

Atherosclerotic cardiovascular disease events among adults with high predicted risk without established risk factors

Nathan Kong^{a,*}, Swati Sakhuja^b, Lisandro D. Colantonio^b, Emily B. Levitan^b, Donald M. Lloyd-Jones^c, Mary Cushman^d, Paul Muntner^e, Tamar S. Polonsky^a

^a Department of Medicine, University of Chicago, Chicago, IL, United States

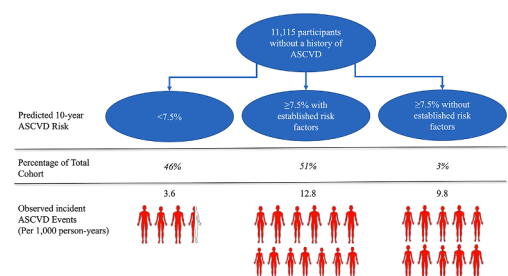
^b Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States

^c Feinberg School of Medicine, Department of Preventive Medicine, Northwestern University, Chicago, IL, United States

^d Department of Medicine, Larner College of Medicine, The University of Vermont, Burlington, VT, United States

^e Office of Science, Center for Disease Control and Prevention, Atlanta, GA, United States

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Cohort study
Preventative cardiology
ASCVD risk

ABSTRACT

Objective: Age is the strongest contributor to 10-year predicted atherosclerotic cardiovascular disease (ASCVD) risk. Some older adults have a predicted ASCVD risk $\geq 7.5\%$, without established risk factors. We sought to compare ASCVD incidence among adults with predicted ASCVD risk $\geq 7.5\%$, with and without established ASCVD risk factors, to adults with predicted risk $< 7.5\%$.

Methods: We analyzed data from REasons for Geographic and Racial Differences in Stroke study participants, 45–79 years old, without ASCVD or diabetes, not taking statins and with low-density lipoprotein cholesterol 70–189 mg/dL. Participants were categorized into 3 groups based on their 10-year predicted ASCVD risk and presence of established risk factors: $< 7.5\%$, $\geq 7.5\%$ with established risk factors and $\geq 7.5\%$ without established risk factors. Established risk factors included smoking, systolic blood pressure ≥ 130 mmHg or antihypertensive medication use, total cholesterol ≥ 200 mg/dL, or high-density lipoprotein cholesterol < 50 mg/dL for women (< 40 mg/dL for men). Participants were followed for ASCVD events.

Results: Among 11,115 participants, 911 incident ASCVD events occurred over a median of 11.1 years. ASCVD incidence rates were 3.6, 12.8, and 9.8 per 1,000 person-years for participants with predicted risk $< 7.5\%$,

Abbreviations: Atherosclerotic cardiovascular disease, (ASCVD); Body mass index, (BMI); Coronary artery calcium, (CAC); High-density lipoprotein cholesterol, (HDL-C); High-sensitivity C-reactive protein, (hs-CRP); Low-density lipoprotein cholesterol, (LDL-C); Myocardial infarction, (MI); Pooled Cohort Equations, (PCE); REasons for Geographic And Racial Differences in Stroke, (REGARDS).

* Corresponding author.

E-mail address: nwkong@gmail.com (N. Kong).

<https://doi.org/10.1016/j.ajpc.2023.100612>

Received 16 July 2023; Received in revised form 27 October 2023; Accepted 20 November 2023

Available online 22 November 2023

2666-6677/© 2023 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

predicted risk $\geq 7.5\%$ with established risk factors and predicted risk $\geq 7.5\%$ without established risk factors, respectively. Compared to adults with predicted risk $< 7.5\%$, hazard ratios for incident ASCVD in participants with risk $\geq 7.5\%$ with and without established risk factors were 3.58 (95% CI 3.03 – 4.21) and 2.72 (95% CI 1.91–3.88), respectively.

Conclusions: Adults with a 10-year predicted ASCVD risk $\geq 7.5\%$ but without established risk factors had a high ASCVD incidence.

1. Introduction

The estimation of atherosclerotic cardiovascular disease (ASCVD) risk with the Pooled Cohort Equations (PCE) is a key step when making decisions for primary prevention [1,2]. Initiation of statin therapy is recommended for adults ages 40 to 75 years with diabetes, low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL, or LDL-C 70 to 189 mg/dL and a 10-year predicted ASCVD risk $\geq 7.5\%$ after considering the presence of selected “risk enhancers” [2]. Age is the strongest contributor to 10-year predicted ASCVD risk [3]. As a result, some older adults have a 10-year predicted ASCVD risk $\geq 7.5\%$, even without established risk factors (i.e.: hypertension, dyslipidemia, and diabetes) [4]. For example, an adult without diabetes mellitus, who does not smoke, with a total cholesterol of 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) of 50 mg/dL, and systolic and diastolic blood pressure of 110/60 mm Hg without the use of antihypertensive medication exceeds a 10-year predicted ASCVD risk $\geq 7.5\%$ at 65 years for White men, 67 years for Black men, 71 years for White women and 72 years for Black women. Some have raised concerns that older individuals who meet thresholds for statin treatment primarily because of age when using the PCE may derive limited benefit [5].

Several observational studies have demonstrated a low incidence of ASCVD events among adults without established risk factors [6]. However, individuals with higher vs lower predicted ASCVD risk have a larger absolute risk reduction with the initiation of lipid-lowering medication, regardless of LDL-C levels [3,7,8]. Therefore, it is important to estimate the ASCVD event rates for adults with ASCVD risk $\geq 7.5\%$ without established risk factors. If adults with ASCVD risk $\geq 7.5\%$ without established risk factors do not experience high event rates, then they may derive little benefit from initiating a statin. In contrast, if adults with ASCVD risk $\geq 7.5\%$ without established risk factors experience a high ASCVD event rate, then initiating a statin may be of benefit.

Using data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study, we compared the incidence of ASCVD events among adults with 10-year predicted ASCVD risk $\geq 7.5\%$ who had established risk factors, adults with ASCVD risk $\geq 7.5\%$ who did not have established risk factors, and adults with ASCVD risk $< 7.5\%$, regardless of the presence of established risk factors. We further investigated whether some ASCVD risk factors not included in the PCE, referred hereafter as “risk modifiers”, were associated with incident ASCVD events within each of these three risk groups [2].

