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Lipoprotein(a) and Family History Predict Cardiovascular Disease Risk

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ABSTRACT

BACKGROUND Elevated lipoprotein(a) (Lp[a]) and family history (FHx) of coronary heart disease (CHD) are individually associated with cardiovascular risk, and Lp(a) is commonly measured in those with FHx.

OBJECTIVES The aim of this study was to determine independent and joint associations of Lp(a) and FHx with atherosclerotic cardiovascular disease (ASCVD) and CHD among asymptomatic subjects.

METHODS Plasma Lp(a) was measured and FHx was ascertained in 2 cohorts. Elevated Lp(a) was defined as the highest race-specific quintile. Independent and joint associations of Lp(a) and FHx with cardiovascular risk were determined using Cox regression models adjusted for cardiovascular risk factors.

RESULTS Among 12,149 ARIC (Atherosclerosis Risk In Communities) participants (54 years, 56% women, 23% black, 44% with FHx), 3,114 ASCVD events were observed during 21 years of follow-up. FHx and elevated Lp(a) were independently associated with ASCVD (hazard ratio [HR]: 1.17; 95% confidence interval [CI]: 1.09 to 1.26, and HR: 1.25; 95% CI: 1.12 to 1.40, respectively), and no Lp(a)-by-FHx interaction was noted ($p = 0.75$). Compared with subjects without FHx and nonelevated Lp(a), those with either elevated Lp(a) or FHx were at a higher ASCVD risk, while those with both had the highest risk (HR: 1.43; 95% CI: 1.27 to 1.62). Similar findings were observed for CHD risk in ARIC, in analyses stratified by premature FHx, and in an independent cohort, the DHS (Dallas Heart Study). Presence of both elevated Lp(a) and FHx resulted in greater improvement in ASCVD and CHD risk reclassification and discrimination indexes than either marker alone.

CONCLUSIONS Elevated plasma Lp(a) and FHx have independent and additive joint associations with cardiovascular risk and may be useful concurrently for guiding primary prevention therapy decisions.
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Lipoprotein (a) (Lp[a]) is an atherogenic lipoprotein composed of a low-density lipoprotein (LDL)-like moiety and a unique glycoprotein, apolipoprotein(a) (apo[a]), that is linked to a single molecule of apolipoprotein B-100 of the LDL moiety (1). Circulating levels of Lp(a) are determined primarily by heredity, including a variety of differences in the *LPA* gene locus (1). Over the past decade, several epidemiological, Mendelian randomization, and genomewide association studies have established Lp(a) as an independent and likely causal risk factor for atherosclerotic cardiovascular disease (ASCVD) (2-6). Similarly, family history (FHx) of coronary heart disease (CHD) is another risk factor that is independently associated with ASCVD risk among asymptomatic subjects, which reflects the inherited and shared environmental predisposition to cardiovascular disease (7).

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ABBREVIATIONS AND ACRONYMS

apo(a) = apolipoprotein(a)
ASCVD = atherosclerotic cardiovascular disease
CHD = coronary heart disease
CI = confidence interval
FHx = family history
HR = hazard ratio
LDL = low-density lipoprotein
Lp(a) = lipoprotein(a)
MI = myocardial infarction

In practice, Lp(a) is frequently measured in those with FHx of CHD.

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The 2018 American multisociety cholesterol management guidelines recognize elevated Lp(a) as a "risk-enhancing" factor during clinician-patient discussions regarding statin initiation for primary ASCVD prevention (8). The 2019 European Society of Cardiology/European Atherosclerosis Society dyslipidemia guidelines recommend considering plasma Lp(a) measurement to reclassify risk in subjects who are between moderate and high ASCVD risk and at least once during the lifetime to identify those with very high levels (>180 mg/dl) (9). Furthermore, plasma Lp(a) testing is recommended by both European and American guidelines among subjects with FHx (9,10).

The association of these 2 nontraditional cardiovascular markers with ASCVD risk is well established, but their independent and joint associations with long-term risk are unclear. To address this knowledge gap, we aimed to determine the independent and joint associations of elevated plasma Lp(a) level and FHx with incident ASCVD and CHD events among asymptomatic participants of 2 multiethnic American population-based cohorts: the ARIC (Atherosclerosis Risk In Communities) study and the DHS (Dallas Heart Study). We hypothesized that an elevated Lp(a) level and FHx have an independent as well as an additive joint association with cardiovascular risk.

METHODS

This study complies with the Declaration of Helsinki and was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center (STU 122017-032). Both ARIC and DHS were approved by Institutional Review Boards at the respective coordinating centers, at each field center, and other central agencies. All participants provided written informed consent at enrollment.

STUDY POPULATION. The study designs of ARIC and DHS have been previously published (11,12). These cohorts are described in detail in the Supplemental Appendix. For the present analysis, we included ARIC and DHS participants who were free of prevalent cardiovascular disease and had information available regarding plasma Lp(a) level, FHx of CHD, cardiovascular risk factors, and adjudicated ASCVD events during follow-up. The final study sample consisted of 12,149 ARIC and 2,756 DHS participants. Participants who were lost to follow-up through December 31, 2016, in ARIC and through December 31, 2012, in DHS were censored in survival analyses.

LIPOPROTEIN MEASUREMENT. Lipoprotein measurements were performed on fasting blood samples in both studies, and serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using enzymatic assays (12,13). LDL cholesterol level was calculated using the Friedewald equation in both ARIC and DHS (12,13).

The apo(a) component of Lp(a) contains a variable number of kringle IV type 2 repeats that can affect

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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plasma Lp(a) levels and apo(a) isoform size (14,15). ARIC investigators measured plasma Lp(a) levels at ARIC visit 1 (reported in milligrams per deciliter) using a kringle IV type 2 repeat–sensitive assay (16). These values were subsequently confirmed about 9 years later at ARIC visit 4 (1996 to 1998) using an automated immunoturbidimetric assay that is insensitive to kringle IV type 2 repeats (Denka Seiken, Tokyo, Japan) (17). For the present analysis, we used Lp(a) values from visit 1 that were standardized using a conversion equation derived from comparison between samples at visit 1 measured by the 2 assays (visit 1 and visit 4) in 100 samples from an entire Lp(a) distribution. There was an excellent correlation (Pearson r = 0.88) between measurements from both assays, without evidence of systematic bias at high or low Lp(a) levels, as previously described (4). We also performed sensitivity analyses using visit 4 Lp(a) levels. Plasma Lp(a) levels among DHS participants (reported in nanomoles per liter) were measured at enrollment using a sandwich enzyme-linked immunosorbent assay that was also insensitive to apo(a) size (18).

