg/m}^2$ †	41.9%	41.8%	43.1%	40.4%	45.2%	17.6%	...	...
Blood cholesterol								
Prevalence, 2017–2020								
TC $\geq 200 \text{ mg/dL}$ ‡	86.4 M (34.7%)	38.9 M (32.8%)	32.5%	27.5%	32.8%	40.7%	...	...
TC $\geq 240 \text{ mg/dL}$ ‡	24.7 M (10.0%)	11.0 M (9.5%)	9.6%	6.9%	9.3%	13.0%	...	...
LDL-C $\geq 130 \text{ mg/dL}$ ‡	63.1 M (25.5%)	30.3 M (25.6%)	25.0%	26.4%	23.7%	31.5%	...	...
HDL-C $< 40 \text{ mg/dL}$ ‡	41.3 M (16.9%)	29.9 M (24.9%)	25.0%	15.3%	29.5%	25.4%	...	...
HBP								
Prevalence, 2017–2020†	122.4 M (46.7%)	62.8 M (50.4%)	48.9%	57.5%	50.3%	50.2%	...	...
Mortality, 2022§	131 454	63 901 (48.6%)¶	44 028	11 665	5132	1861#	861	182
Mortality rate, age adjusted, 2022	31.5 per 100 000	35.4 per 100 000	33.3 per 100 000	67.3 per 100 000	28.0 per 100 000	20.7 per 100 000	34.4 per 100 000	31.5 per 100 000
Diabetes								
Prevalence, 2017–2020								
Diagnosed diabetes†	29.3 M (10.6%)	16.4 M (12.2%)	11.5%	11.8%	14.5%	14.4%	...	...
Undiagnosed diabetes†	9.7 M (3.5%)	4.6 M (3.5%)	2.6%	5.6%	5.3%	5.4%	...	...
Prediabetes†	115.9 M (46.4%)	63.5 M (52.9%)	57.2%	35.3%	50.7%	51.6%	...	...
Incidence, diagnosed diabetes, 2021**	1.2 M	620 000	...	...	...	...	...	...
Mortality, 2022§	101 209	57 557 (56.9%)¶	37 886	9371	7033	1982#	1219	303
Mortality rate, age adjusted, 2022	24.1 per 100 000	30.5 per 100 000	27.6 per 100 000	52.8 per 100 000	34.7 per 100 000	21.5 per 100 000	47.7 per 100 000	49.9 per 100 000

(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* (both sexes)	NH Native Hawaiian or Pacific Islander* (both sexes)
<b>Total CVD</b>								
Prevalence, 2017–2020†	127.9 M (48.6%)	65.4 M (52.4%)	51.2%	58.9%	51.9%	51.5%	...	...
Mortality, 2022§	941 652	494 740 (52.5%)¶	371 064	64 606	37 257	14 106 #	4874	1421
Mortality rate, age adjusted, 2022	224.3 per 100 000	273.9 per 100 000	277.8 per 100 000	379.7 per 100 000	202.4 per 100 000	154.7 per 100 000	193.3 per 100 000	245.8 per 100 000
<b>Stroke</b>								
Prevalence, 2017–2020†	9.4 M (3.3%)	4.0 M (2.9%)	2.7%	4.8%	2.5%	1.8%	...	...
New and recurrent strokes, 1999§	795.0 K	370.0 K (46.5%)¶	325.0 K††	45.0 K††	...	...	...	...
Mortality, 2022§	165 393	71 819 (43.4%)¶	51 042	10 293	6673	2852#	747	298
Mortality rate, age adjusted, 2022	39.5 per 100 000	40.5 per 100 000	38.6 per 100 000	63.5 per 100 000	37.6 per 100 000	31.6 per 100 000	30.3 per 100 000	52.7 per 100 000
<b>CHD</b>								
Prevalence, CHD, 2017–2020†	20.5 M (7.1%)	11.7 M (8.7%)	9.4%	6.2%	6.8%	5.2%	...	...
Prevalence, MI, 2017–2020†	9.3 M (3.2%)	6.1 M (4.5%)	4.8%	4.0%	3.1%	2.8%	...	...
Prevalence, AP, 2017–2020†	10.8 M (3.9%)	5.6 M (4.3%)	4.7%	2.7%	3.6%	2.7%	...	...
Mortality, 2022, CHD§	371 506	223 952 (60.3%)¶	172 181	24 839	16 840	6538	1973	551
Mortality rate, age adjusted, 2022, CHD	87.6 per 100 000	121.9 per 100 000	126.8 per 100 000	144.1 per 100 000	90.7 per 100 000	70.8 per 100 000	76.5 per 100 000	94.1 per 100 000
Mortality, 2022, MI§	103 905	62 571 (60.2%)¶	48 545	6695	4664	1855#	572	164
Mortality rate, age adjusted, 2022, MI	24.5 per 100 000	33.3 per 100 000	35.3 per 100 000	38.2 per 100 000	24.3 per 100 000	19.8 per 100 000	22.3 per 100 000	27.1 per 100 000
<b>HF</b>								
Prevalence, 2017–2020†	6.7M (2.3%)	3.7 M (2.7%)	2.9%	3.8%	1.8%	1.4%	...	...
Mortality, 2022§	87 941	41 657 (47.4%)¶	32 820	5101	2434	835#	354	94
Mortality rate, age adjusted, 2022	21.0 per 100 000	24.2 per 100 000	25.3 per 100 000	32.1 per 100 000	15.0 per 100 000	9.7 per 100 000	14.4 per 100 000	17.1 per 100 000