2. Methods

2.1. Study population

The REGARDS study has been described previously [9]. A total of 30,239 participants aged ≥ 45 years were enrolled from all 48 contiguous United States and the District of Columbia between January 2003 and October 2007. By design, participants living in the “stroke buckle” and “stroke belt” (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) and Black adults were oversampled. All participants completed a computer-assisted telephone interview followed by an in-home examination at baseline. The REGARDS study protocol was approved by the institutional review boards at the participating centers. All participants provided written

informed consent.

For the present analysis, we included REGARDS study participants ages 45 to 79 years, the upper age range of the ASCVD PCE, without a history of ASCVD or diabetes mellitus who were not taking a statin and had fasting LDL-C between 70 and 189 mg/dL ($n = 12,623$). Adults with diabetes or LDL-C ≥ 190 mg/dl were excluded as statins are recommended in this group regardless of their 10-year predicted ASCVD risk. Participants with atrial fibrillation ($n = 705$) or suspected heart failure ($n = 383$) were excluded because individuals with these conditions were not included in the population used to develop the PCE [1]. Participants without follow-up ($n = 177$) or missing data on the PCE components ($n = 243$) were also excluded. After these exclusions, 11,115 participants were included in the current analysis (Fig. 1).

2.2. Baseline data collection

Self-reported information on age, sex, race, region of residence, education, annual household income, cigarette smoking, alcohol use, physical activity, history of diabetes, atrial fibrillation, stroke, coronary heart disease [CHD], and antihypertensive medication use was collected by trained staff through a computer-assisted telephone interview. Participants were asked to fast overnight prior to completing an in-home examination. During the examination, weight, height, waist circumference and blood pressure were measured, blood and spot urine samples were collected, and an electrocardiogram (ECG) was performed. Additionally, the names of all prescription and over-the-counter medications taken during the 2 weeks prior to the in-home visit were recorded based on a pill bottle review. Weight and height were used to calculate body mass index (BMI). Abdominal obesity was defined as a waist circumference ≥ 88 cm among women and ≥ 102 cm among men. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured using blood samples by colorimetric reflectance spectrophotometry. LDL-C was calculated using total cholesterol, HDL-C, and triglycerides using the Sampson equation [10]. High-sensitivity C-reactive protein (hs-CRP) and cystatin C were measured by particle-enhanced immunonephelometry. Albuminuria was defined as a urine albumin to urine creatinine ratio ≥ 30 mg/g. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [11].

A history of ASCVD at baseline was defined as self-report of a physician diagnosis of myocardial infarction (MI) or stroke; a self-report of prior coronary artery bypass, coronary angioplasty, or stenting; a lower extremity revascularization procedure or an aortic aneurysm repair surgery; or evidence of a previous MI on the study ECG. Diabetes was defined by a fasting serum glucose level ≥ 126 mg/dL, a random serum glucose of ≥ 200 mg/dL for the 1621 (14.6%) participants who did not fast for a minimum of 8 h, or self-report of a prior diagnosis by a medical professional with current use of insulin or oral glucose-lowering medications. Prediabetes was defined as fasting serum glucose between 100 and 125 mg/dL or a random serum glucose between 140 and 199 mg/dL among those without diabetes [12]. Atrial fibrillation was defined by self-report or electrocardiogram evidence. Participants were considered to have suspected heart failure if they were taking digoxin in the absence of atrial fibrillation, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker plus beta-blocker in the absence of hypertension, carvedilol, spironolactone, loop diuretics, and/or a combination of hydralazine and nitrates as previously reported [13]. Statin

use was ascertained through medication inventory or by self-reported use of lipid-lowering medications. Diet was assessed using a food frequency questionnaire about the usual dietary intake of each participant over the last year. Physical activity was assessed with a questionnaire to determine the number of times per week vigorous physical activity was performed. Diet and physical activity were categorized into ideal, intermediate, and poor levels based on the AHA Life's Simple 7, as reported previously [14].

2.3. Outcome

The outcome of interest was incident ASCVD. Following the in-home visit, participants or their proxies were contacted twice a year via telephone to identify potential incident ASCVD events. Incident ASCVD was defined as the first event of a nonfatal or fatal stroke or CHD, including nonfatal MI or CHD death event. For MI, medical records were examined

for the presence of signs or symptoms suggestive of ischemia; a rising and/or falling pattern in cardiac troponin level or creatine phosphokinase-MB level over 6 or more hours with a peak level greater than twice the upper limit of normal; and electrocardiogram changes consistent with ischemia or MI, guided by the Minnesota code [15,16]. For stroke, medical records were retrieved for adjudication when stroke symptoms with a subsequent hospitalization, stroke, or heart-related hospitalization were reported. A committee of experts adjudicated strokes according to the World Health Organization definition as “rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin” [17,18]. When deaths were reported, interviews with proxies, medical records in the last year of life, death certificates, and autopsy reports were used to determine whether stroke or CHD was the main underlying cause. We used follow-up data for CHD and stroke events through December 31, 2017.