FHx OF CHD. Parental history of myocardial infarction (MI) at any age was assessed at ARIC visit 1 by self-report and is designated as FHx in this analysis (11). Premature FHx in ARIC was defined as paternal age <55 years or maternal age <60 years at the time of MI diagnosis (19). Data regarding premature FHx were not available for 685 ARIC participants (5.6%), and these subjects were excluded from analyses involving premature FHx as an independent variable or a covariate. In DHS, FHx was obtained using a prespecified questionnaire (20). However, DHS investigators defined FHx as a history of MI in any first-degree relative and premature FHx as MI occurring before 50 years of age in a first-degree male relative or before 55 years of age in a first-degree female relative (20). Premature FHx data were available for all DHS participants.

CARDIOVASCULAR OUTCOMES. Time to first ASCVD event and time to first CHD event were the outcomes of interest in this analysis. Incident ASCVD was defined as the first occurrence of coronary death, nonfatal MI, or stroke (fatal or nonfatal), while incident CHD was defined as the first occurrence of coronary death or nonfatal MI in both study cohorts. The ARIC and DHS methods for assessment of ASCVD and CHD events have been reported previously and are described in the Supplemental Appendix. The mean follow-up period for incident ASCVD was 21.1 ± 8.5 years in ARIC and 10.9 ± 1.9 years in DHS.

STATISTICAL ANALYSIS. Baseline characteristics of ARIC study participants were described across FHx, premature FHx, and plasma Lp(a) levels. Categorical variables are presented as count (proportion) and continuous variables as mean ± SD or median (interquartile range) depending on variable distribution. Categorical variables were compared using the chi-square test, and continuous variables were compared using the unpaired Student's *t*-test or the Mann-Whitney *U* test depending on variable distribution and using the Kruskal-Wallis test across Lp(a) levels. Plasma Lp(a) levels in both studies were stratified into quintiles because a previous seminal analysis from ARIC showed that black and white subjects with Lp(a) levels in the highest quintile are at an increased risk for incident cardiovascular events (4). Given the well-known racial differences in plasma Lp(a) levels (1), we stratified ARIC participants across race-specific Lp(a) quintiles. A similar stratification strategy was used in DHS.

The independent association of race-specific Lp(a) quintiles with time to first ASCVD or CHD event was assessed using Cox proportional hazards regression models in ARIC and DHS separately. These models were adjusted for age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, and statin use at baseline. FHx and premature FHx were added as covariates into 2 different models, and the multiplicative race-specific Lp(a) level (quintile 5 vs. quintiles 1 to 4) by FHx interaction and race-specific Lp(a) level by premature FHx interaction for ASCVD and CHD events were tested. To understand the joint association of elevated Lp(a) and FHx (or premature FHx) with ASCVD and CHD risk, ARIC and DHS participants were separately divided into 4 mutually exclusive groups: group 1, with positive FHx and elevated race-specific Lp(a) level (defined as quintile 5); group 2, with positive FHx and nonelevated race-specific Lp(a) level (defined as quintiles 1 to 4); group 3, with negative FHx and elevated race-specific Lp(a) level; and group 4, with negative FHx and nonelevated race-specific Lp(a) level (referent group). Similar groups were created using premature FHx data. The cumulative incidence of ASCVD and CHD events in these 4 groups was studied using the Kaplan-Meir method. Furthermore, the joint association of elevated Lp(a) level and FHx (or premature FHx) with ASCVD and CHD risk was evaluated using Cox models adjusted for the covariates mentioned previously. The improvement in cardiovascular risk reclassification and discrimination with elevated Lp(a), FHx, and premature FHx was assessed by computing continuous net reclassification improvement, integrated

TABLE 1 Baseline Characteristics of Atherosclerosis Risk In Communities Study Participants Stratified by FHx of Coronary Heart Disease

	All Participants (N = 12,149)	FHx− (n = 6,752)	FHx+ (n = 5,397)	p Value
Age, yrs	53.9 ± 5.7	53.7 ± 5.8	54.1 ± 5.7	**<0.001**
Female	6,811 (56.1)	3,680 (54.5)	3,131 (58.0)	**<0.001**
White	9,326 (76.8)	4,943 (73.2)	4,383 (81.2)	**<0.001**
Black	2,785 (22.9)	1,782 (26.4)	1,003 (18.6)	**<0.001**
Systolic BP, mm Hg	120.5 ± 18.3	120.3 ± 18.5	120.7 ± 18.0	0.094
Diastolic BP, mm Hg	73.4 ± 11.0	73.5 ± 11.1	73.3 ± 10.9	0.533
Antihypertensive use	2,964 (24.4)	1,505 (22.3)	1,459 (27.1)	**<0.001**
Diabetes	1,188 (9.8)	632 (9.4)	556 (10.3)	0.085
Smoking	6,878 (56.6)	3,784 (56.1)	3,094 (57.4)	0.156
Total cholesterol, mg/dl	214.5 ± 41.7	212.3 ± 41.1	217.2 ± 42.3	**<0.001**
HDL cholesterol, mg/dl	52.2 ± 17.0	52.7 ± 17.2	51.7 ± 16.9	**0.001**
Triglycerides, mg/dl	108.0 (78.0–153.0)	105.0 (76.0–149.0)	111.0 (80.0–160.0)	**<0.001**
LDL cholesterol, mg/dl	137.1 ± 39.1	135.2 ± 38.6	139.5 ± 39.6	**<0.001**
Statin use	58 (0.5)	29 (0.4)	29 (0.5)	0.428
Body mass index, kg/m^2	27.4 ± 5.2	27.3 ± 5.1	27.5 ± 5.2	0.207
Lp(a), mg/dl	7.7 (2.9–18.7)	7.6 (2.8–18.4)	7.8 (2.9–19.2)	0.139

Values are mean ± SD, n (%), or median (interquartile range). Divide total cholesterol, HDL cholesterol, and LDL cholesterol by 38.67 and triglycerides by 88.57 to convert to millimoles per liter. **Bold** values indicate statistically significant difference ($p < 0.05$).

BP = blood pressure; FHx = family history; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a).

discrimination index, and change in C statistic. The baseline model for these analyses consisted of covariates used in Cox models.

