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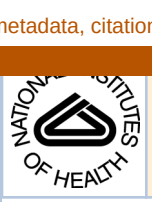

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Associations Between Lipoprotein(a) Levels and Cardiovascular Outcomes in African Americans and Caucasians: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Based on studies with limited statistical power, lipoprotein(a) [Lp(a)] is not considered a risk factor for cardiovascular disease (CVD) in African Americans. We evaluated associations between Lp(a) and incident CVD events in African Americans and Caucasians in the Atherosclerosis Risk in Communities (ARIC) study.

Methods and Results—Plasma Lp(a) was measured in African Americans (n=3,467) and Caucasians (n=9,851). Hazards ratios (HRs) for incident CVD events (coronary heart disease [CHD] and ischemic strokes) were calculated. Lp(a) levels were higher with wider interindividual

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variation in African Americans (median [interquartile range]: 12.8 [7.1–21.7] mg/dl) than Caucasians (4.3 [1.7–9.5] mg/dl; p <0.0001). At 20 years of follow-up, 676 CVD events occurred in African Americans and 1,821 events occurred in Caucasians. Adjusted HRs (95% confidence interval [CI]) per race-specific 1-SD–greater log-transformed Lp(a) were 1.13 (1.04–1.23) for incident CVD, 1.11 (1.00–1.22) for incident CHD, and 1.21 (1.06–1.39) for ischemic strokes in African Americans. For Caucasians, the respective HRs (95% CIs) were 1.09 (1.04–1.15), 1.10 (1.05–1.16), and 1.07 (0.97–1.19). Quintile analyses showed that risk for incident CVD was graded but statistically significant only for the highest compared with the lowest quintile (HR [95%CI] 1.35 [1.06–1.74] for African Americans; HR 1.27 [1.10–1.47] for Caucasians). Similar results were obtained using Lp(a) cut-offs of ≤10 mg/dl, >10–≤20 mg/dl, >20–≤30 mg/dl, and >30 mg/dl.

Conclusions—Lp(a) levels were positively associated with CVD events. Associations were at least as strong, with a larger range of Lp(a) concentrations, in African Americans compared with Caucasians.

Keywords

lipoproteins; cardiovascular diseases; risk factors; race/ethnicity; cardiovascular disease risk factors

Introduction

Although elevated lipoprotein(a) [Lp(a)] is considered a risk factor for cardiovascular disease (CVD) in Caucasians based on its association with measures of atherosclerosis and incident coronary heart disease (CHD) events,[1-9] the association between Lp(a) level and CVD risk in African Americans is not clear,[5,10-14] despite African Americans' having 2–4 times higher Lp(a) levels than Caucasians.[12,15,16] In the meta-analysis performed by the Emerging Risk Factors Collaboration,[1] although Lp(a) was associated with CHD in Caucasians, these associations were not significant in African Americans (261 CHD events occurred in African Americans, compared with 7,540 in Caucasians). The Adult Treatment Panel III guidelines also note that "although Lp(a) levels are higher in African Americans than in Caucasians, an increased risk for CHD associated with higher Lp(a) levels in African Americans has not been documented."[17] Similarly, an European Atherosclerosis Society consensus statement noted that the evidence to date does not answer whether Lp(a) is responsible for the high incidence rate of stroke in African Americans and emphasized the need for further effort to assess atherothrombotic risk due to Lp(a) in different ethnicities.[18]

Few prospective studies have evaluated the associations between Lp(a) levels and incident CVD events in African Americans because African Americans have not been well-represented in established longitudinal cohort studies. The Atherosclerosis Risk in Communities (ARIC) study, given its biracial population, provides an opportunity to study associations between elevated Lp(a) levels and incident CVD events in African Americans. In an earlier publication from the ARIC study evaluating CHD outcomes in up to 10 years of follow-up, although the relative risks (RRs) per 1–standard deviation (SD) higher Lp(a) level for incident CHD were statistically significant for Caucasian men and women, they were not significant for African American men or women.[19] One reason postulated to explain this result was that the number of CHD events was low in African Americans (of a total of 725 CHD events, 90 occurred in African American men and 68 occurred in African American women). Another study in the ARIC cohort showed that although Lp(a) levels were associated positively with ischemic strokes in African American women (RR 1.84, 95% confidence interval [CI] 1.05–3.07), the results were not statistically significant in African American men (RR 1.72, 95% CI 0.86– 3.48).[20] Ascertainment of additional CHD

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events and ischemic strokes in the ARIC cohort since these initial publications provides the opportunity to study the associations between Lp(a) and cardiovascular events in the African American participants with greater statistical power.

