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ORIGINAL ARTICLE

Thirty-Year Atherosclerotic Cardiovascular Disease Risk Among US Adults Aged 30 to 59 Years

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BACKGROUND: The 2023 Predicting Risk of Cardiovascular Disease Events equations estimate 30-year atherosclerotic cardiovascular disease (ASCVD) risk for adults aged 30 to 59 years to inform preventative treatment decisions. We aimed to characterize 30-year ASCVD risk in the eligible US population.

METHODS: We examined adults aged 30 to 59 without known ASCVD who participated in the National Health and Nutrition Examination Survey, 2017 to March 2020 cycle. Using survey weighting to generate nationally representative estimates with 95% CIs, we described 10-year and 30-year ASCVD risk and risk factor control. We then estimated the absolute risk reduction of statin use in populations at high 30-year risk (≥20%.

RESULTS: The cohort included 3229 participants without known ASCVD (mean [SD] age, 44.6 [8.8] years; 49.8% women), representative of 101.9 million (95% CI, 92.2–111.6) US adults. The mean estimated 10-year ASCVD risk was 2.0% (95% CI, 1.9%–2.1%), and the mean 30-year risk was 9.7% (95% CI, 9.4%–10.1%). Of the 9% of the population with high estimated 30-year ASCVD risk, 32.4% (95% CI, 24.0%–40.7%) reported statin use. Most adults with high 30-year ASCVD risk had multiple uncontrolled risk factors, including elevated blood pressure (70.8% [95% CI, 62.4%–79.2%]), obesity (59.9% [95% CI, 52.6%–67.2%]), and elevated total cholesterol (56.2% [95% CI, 45.5%–66.9%]). Expanding primary prevention statins to adults with high 30-year ASCVD risk would change recommendations for 2.5 million (95% CI, 1.9–3.2) adults not currently receiving statins, with an average number needed to treat over 10 years to prevent 1 ASCVD event of 78.3 (95% CI, 74.6–82.0).

CONCLUSIONS: Use of the Predicting Risk of Cardiovascular Disease Events 30-year ASCVD risk equations would identify a population of US adults with low 10-year but high 30-year risk who may warrant enhanced primary prevention strategies.

Key Words: adults ■ atherosclerosis ■ cardiovascular diseases ■ primary prevention ■ risk factors

Estimation of atherosclerotic cardiovascular disease (ASCVD) risk is now central to primary prevention efforts. Traditional 10-year ASCVD risk calculators have been criticized, however, for leading to undertreatment of younger at-risk people.[1,2] Use of risk equations with longer time horizons, such as 30 years or life-time, has been proposed to help guide preventative treatment decisions, including the use of lipid-lowering therapies, for middle-aged and younger adults. For example, the 2019 American Collefe of Cardiology (ACC) and American Heart Association (AHA) guideline on the primary prevention of cardiovascular disease recommends calculation of 30-year or life-time risk as a "communication strategy for reinforcing adherence to lifestyle recommendations"[3] whereas the 2018 AHA/ACC guideline on the management of blood cholesterol recommends 30-year or life-time risk "can be used to inform intensity of primary prevention efforts."[4]

To facilitate this, in 2023, the AHA Cardiovascular-Kidney-Metabolic Scientific Advisory Group developed the

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WHAT IS KNOWN

- Estimation of atherosclerotic cardiovascular disease (ASCVD) risk is central to primary prevention efforts but has largely relied on 10-year risk estimates, which may lead to undertreatment of younger at-risk people.
- The 2023 American Heart Association Predicting Risk of Cardiovascular Disease Events equations include a new 30-year ASCVD risk estimate using the same clinical inputs as for the 10-year ASCVD risk estimate.

WHAT THIS STUDY ADDS

- Applying the Predicting Risk of Cardiovascular Disease Events equations to a nationally representative population of adults aged 30 to 59 years, we found that 9% had an elevated estimated 30-year ASCVD risk of 20% or greater and 44% had an intermediate estimated 30-year risk of 7.5% to 19.9%, with elevated risk highly concentrated among individuals aged 50 to 59 years.
- Among adults with elevated 30-year ASCVD risk, nearly all had at least 2 uncontrolled modifiable risk factors, most commonly elevated blood pressure, body mass index, and total cholesterol.
- Expanding primary prevention statin recommendations to adults with 30-year ASCVD risk of 20% or greater would change recommendations for 2.5 million adults not currently receiving statins, with an average number needed to treat over 10 years to prevent 1 ASCVD event of 78, comparable to the estimated number needed to treat for adults currently recommended but not using primary prevention statins.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
BP	blood pressure
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
NHANES	National Health and Nutrition Examination Survey
PREVENT	Predicting Risk of Cardiovascular Disease Events

Predicting Risk of Cardiovascular Disease Events (PREVENT) equations, which included a new measure for predicting 30-year ASCVD risk using the same clinical inputs as for 10-year ASCVD risk.[5] Compared with the currently recommended pooled cohort equations,[6] the PREVENT equations were developed from a combination of more diverse and contemporary prospective cohorts and routinely collected electronic health record data, removed race, and added measures of renal function and statin use to risk prediction. This novel 30-year risk measure builds on prior calculators to estimate long-term risk based on more limited cohort studies.[7]

The population health implications of routinely estimating 30-year ASCVD risk and incorporating 30-year risk thresholds into primary prevention decisions are not known. One prior study described discordance between 10-year and 30-year PREVENT estimates of overall cardiovascular disease risk (inclusive of heart failure),[8] but there has not been an examination of 30-year ASCVD risk or of the potential population health implications of using these data. Thus, we used data from the National Health and Nutrition Examination Survey (NHANES)[9] to describe 30-year ASCVD risk in adults aged 30 to 59 at the population level and compare 30-year risk estimates to 10-year ASCVD risk estimates generated by the PREVENT equations. We then assessed differences in cardiovascular risk factor control across categories of 30-year ASCVD risk and estimated the potential impact of expanding primary prevention statin recommendations to individuals with elevated 30-year risk.