We performed 3 sensitivity analyses to further evaluate the joint association of Lp(a) and FHx with cardiovascular risk in ARIC. First, the adjusted joint association of elevated Lp(a) level and premature FHx with cardiovascular risk was studied by designating Lp(a) level ≥50 mg/dl as the "elevated" level. Premature FHx and Lp(a) ≥50 mg/dl were chosen because both American and European guidelines recommend Lp(a) measurement in setting of premature FHx (9,10), and Lp(a) ≥50 mg/dl has been designated as an ASCVD risk-enhancing factor in the American guidelines (8). Second, we substituted total cholesterol level with "Lp(a) cholesterol-adjusted total cholesterol" in Cox models by subtracting 30% of the participant's Lp(a) mass from total cholesterol level. This analysis was performed to account for the comeasurement of Lp(a) cholesterol in total cholesterol measurements, and a 30% correction was chosen because the mean cholesterol content of Lp(a) is estimated to be roughly 30% of the total Lp(a) mass (21,22). Last, we used visit 4 Lp(a) levels for conducting survival analyses after excluding participants who experienced ASCVD events between visits 1 and 4. All statistical analyses were performed using SAS version 9.4 (SAS, Cary, North Carolina). A 2-sided p value <0.05 was considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. The mean age of ARIC participants was 53.9 ± 5.7 years, 56.1% were women, 76.8% were White, 22.9% were Black, 44.4% had FHx, and 9.8% had premature FHx (Tables 1 and 2). Participants with FHx were slightly older, more frequently women and White, were taking antihypertensives more frequently, and had unfavorable lipid profiles compared with those without FHx (Table 1). A similar trend was observed when the cohort was stratified by premature FHx, apart from the observation that participants with premature FHx were slightly younger than those without premature FHx (Table 2). Notably, plasma Lp(a) levels among participants with FHx or premature FHx were not significantly different compared with those without FHx or premature FHx, respectively (Tables 1 and 2). When participant characteristics were stratified by race-specific Lp(a) quintiles, there was a trend toward an increasing proportion of women; a decreasing proportion of smokers; increasing age, total, high-density lipoprotein, and LDL cholesterol levels; and decreasing diastolic blood pressure and triglyceride level (Table 3). By design, the racial composition of participants was similar, and Lp(a) levels increased across the 5 groups (Table 3). White participants with Lp(a) >17.92 mg/dl and Black participants with Lp(a) >31.98 mg/dl were in the fifth quintile group. Importantly, the proportion of participants with FHx and

premature FHx increased across race-specific Lp(a) quintiles (Table 3).

DHS participants were younger, with a mean age of 43.6 ± 9.9 years, 56.8% were women, 32.1% were White, 49.6% were Black, 16.1% were Hispanic, 31.1% had FHx, and 10.1% had premature FHx. Baseline characteristics of DHS participants are described in Supplemental Tables 1A and 1B.

INDEPENDENT ASSOCIATIONS OF LP(A) AND FHx WITH CARDIOVASCULAR EVENTS. A total of 3,114 first ASCVD and 2,283 first CHD events occurred during follow-up among ARIC participants. In a multivariate-adjusted Cox model, FHx and elevated Lp(a) level (race-specific quintile 5) were associated with 17% and 25% increased ASCVD risk, respectively (hazard ratio [HR]: 1.17; 95% confidence interval [CI]: 1.09 to 1.26; $p < 0.001$; and HR: 1.25; 95% CI: 1.12 to 1.40; $p < 0.001$, respectively) (Supplemental Table 2). Similarly, 31% and 27% increases in CHD risk with FHx and elevated Lp(a) were observed (HR: 1.31; 95% CI: 1.20 to 1.42; $p < 0.001$; and HR: 1.27; 95% CI: 1.12 to 1.45; $p < 0.001$, respectively) (Supplemental Table 2). In separate Cox models, premature FHx was independently associated with 25% and 43% increases in ASCVD and CHD risk, respectively (HR: 1.25; 95% CI: 1.11 to 1.41; $p < 0.001$; and HR: 1.43; 95% CI: 1.26 to 1.63; $p < 0.001$, respectively).

TABLE 2 Baseline Characteristics of ARIC Study Participants Stratified by Premature FHx of Coronary Heart Disease

	Premature FHx− (n = 10,339)	Premature FHx+ (n = 1,125)	p Value
Age, yrs	53.9 ± 5.8	53.1 ± 5.5	**<0.001**
Female	5,713 (55.3)	669 (59.5)	**0.007**
White	7,891 (76.3)	981 (87.2)	**<0.001**
Black	2,413 (23.3)	142 (12.6)	**<0.001**
Systolic BP, mm Hg	120.3 ± 18.3	120.8 ± 18.2	0.539
Diastolic BP, mm Hg	73.3 ± 11.0	73.7 ± 10.9	0.164
Antihypertensive use	2,453 (23.7)	318 (28.3)	**0.001**
Diabetes	984 (9.5)	119 (10.6)	0.242
Smoking	5,823 (56.3)	662 (58.9)	0.099
Total cholesterol, mg/dl	213.5 ± 41.7	218.8 ± 40.7	**<0.001**
HDL cholesterol, mg/dl	52.3 ± 17.1	51.5 ± 16.5	0.178
Triglycerides, mg/dl	107.0 (77.0–152.0)	112.0 (82.0–165.0)	**<0.001**
LDL cholesterol, mg/dl	136.2 ± 39.0	140.6 ± 38.2	**<0.001**
Statin use	51 (0.5)	5 (0.5)	1.000
Body mass index, kg/m^2	27.4 ± 5.1	27.4 ± 5.2	0.573
Lp(a), mg/dl	7.7 (2.8–18.5)	7.4 (2.7–19.0)	0.433

Values are mean ± SD, n (%), or median (interquartile range). Divide total cholesterol, HDL cholesterol, and LDL cholesterol by 38.67 and triglycerides by 88.57 to convert to millimoles per liter. **Bold** values indicate statistically significant difference ($p < 0.05$).

Abbreviations as in Table 1.