Our aim was thus to study the associations between Lp(a) and incident CVD events, incident CHD events, and incident ischemic strokes in African American and Caucasian ARIC participants at up to 20 years of follow-up from the baseline examination.

Methods

Study population

The ARIC study is a prospective epidemiologic study of CVD incidence primarily among African American and Caucasian adults (n=15,792). ARIC participants were selected to be representative of adults aged 45–64 years living in 4 communities in the United States between 1987 and 1989. A complete description of the study design, objectives, and sampling strategy has been described previously.[21] For the current analyses, we excluded participants with prevalent CHD (n=1,110) or prevalent stroke (n=336) at the baseline ARIC visit (1987–1989), those in whom the self-reported race was not African American or Caucasian or was not known (n=43), African Americans in Minneapolis and Washington County, Maryland (n=48), and those using lipid-lowering medications (n=353) or missing data on lipid-lowering medication use (n=105) at the baseline ARIC visit. Of the remaining 13,797 participants, 13,318 (3,467 African Americans and 9,851 Caucasians) had Lp(a) measurements, and these participants formed the study population for the current analyses. Research protocols were approved by the institutional review board at each participating institution, and all participants provided written informed consent.

Information about covariates of interest was obtained by history and examinations at the baseline visit.[21] Sitting blood pressure and venipuncture were performed using published techniques. Smoking status and the use of antihypertensive and lipid-lowering medications were assessed by a standardized questionnaire. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, prior physician diagnosis of hypertension, or use of antihypertensive medications. Diabetes mellitus was defined as either a self-reported history of diabetes, physician-diagnosed diabetes, the use of prescribed hypoglycemic medications, nonfasting glucose ≥200 mg/dl, or blood glucose ≥126 mg/dl after fasting at least 8 hours.

Baseline laboratory measurements

Lipid assays were performed on 12-hour fasting plasma samples collected on ice using EDTA as the anticoagulant. Cholesterol (total and high-density lipoprotein cholesterol [HDL-C]) and triglycerides were measured enzymatically. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation.[22] The assay characteristics for baseline lipid measurements in the ARIC study have been described previously.[23]

Lp(a) mass was measured at visit 1 using a double-antibody ELISA technique for Lp(a) detection. Lp(a) level was measured as the total protein component (apolipoprotein(a) [apo(a)] + apolipoprotein B). The protein moiety represents approximately one-third of the total Lp(a) lipoprotein mass. Therefore, an Lp(a) protein value of 10 mg/dl is comparable to a total Lp(a) value of approximately 30 mg/dl. The assay reliability (between-person variance divided by the total variance) was 0.90,[24] with essentially no within-person variability (indicative of a largely genetic predisposition), in a small sample of individuals. Most of the measurements were performed within 6 weeks of the receipt of the samples.

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Ascertainment of incident coronary heart disease events and incident ischemic strokes

Our outcome of interest was incident CVD events, which included incident CHD events and incident ischemic strokes. The ascertainment procedure for incident CHD events has been described previously.[25] Briefly, incident CHD events included CHD death, myocardial infarction, silent infarction identified by ECG, coronary artery bypass surgery, and coronary angioplasty occurring on or before December 31, 2007. Death and hospitalization events were ascertained by annual follow-up calls and community hospital surveillance. CHD death was defined as death lacking a probable non-CHD cause and with a recent myocardial infarction, chest pain within 72 hours of death, or a history of CHD.

For the ascertainment of incident ischemic strokes, we surveyed discharges lists from local hospitals and death certificates from state vital statistics offices. An abstractor recorded signs and symptoms and photocopied neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI]) and other diagnostic reports if the discharge diagnoses included a cerebrovascular disease code (International Classification of Diseases, 9th Revision, codes 430 to 438), if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a CT or MRI report. Each eligible case was classified according to criteria adapted from the National Survey of Stroke.[26,27] Qualifying strokes were further classified as definite or probable ischemic (cardioembolic or thrombotic) or hemorrhagic stroke on the basis of neuroimaging studies and autopsy, when available. A stroke was classified as ischemic if a brain CT or MRI revealed acute infarction or showed no evidence of hemorrhage.