METHODS

Data Source

All data are made publicly available at the NHANES website, and all study materials will be made available on reasonable request. Our study analyzed the combined 2017 to March 2020 cycle of the NHANES. NHANES is conducted by the National Center for Health Statistics using a stratified, multistage probability-cluster sampling design.[9,10] Questionnaire, laboratory, and physical examination information is collected via in-home interviews and visits to a mobile examination center. This cross-sectional study was exempt from review and informed consent under the Common Rule, given its use of publicly available aggregated data. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline (Supplemental Material).

Study Population

NHANES participants aged 30 years to 59 years who completed the mobile examination center visit were included in the study population, as this is the target population of the PREVENT 30-year risk equations.[5] Adults with known ASCVD, defined as self-reported history of acute myocardial infarction, angina, coronary artery disease, or stroke, were excluded. Additional exclusions were pregnancy and missing variables used by the PREVENT risk calculators (Figure S1).

ASCVD Risk Estimation

We examined the 2023 PREVENT equations for estimating the 10-year and 30-year risk of ASCVD. The PREVENT 10-year equations have previously been externally validated in

NHANES with moderate-to-strong discrimination and calibration.[11] Both calculators include values for age, sex, total and HDL (high-density lipoprotein) cholesterol, systolic blood pressure (BP), diabetes status, smoking status, estimated glomerular filtration rate, antihypertensive medication use, and statin use. Sex, race, smoking status, and medication use were ascertained by NHANES participant self-report. Diabetes was identified by self-reported history or a hemoglobin A1c ≥6.5%. Total and HDL cholesterol were reported in mg/dL and converted to mmol/L using the conversion factor 0.02586 mg/dL per 1 mmol/L to match calculator units. BP was recorded as the average of up to 3 readings taken after resting for 5 minutes in a seated position, using a validated oscillometric device. Serum creatinine was used to calculate glomerular filtration rate using the 2021 Chronic Kidney Disease Epidemiology Collaboration equations,[12] consistent with PREVENT methodology. We did not examine the expanded PREVENT model with optional variables for hemoglobin A1c, urine albumin-creatinine ratio, and social deprivation index, as prior studies suggest little difference between enhanced and baseline PREVENT models.[5,13] Although PREVENT excluded individuals with outlier values of continuous measurements, we included these individuals and adjusted outlier measurements to calculate cutoffs to be consistent with clinical practice (eg, systolic BP of 205 mm Hg was recategorized to the maximum allowed value of 200 mm Hg).

Eligibility for Primary Prevention Statin

Adults were defined as eligible for primary prevention statin use based on the 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease,[3] which recommends statins for 3 groups of adults aged 40 years to 75 years: those with diabetes, those with a fasting LDL (low-density lipoprotein) cholesterol >190 mg/dL, and those with an estimated 10-year ASCVD risk of ≥7.5%. The guideline further subdivides 10-year ASCVD risk as intermediate (7.5%–19.9%) or high (≥20%). Individuals with an estimated risk <5% are classified as low risk, and those with an estimated risk of 5% to 7.4% as borderline risk; both groups are not routinely recommended pharmacotherapy in the absence of other risk-enhancing factors, and thus are referred to as low risk for this study. As fasting LDL cholesterol data is available for only a subset of NHANES participants and most individuals with an LDL >190 mg/dL also meet criteria for primary prevention by elevated 10-year ASCVD risk,[13] we did not examine LDL cholesterol separately.

Statistical Analysis

All analyses used NHANES mobile examination center weights for the 2017 to March 2020 cycle to result in nationally representative estimate results with 95% CIs.[9] Our analysis consisted of 3 steps. First, we calculated probability density distributions of estimated 10-year and 30-year ASCVD risk overall and across demographic characteristics of sex, age, race and ethnicity, and diabetes status. Then we graphically plotted a cross-tabulation of estimated 10-year and 30-year ASCVD risk using the PREVENT equations.

Second, we calculated the prevalence and control of ASCVD risk factors among adults stratified by the 30-year ASCVD risk categories. We examined the prevalence of hypertension (systolic BP >130 mm Hg or diastolic BP > 80 mm Hg), high total cholesterol (above 200 mg/dL), low HDL cholesterol (<40 mg/dL for mean and <50 mg/dL for women), diabetes (any and with hemoglobin A1c >7.0%), current smoking, obesity (body mass index of ≥30 kg/m^2), and chronic kidney disease (glomerular filtration rate <60 mL/min per 1.83 m^2). We also examined the current use of antihypertensives, statins, and diabetes medications.

Third, we calculated the total numbers of (1) adults aged 40 to 59 years meeting current guideline recommendations for primary prevention statin use based on the 2019 AHA/ACC primary prevention guidelines,[3] (2) adults aged 30 to 39 years with diabetes or 10-year ASCVD risk >7.5% not currently recommended primary prevention statin use because the pooled cohort equations did not estimate 10-year risk in this age group, but for whom 10-year risk is now able to be estimated using PREVENT equations, and (3) individuals not currently recommended primary prevention statin use but with elevated estimated 30-year ASCVD risk, using risk thresholds of 20%, 15%, and 10%. For each group, we calculated the number not currently taking statins and then estimated the number of estimated ASCVD events in 10 years among individuals not currently taking statins and the estimated number of ASCVD events in 10 years if these individuals were taking statins. To conduct these estimations, we multiplied each individual's 10-year estimated ASCVD risk by the expected relative risk reductions of 25% for statin therapy based on prior meta-analyses.[14,15] We then calculated the average absolute risk reduction and average number needed to treat (NNT) across each group.[16] This process was repeated to estimate ASCVD events, absolute risk reduction, and NNT at the 30-year horizon. The underlying PREVENT equations were adjusted for competing risks of death from noncardiovascular causes, and estimated risk reductions similarly accounted for competing risks.[5]

RESULTS

The study sample included 3229 NHANES participants, which was representative of 101.9 million (95% CI, 92.2–111.6) nonpregnant US adults without known ASCVD between the ages of 30 and 59 years after survey weighting. The weighted mean (SD) age of the cohort was 44.6 (8.8) years, 49.8% were female, 6.1% identified as Asian, 10.8% as Black, 9.3% as Mexican American, 8.0% as other Hispanic, and 61.1% as White (Table 1).