Among DHS participants, 161 first ASCVD and 73 first CHD events were observed during follow-up. FHx had an independent association with ASCVD events (HR: 1.65; 95% CI: 1.19 to 2.28; $p = 0.002$),

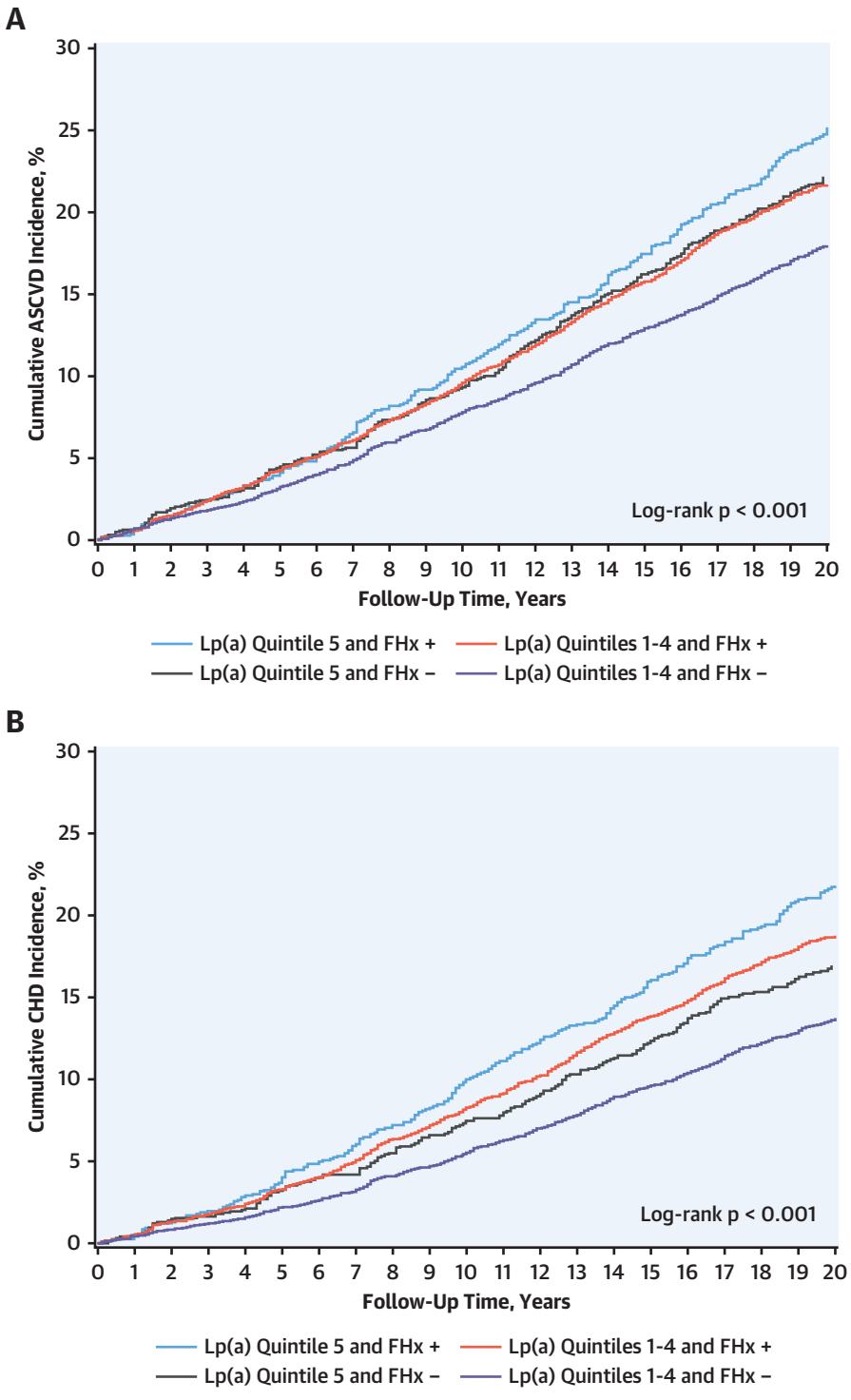
TABLE 3 Baseline Characteristics of ARIC Study Participants Stratified by Race-Specific Lp(a)

	Quintile 1 (n = 2,506)	Quintile 2 (n = 2,400)	Quintile 3 (n = 2,381)	Quintile 4 (n = 2,431)	Quintile 5 (n = 2,431)	p Value
Age, yrs	53.6 ± 5.7	53.7 ± 5.7	54.0 ± 5.7	54.0 ± 5.8	54.1 ± 5.7	**0.002**
Women	1,300 (51.9)	1,292 (53.8)	1,293 (54.3)	1,420 (58.4)	1,506 (61.9)	**<0.001**
White*	1,935 (77.2)	1,840 (76.7)	1,823 (76.6)	1,860 (76.5)	1,868 (76.8)	
Black*	565 (22.6)	551 (23.0)	250 (23.1)	563 (23.2)	556 (22.9)	
Systolic BP, mm Hg	121.0 ± 17.7	119.7 ± 17.9	120.4 ± 18.0	120.7 ± 19.0	120.5 ± 18.7	0.433
Diastolic BP, mm Hg	73.8 ± 10.5	73.4 ± 10.9	73.5 ± 11.1	73.2 ± 11.2	73.1 ± 11.3	**0.024**
Antihypertensive use	614 (24.5)	557 (23.2)	554 (23.3)	598 (24.6)	641 (26.4)	0.065
Diabetes	265 (10.6)	231 (9.6)	222 (9.3)	236 (9.7)	234 (9.7)	0.329
Smoking	1,437 (57.3)	1,405 (58.6)	1,355 (56.9)	1,349 (55.5)	1,332 (54.8)	**0.011**
Total cholesterol, mg/dl	206.1 ± 41.3	209.0 ± 39.9	213.4 ± 40.9	217.6 ± 41.7	226.5 ± 41.7	**<0.001**
HDL cholesterol, mg/dl	51.3 ± 18.2	52.1 ± 16.9	51.9 ± 16.5	52.2 ± 16.3	53.6 ± 17.3	**<0.001**
Triglycerides, mg/dl	114.0 (79.0–170.0)	108.0 (77.0–152.0)	107.0 (78.0–148.0)	104.0 (77.0–149.0)	107.0 (78.0–150.0)	**<0.001**
LDL cholesterol, mg/dl	127.8 ± 38.5	131.4 ± 37.3	137.0 ± 38.0	141.2 ± 39.4	148.1 ± 38.9	**<0.001**
Statin use	12 (0.5)	9 (0.4)	13 (0.6)	7 (0.3)	17 (0.7)	0.434
Body mass index, kg/m^2	27.3 ± 4.9	27.2 ± 5.1	27.5 ± 5.3	27.6 ± 5.2	27.4 ± 5.3	0.328
FHx of CHD	1,067 (42.6)	1,027 (42.8)	1,004 (42.2)	1,113 (45.8)	1,186 (48.8)	**<0.001**
Premature FHx	238 (10.0)	205 (9.0)	190 (8.5)	231 (10.1)	261 (11.5)	**0.048**
Lp(a), mg/dl†						**<0.001**
Blacks	0.02–7.97	8.11–13.55	13.68–20.71	20.84–31.85	31.98–107.56	
Whites	0.02–1.88	2.01–4.00	1.13–7.85	9.98–17.79	17.92–105.84	

Values are mean ± SD, n (%), or median (interquartile range). Divide total cholesterol, HDL cholesterol, and LDL cholesterol by 38.67 and triglycerides by 88.57 to convert to millimoles per liter. **Bold** values indicate statistically significant difference ($p < 0.05$). *Differences in race distribution across Lp(a) quintiles were not tested, because the quintiles are race specific. †The race-specific range for plasma Lp(a) concentrations is provided.