Statistical analyses

Median Lp(a) levels were compared between African American and Caucasians (and between men and women) using analysis of variance test. Using traditional risk factors from baseline data, we defined risk factors for incident CVD events using a Cox proportional-hazards model. The proportional-hazards assumption was confirmed. Multivariable proportional-hazards analysis was performed to assess whether Lp(a) contributed independently to the adjusted models. Adjustment model 1 included age and gender as covariates. Adjustment model 2 included age, gender, current smoking, systolic blood pressure, use of antihypertensive medications, and diabetes. Adjustment model 3 (fully adjusted model) included age, gender, current smoking, systolic blood pressure, use of antihypertensive medications, diabetes, LDL-C, HDL-C, and triglycerides as covariates. First, we performed quintile analyses (separately for African Americans and Caucasians) using the lowest Lp(a) quintile as the referent. Hazard ratios (HRs) were then calculated for the second, third, fourth, and highest quintiles, with adjustment for the covariates. To account for the skewed Lp(a) distribution, HRs associated with a 1-SD increase in log-transformed Lp(a) levels were calculated, followed by adjustment for the covariates of interest. Finally, we calculated HRs using Lp(a) cut-offs of ≤10 mg/dl, >10–≤20 mg/dl, >20–≤30 mg/dl, and >30 mg/dl, using Lp(a) levels ≤10 mg/dl as the referent group and adjusting for the covariates described above.

Analyses were performed using R version 2.11.1. All analyses were performed using 2-tailed tests for significance. A p-value <0.05 was considered statistically significant.

Results

The final analyses included 13,318 participants: 3,467 African Americans (1,304 men, 2,163 women) and 9,851 Caucasians (4,473 men, 5,378 women). Lp(a) was significantly higher in African Americans compared with Caucasians (median levels [interquartile range] and 12.8 [7.1–21.7] mg/dl in African Americans and 4.3 [1.8–10.7] mg/dl in Caucasians, p <0.0001).

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Median Lp(a) levels were significantly higher in women compared with men (African Americans: 13.7 vs. 11.9 mg/dl, p <0.0001; Caucasians: 4.8 vs. 3.9 mg/dl, p <0.0001).

Baseline characteristics

Baseline characteristics of participants across Lp(a) quintiles are described in Table 1. For African Americans, Lp(a) levels in the highest quintile ranged from >24 mg/dl to 81.7 mg/dl (median for the highest quintile = 32.1 mg/dl), whereas Lp(a) levels in the highest quintile for Caucasians ranged from 13.5 mg/dl to 80.3 mg/dl (median for the highest quintile = 20.4 mg/dl). Among both ethnic groups, higher Lp(a) quintiles included a higher proportion of women and lower prevalence of estrogen or progesterone use (in women). With increasing Lp(a) levels, LDL-C and HDL-C levels tended to be higher, whereas triglyceride levels tended to be lower in both groups. African American ARIC study participants in higher Lp(a) quintiles also had a lower prevalence of smoking. Body mass index was not associated with Lp(a) levels. Although participants on lipid-lowering medications (n=335) at baseline were excluded from these analyses, the proportions of participants across Lp(a) quintiles who were on any lipid-lowering medications at ARIC study visit 4 (1996–1998) were 5.5%, 5.6%, 8.5%, 6.3%, and 10.7% for African Americans, and 13.9%, 10.9%, 11.3%, 12.6%, and 18.4% for Caucasians. The proportions of participants across Lp(a) quintiles who were on statins at ARIC study visit 4 were 4.8%, 4.9%, 7.3%, 5.7%, and 2.9% for African Americans, and 10.6%, 7.9%, 8.8%, 10%, and 15.8% for Caucasians.

Lp(a) levels and incident cardiovascular events

At ~20 years of follow-up, there were 676 incident CVD events in African Americans (481 CHD events and 283 ischemic strokes) and 1,821 incident CVD events in Caucasians (1,564 CHD events and 380 ischemic strokes).

Table 2 describes the results of race-specific quintile analyses comparing HRs in the second, third, fourth, and highest quintiles of Lp(a) with those in the lowest quintile. For African Americans, the associations were graded (p for trend = 0.0004, 0.009, and 0.0004 for incident CVD, CHD, and ischemic strokes, respectively), but were statistically significant only for the highest Lp(a) quintile (>24 mg/dl) for incident CVD events and ischemic strokes. Although participants in the highest quintile had increased risk for CHD compared with those in the lowest quintile, this HR was not statistically significant (HR 1.27, 95% CI 0.94–1.71). For Caucasians, the associations were graded for incident CVD (p for trend = 0.001) and CHD (p for trend = 0.002), but not for ischemic strokes (p for trend = 0.25). The HRs for incident CVD and CHD were statistically significant only for the highest quintile of Lp(a) (>13.5 mg/dl). The highest quintile in Caucasians was roughly equivalent to the 50th percentile in African Americans.