The mean estimated 10-year ASCVD risk for the cohort was 2.0% (95% CI, 1.9%–2.1%), and nearly all of the cohort had low (<7.5%) estimated risk (97.4% [95% CI, 96.6%–98.1%]; Figure S2). Of the 10.5% (95% CI 8.9%–12.1%) of the cohort that had diabetes, the majority also had low estimated 10-year risk (79.6% [95% CI, 72.4%–86.9%]).

Thirty-Year Estimated ASCVD Risk

The mean estimated 30-year ASCVD risk across the cohort was 9.7% (95% CI, 9.4%–10.1%), and the Figure depicts the distributions of 30-year risk across demographic groups. Mean 30-year risk was higher in men (11.5% [95% CI, 11.0%–12.0%]) than in women (7.9% [95% CI, 7.5%–8.4%]) and higher with each decade

Table 1. Characteristics of US Adults Aged 30 to 59 Years Without Known Atherosclerotic Cardiovascular Disease, Overall and by 30-Year Atherosclerotic Cardiovascular Disease Risk Category

	Total	Estimated 30-y atherosclerotic cardiovascular disease risk category		
		Low risk (<7.5%)	Intermediate risk (7.5%–19.9%)	High risk (≥20.0%)
Unweighted N	3229	1453	1398	378
Weighted N, millions (95% CI)	101.9 (92.2–111.6)	47.9 (42.9–52.9)	45.0 (40.3–49.6)	9.1 (7.4–10.8)
Characteristic, column % (95% CI)				
Age, y				
30–39	33.7 (31.1–36.4)	62.5 (59.0–65.9)	9.6 (6.4–12.9)	1.5 (0.2–2.8)
40–49	32.5 (30.1–34.9)	32.1 (28.8–35.3)	35.3 (31.7–38.8)	21.5 (13.3–29.7)
50–59	33.7 (31.2–36.3)	5.5 (4.0–6.9)	55.1 (51.2–59.0)	77.0 (68.9–85.1)
Sex				
Female	49.8 (47.5–52.2)	62.0 (59.6–64.4)	40.0 (36.0–44.1)	34.1 (27.6–40.7)
Male	50.2 (47.8–52.5)	38.0 (35.6–40.4)	60.0 (55.9–64.0)	65.9 (59.3–72.4)
Race and ethnicity				
Asian	6.1 (4.0–8.2)	6.9 (4.4–9.3)	5.5 (3.3–7.6)	5.4 (3.1–7.6)
Black	10.8 (8.0–13.5)	10.3 (7.1–13.5)	9.8 (7.6–12.1)	17.9 (11.8–23.9)
Mexican American	9.3 (6.9–11.7)	10.1 (7.2–13.0)	8.5 (6.4–10.6)	9.3 (4.9–13.8)
Other Hispanic	8.0 (6.0–10.0)	8.5 (6.2–10.8)	7.4 (5.2–9.7)	8.5 (4.1–13.0)
White	61.1 (55.4–66.7)	60.1 (53.1–67.0)	63.9 (59.1–68.7)	52.3 (39.4–65.2)
Other*	4.7 (3.7–5.8)	4.3 (2.7–5.8)	4.8 (2.8–6.9)	6.6 (1.7–11.4)
Education				
<12th grade	10.1 (8.5–11.7)	8.4 (6.5–10.3)	10.9 (8.7–13.0)	15.4 (10.0–20.8)
High school graduate	22.5 (19.3–25.8)	18.6 (14.2–23)	24.3 (19.8–28.8)	34.2 (24.9–43.5)
Some college	31.7 (28.7–34.7)	31.8 (27.3–36.3)	32.1 (28.4–35.9)	29.2 (23.3–35.1)
College graduate	35.6 (30.9–40.4)	41.1 (34.2–48.0)	32.7 (27.8–37.6)	21.2 (13.6–28.7)
Health insurance				
Commercial	63.4 (60.1–66.7)	63.5 (58.1–68.8)	65.4 (61.2–69.7)	52.8 (42.5–63.1)
Medicare	1.7 (1.2–2.2)	0.7 (0.2–1.2)	2.0 (1.1–3.0)	5.1 (1.5–8.7)
Medicaid	9.6 (7.9–11.4)	10.2 (8.2–12.3)	9.1 (6.4–11.8)	9.4 (5.7–13.2)
Other insurance	10.5 (7.9–13.2)	9.8 (6.4–13.2)	10.4 (7.5–13.2)	15.1 (7.1–23.1)
Uninsured	14.3 (11.8–16.8)	15.2 (12.0–18.4)	12.8 (10.0–15.7)	17.1 (10.3–23.9)
Missing	0.4 (0.2–0.7)	0.6 (0.2–1.0)	0.3 (0.0–0.5)	0.5 (0.0–1.1)
Access to care				
Routine place for care	82.0 (79.7–84.3)	79.4 (76.1–82.7)	84.1 (80.7–87.5)	85.3 (78.4–92.1)
Care in the past year	81.6 (79.4–83.8)	79.6 (76.8–82.3)	83.0 (79.5–86.4)	85.5 (79.5–91.5)

*Other race per survey includes multiracial.

of age. Among adults aged 30 to 39 years, only 0.4% (95% CI, 0.1%–0.7%]) had a high (≥20%) 30-year risk, compared with 20.3% (95% CI, 17.1%–23.5%) of adults aged 50 to 59 years. Estimated 30-year risk was similar between racial and ethnic groups. Estimated 30-year risk was substantially higher among adults with diabetes (21.2% [95% CI, 20.1%–22.3%]) than among adults without diabetes (8.4% [95% CI, 8.1%–8.7%]).

Overall, 10-year ASCVD risk scores were highly predictive of 30-year ASCVD risk scores (r^2=0.85). A weighted estimate of 9.1 million (95% CI, 7.4–10.8) adults aged 30 to 59 years had a high estimated 30-year risk ≥20% of which 6.6 million (95% CI, 5.0–8.1) had a 10-year risk <7.5% (Figure S3; Table S1). Among adults with low (<7.5%) estimated 10-year ASCVD risk, 48.2% (95% CI, 46.2%–50.3%) also had a low (<7.5%) estimated 30-year ASCVD, 45.2% (95% CI, 43.2%–47.1%) had intermediate (7.5%–19.9%) 30-year risk, and only 6.6% (95% CI, 5.3%–7.9%) had high (≥20%) 30-year risk. Nearly all adults with intermediate 10-year ASCVD risk had high 30-year ASCVD risk.

