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ORIGINAL RESEARCH

Lipoprotein(a) and the Risk for Coronary Heart Disease and Ischemic Stroke Events Among Black and White Adults With Cardiovascular Disease

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BACKGROUND: It is unclear whether lipoprotein(a) is associated with coronary heart disease (CHD) and ischemic stroke events in White and Black adults with atherosclerotic cardiovascular disease (ASCVD).

METHODS AND RESULTS: We conducted a case-cohort analysis, including Black and White REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants ≥45 years of age with prevalent ASCVD (ie, CHD or stroke) at baseline between 2003 and 2007. Baseline lipoprotein(a) molar concentration was measured in participants with ASCVD who experienced a CHD event by December 2017 (n=1166) or an ischemic stroke by September 2019 (n=492) and in a random subcohort of participants with prevalent ASCVD (n=1948). The hazard ratio (HR) for CHD events per 1 SD (1.5 units) higher log-transformed lipoprotein(a) was 1.26 (95% CI, 1.02–1.56) among Black participants and 1.16 (95% CI, 1.02–1.31) among White participants (*P* value comparing HRs, 0.485). The HR for CHD events per 1 SD higher log-lipoprotein(a) within subgroups with hs-CRP (high-sensitivity C-reactive protein) ≥2 and <2 mg/L was 1.31 (95% CI, 0.99–1.73) and 1.23 (95% CI, 0.85–1.80), respectively (*P* value comparing HRs, 0.836), among Black participants, and 1.07 (95% CI, 0.91–1.27) and 1.36 (95% CI, 1.10–1.70), respectively (*P* value comparing HRs, 0.088), among White participants. There was no evidence that the association between lipoprotein(a) and CHD events differed by statin use. There was no evidence of an association between lipoprotein(a) and ischemic stroke events among Black or White participants.

CONCLUSIONS: Higher lipoprotein(a) levels were associated with an increased risk for CHD events in Black and White adults with ASCVD.

Key Words: adults ■ coronary heart disease ■ lipoprotein(a) ■ secondary prevention ■ stroke

Elevated lipoprotein(a) levels have been associated with an increased risk for incident coronary heart disease (CHD)[1–3] and ischemic stroke[1,4] in observational studies. Mendelian randomization analyses also suggest that the association of lipoprotein(a) with incident CHD and ischemic stroke may be causal.[5,6] Adults with a history of atherosclerotic cardiovascular disease (ASCVD) have a high risk for CHD and ischemic stroke events.[7,8] However, there are limited data about whether elevated lipoprotein(a) levels confer an increased risk for CHD and ischemic stroke events in individuals with ASCVD, particularly among Black adults, a population with higher lipoprotein(a) levels versus other racial groups.[9–14] If elevated lipoprotein(a)

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CLINICAL PERSPECTIVE

What Is New?

- Black and White US adults with a history of atherosclerotic cardiovascular disease who had higher lipoprotein(a) levels had an increased risk for future coronary heart disease events.
- The association between lipoprotein(a) and the risk for future coronary heart disease events did not differ by race, statin use, or high-sensitivity C-reactive protein levels.
- There was no association between lipoprotein(a) levels and the risk for ischemic stroke events among Black and White US adults with a history of atherosclerotic cardiovascular disease.

What Are the Clinical Implications?

- Elevated lipoprotein(a) levels can be used to identify Black and White adults with a history of atherosclerotic cardiovascular disease who have an increased risk for future coronary heart disease events and may benefit from more intensive risk reduction interventions, including those taking a statin.

Nonstandard Abbreviations and Acronyms

ApoB	apolipoprotein B
REGARDS	Reasons for Geographic and Racial Differences in Stroke

levels are associated with an increased risk for CHD and ischemic stroke events among Black and White adults with ASCVD, this would support the use of lipoprotein(a) for directing more intensive risk-reduction interventions in this population.

The goal of the current study was to determine the risk for CHD and ischemic stroke events associated with lipoprotein(a) levels among Black and White US adults with ASCVD, defined by a history of CHD or stroke. To accomplish this goal, we conducted a case-cohort analysis using data from Black and White US adults enrolled in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study.[15] Prior studies suggest that the association between lipoprotein(a) and ASCVD events may differ between adults taking versus not taking a statin,[16–18] and among those with versus without high levels of hs-CRP (high-sensitivity C-reactive protein).[19,20] In an exploratory analysis, we determined whether statin use or hs-CRP levels modify the association of lipoprotein(a) with CHD and ischemic stroke events in adults with ASCVD.

METHODS

REGARDS Study

The REGARDS study is a population-based cohort of 30 239 Black and White adults ≥45 years of age from all 48 contiguous US states and the District of Columbia who were enrolled between January 1, 2003, and October 31, 2007.[15] Black adults and residents in the southeastern US states were oversampled by design. The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers, and all participants provided written informed consent. Data used in the current analysis are available from the REGARDS study (https://www.uab.edu/soph/regardsstudy/). Other study information is available from the corresponding author.

Baseline Assessment

All REGARDS study participants completed a computer-assisted telephone interview and an in-home study visit at baseline. Blood samples were collected during the in-home study visit, and serum aliquots were stored at −80 °C.[21] Prevalent ASCVD was defined by a history of CHD or stroke at baseline. A history of CHD was defined by self-report of a prior diagnosis of myocardial infarction or coronary revascularization procedure, or evidence of a previous myocardial infarction on a baseline study ECG obtained during the in-home study visit. History of stroke was defined by self-report of a prior diagnosis. Overall, 2616 Black participants and 4008 White participants had a history of ASCVD at baseline.

Atherosclerotic Cardiovascular Events

Living participants or proxy respondents were contacted every 6 months via telephone to identify hospitalizations related to CHD or stroke events and deaths.[15,22] When hospitalizations were identified, medical records were retrieved for review. Medical records from CHD-related hospitalizations were reviewed independently by 2 study clinicians (M.M.S. and T.M.B.) following published guidelines to determine whether the event was a myocardial infarction based on signs, symptoms, ECGs, and cardiac biomarkers.[23–25] Medical records from stroke-related hospitalizations were reviewed by 2 expert neurologists independently following the World Health Organization stroke definition.[26] Events not meeting this definition but characterized by symptoms lasting <24 hours with neuroimaging consistent with acute infarct or hemorrhage were also classified as strokes. Stroke events were subsequently classified as hemorrhagic or ischemic based on their neuroimaging. When deaths were identified, trained study clinicians determined the underlying cause of death

based on interviews with next of kin, medical records, death certificates, and autopsy reports. For the current analysis, CHD events included a myocardial infarction hospitalization or CHD death (ie, a death suspected to be CHD related without evidence of a noncoronary cause).[22] Ischemic stroke events included fatal or nonfatal ischemic strokes.

Case-Cohort Study Design and Measurement of Lipoprotein(a) and Apolipoprotein B

We used available blood samples collected during the baseline in-home study visit to measure serum lipoprotein(a) molar concentration and apolipoprotein B (ApoB) mass concentration in participants with ASCVD at baseline who had a CHD event between baseline and December 31, 2017 (n=405 Black and 761 White participants), and in participants who had an ischemic stroke between baseline and September 30, 2019 (n=206 Black and 286 White participants). Lipoprotein(a) and ApoB were also measured in a random subcohort of 967 Black and 981 White participants with ASCVD at baseline, selected using an age-, race-, and sex-stratified sampling approach. Figure 1 shows a diagram of the case-cohort study design.

Lipoprotein(a) molar concentration was measured using a particle-enhanced turbidimetric immunoassay (Tina-quant; Roche, Basel, Switzerland) with the calibrator value traceable to the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine reference material 2B.[27] ApoB mass concentration was measured by Siemens reagent (N Antiserum to Human Apolipoprotein B) on a Siemens BNII nephelometer. Non-lipoprotein(a) ApoB mass concentration in mg/dL was calculated as follows: ApoB–lipoprotein(a) molar concentration in nmol/L×0.0513), based on the mass weight of 513 kDa of the ApoB molecule contained in lipoprotein(a) particles.[28,29]

Participant Characteristics

Baseline characteristics of participants analyzed as part of the current study included age, sex, race, geographic region of residence, annual household income, education, physical activity, body mass index, alcohol consumption, current smoking, systolic blood pressure, diabetes, chronic kidney disease, hs-CRP, total cholesterol, high-density lipoprotein cholesterol, triglycerides, low-density lipoprotein cholesterol, and use of aspirin, antihypertensive medication, and statins. Medication dosages at baseline were not recorded in the REGARDS study. The methods used to assess baseline characteristics are provided in Table 1.[30–32]

Statistical Analysis

We calculated the distribution of lipoprotein(a) molar concentration among participants with ASCVD at baseline using data from the random subcohort, overall and by race. We also calculated the distribution of lipoprotein(a) molar concentration among participants

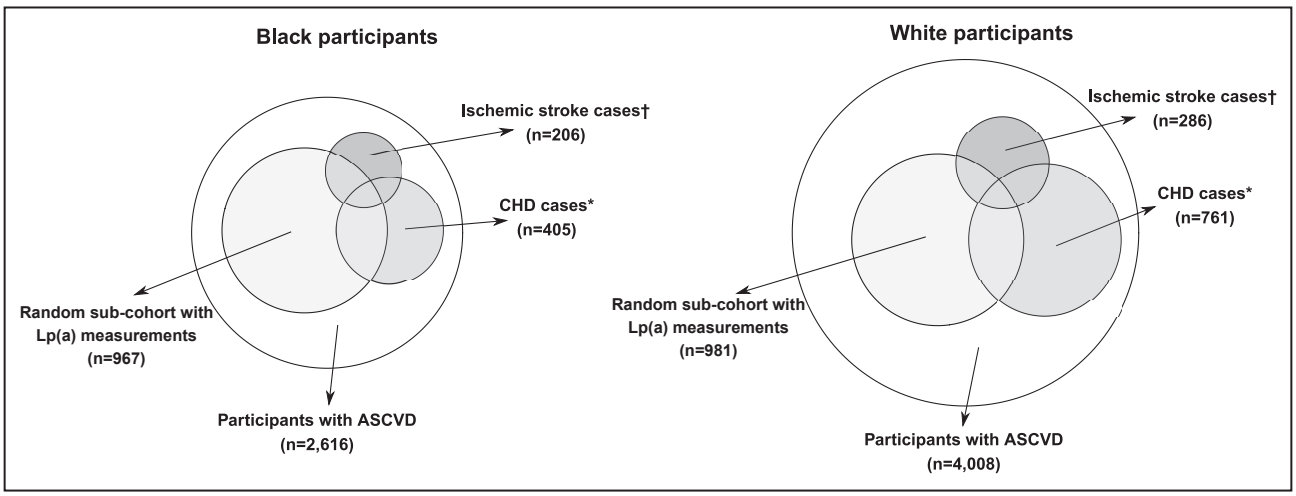

Figure 1. Graphical representation of the case-cohort study design and participants with a history of atherosclerotic cardiovascular disease (ASCVD) included in the current analysis.