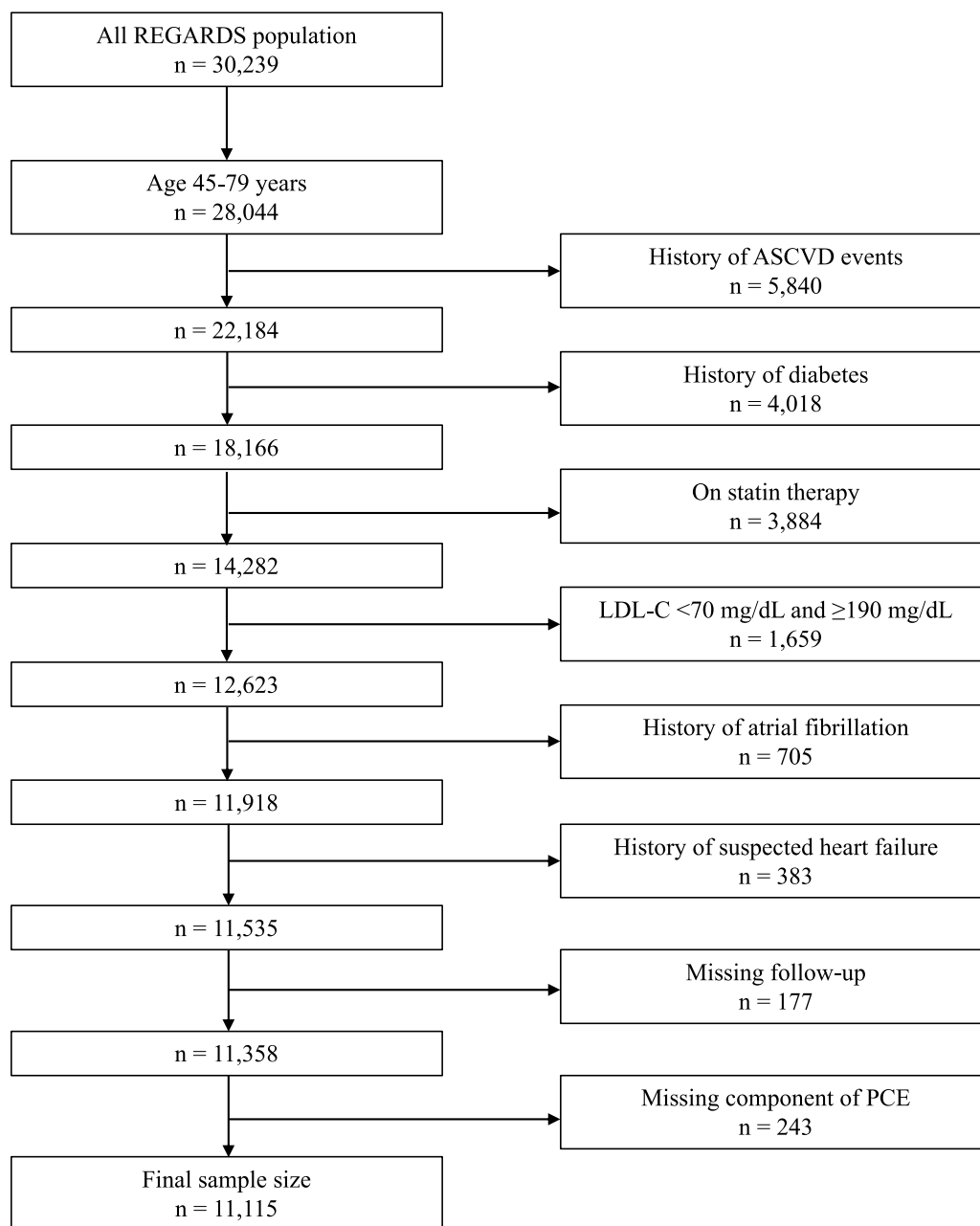


Fig. 1. Exclusion cascade for analysis of 10-year predicted ASCVD risk with and without established risk factors and association with incident ASCVD events. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCE, pooled cohort equations.

2.4. ASCVD risk groups

Each participant’s 10-year ASCVD risk was calculated using the sex- and race-specific PCE. Participants were categorized based on their ASCVD risk: <7.5 %, ≥ 7.5 % with established risk factors, and ≥ 7.5 % without established risk factors. Participants in the risk ≥ 7.5 % without established risk factors were non-smokers with systolic blood pressure (SBP) <130 mm Hg and not taking antihypertensive medication, and had total cholesterol <200 mg/dL, and HDL-C ≥ 50 mg/dL for women or ≥ 40 mg/dL for men. An SBP cutoff of 130 mm Hg was used as this is the level at which antihypertensive medication is recommended in the 2017 ACC/AHA guidelines on the management of blood pressure [19].

2.5. Statistical analysis

Baseline characteristics and the incidence rate per 1000 person years along with 95 % confidence intervals (CI) for composite ASCVD events were calculated for participants in each of the three ASCVD risk groups. Crude hazard ratios (HR) and 95 % CI for the association between the risk ≥ 7.5 % with and without established risk factors groups and incident ASCVD events were estimated using Cox proportional hazard models. The ASCVD risk <7.5 % group served as the reference. The proportional hazards assumption was confirmed using the Schoenfeld residual method. The analysis was conducted for the overall population and stratified by sex. A secondary analysis was performed comparing the risk < 7.5 % and risk ≥ 7.5 % without established risk factors groups using participants in the risk ≥ 7.5 % with established risk factors group as the reference. As adults with and without established risk factors groups may have a different distribution of estimated ASCVD risk, we further stratified participants into smaller estimated risk categories (10-year predicted ASCVD risk groups <5 %, 5 % to <7.5 %, 7.5 % to <10 %, 10 % to <15 %, 15 % to <20 %, and ≥ 20 %). Incidence rates and HRs, with 10-year predicted ASCVD risk 5 to <7.5 % serving as the reference, were then calculated within each subgroup. Hazard ratios were not adjusted for traditional risk factors given that these variables were already incorporated into the PCE. Additionally, results were not adjusted for socioeconomic demographics (i.e. income, education, insurance status) due inability to standardize these measures into clinical care. In a sensitivity analysis, we used an SBP <120 mm Hg without the use of antihypertensive medication, which is considered a normal BP, as the BP criterion in defining risk ≥ 7.5 % without established risk factors group and the incidence rates and HRs were recalculated [19].

2.6. Risk modifiers

Levels of ASCVD risk modifiers not included in the PCE but that could influence ASCVD risk were measured, including diet, physical activity, alcohol use, BMI, eGFR, cystatin C, LDL-C, hs-CRP, triglycerides, albuminuria, and pre-diabetes. The levels were estimated for participants within the three 10-year predicted ASCVD risk groups. Elevated LDL-C, hs-CRP, and triglycerides were also assessed in our study as risk modifiers as they are highlighted in the most recent guidelines [2]. Using *t*-tests or chi-square tests we compared the levels of each risk factor between those who did and did not experience an ASCVD event during follow-up. Two-sided P values of < 0.05 were considered statistically significant. Analyses were conducted using SAS 9.4 (Cary, NC).

3. Results

3.1. Study population and baseline characteristics

The risk <7.5 %, risk ≥ 7.5 % with established risk factors, and risk ≥ 7.5 % without established risk factors groups included 5116 (46.0 %), 5637 (50.7 %), and 362 (3.3 %) participants with a mean age of 56.3 (standard deviation [SD] 5.9), 66.3 (SD 7.1), and 69.9 (SD 5.1) years respectively (Table 1). Compared to participants with risk ≥ 7.5 % with

Table 1
Baseline characteristics* of participants by ASCVD risk group.