Cardiovascular Risk Factor Control

Among adults with high 30-year ASCVD risk, uncontrolled modifiable risk factors were common: 70.8%

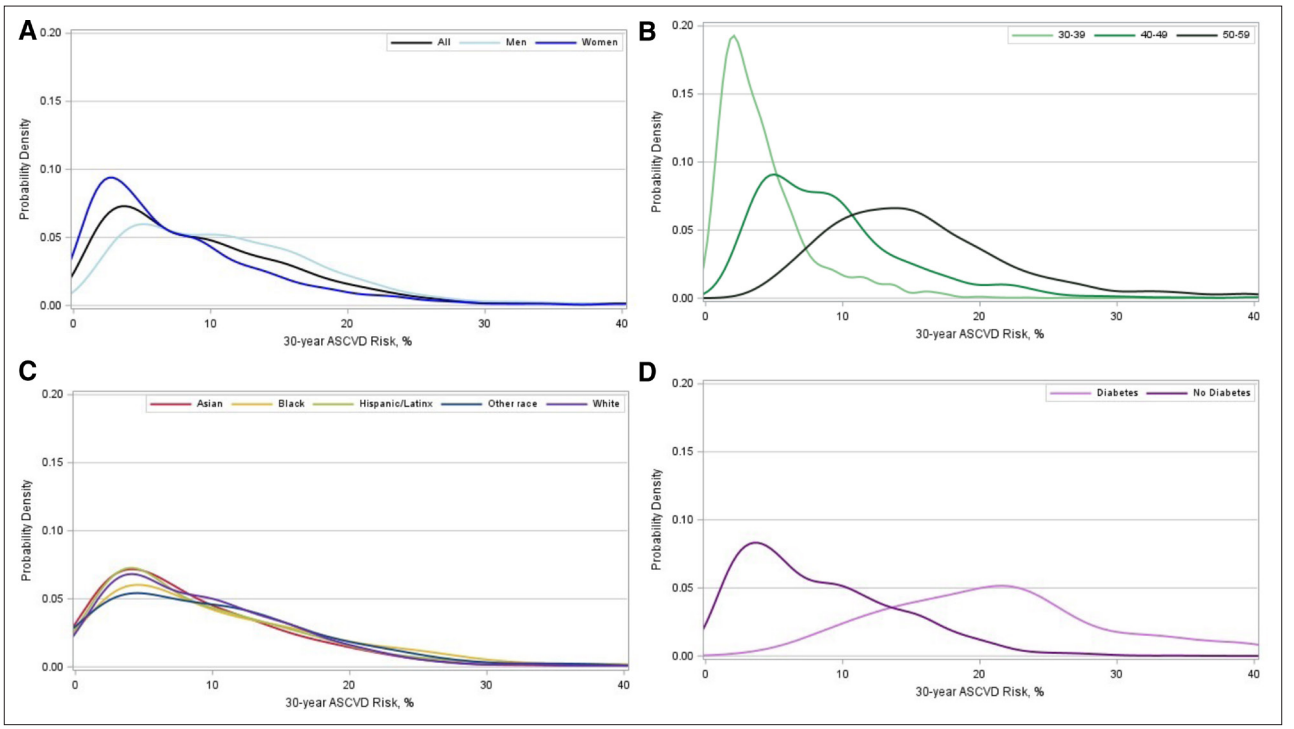

Figure. Marginal distributions of estimated 30-year atherosclerotic cardiovascular disease risk (ASCVD). (**A**) overall and by sex; (**B**) by age; (**C**) by race and ethnicity; and (**D**) by diabetes status. Lines and area under them represent the probability density of 30-year ASCVD risk for each group. Data from the National Health and Nutrition Examination Survey 2017 to 2020 were survey-weighted to the eligible US population.

(95% CI, 62.4%–79.2%) had elevated BP, 59.9% (95% CI, 52.6%–67.2%) had obesity, 56.2% (95% CI, 45.5%–66.9%) had elevated total cholesterol, 53.2% (95% CI, 44.6%–61.8%) had low HDL cholesterol, 31.1% (95% CI, 24.2%–38.5%) reported current smoking, and 31.4% (95% CI, 24.2%–38.5%) had an elevated hemoglobin A1c (Table 2). The prevalence of uncontrolled cardiovascular risk factors was lower among adults with low and intermediate 30-year ASCVD risk, but one-third of low-risk adults and two-thirds of intermediate-risk adults had 2 or more uncontrolled risk factors. In all groups, elevated BP, elevated total cholesterol, and obesity were the most common risk factors. Among individuals with high 30-year ASCVD risk, the presence of ≥3 uncontrolled risk factors was more common in adults aged 30 to 49 years (82.5%; [95% CI, 76.9%–88.1%]) than adults aged 50 to 59 years (68.3% [95% CI, 60.9%–75.8%]), almost no adults in either age category had zero uncontrolled risk factors (Table S2).

Individuals With Low 10-Year and High 30-Year ASCVD Risk

Among individuals with low 10-year ASCVD risk (<7.5%), the majority also had low 30-year ASCVD risk (<20%), but an estimated 6.6 million (95% CI 5.0–8.1 million) individuals had elevated 30-year risk of ≥20% (Table 3). In all key risk factors except sex, individuals with a high 30-year risk (≥20%) but low 10-year risk (<7.5%) had values that were between those whose risk were low for both 10-year and 30-year and those whose risk was high for both. For example, 29.5% (95% CI, 27.0%–31.9%) of those whose risk was low for both were 50 to 59 years old, compared with 72.5% (95% CI, 61.2%–83.9%) of those who were low 10-year but high 30-year and 88.6% (95% CI, 82.3%–94.9%) of those who had high 10-year and 30-year risk. Among adults with low 10-year and high 30-year ASCVD risk, nearly all had at least 2 uncontrolled modifiable risk factors, including 68.8% with elevated BP (95% CI, 59.4%–78.3%), 51.8% with diabetes (95% CI, 42.1%– 61.5%), and 48.7% with elevated cholesterol. In this group with low 10-year ASCVD risk, 35.8% (95% CI, 24.1%–47.4%) were taking statins, and 55.3% (95% CI, 46.7%–63.9%) were taking antihypertensives.