*Coronary heart disease (CHD) cases between the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study baseline and December 31, 2017. †Ischemic stroke cases between the REGARDS study baseline and September 30, 2019. The random subcohort can include participants with a CHD event or an ischemic stroke during follow-up. Specifically, among Black participants included in the random subcohort (n=967), 158 had a CHD event and 84 had an ischemic stroke during follow-up, including 24 participants who had both a CHD event and an ischemic stroke. Among White participants in the random subcohort (n=981), 185 had a CHD event and 70 had an ischemic stroke, including 17 participants who had both a CHD event and an ischemic stroke. Lp(a) indicates lipoprotein(a).

Table 1. Definition of Baseline Characteristics of REGARDS Study Participants Included in the Current Analysis

Baseline characteristic	Definition
Age	Calculated using participants' self-reported date of birth provided during the baseline computer-assisted telephone interview
Sex and race	Based on sex and race self-reported by participants during their baseline computer-assisted telephone interview
Geographic region of residence	Based on the home address provided by participants during their baseline computer-assisted telephone interview and categorized as follows: 1. Stroke buckle: includes coastal North Carolina, South Carolina, and Georgia. 2. Stroke belt: includes the remaining parts of North Carolina, South Carolina, and Georgia, and Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. 3. Other US regions: includes the remaining 40 contiguous US states and the District of Columbia.
Income	Based on the total household annual income from all sources that participants self-reported during their baseline computer-assisted telephone interview
Education	Based on the highest education grade that participants reported have completed during their baseline computer-assisted telephone interview
Low physical activity	Self-reporting not engaging in any weekly activity intense enough to work up a sweat
Body mass index	Calculated using body weight and height measured during the baseline in-home study examination. Specifically, body mass index was calculated as: body weight in kilograms divided by height in meters squared
Alcohol consumption	Based on the number of drinks that participants self-reported having per week during their baseline computer-assisted telephone interview and categorized as follows[30]: 1. No alcohol consumption: 0 drinks per week. 2. Moderate alcohol consumption: >0 to 7 drinks per week for women and >0 to 14 drinks per week for men. 3. Heavy alcohol consumption: >7 drinks per week for women and >14 drinks per week for men.
Current smoking	Having smoked >100 cigarettes in lifetime and currently smoking cigarettes, even occasionally
Systolic blood pressure	Average of the 2 systolic blood pressure measurements taken during the baseline study examination. Blood pressure was measured by a trained health professional using the auscultatory method and an aneroid sphygmomanometer with an appropriately sized cuff. Before their first blood pressure measurement, participants rested for 5 minutes in a seated position with both feet on the floor. At least 30 s elapsed between each blood pressure measurement
Diabetes	Fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, or self-report of a prior diagnosis of diabetes with current use of insulin or oral glucose-lowering medication
Chronic kidney disease	Self-report of being on dialysis, or a calculated estimated glomerular filtration rate <60 mL/min per 1.73 m^2 or urine albumin/creatinine ratio ≥30 mg/g. Estimated glomerular filtration rate was calculated using information on age, sex, race, and serum creatinine and a published equation from the Chronic Kidney Disease Epidemiology Collaboration.[31] Using urine samples, albumin and creatinine were measured and used to calculate the albumin/creatinine ratio as: urinary albumin/urinary creatinine
hs-CRP	Measured by particle-enhanced immunonephelometry using blood samples collected during the baseline examination
Total cholesterol	Measured by colorimetric reflectance spectrophotometry using blood samples collected during the baseline in-home examination
High-density lipoprotein cholesterol	Measured by colorimetric reflectance spectrophotometry using blood samples collected during the baseline in-home examination
Triglycerides	Measured by colorimetric reflectance spectrophotometry using blood samples collected during the baseline in-home examination
Low-density lipoprotein cholesterol	Calculated using baseline total cholesterol, high-density lipoprotein cholesterol, triglycerides, and the Sampson equation.[32]
Use of aspirin	Self-reporting taking aspirin regularly during the baseline computer-assisted telephone interview
Use of antihypertensive medications	Self-reporting taking medication to lower their blood pressure during the baseline computer-assisted telephone interview
Use of statin	Having present any of the following medications in the baseline medication inventory: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin

hs-CRP indicates high-sensitivity C-reactive protein; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

who had a CHD event and an ischemic stroke during follow-up. The rest of the analyses were conducted stratified by race. We calculated summary statistics for baseline characteristics of participants with ASCVD using data from the random subcohort, and among CHD and ischemic stroke cases, separately, by quartiles of the lipoprotein(a) distribution among Black and White participants combined.

We calculated the cumulative incidence of CHD events by lipoprotein(a) quartiles. We also calculated the rate of CHD events per 1000 person-years, overall, and by quartiles of lipoprotein(a). We used the Barlow

method and 4 models with progressive adjustment to calculate hazard ratios (HRs) for CHD events associated with 1-SD higher levels of log-transformed lipoprotein(a).[33] We used log transformation to analyze lipoprotein(a) because values are skewed to the right.[10] Model 1 included adjustment for age, sex, geographic region of residence, education, and income. Model 2 included adjustment for variables in model 1 and physical activity, body mass index, alcohol consumption, and current smoking. Model 3 included adjustment for variables in model 2 and systolic blood pressure, history of CHD, diabetes, chronic kidney disease, hs-CRP, high-density lipoprotein cholesterol, triglycerides, and use of aspirin, antihypertensive medication, and statin. Model 4 included adjustment for variables in model 3 and non-lipoprotein(a) ApoB. We also calculated the HR for CHD events associated with quartiles of lipoprotein(a) using the same 4 levels of adjustment. In a sensitivity analysis, we calculated rates and HRs for CHD events associated with race-specific quartiles of the lipoprotein(a) distribution. We used interaction terms and the approach described by Woodward to test whether HRs for CHD associated with lipoprotein(a) levels were different among Black versus White participants.[34] To test for linear trend across lipoprotein(a) quartiles, we used the median lipoprotein(a) level corresponding to each participant's quartile as the independent variable. The analyses described above were repeated to estimate the cumulative incidence, event rates, and HRs for ischemic stroke associated with lipoprotein(a) levels.

We repeated the calculation of rates and HRs for CHD and ischemic stroke events associated with 1-SD higher log-transformed lipoprotein(a) levels using models 1 to 4 described above among participants with a history of CHD and a history of stroke, separately. In an exploratory analysis, we calculated HRs for CHD and ischemic stroke events associated with 1-SD higher log-transformed lipoprotein(a) levels within subgroups defined by statin use, and hs-CRP levels (<2 or ≥2 mg/L), separately, after adjustment for the variables in model 4 described above. We used interaction terms and the approach described by Woodward to test whether HRs were different across subgroups.[34] All analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, NC), weighted to account for the case-cohort sampling design and extrapolate results to the full REGARDS study population with prevalent ASCVD at baseline.[33]

RESULTS

The median lipoprotein(a) molar concentration was higher in Black than in White participants with prevalent ASCVD (100.1 versus 23.4 nmol/L; $P<0.001$; Figure 2 and Table 2). Among Black participants, those with higher lipoprotein(a) molar concentration were less likely to be men or a current smoker, and more likely to have low physical activity or take aspirin or a statin (Table 3). White participants with higher lipoprotein(a) molar concentration were more likely to take aspirin or a statin. Among CHD and ischemic stroke cases, Black participants had a higher lipoprotein(a) molar concentration than their White counterparts (Figure 3 and Table 4). Baseline characteristics of the CHD and ischemic stroke cases are shown in Tables 5 and 6.

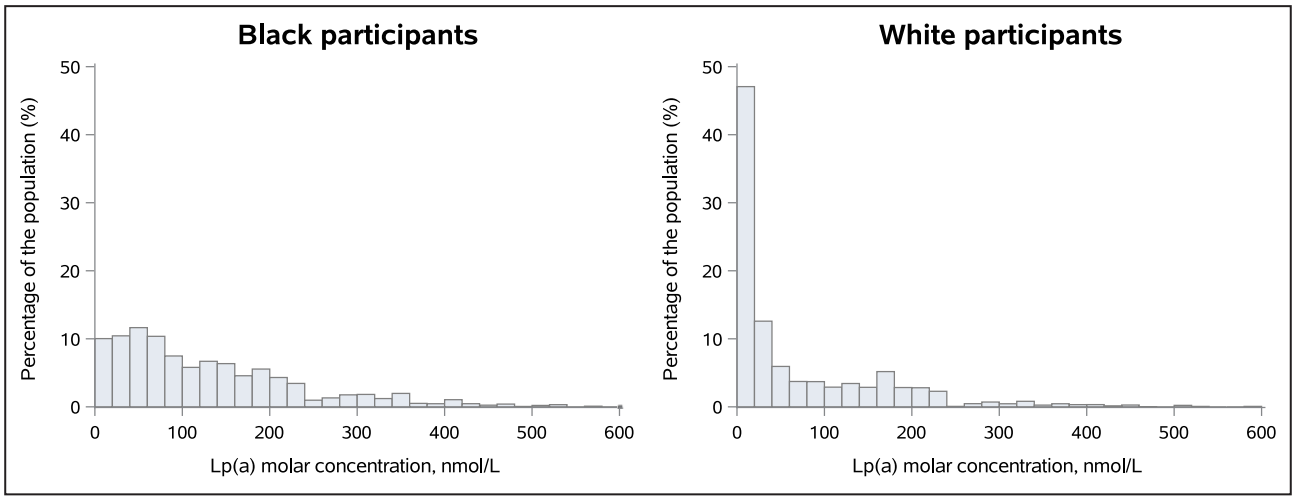

Figure 2. Distribution of lipoprotein(a) (Lp[a]) molar concentration among Black and White REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants with a history of atherosclerotic cardiovascular disease (ASCVD).