We also evaluated HRs for incident CVD events, CHD events, and ischemic strokes per race-specific 1-SD increase in log-transformed Lp(a) levels (Table 3). For African Americans, each 1-SD increase in Lp(a) level in model 3 was associated with a 13% increase in risk for incident CVD events, an 11% increase in risk for CHD events (borderline significant), and a 21% increase in risk for ischemic strokes. Thus, the relationships were numerically stronger for ischemic strokes than for CHD events. For Caucasian participants, each 1-SD increase in Lp(a) was associated with a 9% increase in risk for incident CVD and a 10% increase in risk for CHD events; the 7% increase in risk for ischemic strokes was not statistically significant. It is important to note, however, that the strength of this association was at least as strong in African Americans as in Caucasians.

As it could be argued that the significant association between Lp(a) and incident CVD events seen in African Americans could be a result of differences in SDs of Lp(a) levels in

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African Americans and Caucasians, we also calculated HRs in African Americans and Caucasians using cut-offs with 10-mg/dl increments in Lp(a) levels (Table 4) .The HRs using absolute Lp (a) cut-offs were at least as strong in African Americans as in Caucasians for CVD and CHD, and numerically higher for ischemic strokes at Lp(a) levels >30 mg/dl in African Americans compared with Caucasians.

Stratified analyses on male and female participants (Tables 5–7) showed that Lp(a) levels were associated with increased risk for CVD, CHD, and ischemic strokes in both males and females, with a larger range of relevant Lp(a) concentrations in females compared with males.

We also performed separate analyses for African American women, African American men, Caucasian women, and Caucasian men using Lp(a) quintiles, SD of log-transformed Lp(a) levels, and absolute Lp(a) cut-offs (Supplemental Tables 1–3). Although these analyses were limited given the small number of events in some subgroups, Lp(a) levels were broadly associated with CVD risk in both African American and Caucasian males and females. However, the associations between Lp(a) and risk of ischemic strokes were more robust for African Americans compared with Caucasians (especially Caucasian men).

As one could argue that the Lp(a) assay used in ARIC could be sensitive to apo(a) isoform size, we performed additional analyses using a newer Lp(a) assay that is insensitive to apo(a) isoform size when calibrated with the International Federation of Clinical Chemistry proposed reference material in molar units.[28] Using 100 ARIC visit 1 samples (from the entire Lp(a) distribution based on the original assay with equal representation from both genders and ethnic groups), we compared the results with the original Lp(a) assay with the results of the newer isoform size–insensitive Lp(a) assay. Despite ~23 years of storage at –70°C, our Deming regression analysis (Supplemental Figure 1) showed a good correlation (r=0.88) between the two assays. Similarly, Bland–Altman plots (Supplemental Figure 1) did not show evidence of a systematic bias at high or low Lp(a) levels. Based on these analyses, the clinically relevant cut-off of 30 mg/dl by the original ARIC visit 1 Lp(a) assay is roughly equivalent to 39 mg/dl by the newer isoform size–insensitive Lp(a) assay.

Discussion

In this large population-based study of African Americans and Caucasians followed for up to 20 years, Lp(a) levels were positively associated with risk for incident CVD events in both races. The strength of association for incident CVD events was equivalent for African Americans and Caucasians. The association between ischemic strokes and Lp(a) levels was more robust in African Americans. Although the associations tended to be graded, they were statistically significant only for the highest quintile of Lp(a) levels. The gradient for increase in risk was comparable between both groups, with a larger range of Lp(a) levels in African Americans. Consistent with prior data, median Lp(a) levels were almost 3 times higher in African Americans than in Caucasians.[12,15,16]

Elevated Lp(a) levels have been associated consistently with increased CHD risk in Caucasians but not in African Americans.[5,13,14] Similarly, mendelian randomization studies in Caucasians also support a causal role of Lp(a) in atherosclerosis.[2] Although the exact reasons why elevated Lp(a) levels have not been consistently associated with increased CHD risk in African Americans are not known, some have argued that apo(a) size is an important contributor.[29,30] Small apo(a) isoforms are likely more atherogenic than large apo(a) isoforms,[29] which could partly explain why African Americans may not have increased CHD risk despite elevated Lp(a) levels, as African Americans have lower prevalence of small apo(a) isoforms compared with Caucasians.[31] Paultre et al[30] showed