Estimated Impact of Expanding Primary Prevention Statin Indications

Among adults aged 40 to 59 years, 9.7 million (95% CI, 7.8–11.6 million) meet current guideline criteria for statins for primary prevention, 2.6 million (95% CI, 1.9–3.3 million) due to estimated 10-year ASCVD risk of ≥7.5% and 7.1 million (95% CI, 5.2–9.0 million) due to diabetes with low ASCVD risk (Table S3). Of statin-eligible adults, 5.7

Table 2. Prevalence and Control of Cardiovascular Risk Factors Among US Adults Aged 30 to 59 Years, by 30-Year ASCVD Risk

	30-year ASCVD risk		
	Low (<7.5%)	Intermediate (7.5%–19.9%)	High (≥20.0%)
Unweighted N	1453	1398	378
Weighted N, millions (95% CI)	47.9 (42.9–52.9)	45.0 (40.3–49.6)	9.1 (7.4–10.8)
Cardiovascular risk factors, column % (95% CI)			
Elevated BP			
BP >130/80 mm Hg	19.7 (16.9–22.4)	46.3 (41.5–51.1)	70.8 (62.4–79.2)
Taking any antihypertensive	6.5 (4.9–8.2)	26.3 (23.1–29.5)	57.6 (50.3–64.9)
Taking single antihypertensive	5.0 (3.3–6.7)	19.2 (16.1–22.3)	39.4 (33.0–45.9)
Taking multiple antihypertensives	1.5 0.8–2.3)	7.0 (5.5–8.5)	17.5 (11.6–23.3)
Cholesterol			
Total cholesterol ≥200 mg/dL	30.4 (26.6–34.1)	46.8 (41.5–52.1)	56.2 (45.5–66.9)
Low HDL cholesterol*	23.5 (20.3–26.7)	30.7 (26.9–34.5)	53.2 (44.6–61.8)
Taking statin	2.5 (1.1–3.8)	11.6 (8.7–14.6)	32.4 (24.0–40.7)
Diabetes			
Diabetes	0.5 (0.2–0.8)	10.9 (8.2–13.5)	61.4 (55.2–67.6)
Hemoglobin A1c >7.0%	0.1 (0.0–0.3)	5.2 (3.6–6.8)	31.4 (24.2–38.5)
Taking diabetes medications	1.0 (0.3–1.7)	9.3 (6.2–12.3)	40.4 (33.5–47.3)
Additional risk factors			
Current smoking	14.2 (10.5–17.9)	21.9 (19.4–24.4)	31.1 (23.2–39.0)
BMI >30 kg/m^2	34.9 (30.6–39.2)	48.6 (36.3–53.0)	59.9 (52.6–67.2)
GFR <60 mL/min per 1.73 m^2	0.6 (0.1–1.0)	1.5 (0.5–2.4)	3.6 (1.8–5.4)
No. of uncontrolled risk factors, column % (95% CI)†			
0	28.4 (24.5–32.2)	6.6 (4.3–8.9)	0.2 (0.0–0.6)
1	33.8 (30.7–37.0)	26.3 (23.1–29.4)	5.0 (0.0–10.3)
2	25.6 (23.4–27.9)	36.1 (31.0–41.2)	23.1 (18.5–27.8)
≥3	12.2 (9.8–14.6)	31.0 (26.3–35.7)	71.6 (65.6–77.6)

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; and HDL, high-density lipoprotein.

*Defined as a high-density cholesterol level of <40 mg/dL for men and <50 mg/dL for women.

†Uncontrolled risk factors include BP >130/80 mm Hg, total cholesterol >200 mg/dL, HDL cholesterol <40 mg/dL for men or <50 mg/dL for women, hemoglobin A1c >7.0%, current smoking, BMI >30 kg/m^2, and GFR <60 mL/min per 1.73 m^2.

million (95% CI, 4.5–6.9 million) were not taking statins, the majority of whom were adults with diabetes and low ASCVD risk. By 10-year ASCVD risk category, the mean NNT of using statins for 10 years to prevent 1 ASCVD event was 18.5 (95% CI, 13.7–23.4) for the high-risk group (≥20%), 40.4 (95% CI, 36.7–44.1) for the intermediate-risk group (7.5%–19.9%), and 111.4 (95% CI, 96.3–126.5) for the group with diabetes and low ASCVD risk (<7.5%; Table 4).

Expansion of current primary prevention statin recommendations to adults aged 30 to 39 years would result in an estimated 1.4 million (95% CI, 1.1–1.6 million) adults being newly eligible for statin pharmacotherapy. This group would have a much higher NNT (211.1 [95% CI, 194.5–227.7]) compared with populations currently statin-eligible, as the majority of this group consists of individuals with diabetes and low (<7.5%) ASCVD risk.

Further expanding statin recommendations to adults aged 30 to 59 with ≥20% 30-year ASCVD risk would result in 2.5 million (95% CI, 1.9–3.2 million) adults newly eligible for primary prevention statins not already taking them. This group had an NNT to prevent 1 ASCVD event in 10 years of 78.3 (95% CI, 74.6–82.0). Further expanding recommendations to adults with a 30-year risk between 7.5% and 20% would result in large increases in the population recommended statins, between 8 and 36 million, depending on cutoff used. However, groups with intermediate 30-year risk would have a mean absolute risk reduction <1% resulting in an estimated NNT between 117 and 288.