The Lp(a) molar concentration distribution was calculated using data from Black and White participants in the random subcohort, weighted to the full REGARDS study population with a history of ASCVD at baseline.

Table 2. Distribution of Lipoprotein(a) Molar Concentration Among Black and White REGARDS Study Participants With a History of ASCVD

Variable	All participants (n=1948)	Black participants (n=967)	White participants (n=981)	*P* value*
Lipoprotein(a) molar concentration, nmol/L				
5th Percentile	2.0	9.3	2.0	<0.001
10th Percentile	4.1	19.7	3.1	
25th Percentile	13.2	47.5	8.2	
50th Percentile (ie, median)	52.7	100.1	23.4	
75th Percentile	147.9	185.8	112.9	
90th Percentile	225.3	294.3	197.5	
95th Percentile	315.7	352.9	234.5	
Log-transformed lipoprotein(a) molar concentration				
Mean (SD)	3.7 (1.5)	4.4 (1.1)	3.3 (1.5)	<0.001

The lipoprotein(a) molar concentration distribution was calculated using data from Black and White participants in the random subcohort, weighted to the full REGARDS study population with a history of ASCVD at baseline. ASCVD indicates atherosclerotic cardiovascular disease; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

*Comparing the distribution of lipoprotein(a) molar concentration among Black vs White participants.

Risk for CHD and Ischemic Stroke Events

Among Black and White participants, the cumulative incidence of CHD events was higher at higher lipoprotein(a) levels (Figure 4). There was no evidence of a difference in the cumulative incidence of ischemic stroke events across quartiles of lipoprotein(a). The rate of CHD events was 21.3 (95% CI, 19.2–23.4) and 23.9 (95% CI, 22.2–25.6) per 1000 person-years among Black and White participants, respectively (Table 7). After full multivariable adjustment, each 1-SD higher log-transformed lipoprotein(a) was associated with an increased risk for CHD events among both Black and White participants (HRs, 1.26 [95% CI, 1.02–1.56] and 1.16 [95% CI, 1.02–1.31], respectively; *P* value for the difference between HRs by race, 0.485). There was no evidence of an association between lipoprotein(a) and the risk for ischemic stroke among Black or White participants in multivariable-adjusted models.

The CHD event rate was higher among those in the top versus the bottom quartile of lipoprotein(a) using cut points from Black and White participants with ASCVD combined (Table 8) and when using race-specific cut points (Table 9). There was no evidence of an association between quartiles of lipoprotein(a) and ischemic stroke events.

The multivariable HR for CHD events associated with each SD higher log-transformed lipoprotein(a) was 1.31 (95% CI, 1.03–1.66) and 1.14 (95% CI, 1.00–1.31) among Black and White participants with a history of CHD, respectively (Table 10, top panel; *P* value for the difference between HRs, 0.339). Higher lipoprotein(a) levels were also associated with an increased risk for CHD events among White participants with a history of stroke (HR per 1-SD higher log-transformed lipoprotein(a), 1.44; 95% CI, 1.06–1.96). However, there was no evidence of an association between lipoprotein(a) levels and CHD risk among Black participants with a history of stroke (HR per 1-SD higher log-transformed lipoprotein(a), 0.79; 95% CI, 0.54–1.14). There was no evidence of an association between lipoprotein(a) and the risk for ischemic stroke among Black or White participants with a history of CHD or stroke (Table 10, bottom panel).

Risk for CHD and Ischemic Stroke Events by Statin Use and hs-CRP Levels

There was no evidence of a difference in the association between lipoprotein(a) and the risk for CHD events between participants taking and not taking a statin (Figure 5). Among White participants, the multivariable-adjusted HR for CHD events associated with 1-SD higher log-transformed lipoprotein(a) in those with hs-CRP ≥2 and <2 mg/L was 1.07 (95% CI, 0.91–1.27) and 1.36 (95% CI, 1.10–1.70), respectively (*P* value comparing HRs, 0.088). Among Black participants, the multivariable-adjusted HR for CHD events associated with 1-SD higher log-transformed lipoprotein(a) was 1.31 (95% CI, 0.99–1.73) and 1.23 (95% CI, 0.85–1.80) in those with hs-CRP ≥2 and <2 mg/L, respectively (*P* value comparing HRs, 0.836). There was no evidence of an association between lipoprotein(a) and ischemic stroke events within subgroups defined by statin use or hs-CRP levels.

DISCUSSION

In the current analysis, higher lipoprotein(a) levels were associated with an increased risk for CHD events among Black and White adults with ASCVD. There was no evidence that this association differed by race or by the use of statin therapy or hs-CRP

Table 3. Baseline Characteristics of Black and White REGARDS Study Participants With a History of ASCVD

Characteristic	Black participants				White participants			
	Quartile 1 (n=64)	Quartile 2 (n=209)	Quartile 3 (n=364)	Quartile 4 (n=330)	Quartile 1 (n=354)	Quartile 2 (n=276)	Quartile 3 (n=163)	Quartile 4 (n=188)
Lipoprotein(a) range, nmol/L	<13.2	13.2–<52.7	52.7–<147.9	≥147.9	<13.2	13.2–<52.7	52.7–<147.9	≥147.9
Baseline characteristics								
Age, mean (SD), y	67.7 (9.1)	64.9 (9.0)	67.2 (8.8)	66.7 (9.2)	68.9 (8.7)	70.6 (9.3)	69.1 (8.9)	69.3 (8.8)
Men, %	55.6	52.8	46.0	43.3	65.8	62.8	68.1	66.4
Geographic region of residence, %*								
Stroke belt	22.7	32.0	37.2	27.6	38.6	30.1	37.4	36.0
Stroke buckle	25.1	17.1	15.4	17.7	24.4	26.8	18.8	24.3
Other US regions	52.2	50.9	47.4	54.8	37.0	43.1	43.8	39.7
Less than high school education, %	20.7	23.6	24.9	28.9	11.6	13.1	10.4	11.1
<$25 000 Annual income, %	48.3	48.2	51.5	55.9	31.7	33.2	29.7	29.1
Low physical activity, %†	23.2	41.7	43.9	50.9	38.6	28.0	36.8	37.0
Body mass index, %								
<25 kg/m^2	14.5	19.9	20.4	16.8	27.5	29.1	30.3	26.4
25–<30 kg/m^2	39.5	33.5	33.4	31.7	35.8	39.7	34.9	42.0
≥30 kg/m^2	46.0	46.6	46.3	51.5	36.7	31.2	34.8	31.5
Alcohol consumption, %								
None	66.4	78.9	76.7	76.8	56.6	58.4	61.0	56.8
Moderate	30.4	18.0	20.3	21.7	39.3	37.9	37.1	38.8
Heavy	3.3	3.1	2.9	1.5	4.1	3.7	1.9	4.5
Current smoking, %	29.1	23.5	16.5	15.2	16.2	10.2	12.2	19.1
SBP, mean (SD), mm Hg	133.6 (18.8)	133.8 (17.8)	133.7 (18.0)	133.4 (17.9)	127.9 (16.8)	129.3 (15.9)	129.9 (17.0)	126.6 (15.7)
History of CHD, %	70.8	75.7	71.9	75.5	86.1	87.2	88.1	87.9
History of stroke, %	35.8	35.2	40.3	38.0	22.5	20.8	21.0	22.7
Diabetes, %	41.4	36.2	42.8	44.5	31.1	25.3	23.8	26.1
Chronic kidney disease, %	38.8	30.3	39.7	42.9	29.1	33.5	35.1	36.4
hs-CRP, median (25th–75th percentile), mg/L	2.2 (1.1–4.3)	2.8 (1.2–7.0)	3.3 (1.4–6.8)	2.8 (1.2–7.2)	2.0 (1.0–4.1)	1.9 (1.0–4.3)	1.8 (0.8–4.5)	2.4 (1.0–4.7)
Total cholesterol, mean (SD), mg/dL	175.1 (40.6)	178.4 (39.2)	184.2 (45.4)	187.4 (41.8)	174.0 (37.5)	175.6 (40.0)	173.6 (44.8)	176.6 (35.7)
HDL cholesterol, mean (SD), mg/dL	52.8 (16.3)	48.7 (15.6)	49.8 (14.6)	51.7 (14.6)	45.0 (15.2)	47.6 (14.6)	45.2 (12.7)	47.1 (13.8)
Triglycerides, median (25th–75th percentile), mg/dL	98.0 (71.0–146.0)	117.0 (87.0–161.0)	107.0 (80.0–153.0)	99.0 (75.0–128.0)	145.0 (101.0–214.0)	122.0 (93.0–175.0)	116.0 (90.0–177.0)	120.0 (94.0–164.0)
ApoB, mean (SD), mg/dL	85.3 (28.3)	89.6 (24.7)	93.4 (27.5)	91.8 (26.4)	92.2 (24.0)	92.3 (26.4)	90.5 (27.8)	92.6 (22.9)
Non-lipoprotein(a) ApoB, mean (SD), mg/dL	85.0 (28.3)	87.9 (24.7)	88.5 (27.6)	78.7 (26.0)	91.9 (24.0)	90.9 (26.4)	85.6 (27.9)	80.9 (22.6)
LDL cholesterol, mean (SD), mg/dL	98.6 (33.2)	104.6 (33.2)	110.6 (36.3)	115.0 (36.7)	97.9 (30.3)	102.3 (32.4)	101.8 (34.6)	103.9 (29.7)
Medication use, %								
Aspirin	54.0	56.4	61.6	65.2	69.3	71.1	73.0	76.4
Antihypertensive medication	82.3	78.9	81.5	84.0	62.8	68.7	60.3	63.7
Statin	43.3	40.1	45.3	59.5	54.7	57.8	57.3	70.0

Summary statistics were calculated using data from Black and White participants in the random subcohort, weighted to the full REGARDS study population with a history of ASCVD at baseline. Lipoprotein(a) quartiles were defined using 25th, 50th, and 75th percentiles of the lipoprotein(a) distribution pooling Black and White participants with a history of ASCVD (Table 2). ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; REGARDS, Reasons for Geographic and Racial Differences in Stroke; and SBP, systolic blood pressure.