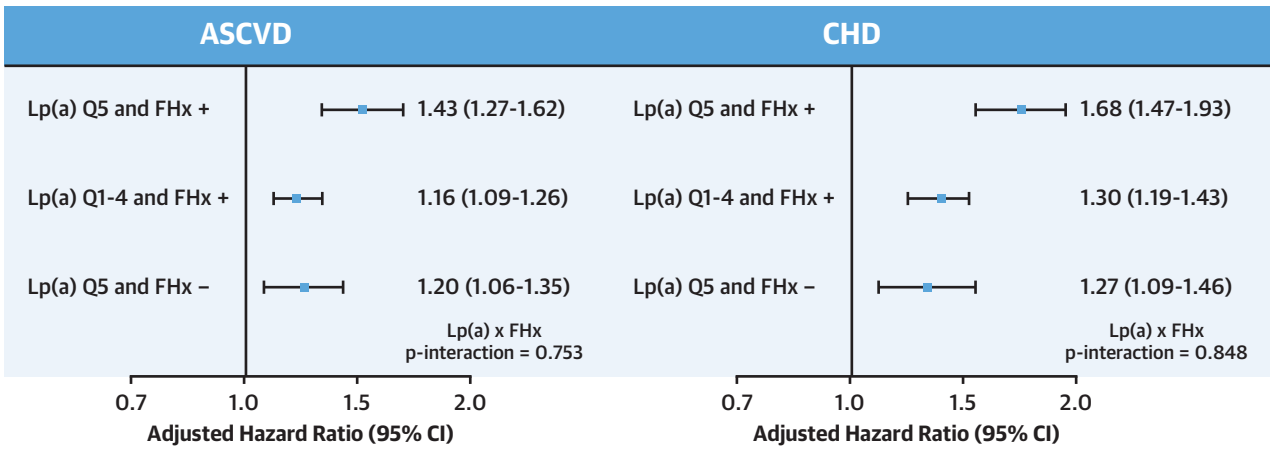
CHD = coronary heart disease; other abbreviations as in Table 1.

FIGURE 1 Cumulative Incidence of ASCVD and CHD Events Across 4 Race-Specific Lp(a) and FHx Groups of ARIC Study Participants



(A) Incidence of atherosclerotic cardiovascular disease (ASCVD). **(B)** Incidence of coronary heart disease (CHD). Group 1 had positive family history (FHx) and elevated race-specific lipoprotein(a) (Lp[a]) (quintile 5); group 2 had positive FHx and nonelevated race-specific Lp(a) (quintiles 1 to 4); group 3 had negative FHx and elevated race-specific Lp(a); and group 4 had negative FHx and nonelevated race-specific Lp(a).

FIGURE 2 Joint Association of Race-Specific Lp(a) and FHx With Incident ASCVD and CHD Among ARIC Study Participants



Cox proportional hazards regression models adjusted for age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, and statin use at baseline. The 4 race-specific Lp(a) and FHx groups are the independent variable, and group 4 is the referent category. CI = confidence interval; other abbreviations as in Figure 1.

while elevated Lp(a) had a nominal association (HR: 1.64; 95% CI: 0.96 to 2.80; p = 0.069). In a separate model, premature FHx also had a nominal association with ASCVD (HR: 1.49; 95% CI: 0.97 to 2.29; p = 0.069). In contrast, elevated Lp(a) (HR: 3.37; 95% CI: 1.41 to 8.06; p = 0.006) and FHx (HR: 2.18; 95% CI: 1.35 to 3.52; p = 0.001) had independent associations with CHD events. Similarly, in a separate model, premature FHx was also independently associated with CHD risk (HR: 2.12; 95% CI: 1.19 to 3.78; p = 0.011).