At a 30-year horizon, the NNT for individuals currently recommended statins to prevent 1 ASCVD event in 30 years of 19.7 (95% CI, 17.9–21.6; Table S4). If statin recommendations were expanded to adults aged 30 to

Table 3. Cardiovascular Risk Factors and Control of US Adults Aged 30 to 59 Years by 10-Year and 30-Year ASCVD Risk

	10-y risk <7.5%		10-y risk ≥7.5% and 30-y risk ≥20%*
	30-y risk <20%	30-y risk ≥20%	
Unweighted N	2847	259	119
Weighted N, millions (95% CI)	92.7 (83.8–101.6)	6.6 (5.0–8.1)	2.5 (1.8–3.2)
Nonmodifiable cardiovascular risk factors, column % (95% CI)			
Age, y			
30–39	36.9 (34.0–39.8)	1.6 (0.0–3.2)	1.3 (0.0–3.6)
40–49	33.7 (31.2–36.1)	25.9 (14.3–37.5)	10.1 (5.1–15.0)
50–59	29.5 (27.0–31.9)	72.5 (61.2–83.9)	88.6 (82.3–94.9)
Sex			
Female	51.4 (48.9–54.0)	32.7 (25.6–39.8)	37.8 (20.5–55.2)
Male	48.6 (46.0–51.1)	67.3 (60.2–74.4)	62.2 (44.8–79.5)
Modifiable cardiovascular risk factors, column % (95% CI)			
Elevated BP			
BP >130/80 mm Hg	32.5 (29.2–35.8)	68.8 (59.4–78.3)	75.9 (60.4–91.4)
Taking antihypertensive	16.0 (14.3–17.7)	55.3 (46.7–63.9)	63.7 (50.5–76.9)
Cholesterol			
Total cholesterol ≥200 mg/dL	38.3 (34.8–41.8)	48.7 (35.8–61.6)	75.6 (64.3–87.0)
Low HDL cholesterol†	27.0 (23.9–30.2)	53.7 (44.1–63.4)	51.9 (37.5–66.2)
Taking statin	6.9 (5.3–8.5)	35.8 (24.1–47.4)	23.6 (15.3–31.8)
Diabetes			
Diabetes	5.5 (4.2–6.8)	51.8 (42.1–61.5)	86.3 (78.4–94.1)
Hemoglobin A1c >7.0%	2.6 (1.8–3.4)	25.7 (17.0–34.4)	46.1 (32.0–60.2)
Taking diabetes medications	5.0 (3.5–6.5)	37.2 (27.7–46.7)	48.8 (35.4–62.1)
Additional risk factors			
Current smoking	18 (15.4–20.5)	27.7 (16.4–39)	40.0 (25.2–54.9)
BMI >30 kg/m^2	41.5 (38.0–45.0)	57.0 (47.3–66.7)	67.3 (56.6–78.1)
GFR <60 mL/min per 1.73 m^2	0.8 (0.4–1.3)	1.1 (0.0–2.2)	10.2 (3.3–17.1)
No. of uncontrolled risk factors, column % (95% CI)‡			
0	17.9 (15.4–20.3)	0.2 (0.0–0.5)	0.4 (0.3–0.6)
1	30.2 (28.3–32.2)	7.0 (0.0–14.1)	0.0 (0.0–0.0)
2	30.7 (27.9–33.6)	28.7 (22.6–34.7)	8.8 (1.9–15.7)
≥3	21.2 (18.1–24.2)	64.2 (56.3–72.1)	90.7 (83.8–97.7)

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; and HDL, high-density lipoprotein.

*The group of 10-year ASCVD risk≥7.5% and 30-year ASCVD risk <20% was only an unweighted sample size of 4 (weighted, millions [95% CI]: 0.1 [0.0–0.3]), so it was not included in this table.

†Defined as a high-density cholesterol level of <40 mg/dL for men and <50 mg/dL for women.

‡Uncontrolled risk factors include BP >130/80 mm Hg, total cholesterol > 200 mg/dL, HDL cholesterol <40 mg/dL for men or <50 mg/dL for women, hemoglobin A1c >7.0%, current smoking, BMI >30 kg/m^2, and GFR <60 mL/min per 1.73 m^2.

59 years with ≥20% 30-year ASCVD risk, the NNT to prevent 1 ASCVD event in 30 years would be 17.8 (95% CI, 17.3–18.2).

DISCUSSION

In this cross-sectional study of applying the 2023 PREVENT equations to a nationally representative population of adults aged 30 to 59 years without known ASCVD, we found that 9% had a high estimated 30-year risk (≥20.0%) and 44% had an intermediate estimated 30-year risk (7.5%–19.9%). Elevated 30-year risk was highly concentrated among the oldest ages in our cohort (ages, 50–59 years), with <1% of adults aged 30 to 39 years estimated to have elevated 30-year risk and over 20% of those aged 50 to 59 years. Treating by 30-year ASCVD risk always has a lower 10-year absolute risk reduction than treating by 10-year risk, but similar risk reductions to patients with diabetes with low 10-year ASCVD risk who are currently statin eligible. All scenarios

Table 4. Impact of Primary Prevention Statin Use Among US Adults Aged 30 to 59 Years Not Currently Taking Statins, by Risk Category

	No. not currently receiving statins, thousands (95% CI)	Mean estimated 10-y ASCVD risk, % (95% CI)	Mean 10-y absolute risk reduction, % (95% CI)	NNT for 10 y to prevent 1 ASCVD event, N (95% CI)
Currently recommended primary prevention statins				
Overall: ages 40–59 y currently recommended statins	5690.9 (4478.0–6903.8)	6.5 (6.0–7.1)	1.6 (1.5–1.8)	86.5 (74.2–98.7)
Ages 40–59 y with 10-y ASCVD risk ≥20%	53.0 (0.0–208.2)	22.3 (13.9–29.8)	5.6 (3.7–7.5)	18.5 (13.7–23.4)
Ages 40–59 y with 10-y ASCVD risk 7.5%–19.9%	1926.6 (1317.9–2535.3)	10.5 (9.5–11.5)	2.6 (2.4–2.9)	40.4 (36.7–44.1)
Ages 40–59 y with diabetes and 10-y risk <7.5%	3711.3 (2614.7–4807.9)	4.3 (3.9–4.6)	1.1 (1.0–1.1)	111.4 (96.3–126.5)
Expanding current recommendations to ages 30–39 y				
Ages 30–39 with diabetes or 10-y risk ≥7.5%	1379.9 (1120.1–1639.7)	2.5 (2.3–2.8)	0.6 (0.6–0.7)	211.1 (194.5–227.7)
Expanding recommendations based on estimated 30-y ASCVD risk*				
Ages 30–59 y with 30-y ASCVD risk ≥20%	2492.9 (1878.2–3197.6)	5.3 (5.0–5.5)	1.3 (1.3–1.4)	78.3 (74.6–82.0)
Ages 30–59 y with 30-y ASCVD risk 15% -19.9%	8519.6 (6912.2–10 126.9)	3.5 (3.4–3.7)	0.9 (0.8–0.9)	116.6 (112.2–121.1)
Ages 30–59 y with 30-y ASCVD risk 10%–14.9%	17 319.5 (14 776.5–19 862.4)	2.2 (2.1–2.3)	0.5 (0.5–0.6)	191.3 (184.7–197.8)
Ages 30–59 y with 30-y ASCVD risk 7.5%–9.9%	10 642.9 (9230.8–12 055.3)	1.4 (1.4–1.4)	0.4 (0.3–0.4)	288.3 (282.1–294.4)