Participant characteristics	Risk <7.5 % (n = 5116)	Risk ≥ 7.5 % with established risk factors (n = 5637)	Risk ≥ 7.5 % without established risk factors (n = 362)
Age, years	56.2 (5.9)	66.3 (7.1)	69.9 (5.1)
Men, %	21.9	57.2	76.2
Black, %	32.4	41.9	22.9
Geographic region, %			
Stroke belt	34.7	35.7	27.9
Stroke buckle	23.1	17.8	17.7
Other US regions	42.2	46.5	54.4
Less than high school education, %	4.5	11.5	5.3
Annual household income <\$25,000, %	18.4	29.4	15.7
Body mass index (kg/m ²), %			
Normal (<25)	32.4	25.6	46.7
Overweight (25 to <30)	35.2	40.7	40.0
Obese (≥ 30)	32.4	33.7	14.4
Abdominal obesity present, %	39.3	43.1	20.7
Current smoker, %	9.4	21.3	0.0
Alcohol drinker, %			
None	55.8	52.8	59.5
Moderate	39.3	42.0	35.8
Heavy	4.8	5.2	4.7
Diet Score			
Ideal/Intermediate	22.9	17.9	22.8
Poor	77.1	82.1	77.2
Physical activity score, %			
Ideal	30.2	33.0	41.9
Intermediate	41.9	36.9	32.2
Poor	27.9	30.1	25.8
Total cholesterol, mg/dL	202 (31)	204 (32)	179 (15)
LDL-C, mg/dL	123.9 (27.0)	129.4 (26.9)	107.4 (15.1)
Triglycerides, mg/dL	112.4 (63.2)	135.4 (79.2)	92.6 (40.1)
HDL-C, mg/dL	58 (16)	51 (16)	55 (11)
Cystatin C, mg/L	0.9 (0.2)	1.0 (0.3)	0.9 (0.2)
LDL-C ≥ 160 mg/dL, %	11.2	14.6	0.0
hs-CRP ≥ 2 mg/L, %	48.0	54.3	39.5
Triglycerides ≥ 150 mg/dL, %	19.1	30.1	7.5
eGFR < 60 mL/min/1.73m ² , %	1.8	7.6	3.9
Albuminuria, %	5.4	11.3	5.9
Prediabetes, %	15.8	23.0	16.6
Systolic blood pressure, mm Hg	118 (13)	132 (16)	118 (8)
Diastolic blood pressure, mm Hg	75 (9)	79 (10)	72 (8)
Antihypertensive medication use, %	22.9	48.8	0.0
10-year predicted ASCVD risk %	3.6 [2.0–5.5]	14.1 [10.4–19.6]	12.0 [9.3–15.6]

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; ASCVD, atherosclerotic cardiovascular disease.

* Results reported as mean (standard deviation) or median (inter-quartile range) for 10-year predicted atherosclerotic cardiovascular disease risk as it was not non-normally distributed.

established risk factors, participants with risk ≥ 7.5 % without established risk factors were more likely to be male, have a BMI < 25 kg/m², an ideal/intermediate diet, and have an ideal physical activity level. Ideal or intermediate diet scores were observed in fewer than ¼ of the

participants, with the smallest proportion in the risk $\geq 7.5\%$ with established risk factors group (Table 1). The risk $\geq 7.5\%$ without established risk factors group had the highest proportion of adults with ideal physical activity scores (Table 1). The risk $\geq 7.5\%$ without established risk factors had a lower percentage of black participants (22.9%) compared to the risk $<7.5\%$ (32.4%) and the risk $\geq 7.5\%$ with established risk factors (41.9%). Participant characteristics when 10-year predicted risk groups were further divided into smaller subgroups are presented in Supplemental Table 1. Predicted 10-year ASCVD risk overlapped between those in risk $\geq 7.5\%$ with and without established risk factors groups (Fig. 2).

3.2. Incident cardiovascular events

A total of 911 incident ASCVD events occurred over a median follow-up of 11.1 years. The incidence rate per 1000 person-years among the risk $<7.5\%$ group was 3.6 (95% CI 3.1 to 4.1), compared to 12.8 (95% CI 11.8 to 13.7) in the risk $\geq 7.5\%$ with established risk factors group and 9.8 (95% CI 6.9 to 13.2) in the risk $\geq 7.5\%$ without established risk factors group (Central Illustration). Adults in the risk $\geq 7.5\%$ with established risk factors group had a HR of 3.58 (95% CI 3.03 to 4.21), and the risk $\geq 7.5\%$ without established risk factors group had a HR of 2.72 (95% CI 1.91 to 3.88), each compared to the risk $<7.5\%$ group (Table 2). When using the risk $\geq 7.5\%$ with established risk factors as the reference group, the HR for ASCVD events was 0.76 (95% CI 0.55 to 1.06) for the risk $\geq 7.5\%$ without established risk factors group. The risk $\geq 7.5\%$ with established risk factors group had a HR of 3.58 (95% CI 2.91 to 4.41) while the risk $\geq 7.5\%$ without established risk factors group had a HR of 2.62 (95% CI 1.29 to 5.37) compared to the risk $<7.5\%$ group in women. In men, the risk $\geq 7.5\%$ with established risk factors group had a HR of 3.07 (95% CI 2.29 to 4.11) and the risk $\geq 7.5\%$ without established risk factors group had a HR of 2.31 (95% CI 1.46 to 4.11) compared to the risk $<7.5\%$ group (Supplemental Table 2).

The incidence rates in the risk $\geq 7.5\%$ with established risk factors were 6.3, 10.3, 14.1, and 22.2 per 1000 person-years for participants with a 10-year predicted ASCVD risk of 7.5% to $<10\%$, 10% to $<15\%$, 15% to $<20\%$, and $\geq 20\%$, respectively (Supplemental Table 3). The incidence rates in the risk $\geq 7.5\%$ without established risk factors were 7.6, 8.4, 11.3, and 22.0 per 1000 person-years for participants with a 10-year predicted ASCVD risk of 7.5% to $<10\%$, 10% to $<15\%$, 15% to

Table 2
Incidence rates and hazard ratios for atherosclerotic cardiovascular disease associated with 10-year predicted risk groups.

	Risk $<7.5\%$	Risk $\geq 7.5\%$ with established risk factors	Risk $\geq 7.5\%$ without established risk factors
Number of participants	5116	5637	362
ASCVD events, n (%)	183 (3.6)	691 (12.3)	37 (10.2)
CHD events, n (%)	107 (2.1)	371 (6.6)	19 (5.3)
Stroke event, n (%)	79 (1.5)	324 (5.8)	18 (4.9)
Person-years of follow-up	51,402.4	54,142.3	3765.6
Incidence rate per 1000 person-years (95% CI)	3.6 (3.1–4.1)	12.8 (11.8–13.7)	9.8 (6.9–13.2)
Hazard ratio (95% CI)	1 (reference)	3.58 (3.03–4.21)	2.72 (1.91–3.88)
Hazard ratio (95% CI)	0.28 (0.24–0.33)	1 (reference)	0.76 (0.55–1.06)

ASCVD, atherosclerotic cardiovascular disease.