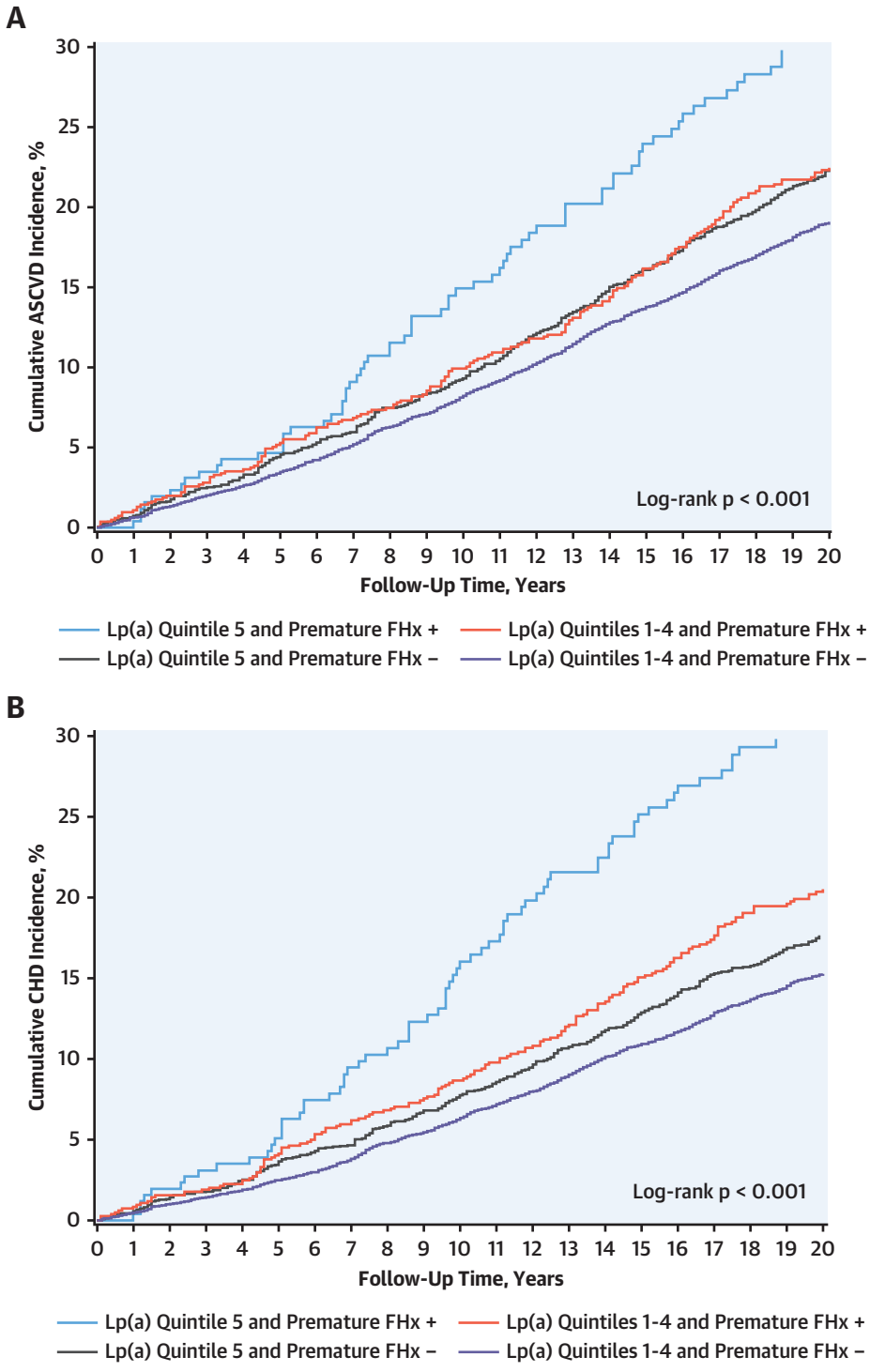
JOINT ASSOCIATION OF LP(A) AND FHx WITH CARDIOVASCULAR EVENTS. ARIC participants were stratified into 4 mutually exclusive groups on the basis of elevated or nonelevated Lp(a) level and presence or absence of FHx to evaluate the joint association of Lp(a) and FHx with cardiovascular risk. The four groups consisted of participants with elevated Lp(a) and positive FHx (group 1), positive FHx alone (group 2), elevated Lp(a) alone (group 3), and nonelevated Lp(a) and negative FHx (group 4). The cumulative incidence of ASCVD and CHD events across the 4 groups is described in **Figures 1A and 1B**. ASCVD and CHD incidence was higher with either elevated Lp(a) or positive FHx compared with subjects with neither, but the highest incidence was observed in those with both elevated Lp(a) and positive FHx. The 10-, 15-, and 20-year ASCVD and CHD cumulative incidence rates across the 4 groups are reported in Supplemental Table 3.

In multivariate-adjusted Cox modes, ARIC participants in group 1 were at 43% and 68% increased risk for ASCVD and CHD events, respectively, compared with participants in group 4 (**Figure 2**). The corresponding HRs for participants in group 2 and group 3 were numerically smaller but were each statistically significant (**Figure 2**). Furthermore, the association of elevated Lp(a) level with ASCVD and CHD was not modified by FHx (p for interaction = 0.753 and 0.848, respectively).

The cumulative incidence of ASCVD and CHD events across the 4 groups created using premature FHx is described in **Figures 3A and 3B**. Similar to the observations described earlier, ASCVD and CHD incidence was higher in groups 1, 2, and 3 compared with group 4. It is worth noting that the 10-, 15-, and 20-year ASCVD and CHD incidence in group 1 was 1.5- to 2.5-fold higher compared with group 4 (Supplemental Table 3). We also observed a nominal multiplicative interaction between elevated Lp(a) and premature FHx for ASCVD (p = 0.096) and CHD (p = 0.077) in multivariate-adjusted Cox models. Participants in group 1 were at a 74% and 114% increased risk for ASCVD and CHD events, respectively, compared with group 4 participants (**Figure 4**).

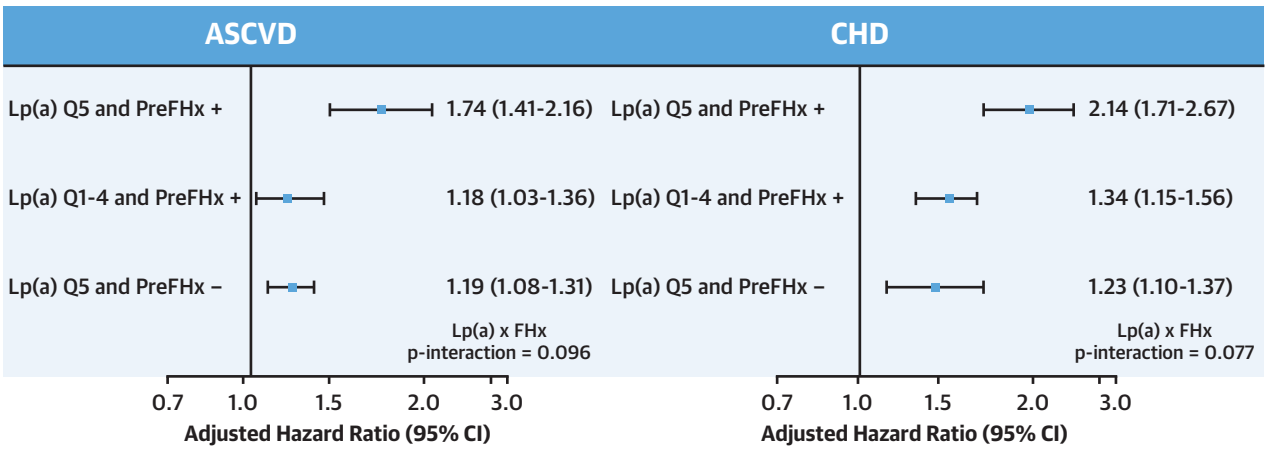
DHS participants were stratified into similar Lp(a)/FHx and Lp(a)/premature FHx groups. Unlike ARIC, we observed significant multiplicative interactions between elevated Lp(a) and FHx and between elevated Lp(a) and premature FHx for ASCVD (p = 0.043 and

FIGURE 3 Cumulative Incidence of ASCVD and CHD Events Across 4 Race-Specific Lp(a) and Family History Groups of ARIC Study Participants



(A) Incidence of ASCVD. **(B)** Incidence of CHD. Group 1 had positive premature FHx and elevated race-specific Lp(a) (quintile 5), group 2 had positive premature FHx and nonelevated race-specific Lp(a) (quintiles 1 to 4), group 3 had negative premature FHx and elevated race-specific Lp(a), and group 4 had negative premature FHx and nonelevated race-specific Lp(a). Abbreviations as in Figure 1.