*Stroke buckle includes coastal North Carolina, South Carolina, and Georgia. Stroke belt includes the remaining parts of North Carolina, South Carolina, and Georgia, and Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Other US regions include the remaining 40 contiguous US states and the District of Columbia.

†Low physical activity was defined by not engaging in any weekly activity intense enough to work up a sweat and was assessed by self-report.

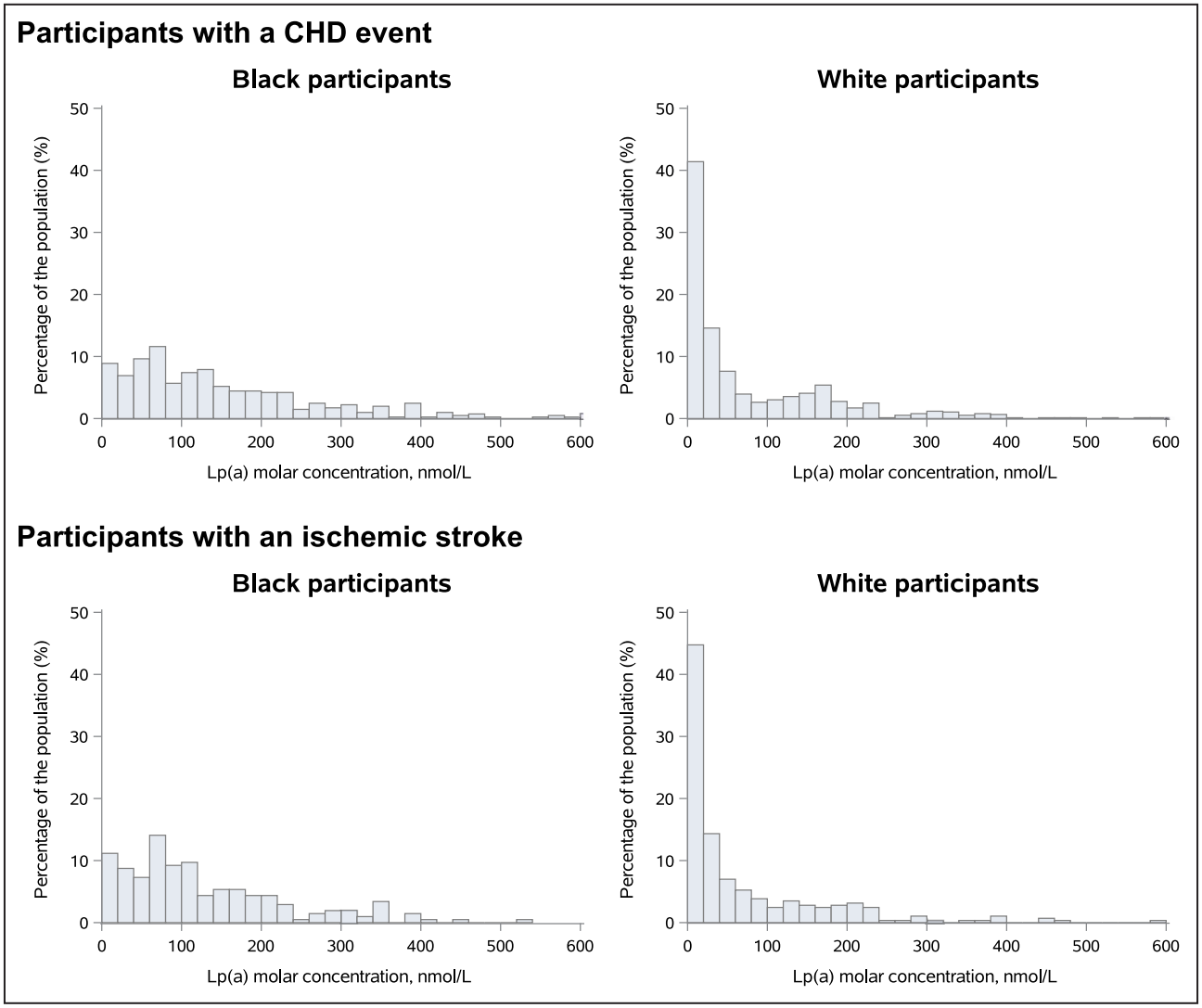

Figure 3. Distribution of lipoprotein(a) (Lp[a]) molar concentration among Black and White REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants with a history of atherosclerotic cardiovascular disease who had a coronary heart disease (CHD) event (top panel) and an ischemic stroke (bottom panel) during follow-up.

levels. Lipoprotein(a) was not associated with the risk for ischemic stroke among Black and White participants with prevalent ASCVD, including those with a history of stroke. These results suggest that elevated lipoprotein(a) levels can be used to identify Black and White adults with ASCVD who have an increased risk for CHD events.

Most prior analyses on the risk for ASCVD events associated with lipoprotein(a) in adults with prevalent ASCVD were restricted to individuals who underwent a percutaneous coronary intervention at a single health care center or were taking a statin.[11–14] In a prior analysis of the UK Biobank, the age-, sex-, and race-adjusted HR for CHD events associated with lipoprotein(a) ≥150 versus <150 nmol/L among UK adults with ASCVD was 1.23 (95% CI, 1.10–1.37).[16] However, most participants included in the analysis were White individuals, and results for those of other race were not reported separately. In the current analysis, higher lipoprotein(a) levels were associated with an increased risk for CHD events among US Black and White adults with prevalent ASCVD after multivariable adjustment for sociodemographic variables and many cardiovascular risk factors, overall and restricted to those with a history of CHD. Also, elevated lipoprotein(a) was associated with an increased risk for CHD events among White participants but not among Black participants with a history of stroke. Future studies should confirm whether no association exists between lipoprotein(a) and the risk for CHD events in Black adults with a history of stroke.

Prior studies suggest that the association of lipoprotein(a) with ischemic stroke may be weaker than the

Table 4. Lipoprotein(a) Levels Among REGARDS Study Participants With a History of ASCVD Who Had a CHD Event and an Ischemic Stroke

Variable	All participants	Black participants	White participants	*P* value*
Participants who had a CHD event, n	1166	405	761	
Lipoprotein(a) molar concentration, nmol/L				
5th Percentile	3.0	11.5	2.0	<0.001
10th Percentile	5.2	21.5	4.1	
25th Percentile	15.1	59.1	10.0	
50th Percentile (ie, median)	57.8	119.0	30.2	
75th Percentile	161.0	213.5	130.5	
90th Percentile	270.4	346.5	208.0	
95th Percentile	353.2	423.5	310.2	
Log-transformed lipoprotein(a) molar concentration				
Mean (SD)	3.8 (1.5)	4.6 (1.1)	3.4 (1.5)	<0.001
Participants who had an ischemic stroke, n	492	206	286	
Lipoprotein(a) molar concentration, nmol/L				
5th Percentile	3.3	10.4	2.0	<0.001
10th Percentile	5.1	18.2	3.8	
25th Percentile	15.0	53.8	9.6	
50th Percentile (ie, median)	60.2	97.4	25.1	
75th Percentile	141.9	176.3	98.8	
90th Percentile	230.0	296.0	202.7	
95th Percentile	315.7	351.3	254.4	
Log-transformed lipoprotein(a) molar concentration				
Mean (SD)	3.8 (1.4)	4.4 (1.1)	3.3 (1.5)	<0.001

ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

*Comparing the distribution of lipoprotein(a) molar concentration among Black vs White participants.

association with CHD events.[3,6,16] For example, among adults with ASCVD or high ASCVD risk in the UK Biobank, the HR associated with 1 SD higher levels of log-transformed lipoprotein(a) molar concentration was 1.06 (95% CI, 1.00–1.11) for ischemic stroke versus 1.11 (95% CI, 1.09–1.14) for CHD events.[3] However, these prior studies included mostly White participants.[3,6] Prior analyses of the REGARDS study and the ARIC (Atherosclerosis Risk in Communities) study suggest that the risk for incident ischemic stroke associated with lipoprotein(a) may be stronger among Black versus White adults.[2,4] Among Black and White REGARDS study participants, the HR for incident ischemic stroke associated with lipoprotein(a) in the top versus the bottom race-specific quartile was 1.96 (95% CI, 1.10–3.46) and 1.14 (95% CI, 0.64–2.04), respectively.[4] In the current analysis, there was no evidence of an association between lipoprotein(a) and the risk for ischemic stroke among Black or White REGARDS study participants with prevalent ASCVD. However, 95% CIs do not exclude a small association between lipoprotein(a) and the risk for ischemic stroke in adults with ASCVD.

The 2018 American Heart Association/American College of Cardiology multisociety cholesterol guideline recommends all adults with ASCVD take a high-intensity statin or the maximally tolerated statin dosage.[7] This guideline also recommends the initiation of ezetimibe and/or a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor among high-risk patients with ASCVD with a low-density lipoprotein cholesterol ≥70 mg/dL despite taking maximally tolerated statin therapy. In the current study, higher lipoprotein(a) was associated with an increased risk for CHD events among adults with ASCVD taking a statin. Patients with ASCVD taking a statin who have elevated lipoprotein(a) may benefit from more intensive lipid management to reduce their risk for future cardiovascular events.[35]

In a secondary analysis of the ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes) trial, the multivariable-adjusted HR for ASCVD events per 1-unit higher log-transformed lipoprotein(a) molar concentration was 1.13 (95% CI, 1.05–1.22) among participants with hs-CRP ≥2 mg/L and 0.95 (95% CI, 0.87–1.05) in those with hs-CRP <2 mg/L (*P* value comparing HRs, 0.008).[19] The authors hypothesized that higher lipoprotein(a) may be a risk factor for ASCVD events only in

Table 5. Baseline Characteristics of Black and White REGARDS Study Participants With a History of ASCVD Who Had a CHD Event During Follow-Up