There were $n = 7$ participants who had both stroke and CHD events on same date and have been included for both stroke and CHD event rows. Therefore, the number and percents may be more than the total number and percent of ASCVD events.

$<20\%$, and $\geq 20\%$, respectively. The incidence rates of the risk $<5\%$ and risk 5% to $<7.5\%$ was 2.6 and 5.6 respectively. Within each subgroup of estimated ASCVD risk, the HR for incident ASCVD is reported in both the risk $\geq 7.5\%$ with and without established risk factors groups and presented in Supplemental Table 3.

3.3. Sensitivity analysis

When requiring an SBP <120 mm Hg without the use of antihypertensive medication for the risk $\geq 7.5\%$ without established risk factors group, 1.6% of participants met the definition of having risk $\geq 7.5\%$ without established risk factors. The incidence rates were 3.6 (95% CI 3.1 to 4.1), 12.7 (95% CI 11.8 to 13.6), and 9.1 (95% CI 5.3 to 13.9) per

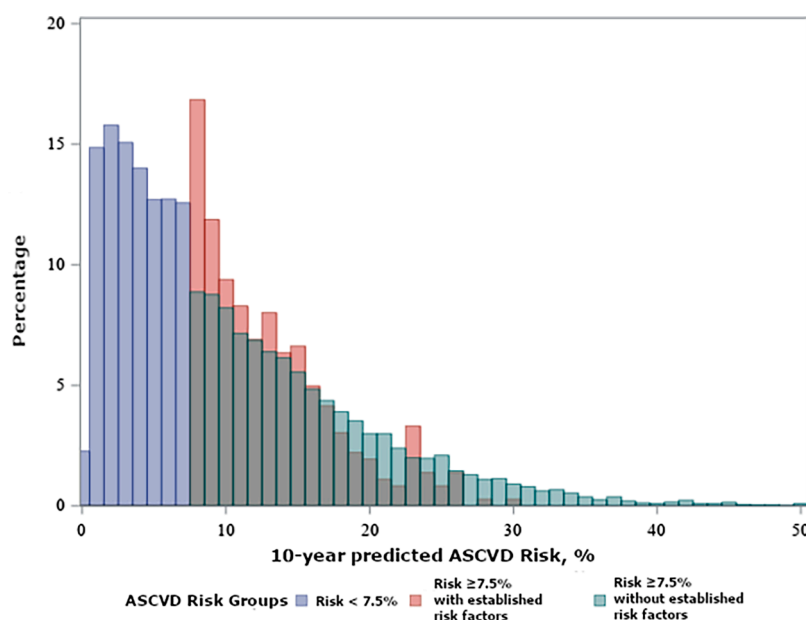


Fig. 2. Distribution of 10-year predicted atherosclerotic risk by ASCVD risk groups. ASCVD: Atherosclerotic cardiovascular disease.

1000 person-years for the risk <7.5 %, and risk ≥ 7.5 % with and without established risk factors groups, respectively (Supplemental Table 4). The HRs for ASCVD were 3.55 (95 % CI 3.02 to 4.18) and 2.52 (95 % CI 1.53 to 4.14) for the risk ≥ 7.5 % with and without established risk factors, respectively, using the risk <7.5 % group as reference.

3.4. Association of risk modifiers with ASCVD risk

In the risk <7.5 % group, participants who experienced an incident ASCVD event during follow-up were more likely to have an eGFR <60 mL/min/1.73m² and higher cystatin C level (Table 3). In the risk ≥ 7.5 % with established risk factors group, participants who had ASCVD events during follow-up were more likely to have an eGFR <60 mL/min/1.73m², higher cystatin C, hs-CRP ≥ 2 mg/L, triglycerides ≥ 150 mg/dL, and albuminuria. There was no statistical difference in risk modifiers between those that did and did not experience ASCVD events in the risk ≥ 7.5 % without established risk factors group.

4. Discussion

In a large, contemporary, cohort of Black and White U.S. adults, only 3.3 % of participants had a predicted 10-year ASCVD risk ≥ 7.5 % based primarily on age. Those with 10-year predicted risk ≥ 7.5 % both with and without established risk factors had a substantially higher risk for incident ASCVD compared to those with a 10-year predicted risk <7.5 % across the spectrum of predicted ASCVD risk. The results were consistent among women and men and when evaluating a lower threshold of an untreated SBP <120 mm Hg.

It is notable that the risk ≥ 7.5 % without established risk factors group comprised only 3 % of the entire cohort. The percentage of risk ≥ 7.5 % based primarily on age is likely to be even smaller than 3 % in the general population as we excluded those with a history of ASCVD or diabetes, and those already taking a statin. Age is the biggest contributor to ASCVD risk [20,21]. As a result, many critics of risk estimation for

primary prevention cite the reliance on age, and the “inevitability” of statin treatment as potential short-comings [5,22]. However, not only do the current results demonstrate that the group of adults who have risk ≥ 7.5 % primarily because of age is quite small, but also that this group has high ASCVD risk. These results support the concept that age is a powerful risk predictor because it integrates the cumulative exposures to even moderate elevations in risk factors [23–25]. For example, Liu et al. found that among adults treated with antihypertensive medication, a cumulative SBP exposure of >3000 mmHg-years (i.e. 120 mm Hg over 25 years) was associated with higher left ventricular mass than adults who achieved an SBP <120 mm Hg without medication [26]. Studies of LDL-C have also demonstrated that higher cumulative LDL-C levels are associated with a higher incidence of cardiovascular events [27,28].

It is worth noting that among the adults with risk ≥ 7.5 % primarily because of age, more than three-fourths had poor diet scores and more than half did not meet recommendations for ideal levels of physical activity. The high prevalence of a poor diet and inadequate physical activity within the risk ≥ 7.5 % without established risk factors group supports the hypothesis that their elevated risk derives from long-term accumulated exposures to subclinical risk factors. Multiple observational studies have demonstrated associations between consumption of a heart healthy diet and more physical activity with a lower risk for incident ASCVD, even after adjusting for traditional risk factors [29–34]. The results from the current study highlight the need for public health measures to help adults maintain ideal cardiovascular health.