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that elevated levels of Lp(a) combined with small apo(a) isoforms were associated with the angiographic extent of coronary artery disease in both African American and Caucasian men. However, most studies showing associations between small apo(a) and CHD events did not adjust for total Lp(a) levels,[32] and smaller apo(a) isoforms are associated with higher total Lp(a) levels.[33] In addition, a recent analysis showed that although total Lp(a) levels were associated with CHD events after adjustment for apo(a) isoform size, the reverse was not true.[34] Similarly, lower LDL-C and higher HDL-C levels in African Americans might protect against risk conferred by elevated Lp(a) levels,[35-37] since treatment of elevated LDL-C in individuals with elevated Lp(a) has been shown to attenuate the increased risk for CHD events.[38]

Our analyses extend the previously observed associations between small apo(a) isoforms and CVD events to show that total Lp(a) levels were also associated with incident CVD events in African Americans. Prior studies included few African American participants and consequently few CVD events, leading to limited statistical power. The sizeable number of African American participants and careful ascertainment of CVD events over multiple visits in ARIC provided us with greater statistical power to evaluate associations between Lp(a) levels and CVD events in African Americans. Our analyses showed that elevated Lp(a) levels were associated with both CHD events and ischemic strokes in African Americans, and the magnitude of risk associated with each race-specific 1-SD increment in log Lp(a) level was comparable to that in Caucasians. The higher risk estimates for ischemic strokes than for incident CHD events in our study suggest that elevated Lp(a) in African Americans might confer higher risk for a cerebrovascular event than for a coronary vascular event, which may also contribute to the lack of association in smaller studies that assessed only CHD as the outcome.[5,13,14] Our findings of increased CVD risk in individuals with Lp(a) levels >30 mg/dl are broadly consistent with the recommendation of a consensus statement from the European Atherosclerosis Society.[18] This consensus statement recommends desirable Lp(a) levels to be <80th percentile (< ~50 mg/dl), and our findings (Table 4) support these cut-offs (30 mg/dl by the original ARIC visit 1 assay is roughly equivalent to 39 mg/dl by the newer isoform size–insensitive assay).

To our knowledge, this is the largest epidemiologic study to date evaluating the associations between Lp(a) and CVD events in African Americans. Our study has limitations. The Lp(a) mass assay used in the ARIC study measured the total protein mass and could be affected by variations in apo(a) size secondary to variable numbers of kringle 4 type 2 repeats. The number of kringle 4 type 2 repeats can vary from 3 to 40 per apo(a) particle, is genetically determined, and affects the measurement obtained with the assay.[33] A newer molar assay developed by Marcovina,[31,39,40] which is directed towards kringle 4 type 9 and is not affected by the number of kringle 4 type 2 repeats, is available but was not originally used in the ARIC study. However, our analyses showed good correlation between the original Lp(a) assay used on ARIC visit 1 samples and a newer assay insensitive to apo(a) isoform size. It is also interesting to note that in the meta-analysis conducted by the Emerging Risk Factors Collaboration,[1] relative risk for CHD was increased regardless of the apo(a) isoform sensitivity of the assay. Apo(a) isoform information is not available for the ARIC cohort; small apo(a) isoforms, in addition to being associated with higher plasma Lp(a) levels,[33] may be more atherogenic than large apo(a) isoforms.[41] Another limitation is that we examined only associations, and did not perform tests for discrimination, calibration, and reclassification.

In conclusion, elevated Lp(a) levels were associated with incident CVD events in African Americans in the ARIC study, and this risk was comparable to that in Caucasians. Elevated Lp(a) levels should therefore be considered a risk factor for CVD in African Americans.

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Supplementary Material

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Based on observational and prospective studies with limited statistical power, lipoprotein(a) [Lp(a)] is not considered a risk factor for cardiovascular disease (CVD) in African Americans. The Adult Treatment Panel III guidelines also note that “although Lp(a) levels are higher in African Americans than in Caucasians, an increased risk for coronary heart disease (CHD) associated with higher Lp(a) levels in African Americans has not been documented.” This is despite the fact that Lp(a) levels in African Americans are 2–4 times higher than those in Caucasians. In these analyses, we evaluated the association between plasma Lp(a) levels and the risk of incident CVD events (incident CHD and incident ischemic strokes) in 3,467 African American and 9,851 Caucasians participants of the Atherosclerosis Risk in Communities (ARIC) study over a 20-year follow-up period. Our analyses show that Lp(a) levels were positively associated with CVD events in both races. Associations were at least as strong in African Americans, with a larger range of relevant Lp(a) concentrations in African Americans compared with Caucasians. Elevated Lp(a) levels should therefore be considered to be associated with an increased CVD risk in African Americans.