	Black participants				White participants			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Characteristic	(n=22)	(n=69)	(n=156)	(n=158)	(n=236)	(n=228)	(n=135)	(n=162)
Lipoprotein(a) range, nmol/L	<13.2	13.2–<52.7	52.7–<147.9	≥147.9	<13.2	13.2–<52.7	52.7–<147.9	≥147.9
Baseline characteristics								
Age, mean (SD), y	67.8 (9.1)	67.1 (7.7)	67.8 (8.7)	66.5 (8.4)	69.8 (8.3)	72.0 (9.1)	70.8 (8.5)	69.3 (9.2)
Men, %	63.6	59.4	57.7	42.4	77.1	75.4	80.0	65.4
Geographic region of residence, %*								
Stroke belt	22.7	34.8	34.6	25.9	40.7	30.7	29.6	32.7
Stroke buckle	27.3	15.9	19.9	15.8	22.5	25.0	23.7	23.5
Other US regions	50.0	49.3	45.5	58.2	36.9	44.3	46.7	43.8
Less than high school education, %	9.1	30.9	28.8	29.7	14.9	11.0	8.9	11.1
<$25 000 Annual income, %	45.5	57.8	61.1	60.0	25.7	33.2	31.3	34.8
Low physical activity, %†	36.4	49.3	43.5	58.0	38.4	41.0	42.5	45.3
Body mass index, %								
<25 kg/m^2	13.6	10.3	17.8	14.0	18.6	20.3	23.1	23.3
25–<30 kg/m^2	36.4	38.2	32.2	35.0	39.0	42.7	37.3	39.6
≥30 kg/m^2	50.0	51.5	50.0	51.0	42.4	37.0	39.6	37.1
Alcohol consumption, %								
None	63.6	67.6	83.8	79.6	63.2	62.7	57.5	70.0
Moderate	31.8	26.5	15.6	19.7	34.2	36.0	40.3	27.5
Heavy	4.5	5.9	0.6	0.7	2.6	1.3	2.2	2.5
Current smoking, %	23.8	23.5	19.9	22.8	18.6	12.7	11.1	19.9
SBP, mean (SD), mm Hg	141.5 (17.6)	136.0 (18.9)	136.0 (19.2)	137.3 (21.6)	131.0 (18.2)	131.0 (17.3)	129.5 (16.3)	127.6 (17.2)
History of CHD, %	81.8	88.4	83.2	86.6	92.7	89.0	91.9	93.2
History of stroke, %	36.4	36.2	30.1	29.5	16.9	24.4	20.9	19.8
Diabetes, %	59.1	63.2	51.7	53.2	39.4	39.8	43.0	28.8
Chronic kidney disease, %	68.2	52.2	55.5	54.4	41.7	48.7	44.4	35.8
hs-CRP, median (25th–75th percentile), mg/L	2.1 (1.0–4.4)	3.9 (2.1–7.6)	3.4 (1.4–7.8)	3.7 (1.4–8.4)	2.4 (1.0–4.7)	2.7 (1.1–5.6)	2.3 (1.0–5.3)	2.1 (1.1–5.0)
Total cholesterol, mean (SD), mg/dL	173.3 (35.3)	170.2 (34.5)	176.6 (41.2)	193.3 (51.2)	170.9 (36.0)	172.9 (41.4)	176.7 (42.6)	184.3 (45.7)
HDL cholesterol, mean (SD), mg/dL	47.8 (11.5)	45.7 (14.3)	47.8 (12.2)	50.2 (13.5)	41.6 (13.1)	42.9 (13.8)	42.4 (11.8)	44.6 (12.4)
Triglycerides, median (25th–75th percentile), mg/dL	111.5 (88.0–153.0)	117.0 (86.0–162.0)	106.0 (74.0–143.0)	97.5 (77.0–138.0)	151.0 (100.0–231.0)	141.5 (96.0–205.0)	139.0 (99.0–202.0)	134.0 (94.0–205.5)
ApoB, mean (SD), mg/dL	87.2 (23.6)	90.0 (25.5)	89.0 (25.9)	96.9 (29.1)	93.9 (24.2)	92.9 (26.5)	94.6 (29.1)	98.5 (27.7)
Non-lipoprotein(a) ApoB, mean (SD), mg/dL	86.8 (23.6)	88.3 (25.5)	84.0 (25.9)	81.9 (28.9)	93.6 (24.2)	91.5 (26.5)	89.6 (29.2)	85.8 (27.8)
LDL cholesterol, mean (SD), mg/dL	101.2 (34.5)	100.3 (29.9)	107.2 (37.3)	121.1 (43.8)	96.6 (28.9)	100.7 (31.6)	105.3 (35.6)	109.2 (35.8)
Medication use, %								
Aspirin	68.2	65.2	66.0	66.9	73.7	73.6	80.0	77.2
Antihypertensive medication	86.4	89.6	82.9	88.3	65.8	71.4	67.4	71.8
Statin	59.1	43.5	50.6	64.6	58.9	62.7	59.3	72.2

Summary statistics were calculated using data from Black and White participants with a history of ASCVD at baseline who had a CHD event through December 31, 2017. Lipoprotein(a) quartiles were defined using 25th, 50th, and 75th percentiles of the lipoprotein(a) distribution pooling Black and White participants with a history of ASCVD (Table 2). ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; REGARDS, Reasons for Geographic and Racial Differences in Stroke; and SBP, systolic blood pressure.

*Stroke buckle includes coastal North Carolina, South Carolina, and Georgia. Stroke belt includes the remaining parts of North Carolina, South Carolina, and Georgia, and Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Other US regions include the remaining 40 contiguous US states and the District of Columbia.

†Low physical activity is defined by self-reporting not engaging in any weekly activity intense enough to work up a sweat.

Table 6. Baseline Characteristics of Black and White REGARDS Study Participants With a History of ASCVD Who Had an Ischemic Stroke Event During Follow-Up

	Black participants				White participants			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Characteristics	(n=13)	(n=36)	(n=90)	(n=67)	(n=95)	(n=88)	(n=52)	(n=51)
Lipoprotein(a) range, nmol/L	<13.2	13.2–<52.7	52.7–<147.9	≥147.9	<13.2	13.2–<52.7	52.7–<147.9	≥147.9
Baseline characteristics								
Age, mean (SD), y	70.4 (7.9)	67.7 (6.5)	67.7 (8.8)	67.2 (6.7)	69.9 (8.2)	73.0 (8.6)	73.0 (8.1)	68.4 (8.9)
Men, %	53.8	55.6	50.0	35.8	57.9	71.6	53.8	60.8
Geographic region of residence, %*								
Stroke belt	7.7	25.0	30.0	28.4	44.2	33.0	32.7	35.3
Stroke buckle	46.2	19.4	21.1	17.9	17.9	21.6	19.2	37.3
Other US regions	46.2	55.6	48.9	53.7	37.9	45.5	48.1	27.5
Less than high school education, %	23.1	19.4	25.6	31.3	8.4	8.0	7.7	19.6
<$25 000 Annual income, %	76.9	60.6	56.6	69.2	34.4	25.9	27.1	38.8
Low physical activity, %†	38.5	35.3	46.7	47.8	40.4	38.4	43.1	43.1
Body mass index, %								
<25 kg/m^2	7.7	19.4	14.4	22.7	32.6	26.1	32.7	27.5
25–<30 kg/m^2	53.8	30.6	42.2	31.8	37.9	40.9	44.2	45.1
≥30 kg/m^2	38.5	50.0	43.3	45.5	29.5	33.0	23.1	27.5
Alcohol consumption, %								
None	61.5	71.4	81.8	87.7	66.7	64.8	65.4	68.0
Moderate	38.5	25.7	18.2	12.3	30.1	30.7	28.8	32.0
Heavy		2.9			3.2	4.5	5.8	
Current smoking, %	23.1	25.7	17.8	24.2	20.0	10.2	13.5	23.5
SBP, mean (SD), mm Hg	147.8 (21.0)	136.1 (18.1)	139.0 (21.6)	134.8 (17.8)	129.6 (16.6)	130.4 (16.0)	133.9 (19.3)	127.6 (14.1)
History of CHD, %	53.8	72.2	66.3	72.7	78.7	86.2	78.8	82.0
History of stroke, %	61.5	38.9	48.9	52.2	41.1	31.4	38.5	35.3
Diabetes, %	38.5	41.7	50.6	44.8	36.8	34.5	36.5	31.4
Chronic kidney disease, %	53.8	41.7	60.7	50.7	37.9	54.5	40.4	27.5
hs-CRP, median (25th–75th percentile), mg/L	2.8 (1.2–6.7)	1.4 (0.7–6.5)	2.9 (1.0–8.4)	3.2 (1.3–8.9)	2.0 (1.1–4.2)	2.3 (1.0–5.8)	4.5 (1.8–8.0)	2.5 (0.9–5.0)
Total cholesterol, mean (SD), mg/dL	190.8 (39.5)	184.8 (40.3)	180.0 (41.1)	188.2 (47.4)	176.2 (40.5)	174.8 (39.9)	174.8 (34.9)	174.5 (37.6)
HDL cholesterol, mean (SD), mg/dL	53.2 (23.0)	51.1 (22.4)	47.6 (13.1)	51.9 (14.9)	44.7 (14.8)	44.0 (14.2)	46.6 (11.2)	46.7 (14.9)
Triglycerides, median (25th–75th percentile), mg/dL	119.0 (98.0–254.0)	107.0 (86.0–178.5)	111.0 (84.0–149.0)	85.0 (67.0–121.0)	156.0 (94.0–239.0)	141.0 (102.0–214.0)	135.5 (99.5–185.0)	123.0 (90.0–168.0)
ApoB, mean (SD), mg/dL	97.5 (27.1)	94.9 (24.5)	91.5 (27.1)	92.6 (29.0)	93.8 (26.2)	95.5 (26.3)	90.4 (24.6)	90.9 (25.1)
Non-lipoprotein(a) ApoB, mean (SD), mg/dL	97.1 (27.0)	93.4 (24.5)	86.8 (27.1)	79.8 (29.0)	93.5 (26.2)	94.1 (26.3)	85.6 (24.5)	78.3 (25.4)
LDL cholesterol, mean (SD), mg/dL	96.5 (27.7)	107.1 (30.4)	110.6 (36.6)	116.7 (40.6)	99.1 (32.2)	101.6 (33.6)	101.5 (29.5)	101.4 (31.0)
Medication use, %								
Aspirin	76.9	58.3	72.2	62.7	63.8	62.5	76.9	74.5
Antihypertensive medication	92.3	79.4	89.9	82.5	71.3	69.0	73.1	59.6
Statin	53.8	33.3	47.8	59.7	49.5	63.6	61.5	76.5

Summary statistics were calculated using data from Black and White participants with a history of ASCVD at baseline who had an ischemic stroke event through September 30, 2019. Lipoprotein(a) quartiles were defined using 25th, 50th, and 75th percentiles of the lipoprotein(a) distribution pooling Black and White participants with a history of ASCVD (Table 2). ApoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; HDL, high-density lipoprotein; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein; REGARDS, Reasons for Geographic and Racial Differences in Stroke; and SBP, systolic blood pressure.