FIGURE 4 Joint Association of Race-Specific Lp(a) and Premature FHx With Incident ASCVD and CHD Among ARIC Study Participants



Cox proportional hazards regression models adjusted for age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, and statin use at baseline. The 4 race-specific Lp(a) and premature FHx groups are the independent variable, and group 4 is the referent category. Q = quintile; other abbreviations as in Figures 1 and 2.

p = 0.016, respectively) and CHD (p = 0.006 and p = 0.004, respectively) in multivariate-adjusted Cox models. Thus, the presence of both elevated Lp(a) and positive FHx or premature FHx was associated with a 2- to 3-fold increased ASCVD risk and a 5- to 8-fold increased CHD risk (Table 4).

CARDIOVASCULAR RISK RECLASSIFICATION AND DISCRIMINATION WITH LP(A) AND FHx. Adding elevated Lp(a) or FHx resulted in increases in net reclassification improvement and integrated discrimination index for both ASCVD and CHD events when added to a traditional risk factor model among ARIC participants (Table 5). However, the improvements in both metrics, as well as for change in C statistic, were numerically greater when both elevated Lp(a) and FHx were included in the respective models. The improvements in the various metrics were of lesser magnitude in each of the models when premature FHx was substituted for FHx, but the presence of both elevated Lp(a) and premature FHx led to improvement in all metrics for CHD risk prediction (Table 5).

SENSITIVITY ANALYSES. Lp(a) ≥50 mg/dl was observed infrequently (2.5%) among ARIC participants. Nonetheless, the presence of both Lp(a) ≥50 mg/dl and premature FHx was associated with a >2-fold risk for ASCVD and CHD events (Supplemental Table 4). After substituting total cholesterol levels with Lp(a) cholesterol-adjusted total cholesterol levels in Cox models, our observations regarding elevated ASCVD and CHD hazard for groups 1, 2, and 3 participants remained largely unchanged (Supplemental Table 5). Last, when Lp(a) levels from visit 4 were used (n = 8,844, mean follow-up duration 15.3 years, with 1,805 ASCVD and 1,324 CHD events), participants in group 1 continued to have the highest hazard for ASCVD and CHD events (Supplemental Table 6). Lp(a) ≥50 mg/dl was noted among 18.2% participants at visit 4. The presence of elevated Lp(a), defined using this cutoff, and premature FHx was associated with a nominally increased ASCVD risk and significantly increased CHD risk during follow-up, effect estimates that were higher than for Lp(a) ≥50 mg/dl or premature FHx alone for both outcomes (Supplemental Table 7).

DISCUSSION

We report 3 important findings in this study of the independent and joint associations of circulating Lp(a) levels and FHx with cardiovascular risk involving 2 different population-based cohorts. First, elevated plasma Lp(a) level (defined as race-specific quintile 5), FHx, and premature FHx had independent associations with long-term ASCVD and CHD risk among asymptomatic subjects. Second, subjects with elevated Lp(a) levels and FHx (or premature FHx)

TABLE 4 Joint Associations of Race-Specific Lipoprotein(a) and FHx/Premature FHx With Incident ASCVD and CHD Events Among Dallas Heart Study Participants

	ASCVD*	CHD†
	HR (95% CI)	HR (95% CI)
Elevated Lp(a) and FHx+ (n = 170)	2.57 (1.52–4.34)	5.49 (2.85–10.60)
Nonelevated Lp(a) and FHx+ (n = 686)	1.51 (1.06–2.15)	1.62 (0.93–2.84)
Elevated Lp(a) and FHx− (n = 380)	1.00 (0.57–1.77)	1.04 (0.45–2.44)
Nonelevated Lp(a) and FHx− (n = 1,520)	Referent	Referent
Elevated Lp(a) and premature FHx+ (n = 55)	3.35 (1.66–6.74)	7.96 (3.60–17.59)
Nonelevated Lp(a) and premature FHx+ (n = 222)	1.14 (0.69–1.89)	1.29 (0.60–2.79)
Elevated Lp(a) and premature FHx− (n = 496)	0.88 (0.55–1.40)	1.24 (0.66–2.33)
Nonelevated Lp(a) and premature FHx− (n = 1,983)	Referent	Referent

Cox proportional hazards regression models adjusted for age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, and statin use at baseline. *Elevated Lp(a) × FHx and elevated Lp(a) × premature FHx p for interaction for ASCVD = 0.043 and 0.016, respectively. †Elevated Lp(a) × FHx and elevated Lp(a) × premature FHx p for interaction for CHD = 0.006 and 0.004, respectively.

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; HR = hazard ratio; Q = quintile; other abbreviations as in Tables 1 and 3.

were at a significantly higher risk for incident ASCVD and CHD compared with those having neither risk factor. Last, the addition of an elevated Lp(a) level and FHx (or premature FHx) to a traditional risk factor model improved ASCVD and CHD risk reclassification and discrimination indexes, which were of higher magnitude than observed after adding each marker alone. These results suggest that both Lp(a) and FHx are at least additive, and in some cases multiplicative, for cardiovascular risk assessment.

Elevated plasma Lp(a) levels are associated with increased risk for cardiovascular events in diverse patient populations (2–5). Several studies have also shown that race is an important determinant of circulating Lp(a) levels, with Black subjects having higher levels compared with other race groups (1). A seminal study from ARIC previously showed that the association of Lp(a) levels with incident cardiovascular events is similar among Whites and Blacks in quintile-based analyses (4). This was the rationale behind our approach of pooling participants across race-specific Lp(a) quintiles. Herein, we have demonstrated that an elevated Lp(a) level (race-specific quintile 5) is associated with cardiovascular risk among asymptomatic participants of 2 population-based, ethnically diverse American epidemiological cohorts.

FHx of CHD and premature FHx have long been regarded as risk factors for ASCVD development among asymptomatic subjects (7,23). Our results are consistent with prior studies and show that both FHx and premature FHx are independently associated with increased long-term ASCVD and CHD risk. Notably, the proportion of participants with FHx and premature FHx increased across race-specific Lp(a) quintiles, showing that both FHx and premature FHx have associations with circulating Lp(a) levels (Table 3). The lack of an association of Lp(a) with FHx when not accounting for race (Tables 1 and 2) is probably due to reverse confounding, with higher Lp(a) but lower prevalence of FHx in Black subjects.