The decision to initiate statin therapy for primary prevention in adults who have a 10-year estimated ASCVD risk ≥ 7.5 % based primarily on age can be challenging. Many older adults in this cohort may feel that they do not need a statin since they do not have other established cardiovascular risk factors. However, the current study demonstrated that adults with 10-year predicted ASCVD risk ≥ 7.5 % without established risk factors experience event rates above 7.5 %, the clinical trial-supported threshold for benefit of statin therapy [2]. An elevated ASCVD event rate was present even among adults with predicted risk of

Table 3

Risk modifiers among participants who experienced and did not experience an incident atherosclerotic cardiovascular disease event by ASCVD risk group.

	Risk < 7.5 %			Risk ≥ 7.5 % with established risk factors			Risk ≥ 7.5 % without established risk factors		
	No ASCVD Events (n = 4933)	ASCVD Events (n = 183)	p-value	No ASCVD Events (n = 4946)	ASCVD Events (n = 691)	p-value	No ASCVD Events (n = 325)	ASCVD Events (n = 37)	p-value
Diet score									
Ideal/Intermediate	23 %	20 %	0.400	18 %	17 %	0.468	24 %	13 %	0.193
Poor	77 %	80 %		82 %	83 %		76 %	87 %	
Physical Activity Score									
Ideal	30 %	31 %	0.635	33 %	35 %	0.476	43 %	37 %	0.353
Intermediate	42 %	39 %		37 %	35 %		31 %	43 %	
Poor	28 %	30 %		30 %	30 %		27 %	20 %	
Alcohol drinker, %									
None	56 %	59 %	0.113	52 %	62 %	0.486	59 %	62 %	0.343
Moderate	40 %	34 %		43 %	32 %		36 %	34 %	
Heavy	5 %	7 %		5 %	6 %		5 %	4 %	
Body mass index (kg/m ²)									
Normal (<25)	32 %	33 %	0.979	26 %	27 %	0.513	47 %	43 %	0.611
Overweight (25–<30)	35 %	35 %		41 %	42 %		38 %	46 %	
Obese (≥ 30)	32 %	32 %		34 %	32 %		15 %	11 %	
eGFR <60 mL/min/1.73m ²	1.7 %	6.0 %	<0.001	7.1 %	11.3 %	<0.001	3.4 %	8.1 %	0.163
Cystatin C, mg/L*	0.9 (0.2)	1.0 (0.6)	0.013	1.0 (0.3)	1.1 (0.3)	<0.001	0.9 (0.2)	0.9 (0.2)	0.374
LDL-C ≥ 160 mg/dL	11 %	13 %	0.550	15 %	13 %	0.226	0 %	0 %	–
hs-CRP ≥ 2 mg/L	48 %	51 %	0.479	54 %	59 %	0.005	40 %	38 %	0.828
Triglycerides ≥ 150 mg/dL	19 %	25 %	0.055	29 %	35 %	0.003	7 %	11 %	0.503
Albuminuria	5 %	8 %	0.072	10 %	19 %	<0.001	6 %	10 %	0.460
Prediabetes	16 %	21 %	0.062	23 %	22 %	0.563	17 %	16 %	0.951

ASCVD, atherosclerotic cardiovascular disease.

* Numbers for cystatin C represent mean (standard deviation).

7.5 % to <10 %. Large meta-analyses and retrospective studies in primary prevention populations have shown conflicting results with the use of statins in individuals >75 years old with some showing benefit and others showing no effect [35,36]. The Cholesterol Treatment Trialists' Collaboration showed a significant association between statin therapy and reduction in major vascular events in the age groups of 66–75 years of age [36]. The Pragmatic Evaluation of Events and Benefits of Lipid-lowering in Older Adults (PREVENTABLE) trial will randomize atorvastatin 40 mg versus placebo in US adults \geq 75 years without established clinical ASCVD with a primary outcome of dementia and persistent disability free survival (NCT04262206) [37]. The Statin Therapy for Reducing Events in the Elderly (STAREE) trial will randomize atorvastatin 40 mg versus placebo in Australian adults \geq 70 years without clinical ASCVD with a primary outcome of disability free survival and major cardiovascular events (NCT02099123) [38]. The results of these two randomized controlled trials may provide further clarity on this population.

We examined multiple laboratory biomarkers, including LDL-C, triglycerides, and hs-CRP, that were highlighted in recent guidelines as potentially elevating an individual's estimated ASCVD risk [2]. Among the risk \geq 7.5 % without established risk factors group, we did not find significant differences in the levels of risk biomarkers between those who did and did not experience ASCVD events, however we may have been underpowered. For example, participants in the risk \geq 7.5 % without established risk factors group who experienced ASCVD events were nearly twice as likely to have albuminuria (10.8 % vs 5.7 %, $p = 0.46$) and more than twice as likely to have an eGFR < 60 mL/min/1.73m² (8.1 % vs 3.4 %, $p = 0.16$) compared to participants who did not experience ASCVD events. Among the risk < 7.5 % and the risk \geq 7.5 % with established risk factors groups, those who experienced ASCVD events were significantly more likely to have a lower eGFR and higher cystatin C, markers of decreased renal function. The use of coronary artery calcium (CAC) scoring could enhance risk assessment in the risk \geq 7.5 % without established risk factors subgroup. In a combined analysis of 4778 participants from 3 U.S. cohorts, Yano et al. found that 31 % of adults aged 60 years and older had a CAC score of 0, suggesting that it could help identify older adults with higher and lower ASCVD risk [39]. Further study is warranted to determine whether other subclinical markers of disease, such as abdominal adiposity or high-sensitivity troponin, could help guide risk assessment in older adults without established risk factors.

4.1. Limitations

The current study has several strengths, including its large sample size, extensive data collection at baseline and rigorous follow-up and adjudication of ASCVD events. However, the results of our study should be interpreted in the context of its known and potential limitations. Participants' 10-year predicted risk was assessed at baseline only. Therefore, some participants who were classified as being without established risk factors may have developed risk factors during follow-up. The modest sample size of participants in the risk \geq 7.5 % without established risk factors group resulted in wide confidence intervals for some estimates, and we were underpowered to detect differences in risk modifiers among those who did and did not experience ASCVD events. CAC score, a potentially useful risk marker as discussed previously, was unfortunately not available in the REGARDS study. In addition, other factors highlighted in the most recent guidelines as risk modifiers (i.e.: ApoB, pre-mature menopause, pre-eclampsia, significant family history of ASCVD) were not available in the REGARDS study and thus could not be assessed. Lp(a) was available for only a very small percentage of participants included in a case-cohort study and thus was not included for analysis. We excluded participants with diabetes because statins are already indicated for this population. However, this removed many individuals at higher risk of incident ASCVD from the study population. It is likely that the exclusion of these individuals resulted in the under-

estimation of risk in the risk \geq 7.5 % with established risk factors group.