*Stroke buckle includes coastal North Carolina, South Carolina, and Georgia. Stroke belt includes the remaining parts of North Carolina, South Carolina, and Georgia, and Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Other US regions include the remaining 40 contiguous US states and the District of Columbia.

†Low physical activity is defined by self-reporting not engaging in any weekly activity intense enough to work up a sweat.

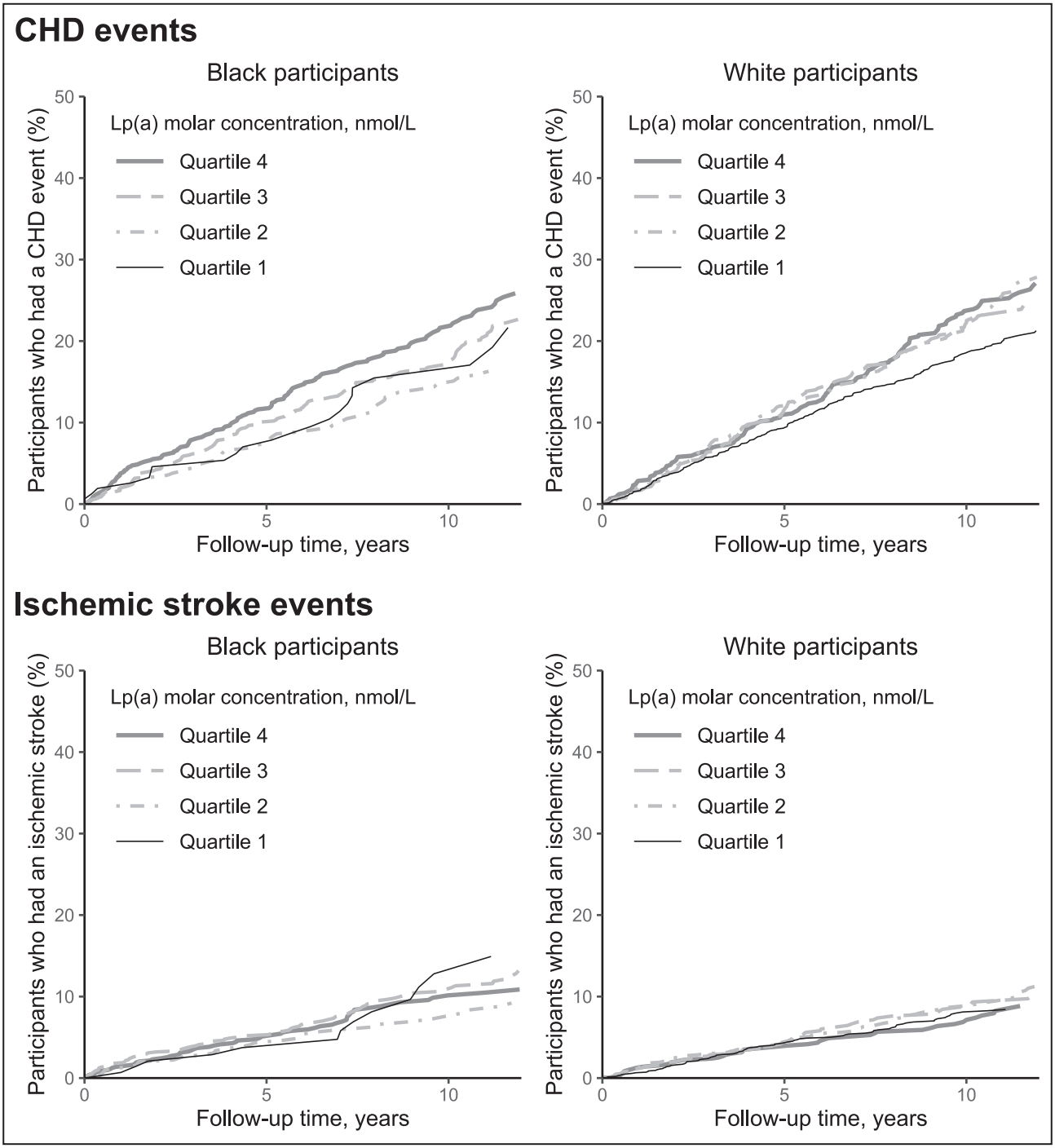

Figure 4. Cumulative incidence of coronary heart disease (CHD) and ischemic stroke events by lipoprotein(a) (Lp[a]) levels among REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants with a history of atherosclerotic cardiovascular disease (ASCVD).

Lp(a) quartiles were defined using 25th, 50th, and 75th percentiles of the Lp(a) distribution, pooling Black and White participants with a history of ASCVD. Lp(a) molar concentration range by quartiles:

1. Quartile 1: <13.2 nmol/L.
2. Quartile 2: 13.2 to <52.7 nmol/L.
3. Quartile 3: 52.7 to <147.9 nmol/L.
4. Quartile 4: ≥147.9 nmol/L.

Table 7. Risk for CHD and Ischemic Stroke Events Associated With 1-SD Higher Level of Log-Transformed Lipoprotein(a) Among REGARDS Study Participants With a History of ASCVD

Variable	Black participants	White participants	*P* value*
CHD events			
Events/person-years	405/19 008	761/31 883	
Rate (95% CI) per 1000 person-years	21.3 (19.2–23.4)	23.9 (22.2–25.6)	
Hazard ratio (95% CI)			
Model 1 (AIC: Black=5467.2; White=11 235.4)	1.32 (1.09–1.59)	1.11 (1.00–1.23)	0.123
Model 2 (AIC: Black=5119.7; White=10 673.8)	1.33 (1.09–1.63)	1.14 (1.02–1.27)	0.190
Model 3 (AIC: Black=4635.3; White=9887.1)	1.27 (1.03–1.56)	1.15 (1.02–1.31)	0.462
Model 4 (AIC: Black=4635.6; White=9887.8)	1.26 (1.02–1.56)	1.16 (1.02–1.31)	0.485
Ischemic stroke events			
Events/person-years	206/20 244	286/34 802	
Rate (95% CI) per 1000 person-years	10.2 (8.8–11.6)	8.2 (7.3–9.2)	
Hazard ratio (95% CI)			
Model 1 (AIC: Black=2808.3; White=4289.4)	1.02 (0.83–1.27)	1.02 (0.89–1.16)	0.962
Model 2 (AIC: Black=2647.8; White=4123.2)	1.08 (0.86–1.35)	1.03 (0.89–1.18)	0.714
Model 3 (AIC: Black=2394.6; White=3669.8)	1.05 (0.83–1.33)	1.06 (0.91–1.23)	0.964
Model 4 (AIC: Black=2396.1; White=3671.5)	1.05 (0.83–1.33)	1.05 (0.90–1.23)	0.970

The SD of log-transformed lipoprotein(a) molar concentration in the overall population of Black and White participants with a history of ASCVD was 1.5 (Table 2). Model 1 includes adjustment for age, sex, geographic region of residence, education, and income. Model 2 includes adjustment for variables in model 1 and physical activity, body mass index, alcohol consumption, and current smoking. Model 3 includes adjustment for variables in model 2 and systolic blood pressure, history of CHD, diabetes, chronic kidney disease, hs-CRP (high-sensitivity C-reactive protein), high-density lipoprotein cholesterol, triglycerides, and use of aspirin, antihypertensive medication, and statin. Model 4 includes adjustment for variables in model 3 plus non-lipoprotein(a) apolipoprotein B. AIC indicates Akaike information criterion; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

*Comparing hazard ratios among Black vs White participants.

adults with high hs-CRP levels. However, these results were conducted among optimally treated participants enrolled in a trial of evacetrapib and may not be generalizable to all adults with ASCVD. In the MESA (Multi-Ethnic Study of Atherosclerosis), the multivariable-adjusted HR for incident ASCVD per 1-unit higher log-transformed lipoprotein(a) was 1.32 (95% CI, 1.05–1.65) among participants with hs-CRP ≥2 mg/L, and 1.02 (95% CI, 0.81–1.27) in those with hs-CRP <2 mg/L (*P* value comparing HRs, 0.04).[20] However, 95% CIs were wide and the MESA only included participants without clinical ASCVD at baseline. Results from the current analysis of a population-based cohort of US adults with a history of ASCVD do not support that higher lipoprotein(a) is associated with an increased risk for CHD events only among those with hs-CRP ≥2 mg/L. Further studies are needed to determine whether hs-CRP modifies the association between lipoprotein(a) and ASCVD events, and, if effect modification is present, the biological mechanisms underlying this relationship.