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. Combined because of low numbers in these categories.

†Age ≥20 years.

‡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.

§All ages.

||Mortality for Hispanic people, NH American Indian or Alaska Native people, NH Asian people, and NH Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese people, Filipino people, Japanese people, and other Asian people.

\*\*Age ≥18 years.

††Estimates include Hispanic males and NH males. Estimates for White males include other non-Black races.

**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* (both sexes)	NH Native Hawaiian or Pacific Islander* (both sexes)
Overweight and obesity								
Prevalence, 2017–2020								
Obesity, BMI $\geq 30.0$ kg/m <sup>2</sup> †	41.9%	41.8%	39.6%	57.9%	45.7%	14.5%	...	...
Blood cholesterol								
Prevalence, 2017–2020								
TC $\geq 200$ mg/dL‡	86.4 M (34.7%)	47.5 M (36.2%)	37.2%	29.6%	33.6%	37.7%	...	...
TC $\geq 240$ mg/dL‡	24.7 M (10.0%)	13.7 M (10.4%)	10.7%	9.3%	10.0%	8.7%	...	...
LDL-C $\geq 130$ mg/dL‡	63.1 M (25.5%)	32.8 M (25.4%)	24.0%	22.5%	27.5%	25.3%	...	...
HDL-C <40 mg/dL‡	41.3 M (16.9%)	11.4 M (9.3%)	8.8%	7.9%	11.8%	6.9%	...	...
HBP								
Prevalence, 2017–2020†	122.4 M (46.7%)	59.6 M (43.0%)	42.6%	58.4%	35.3%	37.6%	...	...
Mortality, 2022§	131 454	67 553 (51.4%)¶	49 115	10 647	4694	2146#	861	182
Mortality rate, age adjusted, 2022	31.5 per 100 000	27.6 per 100 000	26.8 per 100 000	44.7 per 100 000	20.4 per 100 000	17.0 per 100 000	34.4 per 100 000	31.5 per 100 000
Diabetes								
Prevalence, 2017–2020								
Diagnosed diabetes†	29.3 M (10.6%)	12.9 M (9.1%)	7.7%	13.3%	12.3%	9.9%	...	...
Undiagnosed diabetes†	9.7 M (3.5%)	5.1 M (3.5%)	2.8%	3.2%	4.5%	5.2%	...	...
Prediabetes†	115.9 M (46.4%)	52.4 M (40.0%)	38.8%	35.7%	41.3%	40.2%	...	...
Incidence, diagnosed diabetes, 2021**	1.2 M	591 000	...	...	...	...	...	...
Mortality, 2022§	101 209	43 652 (43.1%)¶	26 815	8583	5475	1727#	1219	303
Mortality rate, age adjusted, 2022	24.1 per 100 000	18.8 per 100 000	16.0 per 100 000	35.5 per 100 000	22.9 per 100 000	13.9 per 100 000	47.7 per 100 000	49.9 per 100 000
Total CVD								
Prevalence, 2017–2020†	127.9 M (48.6%)	62.5 M (44.8%)	44.6%	59.0%	37.3%	38.5%	...	...
Mortality, 2022§	941 652	446 912 (47.5%)¶	338 610	58 860	30 676	13 150#	4874	1421
Mortality rate, age adjusted, 2022	224.3 per 100 000	183.1 per 100 000	186.2 per 100 000	246.9 per 100 000	133.0 per 100 000	104.9 per 100 000	193.3 per 100 000	245.8 per 100 000
Stroke								
Prevalence, 2017–2020†	9.4 M (3.3%)	5.4 M (3.6%)	3.6%	5.4%	2.5%	1.5%	...	...
New and recurrent strokes, 1999§	795.0 K	425.0 K (53.5%)¶	365.0 K††	60.0 K††	...	...	...	...
Mortality, 2022§	165 393	93 574 (56.6%)¶	68 887	12 363	7551	3630#	747#	298
Mortality rate, age adjusted, 2022	39.5 per 100 000	38.2 per 100 000	37.5 per 100 000	52.2 per 100 000	33.0 per 100 000	29.0 per 100 000	30.3 per 100 000	52.7 per 100 000
CHD								
Prevalence, CHD, 2017–2020†	20.5 M (7.1%)	8.8 M (5.8%)	5.9%	6.3%	6.1%	3.9%	...	...
Prevalence, MI, 2017–2020†	9.3 M (3.2%)	3.2 M (2.1%)	2.2%	2.3%	1.9%	0.5%	...	...
Prevalence, AP, 2017–2020†	10.8 M (3.9%)	5.2 M (3.6%)	3.5%	4.1%	4.3%	2.7%	...	...
Mortality, 2022, CHD§	371 506	147 554 (39.7%)¶	112 164	18 264	10 754	4418	1973	551
Mortality rate, age adjusted, 2022, CHD	87.6 per 100 000	60.3 per 100 000	61.9 per 100 000	75.8 per 100 000	46.7 per 100 000	35.2 per 100 000	76.5 per 100 000	94.1 per 100 000
Mortality, 2022, MI§	103 905	41 334 (39.8%)¶	31 205	5193	3141	1278#	572	164
Mortality rate, age adjusted, 2022, MI	24.5 per 100 000	17.2 per 100 000	17.7 per 100 000	21.5 per 100 000	13.5 per 100 000	10.2 per 100 000	22.3 per 100 000	27.1 per 100 000