ASCVD indicates atherosclerotic cardiovascular disease; and NNT, number needed to treat.
*Excludes adults with diabetes, or 10-year ASCVD risk ≥7.5% who are already recommended primary prevention statins.

of expanding current primary prevention statin eligibility would result in lower 10-year absolute risk reduction compared with increasing uptake of statin therapy among the ≈2 million adults with high and intermediate 10-year risk who are currently eligible but not receiving primary prevention pharmacotherapy.

The PREVENT 30-year risk equations build on prior long-term risk estimates[7,17,18] using more contemporary prospective cohort and electronic health record data and including additional risk factors and modifiers, including kidney function and statin use. Our study builds on a recent brief report describing 30-year cardiovascular disease risk estimated by PREVENT equations, which found that 1 in 7 patients had 30-year risk >20%.[8] The PREVENT cardiovascular disease risk estimates are based on different equations than the PREVENT ASCVD equations and include the development of heart failure as an outcome. We focused on ASCVD risk, which has more direct implications for guiding preventative lipid-lowering therapy decisions.

Despite state-of-the-art methods, the accuracy of the PREVENT 30-year risk estimation in today's population is difficult to accurately assess. Average follow-up in the PREVENT equations was <5 years, and maximal follow-up was 15 years, so 30-year risk estimates were developed by combining shorter risk assessments.[5] The PREVENT equations were modeled using age as a time scale, which may result in an overestimation of 30-year risk, since improving medical care will likely make ASCVD risk in the coming 30 years lower than what was observed in the cohorts informing PREVENT, though they did account for competing risks of noncardiovascular death. In addition, although the 10-year PREVENT equations have been externally validated in NHANES, the 30-year equations have not been examined.[11] Furthermore, potential errors and missing data in the electronic health record data that provided the majority of data on which the PREVENT equations were based could alter the equations' results, but the direction of possible bias is unknown.

Current guideline recommendations differ for adults aged 30 to 39 years, and the precise clinical use of 30-year risk in this population is undetermined. The 2018 AHA/ACC guideline on cholesterol management recommends estimating long-term ASCVD risk in younger adults to inform intensity of primary prevention efforts, and considering primary prevention statins in younger adults with a family history of premature ASCVD, in people whose LDL is above 160, and in patients with diabetes of >10 years duration or with evidence of nephropathy, retinopathy, neuropathy or peripheral vascular disease.[4] The 2019 AHA/ACC primary prevention guideline emphasizes the role of 30-year risk as being to improve communication and encourage medication adherence,[3] whereas the 2022 US Preventive Services Task Force makes no clinical recommendations for younger adults or on the use of long-term risk calculation.[19] The US Preventive Services Task Force does identify the need for more studies on the efficacy and safety of statin use in younger populations, particularly those with elevated long-term risk.

This study demonstrates that the estimated 30-year risk is closely correlated but does not precisely mirror 10-year risk, so there are adults with high 30-year-risk, but relatively low or moderate 10-year risk. However, the primary determinant of 30-year risk is age, not individual risk factors. Some clinicians encourage early treatment for individuals with high 30-year and life-time risk with statins and aggressive BP reduction. This is due to the possibility of legacy effects, where early treatment might have cumulative benefit when people are at higher risk later in life.[20] The legacy effect has not been clearly seen in randomized trials, though those are usually brief.[20–22] It

is observed in Mendelian randomization studies, observational cohorts, and it is biologically plausible.[23] An important concern about guiding statin treatment using 30-year risk is that statins increase diabetes risk.[24] If the increase in diabetes risk accumulates with prolonged statin use, this could be an unexpected harm of early statin use and warrants further study. Furthermore, the burden of recommending life-long preventative medications in younger adults is not well-established and may impact acceptance and adherence to other preventative cardiovascular medications (eg, antihypertensives).

Clinical Implications

The clinical implications of this study are broad. Individuals with elevated 30-year ASCVD risk will most importantly benefit from counseling on strategies to optimize lifestyle factors, including physical activity, diet quality, smoking cessation, and weight loss, for the more than half of the patients in this group who were obese. Statins and BP-lowering medications are already among the most used medications in the world, and the introduction of 30-year risk into clinical practice could broaden that use to millions more Americans. These medications' relatively low costs and good safety profile make them practical, though their appropriateness compared with nonpharmacological lifestyle modifications is unclear. As statins have been observed to have a consistent relative risk reduction across baseline levels of ASCVD risk, broadening treatment recommendations to lower risk groups will be less efficient than increasing uptake in groups with elevated 10-year risk who are not currently receiving statins.

Study Limitations

Our study has limitations. The 2017 to 2020 NHANES cycle response rate was 47% but was adjusted by NHANES to account for nonresponse. The 10-year PREVENT equations were developed to estimate risk for adults aged 30 to 79 years. We focused on the subset of adults aged 30 to 59 years for whom the PREVENT equations also estimate 30-year ASCVD risk. Estimates of clinical outcomes resulting from scenarios of statin eligibility expansion were based on assumptions of consistent relative risk reductions from meta-analysis; however, actual risk reductions may vary with medication adherence, dosage, and other clinical characteristics of patients. We did not examine other risk enhancers (eg, family history, additional biomarkers, or coronary calcium), as this data is not fully available in NHANES, but these factors may guide decision-making for patients with borderline risk. We did not examine the population health impact of lowering currently accepted 10-year ASCVD risk thresholds for treatment, which has also been proposed,[25] and acknowledge that guideline-recommended thresholds are typically the result of expert opinion and may vary, as demonstrated by current differences between USPSTF and AHA/ACC guidelines. We did not examine the broader PREVENT equations for estimating 10-year and 30-year risk of cardiovascular disease, which is a composite of ASCVD and heart failure, as primary prevention strategies for heart failure are not clearly established and may differ from the prevention of ASCVD. Finally, given the cross-sectional nature of this study, we are unable to test the legacy effect of early treatment. If the legacy effect is large, this could alter the results meaningfully.