The current analysis has several strengths. We used data from the REGARDS study, a large population-based cohort of Black and White adults who resided in all 48 contiguous US states and the District of Columbia with rigorous adjudication of CHD and ischemic stroke events. Therefore, results from the current study have a high degree of generalizability to US adults with a history of ASCVD, regardless of whether they are receiving health care, or their treatment. Many participants with a history of ASCVD included in the current study were not taking aspirin or a statin at baseline in 2003 to 2007, which is consistent with prior reports from the National Health and Nutrition Examination Surveys.[36,37] We used a case-cohort design, an efficient approach that provides unbiased estimations of HRs for exposure-outcome associations.[33,38] We measured the lipoprotein(a) molar concentration calibrated to the World Health Organization/International Federation of Clinical Chemistry and Laboratory Medicine reference material. Using standardized molar concentration provides values that are comparable across different laboratories and study populations, which may improve the clinical interpretation of the risk associated with lipoprotein(a).[39,40] Despite these strengths, the current study has known and potential limitations. The REGARDS study did not collect data on the statin dosage taken by participants at baseline, and whether participants were taking a maximally tolerated statin dosage or taking the statins as prescribed. The current study lacks statistical power to detect a small association between lipoprotein(a) and the risk for ischemic stroke by race groups. Finally,

Table 8. Risk for CHD and Ischemic Stroke Events Associated With Lipoprotein(a) Quartiles Among REGARDS Study Participants With a History of ASCVD

Variable	Quartiles of lipoprotein(a)				*P* trends*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Lipoprotein(a) range, nmol/L	<13.2	13.2–<52.7	52.7–<147.9	≥147.9	
CHD events					
Black participants					
Events/person-years	22/1206	69/4407	156/7273	158/6121	
Rate (95% CI)†	18.2 (10.6–25.9)	15.7 (12.0–19.4)	21.4 (18.1–24.8)	25.8 (21.8–29.8)	
Hazard ratio (95% CI)					
Model 1 (AIC: 5474.0)	1 (Reference)	0.91 (0.51–1.62)	1.24 (0.72–2.14)	1.44 (0.84–2.47)	0.012
Model 2 (AIC: 5125.2)	1 (Reference)	0.85 (0.46–1.58)	1.25 (0.70–2.23)	1.41 (0.79–2.52)	0.014
Model 3 (AIC: 4641.0)	1 (Reference)	0.96 (0.49–1.89)	1.25 (0.67–2.36)	1.43 (0.77–2.67)	0.052
Model 4 (AIC: 4641.4)	1 (Reference)	0.98 (0.49–1.93)	1.25 (0.66–2.35)	1.45 (0.78–2.69)	0.049
White participants					
Events/person-years	236/11 502	228/8697	135/5505	162/6179	
Rate (95% CI)†	20.5 (17.9–23.1)	26.2 (22.8–29.6)	24.5 (20.4–28.7)	26.2 (22.2–30.3)	
Hazard ratio (95% CI)					
Model 1 (AIC: 11 241.9)	1 (Reference)	1.19 (0.91–1.57)	1.12 (0.82–1.54)	1.26 (0.93–1.70)	0.249
Model 2 (AIC: 10 679.4)	1 (Reference)	1.33 (0.98–1.80)	1.26 (0.90–1.76)	1.33 (0.96–1.84)	0.203
Model 3 (AIC: 9893.4)	1 (Reference)	1.35 (0.97–1.87)	1.31 (0.91–1.88)	1.35 (0.93–1.96)	0.241
Model 4 (AIC: 9894.6)	1 (Reference)	1.34 (0.97–1.86)	1.32 (0.92–1.89)	1.36 (0.93–1.98)	0.223
Ischemic stroke events					
Black participants					
Events/person-years	13/1231	36/4711	90/7669	67/6633	
Rate (95% CI)†	10.6 (4.8–16.3)	7.6 (5.1–10.1)	11.7 (9.3–14.2)	10.1 (7.7–12.5)	
Hazard ratio (95% CI)					
Model 1 (AIC: 2808.8)	1 (Reference)	0.78 (0.39–1.54)	1.13 (0.61–2.11)	0.98 (0.52–1.84)	0.667
Model 2 (AIC: 2645.5)	1 (Reference)	0.68 (0.33–1.39)	1.18 (0.62–2.24)	0.98 (0.51–1.90)	0.478
Model 3 (AIC: 2393.8)	1 (Reference)	0.70 (0.33–1.48)	1.15 (0.58–2.27)	0.98 (0.50–1.92)	0.591
Model 4 (AIC: 2395.6)	1 (Reference)	0.70 (0.33–1.50)	1.14 (0.58–2.25)	0.98 (0.50–1.93)	0.580
White participants					
Events/person-years	95/12 667	88/9460	52/5870	51/6804	
Rate (95% CI)†	7.5 (6.0–9.0)	9.3 (7.4–11.2)	8.9 (6.5–11.3)	7.5 (5.4–9.6)	
Hazard ratio (95% CI)					
Model 1 (AIC: 4292.8)	1 (Reference)	1.12 (0.79–1.58)	1.07 (0.71–1.63)	0.99 (0.66–1.48)	0.818
Model 2 (AIC: 4125.4)	1 (Reference)	1.23 (0.85–1.77)	1.13 (0.73–1.76)	1.03 (0.68–1.56)	0.863
Model 3 (AIC: 3669.0)	1 (Reference)	1.38 (0.91–2.09)	1.39 (0.86–2.25)	1.05 (0.65–1.69)	0.890
Model 4 (AIC: 3670.4)	1 (Reference)	1.40 (0.92–2.13)	1.39 (0.86–2.24)	1.04 (0.65–1.68)	0.852

Quartiles of lipoprotein(a) were defined using 25th, 50th, and 75th percentiles of the lipoprotein(a) distribution among Black and White participants with a history of ASCVD combined (Table 2). Model 1 includes adjustment for age, sex, geographic region of residence, education, and income. Model 2 includes adjustment for variables in model 1 and physical activity, body mass index, alcohol consumption, and current smoking. Model 3 includes adjustment for variables in model 2 and systolic blood pressure, history of CHD, diabetes, chronic kidney disease, hs-CRP (high-sensitivity C-reactive protein), high-density lipoprotein cholesterol, triglycerides, and use of aspirin, antihypertensive medication, and statin. Model 4 includes adjustment for variables in model 3 plus non-lipoprotein(a) apolipoprotein B. *P* values comparing hazard ratios for CHD events associated with quartiles of lipoprotein(a) among Black vs White participants: model 1=0.337; model 2=0.210; model 3=0.536; model 4=0.596. *P* values comparing hazard ratios for ischemic stroke events associated with quartiles of lipoprotein(a) among Black vs White participants: model 1=0.574; model 2=0.234; model 3=0.304; model 4=0.290. AIC indicates Akaike information criterion; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

**P* trends were calculated using the median lipoprotein(a) level corresponding to each participant's quartile as the independent variable.

†Rates are expressed per 1000 person-years.

we used stored samples to measure lipoprotein(a) at baseline, which may affect the stability of lipoprotein(a) particles.[41] However, the median lipoprotein(a) molar concentration among Black and White REGARDS study participants included in the current analysis was higher than those reported in apparently healthy

Table 9. Risk for CHD and Ischemic Stroke Events Associated With Race-Specific Lipoprotein(a) Quartiles Among REGARDS Study Participants With a History of ASCVD

Variable	Quartiles of lipoprotein(a)				*P* trends*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
CHD events					
Black participants					
Lipoprotein(a) range, nmol/L	<47.5	47.5–<100.1	100.1–<185.8	≥185.8	
Events/person-years	77/4919	96/4984	107/4626	125/4478	
Rate (95% CI)†	15.7 (12.2–19.2)	19.3 (15.4–23.1)	23.1 (18.7–27.5)	27.9 (23.0–32.8)	
Hazard ratio (95% CI)					
Model 1 (AIC: 5469.9)	1 (Reference)	1.23 (0.86–1.76)	1.45 (1.01–2.08)	1.73 (1.21–2.46)	0.002
Model 2 (AIC: 5121.7)	1 (Reference)	1.27 (0.86–1.86)	1.47 (1.00–2.16)	1.80 (1.24–2.61)	0.002
Model 3 (AIC: 4637.2)	1 (Reference)	1.27 (0.83–1.93)	1.38 (0.92–2.08)	1.69 (1.13–2.53)	0.013
Model 4 (AIC: 4637.5)	1 (Reference)	1.24 (0.81–1.90)	1.36 (0.90–2.04)	1.68 (1.12–2.52)	0.011
White participants					
Lipoprotein(a) range, nmol/L	<8.2	8.2–<23.4	23.4–<112.9	≥112.9	
Events/person-years	168/8121	165/7820	213/7840	215/8102	
Rate (95% CI)†	20.7 (17.6–23.8)	21.1 (17.9–24.3)	27.2 (23.5–30.8)	26.5 (23.0–30.1)	
Hazard ratio (95% CI)					
Model 1 (AIC: 11 239.7)	1 (Reference)	1.02 (0.74–1.40)	1.23 (0.91–1.67)	1.26 (0.93–1.71)	0.135
Model 2 (AIC: 10 676.6)	1 (Reference)	1.12 (0.79–1.58)	1.45 (1.03–2.03)	1.34 (0.96–1.86)	0.154
Model 3 (AIC: 9892.4)	1 (Reference)	1.06 (0.72–1.54)	1.39 (0.96–2.02)	1.33 (0.92–1.92)	0.151
Model 4 (AIC: 9893.3)	1 (Reference)	1.05 (0.72–1.53)	1.38 (0.95–2.01)	1.34 (0.92–1.94)	0.137
Ischemic stroke events					
Black participants					
Lipoprotein(a) range, nmol/L	<47.5	47.5–<100.1	100.1–<185.8	≥185.8	
Events/person-years	45/5185	59/5178	55/5114	47/4766	
Rate (95% CI)†	8.7 (6.1–11.2)	11.4 (8.5–14.3)	10.8 (7.9–13.6)	9.9 (7.0–12.7)	
Hazard ratio (95% CI)					
Model 1 (AIC: 2811.1)	1 (Reference)	1.23 (0.78–1.94)	1.20 (0.76–1.89)	1.12 (0.71–1.79)	0.814
Model 2 (AIC: 2649.3)	1 (Reference)	1.40 (0.87–2.26)	1.38 (0.86–2.23)	1.26 (0.77–2.06)	0.564
Model 3 (AIC: 2395.0)	1 (Reference)	1.54 (0.92–2.59)	1.24 (0.74–2.09)	1.29 (0.77–2.17)	0.675
Model 4 (AIC: 2396.8)	1 (Reference)	1.52 (0.91–2.56)	1.23 (0.73–2.07)	1.29 (0.77–2.17)	0.662
White participants					
Lipoprotein(a) range, nmol/L	<8.2	8.2–<23.4	23.4–<112.9	≥112.9	
Events/person-years	63/8772	75/8591	80/8552	68/8887	
Rate (95% CI)†	7.2 (5.4–9.0)	8.7 (6.8–10.7)	9.4 (7.3–11.4)	7.7 (5.8–9.5)	
Hazard ratio (95% CI)					
Model 1 (AIC: 4293.1)	1 (Reference)	1.08 (0.71–1.63)	1.10 (0.74–1.63)	1.01 (0.68–1.52)	0.874
Model 2 (AIC: 4125.9)	1 (Reference)	1.14 (0.74–1.75)	1.20 (0.79–1.84)	1.02 (0.67–1.57)	0.757
Model 3 (AIC: 3671.8)	1 (Reference)	1.06 (0.66–1.72)	1.31 (0.80–2.13)	1.02 (0.64–1.63)	0.845
Model 4 (AIC: 3673.4)	1 (Reference)	1.07 (0.66–1.73)	1.32 (0.81–2.15)	1.01 (0.64–1.62)	0.809