(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* (both sexes)	NH Native Hawaiian or Pacific Islander* (both sexes)
HF								
Prevalence, 2017–2020†	6.7 M (2.3%)	3.0 M (1.9%)	1.6%	3.3%	1.6%	0.5%	...	...
Mortality, 2022§	87 941	46 284 (52.6%)¶	37 152	5375	2478	883#	354	94
Mortality rate, age adjusted, 2022	21.0 per 100 000	18.5 per 100 000	19.6 per 100 000	22.7 per 100 000	11.0 per 100 000	7.0 per 100 000	14.4 per 100 000	17.1 per 100 000

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. Combined because of low numbers in these categories.

†Age ≥20 years.

‡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.

§All ages.

||Mortality for Hispanic people, NH American Indian or Alaska Native people, NH Asian people, and NH Native Hawaiian or Other Pacific Islander people should be interpreted with caution because of inconsistencies in reporting.

¶These percentages represent the portion of total incidence or mortality that is for males vs females.

#Includes Chinese people, Filipino people, Japanese people, and other Asian people.

\*\*Age ≥18 years.

††Estimates include Hispanic females and NH females. Estimates for White females include other non-Black races.

##Estimate considered unreliable or does not meet standards of reliability or precision.

**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														
Obesity, 2–19 y of age*	19.7%	20.9%	18.5%	17.6%	15.4%	18.8%	30.8%	29.3%	23.0%	13.1%	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, 2022†‡§	3213	1758 (54.7%)§	1455 (45.3%)§	1078	844	277	257	306	265	49	41			
Mortality rate, age adjusted, per 100 000, 2022	1.0	1.1	0.9	1.2	0.9	1.4	1.2	0.9	0.8	0.6	0.5			

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 people, American Indian or Alaska Native people, NH Asian people, and NH Native Hawaiian or Other 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 or Alaska Native, mortality: 22; NH Native Hawaiian or Other Pacific Islander, mortality: 10.

## REFERENCE

- Stierman B, Afful J, Carroll M, Chen T, Davy O, Fink S, Fryar C, Gu Q, Hales C, Hughes J, et al. National Health and Nutrition Examination Survey 2017–March 2020 prepandemic 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) and sponsors the Healthcare Cost and Utilization Project (HCUP; 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 2025 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 2025. 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; 1992–2022)
- 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, 111, 113, 120–151)*—Classification that 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."
  - *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.
  - *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.
- *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 ( $\geq 130$  mm Hg systolic blood pressure,  $\geq 85$  mm Hg 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 people, Black people, American Indian or Alaska Native people, 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.