5. Conclusion

In a large, contemporary, cohort of Black and white U.S. adults, only 3 % of participants had 10-year predicted ASCVD risk \geq 7.5 % in the absence of established risk factors. Among the participants with risk \geq 7.5 % without established risk factors, the incidence rate of ASCVD events was above the trial-supported threshold in which benefit from statin therapy is seen.

Disclosures

Lisandro D. Colantonio, Paul Muntner and Emily B. Levitan receive grant support from Amgen, Inc. The remaining authors have nothing to disclose.

Data availability

To abide by its obligations with NIH/NINDS and the IRB of the University of Alabama at Birmingham, REGARDS facilitates data sharing through formal data use agreements. Any investigator is welcome to request the REGARDS data and documentation through this process. Requests for data access may be sent to the REGARDS study at regard-admin@uab.edu.

Author agreement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. This research project is supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service. We wish to report that Lisandro D. Colantonio, Paul Muntner and Emily B. Levitan receive grant support from Amgen, Inc. None of the remaining authors have anything to disclose.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author. All the co-authors have approved of the final version of this manuscript including the re-submission and reviewer edits.

CRediT authorship contribution statement

Nathan Kong: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Swati Sakhuja:** Methodology, Formal analysis, Writing – review & editing, Visualization. **Lisandro D. Colantonio:** Methodology, Writing – review & editing. **Emily B. Levitan:** Writing – review & editing. **Donald M. Lloyd-Jones:** Writing – review & editing. **Mary Cushman:** Writing – review & editing, Funding acquisition. **Paul Muntner:** Methodology, Writing – review & editing.

Tamar S. Polonsky: Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Mary Cushman reports financial support was provided by National Institute of Neurological Disorders and Stroke and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service. Lisandro Colantonio, Paul Muntner, Emily Levitan reports a relationship with Amgen Inc that includes: funding grants.

Acknowledgments

We thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions and further information about the study can be found at <http://www.regardsstudy.org>.

Sources of funding

This research project is supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS or the NIA. Representatives of the NINDS were involved in the review of the manuscript but were not directly involved in the collection, management, analysis or interpretation of the data. The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at: <https://www.uab.edu/soph/regardsstudy/>

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ajpc.2023.100612](https://doi.org/10.1016/j.ajpc.2023.100612).

References

- Goff DC, DM Lloyd-Jones, 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. *Circulation* 2014;129:S49–73. <https://doi.org/10.1161/01.cir.0000437741.48606.98>.
- Grundey SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 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* 2019;139:e1082–143. <https://doi.org/10.1161/CIR.0000000000000625>.
- Lloyd-Jones DM, Huffman MD, Karmali KN, Sanghavi DM, Wright JS, Pelsler C, Gulati M, Masoudi FA, Goff Jr 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:e793–813. <https://doi.org/10.1161/cir.0000000000000467>.
- Karmali KN, Goff Jr DC, Ning H, Lloyd-Jones DM. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. *J Am Coll Cardiol* 2014;64:959–68. <https://doi.org/10.1016/j.jacc.2014.06.1186>.
- Ridker PM, Cook NR. The pooled cohort equations 3 years on. *Circulation* 2016;134:1789–91. <https://doi.org/10.1161/CIRCULATIONAHA.116.024246>.
- Daviglus ML, Stamler J, Pirzada A, Yan LL, Garside DB, Liu K, Wang R, Dyer AR, Lloyd-Jones DM, Greenland P. Favorable cardiovascular risk profile in young women and long-term risk of cardiovascular and all-cause mortality. *JAMA* 2004;292:1588–92. <https://doi.org/10.1001/jama.292.13.1588>.
- Sheppard JP, Stevens S, Stevens R, Martin U, Mant J, Hobbs FDR, McManus RJ. Benefits and harms of antihypertensive treatment in low-risk patients with mild hypertension. *JAMA Intern Med* 2018;178:1626–34. <https://doi.org/10.1001/jamainternmed.2018.4684>.
- Bohula EA, Morrow DA, Giugliano RP, Blazing MA, He P, Park JG, Murphy SA, White JA, Kesaniemi YA, Pedersen TR, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. *J Am Coll Cardiol* 2017;69:911–21. <https://doi.org/10.1016/j.jacc.2016.11.070>.
- Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, Graham A, Moy CS, Howard G. The reasons for geographic and racial differences in stroke study: objectives and design. *Neuroepidemiology* 2005;25:135–43. <https://doi.org/10.1159/000086678>.
- Sampson M, Ling C, Sun Q, Harb R, Ashmaig M, Warnick R, Sethi A, Fleming JK, Otvos JD, Meeusen JW, et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. *JAMA Cardiol* 2020;5:540–8. <https://doi.org/10.1001/jamacardio.2020.0013>.
- Levey AS, Stevens LA. Estimating GFR using the CKD epidemiology collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis* 2010;55:622–7. <https://doi.org/10.1053/j.ajkd.2010.02.337>.
- Carson AP, Muntner P, Kissela BM, Kleindorfer DO, Howard VJ, Meschia JF, Williams LS, Prineas RJ, Howard G, Safford MM. Association of prediabetes and diabetes with stroke symptoms: the reasons for geographic and racial differences in stroke (REGARDS) study. *Diabetes Care* 2012;35:1845–52. <https://doi.org/10.2337/dc11-2140>.
- Goyal P, Mefford MT, Chen L, Sterling MR, Durant RW, Safford MM, Levitan EB. Assembling and validating a heart failure-free cohort from the reasons for geographic and racial differences in stroke (REGARDS) study. *BMC Med Res Methodol* 2020;20:53. <https://doi.org/10.1186/s12874-019-0890-x>.
- Akinyelure OP, Sakhujia S, Colvin CL, Clark D, Jaeger BC, Hardy ST, Howard G, Cohen LP, Irvin MR, Tanner R, et al. Cardiovascular health and transition from controlled blood pressure to apparent treatment resistant hypertension. *Hypertension* 2020;76:1953–61. <https://doi.org/10.1161/HYPERTENSIONAHA.120.15890>.
- Prineas RJ, Crow RS, Zhang ZM. *The Minnesota code manual of electrocardiographic findings: including measurement and comparison with the Novacode; standards and procedures for ECG measurement in epidemiologic and clinical trials*. 2nd ed. London: Springer; 2010.
- Safford MM, Brown TM, Muntner PM, Durant RW, Glasser S, Halanich JH, Shikany JM, Prineas RJ, Samdarshi T, Bittner VA, et al. Association of race and sex with risk of incident acute coronary heart disease events. *JAMA* 2012;308:1768–74. <https://doi.org/10.1001/jama.2012.14306>.
- Stroke–1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO task force on stroke and other cerebrovascular disorders. *Stroke* 1989;20:1407–31. <https://doi.org/10.1161/01.str.20.10.1407>.
- Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, Cushman M, Moy CS, Soliman EZ, Kissela BM, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol* 2011;69:619–27. <https://doi.org/10.1002/ana.22385>.
- Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Hypertension* 2018;71:e13–115. <https://doi.org/10.1161/HYP.0000000000000065>.
- Bress AP, Colantonio LD, Booth 3rd JN, Spruill TM, Ravenell J, Butler M, Shallcross AJ, Seals SR, Reynolds K, Ogedegbe G, et al. Modifiable risk factors versus age on developing high predicted cardiovascular disease risk in blacks. *J Am Heart Assoc* 2017;6. <https://doi.org/10.1161/jaha.116.005054>.
- Leening MJG, Cook NR, Ridker PM. Should we reconsider the role of age in treatment allocation for primary prevention of cardiovascular disease? *Eur Heart J* 2017;38:1542–7. <https://doi.org/10.1093/eurheartj/ehw287>.
- Kannel WB, Vasan RS. Is age really a non-modifiable cardiovascular risk factor? *Am J Cardiol* 2009;104:1307–10. <https://doi.org/10.1016/j.amjcard.2009.06.051>.
- Sniderman AD, Furberg CD. Age as a modifiable risk factor for cardiovascular disease. *Lancet* 2008;371:1547–9. [https://doi.org/10.1016/S0140-6736\(08\)60313-X](https://doi.org/10.1016/S0140-6736(08)60313-X).
- Jackson R, Kerr A, Wells S. 'Should we reconsider the role of age in treatment allocation for primary prevention of cardiovascular disease?' No, but we can improve risk communication metrics. *Eur Heart J* 2017;38:1548–52. <https://doi.org/10.1093/eurheartj/ehw322>.
- Liu K, Colangelo LA, Daviglus ML, Goff DC, Pletcher M, Schreiner PJ, Sibley CT, Burke GL, Post WS, Michos ED, et al. Can antihypertensive treatment restore the risk of cardiovascular disease to ideal levels? *J Am Heart Assoc* 2015;4:e002275. <https://doi.org/10.1161/JAHA.115.002275>.
- Domanski MJ, Tian X, Wu CO, Reis JP, Dey AK, Gu Y, Zhao L, Bae S, Liu K, Hasan AA, et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. *J Am Coll Cardiol* 2020;76:1507–16. <https://doi.org/10.1016/j.jacc.2020.07.059>.
- Zhang Y, Pletcher MJ, Vittinghoff E, Clemons AM, Jacobs Jr 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;6:1406–13. <https://doi.org/10.1001/jamacardio.2021.3508>.
- Chomistek AK, Manson JE, Stefanick ML, Lu B, Sands-Lincoln M, Going SB, Garcia L, Allison MA, Sims ST, LaMonte MJ, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the