Quartiles of lipoprotein(a) were defined using 25th, 50th, and 75th percentiles of the lipoprotein(a) distribution among Black and White participants with a history of ASCVD, separately (Table 2). Model 1 includes adjustment for age, sex, geographic region of residence, education, and income. Model 2 includes adjustment for variables in model 1 and physical activity, body mass index, alcohol consumption, and current smoking. Model 3 includes adjustment for variables in model 2 and systolic blood pressure, history of CHD, diabetes, chronic kidney disease, hs-CRP (high-sensitivity C-reactive protein), high-density lipoprotein cholesterol, triglycerides, and use of aspirin, antihypertensive medication, and statin. Model 4 includes adjustment for variables in model 3 plus non-lipoprotein(a) apolipoprotein B. *P* values comparing hazard ratios for CHD events associated with quartiles of lipoprotein(a) among Black vs White participants: model 1=0.625; model 2=0.613; model 3=0.745; model 4=0.760. *P* values comparing hazard ratios for ischemic stroke events associated with quartiles of lipoprotein(a) among Black vs White participants: model 1=0.978; model 2=0.917; model 3=0.580; model 4=0.585. AIC indicates Akaike information criterion; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

**P* trends were calculated using the median lipoprotein(a) level corresponding to each participant's quartile as the independent variable.

†Rates are expressed per 1000 person-years.

Table 10. Risk for CHD and Ischemic Stroke Events Associated With 1-SD Higher Level of Log-Transformed Lipoprotein(a) Among REGARDS Study Participants With a History of CHD and Ischemic Stroke, Separately

Variable	Black participants	White participants	*P* value*
CHD events			
Participants with a history of CHD			
Events/person-years	344/13 897	695/27 968	
Rate (95% CI) per 1000 person-years	24.8 (22.1–27.4)	24.8 (23.0–26.7)	
Hazard ratio (95% CI)			
Model 1 (AIC: Black=4418.2; White=10 093.1)	1.32 (1.07–1.62)	1.10 (0.99–1.23)	0.141
Model 2 (AIC: Black=4142.6; White=9563.8)	1.34 (1.07–1.68)	1.14 (1.01–1.29)	0.218
Model 3 (AIC: Black=3795.1; White=8917.6)	1.31 (1.03–1.66)	1.14 (0.99–1.30)	0.310
Model 4 (AIC: Black=3796.7; White=8915.7)	1.31 (1.03–1.66)	1.14 (1.00–1.31)	0.339
Participants with a history of stroke			
Events/person-years	126/7028	155/6356	
Rate (95% CI)†	17.9 (14.8–21.1)	24.4 (20.5–28.2)	
Hazard ratio (95% CI)			
Model 1 (AIC: Black=1517.6; White=1783.8)	1.02 (0.74–1.41)	1.39 (1.10–1.75)	0.137
Model 2 (AIC: Black=1436.6; White=1690.9)	0.96 (0.69–1.35)	1.29 (1.00–1.68)	0.176
Model 3 (AIC: Black=1221.7; White=1503.6)	0.79 (0.55–1.14)	1.40 (1.04–1.89)	0.018
Model 4 (AIC: Black=1222.9; White=1502.1)	0.79 (0.54–1.14)	1.44 (1.06–1.96)	0.014
Ischemic stroke events			
Participants with a history of CHD			
Events/person-years	138/14 998	231/30 558	
Rate (95% CI) per 1000 person-years	9.2 (7.7–10.7)	7.6 (6.6–8.5)	
Hazard ratio (95% CI)			
Model 1 (AIC: Black=1815.6; White=3402.2)	1.04 (0.80–1.34)	1.03 (0.89–1.19)	0.955
Model 2 (AIC: Black=1709.4; White=3247.4)	1.08 (0.82–1.41)	1.04 (0.89–1.21)	0.810
Model 3 (AIC: Black=1558.5; White=2982.9)	1.06 (0.79–1.41)	1.03 (0.87–1.21)	0.883
Model 4 (AIC: Black=1560.2; White=2983.1)	1.05 (0.79–1.40)	1.03 (0.88–1.22)	0.927
Participants with a history of stroke			
Events/person-years	101/7205	104/6590	
Rate (95% CI)†	14.0 (11.3–16.8)	15.8 (12.7–18.8)	
Hazard ratio (95% CI)			
Model 1 (AIC: Black=1199.9; White=1240.0)	1.02 (0.72–1.45)	1.01 (0.78–1.30)	0.990
Model 2 (AIC: Black=1150.2; White=1201.3)	1.05 (0.73–1.51)	0.96 (0.73–1.27)	0.734
Model 3 (AIC: Black=1039.8; White=1027.3)	0.96 (0.65–1.41)	1.05 (0.74–1.50)	0.742
Model 4 (AIC: Black=1040.7; White=1023.6)	0.98 (0.65–1.46)	0.99 (0.68–1.43)	0.997

The SD of log-transformed lipoprotein(a) molar concentration in the overall population of Black and White participants with a history of atherosclerotic cardiovascular disease was 1.5 (Table 2). Model 1 includes adjustment for age, sex, geographic region of residence, education, and income. Model 2 includes adjustment for variables in model 1 and physical activity, body mass index, alcohol consumption, and current smoking. Model 3 includes adjustment for variables in model 2 and systolic blood pressure, history of CHD, diabetes, chronic kidney disease, hs-CRP (high-sensitivity C-reactive protein), high-density lipoprotein cholesterol, triglycerides, and use of aspirin, antihypertensive medication, and statin. Model 4 includes adjustment for variables in model 3 plus non-lipoprotein(a) apolipoprotein B. AIC indicates Akaike information criterion; CHD, coronary heart disease; and REGARDS, Reasons for Geographic and Racial Differences in Stroke.

*Comparing hazard ratios among Black vs White participants.

†Rates are expressed per 1000 person-years.

individuals[10] and similar to those in adults with a history of ASCVD.[16]

In conclusion, the current study suggests that higher lipoprotein(a) levels are associated with an increased risk for CHD events in Black and White adults with prevalent ASCVD. This association does not appear to be modified by statin use or hs-CRP levels. Lipoprotein(a) levels could be used to inform the need for more intensive risk-reduction interventions in Black and White adults with ASCVD.

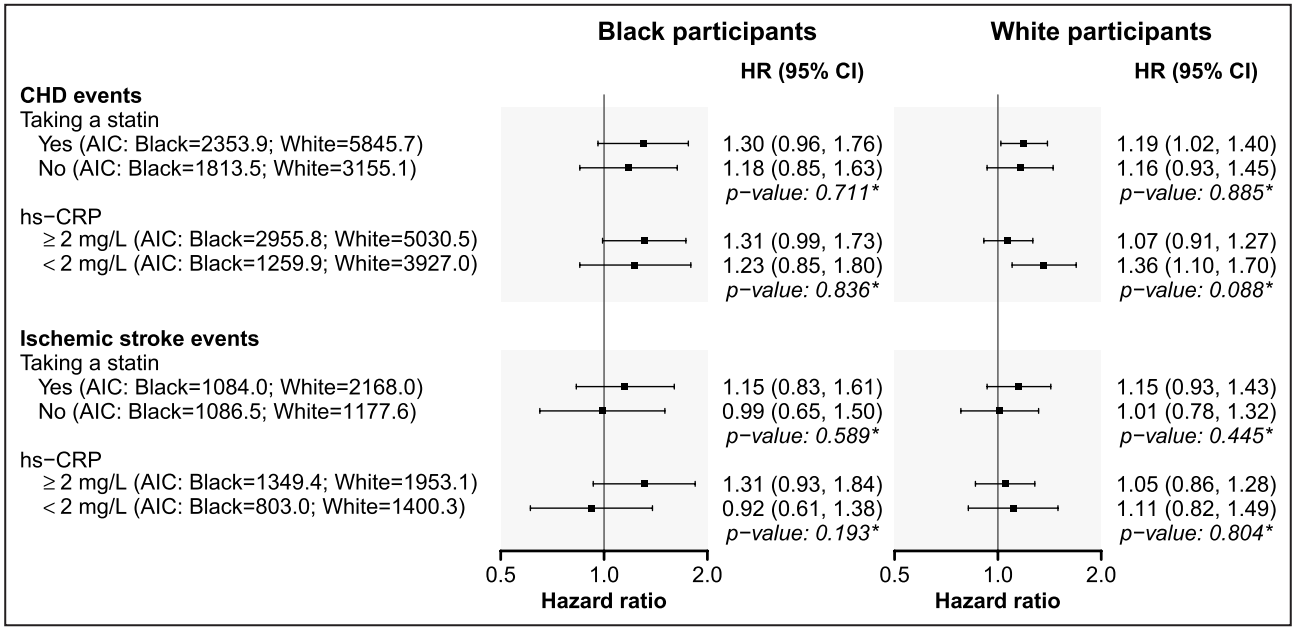

Figure 5. Risk for coronary heart disease (CHD) and ischemic stroke events associated with a 1-SD higher level of log-transformed lipoprotein(a) (Lp[a]) among REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants with a history of atherosclerotic cardiovascular disease (ASCVD), stratified by statin use and hs-CRP (high-sensitivity C-reactive protein) levels.

*Comparing hazard ratios (HRs) across subgroups defined by statin use and hs-CRP levels. The SD of log-transformed Lp(a) molar concentration in the overall population of Black and White participants with a history of ASCVD was 1.5 (Table 2). HRs include adjustment for age, sex, geographic region of residence, education, income, physical activity, body mass index, alcohol consumption, current smoking, systolic blood pressure, history of CHD, diabetes, chronic kidney disease, hs-CRP (in models stratified by statin use), high-density lipoprotein cholesterol, triglycerides, and use of aspirin, antihypertensive medication, statin (in models stratified by hs-CRP levels), and non-Lp(a) apolipoprotein B. AIC indicates Akaike information criterion.

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