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Table 1

Baseline characteristics across Lp(a) quintiles in ARIC participants.

African Americans (n=3,467):

Characteristics	Lp(a) Quintiles, mg/dl					p for linear trend
	1 0.1–≤6.1	2 >6.1–≤10.3	3 >10.3–≤15.8	4 >15.8–≤24	5 >24–81.7	
N	710	680	698	686	693	—
Age, years	53	53	53	53	54	0.02
Women, %	56.9	61.9	59.9	64.0	69.4	<0.001
Body mass index, kg/m^2	29	29	30	30	30	0.08
Systolic blood pressure, mm Hg	128	128	129	129	129	0.42
Diastolic blood pressure, mm Hg	80	80	80	79	80	0.88
Hypertension, %	50.4	49.7	52.9	49.1	58.1	0.005
Antihypertensive medication use, %	37.6	38.9	39.8	41.5	48.0	<0.001
Estrogen or progesterone use, *%	17.7	19.0	11.2	13.6	10.8	0.001
Current smoking, %	34.1	30.7	26.1	29.0	25.8	0.007
Diabetes, %	17.3	16.6	19.7	17.1	18.9	0.60
LDL-C, mg/dl	124	128	136	144	154	<0.001
HDL-C, mg/dl	54	56	55	56	57	0.008
Triglycerides, mg/dl	99	94	93	95	93	<0.001

Caucasians (n=9,851):

Characteristics	Lp(a) Quintiles, mg/dl					p for linear trend
	1 0.1–≤1.5	2 >1.5–≤3.1	3 >3.1–≤6.0	4 >6.0–≤13.5	5 >13.5–80.3	
N	2061	1955	1901	1963	1971	—
Age, years	54	54	54	54	54	0.32
Women, %	50.9	51.8	53.7	56.7	60.0	<0.001
Body mass index, kg/m^2	27	27	27	27	27	0.71
Systolic blood pressure, mm Hg	119	118	118	118	118	0.01
Diastolic blood pressure, mm Hg	72	72	72	71	71	0.007
Hypertension, %	28.5	26.9	27.6	28.0	28.7	0.76
Antihypertensive medication use, %	23.0	21.8	21.5	22.6	21.8	0.79
Estrogen or progesterone use, *%	24.1	22.8	20.8	19.0	19.9	0.03
Current smoking, %	25.4	23.2	25.7	24.3	24.1	0.38
Diabetes, %	9.3	7.7	7.3	7.3	7.5	0.09
LDL-C, mg/dl	128	132	137	139	145	<0.001
HDL-C, mg/dl	51	51	51	51	53	<0.001
Triglycerides, mg/dl	119	113	110	108	111	<0.001

Values expressed as means except percentages and triglycerides (median).

*Women only

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

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Table 2

Hazard ratios* for incident CVD events for race-specific Lp(a) quintiles.

African Americans:

Incident Events	HR (95% CI); Number of Events					p for linear trend
	Quintile 1 0.1–≤6.1 mg/dl	**Quintile 2 >6.1–≤10.3 mg/dl**	**Quintile 3 >10.3–≤15.8 mg/dl**	**Quintile 4 >15.8–≤24 mg/dl**	**Quintile 5 >24 mg/dl**	
CVD	Reference; 122	1.008 (0.78–1.31); 115	1.21 (0.95–1.55); 142	1.10 (0.85–1.41); 131	1.35 (1.06–1.74); 166	0.0004
CHD	Reference; 87	1.03 (0.76–1.39); 82	1.24 (0.92–1.66); 104	1.07 (0.79–1.44); 93	1.27 (0.94–1.71); 115	0.009
Ischemic strokes	Reference; 49	0.95 (0.63–1.43); 45	1.21 (0.82–1.78); 57	1.09 (0.73–1.63); 53	1.60 (1.10–2.34); 79	0.0004

Caucasians:

Incident Events	HR (95% CI); Number of Events					p for linear trend
	Quintile 1 0.1–≤1.5 mg/dl	**Quintile 2 >1.5–≤3.1 mg/dl**	**Quintile 3 >3.1–≤6.0 mg/dl**	**Quintile 4 >6.0–≤13.5 mg/dl**	**Quintile 5 >13.5 mg/dl**	
CVD	Reference; 383	0.94 (0.81– 1.09); 327	1.01 (0.87–1.17); 339	1.05 (0.90–1.22); 363	1.27 (1.10–1.47); 409	0.001
CHD	Reference; 330	0.91 (0.78–1.08); 274	0.99 (0.84–1.16); 285	1.09 (0.93–1.28); 322	1.28 (1.10–1.50); 353	0.002
Ischemic strokes	Reference; 77	1.03 (0.74–1.44); 72	1.17 (0.85–1.62); 81	0.87 (0.62–1.23); 64	1.27 (0.92–1.76); 86	0.25

*Adjusted for age, gender, smoking, systolic blood pressure, antihypertensive medication use, diabetes, LDL-C, HDL-C, and triglycerides.

HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

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Table 3

Hazard ratios for incident CVD events per standard deviation increase* in log-transformed Lp(a) levels.

African Americans:

	HR (95% CI); Number of Events		
Incident Events	**Model 1**	**Model 2**	**Model 3**
CVD	1.17 (1.07–1.23)	1.18 (1.09–1.28)	1.13 (1.04–1.23)
CHD	1.17 (1.06–1.28)	1.17 (1.07–1.29)	1.11 (1.00–1.22)
Ischemic strokes	1.21 (1.06–1.37)	1.20 (1.06–1.37)	1.21 (1.06–1.39)

Caucasians:

	HR (95% CI); Number of Events		
Incident Events	**Model 1**	**Model 2**	**Model 3**
CVD	1.09 (1.04–1.14)	1.12 (1.07–1.18)	1.09 (1.04–1.15)
CHD	1.10 (1.05–1.16)	1.13 (1.08–1.19)	1.10 (1.05–1.16)
Ischemic strokes	1.06 (0.96–1.18)	1.09 (0.99–1.21)	1.07 (0.97–1.19)

Model 1 adjusted for age and gender; Model 2 adjusted for model 1 plus smoking, systolic blood pressure, antihypertensive medication use, and diabetes; Model 3 adjusted for model 2 plus LDL-C, HDL-C, and triglycerides.

*Race-specific standard deviation of log Lp(a) levels = 0.90 for African Americans and 1.15 for Caucasians.

Abbreviations as in Table 2.

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Table 4

Hazard ratios* for incident CVD events per 10-mg/dl increase in Lp(a).

African Americans:

	HR (95% CI); Number of Events				
Incident Events	**≤10 mg/dl**	**>10–≤20 mg/dl**	**>20–≤30 mg/dl**	**>30 mg/dl**	**p for linear trend**
CVD	Reference; 228	1.08 (0.89–1.30); 217	1.16 (0.92–1.46); 120	1.58 (1.24–2.01); 111	<0.0001
CHD	Reference; 164	1.06 (0.85–1.32); 155	1.17 (0.89–1.53); 88	1.33 (1.00–1.78); 74	0.008
Ischemic strokes	Reference; 90	1.14 (0.85–1.54); 89	1.15 (0.80–1.64); 49	2.12 (1.48–3.03); 55	<0.0001

Caucasians:

	HR (95% CI); Number of Events				
Incident Events	**≤10 mg/dl**	**>10–≤20 mg/dl**	**>20–≤30 mg/dl**	**>30 mg/dl**	**p for linear trend**
CVD	Reference; 1265	1.25 (1.11–1.41); 340	1.27 (1.06–1.51); 137	1.42 (1.12–1.79); 79	0.014
CHD	Reference; 1078	1.29 (1.13–1.47); 300	1.35 (1.12–1.63); 124	1.35 (1.04–1.75); 62	0.14
Ischemic strokes	Reference; 270	1.05 (0.79–1.39); 61	1.11 (0.74–1.67); 27	1.65 (1.04–2.61); 22	0.014

* Adjusted for age, gender, smoking, systolic blood pressure, antihypertensive medication use, diabetes, LDL-C, HDL-C, and triglycerides.

Abbreviations as in Table 2.

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Table 5

Hazard ratios* for incident CVD events for Lp(a) quintiles.

Women:

Incident Events	HR (95% CI); Number of Events					p for linear trend
	Quintile 1 0.1–≤2.1 mg/dl	Quintile 2 >2.1–≤4.9 mg/dl	Quintile 3 >4.9–≤9.6 mg/dl	Quintile 4 >9.6–≤18.6 mg/dl	Quintile 5 >18.6–81.7 mg/dl	
CVD	Reference; 168	1.03 (0.83–1.28); 178	0.99 (0.80–1.22); 185	1.09 (0.88–1.35); 205	1.31 (1.06–1.60); 254	<0.0001
CHD	Reference; 137	0.94 (0.74–1.19); 134	0.93 (0.73–1.18); 141	1.01 (0.80–1.29); 155	1.15 (0.91–1.45); 186	<0.0001
Ischemic strokes	Reference; 42	1.44 (0.95–2.16); 58	1.23 (0.82–1.86); 55	1.46 (0.98–2.18); 69	2.07 (1.41–3.03); 102	<0.0001