- women's health initiative. *J Am Coll Cardiol* 2013;61:2346–54. <https://doi.org/10.1016/j.jacc.2013.03.031>.
- [29] Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, et al. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;378:e34. <https://doi.org/10.1056/NEJMoa1800389>.
- [30] Reedy J, Krebs-Smith SM, Miller PE, Liese AD, Kahle LL, Park Y, Subar AF. Higher diet quality is associated with decreased risk of all-cause, cardiovascular disease, and cancer mortality among older adults. *J Nutr* 2014;144:881–9. <https://doi.org/10.3945/jn.113.189407>.
- [31] Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease. *Circulation* 2011;124:789–95. <https://doi.org/10.1161/CIRCULATIONAHA.110.010710>.
- [32] Sotos-Prieto M, Bhupathiraju SN, Mattei J, Fung TT, Li Y, Pan A, Willett WC, Rimm EB, Hu FB. Association of changes in diet quality with total and cause-specific mortality. *N Engl J Med* 2017;377:143–53. <https://doi.org/10.1056/NEJMoa1613502>.
- [33] Kong NW, Ning H, Zhong VW, Paluch A, Wilkins JT, Lloyd-Jones D, Allen NB. Association between diet quality and incident cardiovascular disease stratified by body mass index. *Am J Prevent Cardiol* 2021;8:100298. <https://doi.org/10.1016/j.ajpc.2021.100298>.
- [34] Orkaby AR, Driver JA, Ho YL, Lu B, Costa L, Honerlaw J, Galloway A, Vassy JL, Forman DE, Gaziano JM, et al. Association of statin use with all-cause and cardiovascular mortality in US veterans 75 years and older. *JAMA* 2020;324:68–78. <https://doi.org/10.1001/jama.2020.7848>.
- [35] Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019;393:407–15. [https://doi.org/10.1016/s0140-6736\(18\)31942-1](https://doi.org/10.1016/s0140-6736(18)31942-1).
- [36] Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs: Drugs Devices Other Intervent* 2008;8:373–418. <https://doi.org/10.2165/0129784-200808060-00004>.
- [37] Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *J Am Geriatr Soc* 2014;62:2261–72. <https://doi.org/10.1111/jgs.13153>.
- [38] Hoel RW, Giddings Connolly RM, Takahashi PY. Polypharmacy management in older patients. *Mayo Clin Proc* 2021;96:242–56. <https://doi.org/10.1016/j.mayocp.2020.06.012>.
- [39] Yano Y, O'Donnell CJ, Kuller L, Kavousi M, Erbel R, Ning H, D'Agostino R, Newman AB, Nasir K, Hofman A, et al. Association of coronary artery calcium score vs age with cardiovascular risk in older adults: an analysis of pooled population-based studies. *JAMA Cardiol* 2017;2:986–94. <https://doi.org/10.1001/jamacardio.2017.2498>.