Conclusions

Use of the PREVENT 30-year ASCVD risk equations would identify a population of US adults with low 10-year but high 30-year risk who may warrant enhanced primary prevention strategies. However, guiding treatment by 30-year risk prevents fewer events per year of treatment than guiding treatment by 10-year risk, indicating a larger population benefit from increasing primary prevention uptake among individuals currently recommended primary prevention pharmacotherapy due to elevated 10-year risk.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S3
STROBE Statement

REFERENCES

1. Stone NJ, Smith SC, Orringer CE, Rigotti NA, Navar AM, Khan SS, Jones DWD, Goldberg R, Mora S, Blaha M, et al. Managing atherosclerotic cardiovascular risk in young adults: JACC state-of-the-art review. *J Am Coll Cardiol.* 2022;79:819–836. doi: 10.1016/j.jacc.2021.12.016

2. Thanassoulis G, Sniderman AD, Pencina MJ. A long-term benefit approach vs standard risk-based approaches for statin eligibility in primary prevention. *JAMA Cardiol*. 2018;3:1090–1095. doi: 10.1001/jamacardio.2018.3476
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
5. Khan SS, Matshushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Kovesdy CP, et al. Chronic Kidney Disease Consortium and the American Heart Association Cardiovascular-Kidney-Metabolic Science Advisory Group. Development and validation of the American Heart Association's PREVENT equations. *Circulation*. 2024;149:430–449. doi: 10.1161/CIRCULATIONAHA.123.067626
6. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2935–2959. doi: 10.1016/j.jacc.2013.11.005
7. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the thirty-year risk of cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:3078. doi: 10.1161/CIRCULATIONAHA.108.816694
8. Krishnan V, Huang X, Perak AM, Coresh J, Ndumele CE, Greenland P, Lloyd-Jones DM, Khan SS. Discordance of 10- and 30-year predicted risk for cardiovascular disease in US adults. *JAMA*. 2025;333:1828. doi: 10.1001/jama.2025.2868
9. Centers for Disease Control and Prevention. About the National Health and Nutrition Examination Survey. Accessed October 25, 2024. https://www.cdc.gov/nchs/nhanes/about/index.html
10. Akinbami LJ, Chen TC, Davy O, Ogden CL, Fink S, Clark J, Riddles MK, Mohadjer LK. National Health and Nutrition Examination Survey, 2017–March 2020 prepandemic file: sample design, estimation, and analytic guidelines. *Vital Health Stat 1*. 2022;2:1–36. doi: 10.15620/cdc:115434
11. Scheuermann B, Brown A, Colburn T, Hakeem H, Chow CH, Ade C. External validation of the American Heart Association PREVENT cardiovascular disease risk equations. *JAMA Netw Open*. 2024;7:e2438311. doi: 10.1001/jamanetworkopen.2024.38311
12. Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, Mendu ML, Miller WG, Moxey-Mims MM, Roberts GV, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. *Am J Kidney Dis*. 2022;79:268.e1–288.e1. doi: 10.1053/j.ajkd.2021.08.003
13. Anderson TS, Wilson LM, Sussman JB. Atherosclerotic cardiovascular disease risk estimates using the predicting risk of cardiovascular disease events equations. *JAMA Intern Med*. 2024;184:963–970. doi: 10.1001/jamainternmed.2024.1302
14. Lloyd-Jones DM, Huffman MD, Karmali KN, Sanghavi DM, Wright JS, Pelser C, Gulati M, Masoudi FA, Goff DC. Estimating longitudinal risks and benefits from cardiovascular preventive therapies among Medicare patients: the Million Hearts Longitudinal ASCVD Risk Assessment tool: a special report from the American Heart Association and American College of Cardiology. *Circulation*. 2017;135:e793–e813. doi: 10.1161/CIR.0000000000000467
15. Karmali KN, Lloyd-Jones DM, Berendsen MA, Goff DC, Sanghavi DM, Brown NC, Korenovska L, Huffman MD. Drugs for primary prevention of atherosclerotic cardiovascular disease: an overview of systematic reviews. *JAMA Cardiol*. 2016;1:341–349. doi: 10.1001/jamacardio.2016.0218
16. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ*. 1995;310:452–454. doi: 10.1136/bmj.310.6977.452
17. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP, Lloyd-Jones DM. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321–329. doi: 10.1056/NEJMoa1012848
18. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA*. 2012;308:1795–1801. doi: 10.1001/jama.2012.14312
19. US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2022;323:746–753. doi: 10.1001/jama.2022.13044
20. Navar-Boggan AM, Peterson ED, D'Agostino RB, Neely D, Sniderman AD, Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. *Circulation*. 2015;131:451–458. doi: 10.1161/CIRCULATIONAHA.114.012477
21. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388:2532–2561. doi: 10.1016/S0140-6736(16)31357-5
22. Zhang Y, Pletcher MJ, Vittinghoff E, Clemons AM, Jacobs DR, Allen NB, Alonso A, Bellows BK, Oelsner EC, Zeki Al Hazzouri A, et al. Association between cumulative low-density lipoprotein cholesterol exposure during young adulthood and middle age and risk of cardiovascular events. *JAMA Cardiol*. 2021;6:1406–1413. doi: 10.1001/jamacardio.2021.3508
23. Sauser K, Levine DA, Hayward RA. A review of the clinical evidence related to early treatment of elevated LDL for cardiovascular primary prevention. *Evid Based Med*. 2015;20:162–169. doi: 10.1136/ebmed-2015-110170
24. Cholesterol Treatment Trialists' (CTT) Collaboration. Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis. *Lancet Diabetes Endocrinol*. 2024;12:306–319. doi: 10.1016/S2213-8587(24)00040-8
25. Khan SS, Lloyd-Jones DM. Statins for primary prevention of cardiovascular disease-with PREVENT, what's a clinician to do? *JAMA*. 2024;332:961–962. doi: 10.1001/jama.2024.13887