Men:

Incident Events	HR (95% CI); Number of Events					p for linear trend
	Quintile 1 0.1–≤1.7 mg/dl	Quintile 2 >1.7–≤3.7 mg/dl	Quintile 3 >3.7–≤7.4 mg/dl	Quintile 4 >7.4–≤15.2 mg/dl	Quintile 5 >15.2–80.3 mg/dl	
CVD	Reference; 277	1.04 (0.88– 1.23); 285	1.01 (0.85–1.20); 281	1.21 (1.03–1.43); 330	1.21 (1.02–1.43); 334	0.001
CHD	Reference; 241	1.03 (0.86–1.24); 247	1.00 (0.83–1.20); 241	1.21 (1.02–1.45); 286	1.15 (0.96–1.38); 277	0.024
Ischemic strokes	Reference; 53	1.03 (0.70–1.52); 54	1.26 (0.87–1.82); 71	1.25 (0.87–1.80); 71	1.50 (1.05–2.14); 88	0.0001

* Adjusted for age, race, smoking, systolic blood pressure, antihypertensive medication use, diabetes, LDL-C, HDL-C, and triglycerides.

Abbreviations as in Table 2.

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Table 6

Hazard ratios for incident CVD events per standard deviation increase* in log-transformed Lp(a) levels.

Women:

	HR (95% CI); Number of Events		
Incident Events	**Model 1**	**Model 2**	**Model 3**
CVD	1.10 (1.03–1.18)	1.11 (1.03–1.19)	1.09 (1.01–1.17)
CHD	1.14 (1.06–1.23)	1.12 (1.03–1.21)	1.09 (1.01–1.18)
Ischemic strokes	1.11 (0.98–1.26)	1.10 (0.97–1.24)	1.12 (0.98–1.28)

Men:

	HR (95% CI); Number of Events		
Incident Events	**Model 1**	**Model 2**	**Model 3**
CVD	1.12 (1.06–1.18)	1.16 (1.09–1.22)	1.12 (1.06–1.19)
CHD	1.12 (1.06–1.19)	1.16 (1.09–1.23)	1.12 (1.05–1.19)
Ischemic strokes	1.13 (1.00–1.27)	1.17 (1.04–1.32)	1.13 (1.00–1.28)

Model 1 adjusted for age, race

Model 2 adjusted for model 1 plus smoking, systolic blood pressure, antihypertensive medication use, and diabetes.

Model 3 adjusted for model 2 plus LDL-C, HDL-C, and triglycerides.

*Gender-specific standard deviation of log Lp(a) levels = 1.167 for females and 1.164 for males.

Abbreviations as in Table 2.

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Table 7

Hazard ratios* for incident CVD events per 10-mg/dl increase in Lp(a).

Women:

	HR (95% CI); Number of Events				p for linear trend
Incident Events	**≤10 mg/dl**	**>10–≤20 mg/dl**	**>20–≤30 mg/dl**	**>30 mg/dl**	
CVD	Reference; 539	1.13 (0.96–1.34); 222	1.14 (0.93–1.41); 120	1.55 (1.24–1.93); 109	<0.0001
CHD	Reference; 417	1.17 (0.97–1.41); 168	1.23 (0.97–1.57); 94	1.42 (1.09–1.84); 74	0.0002
Ischemic strokes	Reference; 159	1.02 (0.80–1.36); 73	1.06 (0.74–1.52); 43	1.91 (1.35–2.71); 51	<0.0001

Men:

	HR (95% CI); Number of Events				p for linear trend
Incident Events	**≤10 mg/dl**	**>10–≤20 mg/dl**	**>20–≤30 mg/dl**	**>30 mg/dl**	
CVD	Reference; 954	1.24 (1.09–1.42); 335	1.33 (1.10–1.60); 137	1.46 (1.15–1.86); 81	<0.0005
CHD	Reference; 825	1.27 (1.10–1.46); 287	1.37 (1.13–1.68); 118	1.32 (1.01–1.74); 62	0.049
Ischemic strokes	Reference; 201	1.13 (0.86–1.49); 77	1.13 (0.77–1.67); 33	1.84 (1.19–2.87); 26	0.0001

* Adjusted for age, race, smoking, systolic blood pressure, antihypertensive medication use, diabetes, LDL-C, HDL-C, and triglycerides.

Abbreviations as in Table 2.