Circulating Lp(a) levels are primarily determined genetically, and FHx loosely captures the polygenic predisposition to cardiovascular disease. It seems plausible that both these markers might provide redundant information regarding cardiovascular risk in the general population. In a small prior case-control study of White men, apo(a) concentration accounted for much of the familial predisposition to CHD, and apo(a) and FHx were interchangeable as factors associated with CHD risk (24). However, the additive effects of apo(a) and FHx were not explored in that study. Contrary to the hypothesis that Lp(a) and FHx provide redundant prognostic information, and perhaps most important, our results indicate that the simultaneous presence of these 2 "risk-enhancing factors" is independently associated with increased long-term cardiovascular risk in the ARIC cohort. The strength of this joint association was higher than what was observed with either risk factor alone. Furthermore, these additive joint associations were unchanged in sensitivity analyses in which Lp(a) level ≥50 mg/dl and premature FHx were considered together, and total cholesterol levels used in Cox models were adjusted for comeasurement of Lp(a) cholesterol. Last, the presence of both elevated Lp(a) and FHx (or premature FHx) resulted in improvement in ASCVD and CHD risk reclassification and discrimination indexes.

It is also worth mentioning that the joint association of elevated Lp(a) and FHx (or premature FHx) was multiplicative for ASCVD and CHD risk in the DHS cohort, with a several-fold increased cardiovascular risk observed in those with both elevated Lp(a) and FHx of CHD. It is plausible that the smaller number of events, younger age, and relatively short duration of follow-up are responsible for this multiplicative joint association.

CLINICAL IMPLICATIONS. Our findings are highly relevant in the context of the current landscape of primary ASCVD prevention. Lp(a) is commonly measured in clinical settings for subjects with FHx. In fact, both American and European medical societies endorse measurement of Lp(a) in this setting

TABLE 5 Improvement in ASCVD and CHD Risk Reclassification and Discrimination With Lp(a), FHx of CHD, and Premature FHx of CHD

	NRI (95% CI)	p Value	IDI (95% CI)	p Value	Delta C Statistic (95% CI)	p Value
ASCVD events						
Elevated Lp(a)	**0.086 (0.042 to 0.130)**	<0.001	**0.002 (0.0006 to 0.003)**	0.001	0.001 (−0.0003 to 0.002)	0.136
FHx	**0.132 (0.087 to 0.178)**	<0.001	**0.001 (0.0005 to 0.002)**	0.002	0.001 (−0.0004 to 0.002)	0.204
Premature FHx	0.092 (−0.007 to 0.190)	0.071	0.0001 (−0.0001 to 0.001)	0.903	0.001 (−0.0003 to 0.0015)	0.1661
Elevated Lp(a) and FHx	**0.154 (0.103 to 0.205)**	<0.001	**0.003 (0.002 to 0.004)**	<0.001	0.002 (−0.00002 to 0.003)	0.052
Elevated Lp(a) and premature FHx	**0.089 (0.034 to 0.144)**	0.002	**0.002 (0.0004 to 0.003)**	0.011	0.002 (−0.00004 to 0.003)	0.056
CHD events						
Elevated Lp(a)	**0.120 (0.068 to 0.173)**	<0.001	**0.003 (0.002 to 0.004)**	<0.001	0.001 (−0.0002 to 0.003)	0.093
FHx	**0.192 (0.151 to 0.234)**	<0.001	**0.004 (0.003 to 0.006)**	<0.001	**0.003 (0.001 to 0.005)**	0.012
Premature FHx	**0.093 (0.005 to 0.181)**	0.041	**0.002 (0.00001 to 0.003)**	0.047	**0.002 (0.0005 to 0.004)**	0.016
Elevated Lp(a) and FHx	**0.214 (0.168 to 0.260)**	<0.001	**0.007 (0.005 to 0.009)**	<0.001	**0.004 (0.001 to 0.007)**	0.004
Elevated Lp(a) and premature FHx	**0.151 (0.087 to 0.216)**	<0.001	**0.004 (0.002 to 0.006)**	<0.001	**0.004 (0.001 to 0.006)**	0.006

Change in risk reclassification (continuous NRI) and risk discrimination (IDI and delta C statistic) after adding elevated Lp(a), FHx, and premature FHx individually and in combination to a baseline risk prediction model comprising age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, and statin use at baseline. **Bold** indicates statistically significant values.

IDI = integrated discrimination index; NRI = net reclassification improvement; other abbreviations as in Tables 1, 3, and 4.

(9,25). However, it was previously not well characterized if Lp(a) measurement was additive to the cardiovascular risk information conveyed by FHx. Our results demonstrate that these 2 factors are independent and at least additive in their association with incident cardiovascular events. For instance, the 10-year cumulative ASCVD incidence among ARIC participants with both elevated Lp(a) and FHx (or premature FHx) was about 10%, which is higher than the American multisociety guideline-recommended statin initiation threshold of 7.5% (8). Finally, the presence of both elevated Lp(a) and FHx or premature FHx improves ASCVD and CHD risk reclassification and discrimination beyond traditional risk factors. Taken together, an elevated Lp(a) level and FHx may be useful for informing cardiovascular disease prevention strategies among asymptomatic subjects.

STUDY LIMITATIONS. This is the first study analyzing the independent and joint association of elevated Lp(a) level and FHx with cardiovascular risk among asymptomatic participants of 2 well-established American community-based epidemiological cohorts. Our study cohorts consisted of multiethnic participants who were followed for a long time period for adjudicated ASCVD and CHD events.

The results of our study should be interpreted in the context of several limitations. First, we report findings from observational cohorts of American adults 30 to 65 years of age at the time of blood draw for measurement of Lp(a), and as such our results may not be generalizable to other populations outside the United States. However, the multiethnic nature of our cohorts does enhance the application to diverse populations.

Second, the definition of FHx (at any age and premature) was cohort specific, and data were obtained using self-report at enrollment. Information regarding FHx in multiple first-degree and/or second-degree relatives was not collected. However, the consistency of our results across different FHx definitions between the cohorts enhances the fidelity of our findings.

Third, the prospective impact of statin and cardiovascular risk reduction therapy use in participants with elevated Lp(a) level and FHx (or premature FHx) was not evaluated in this study.

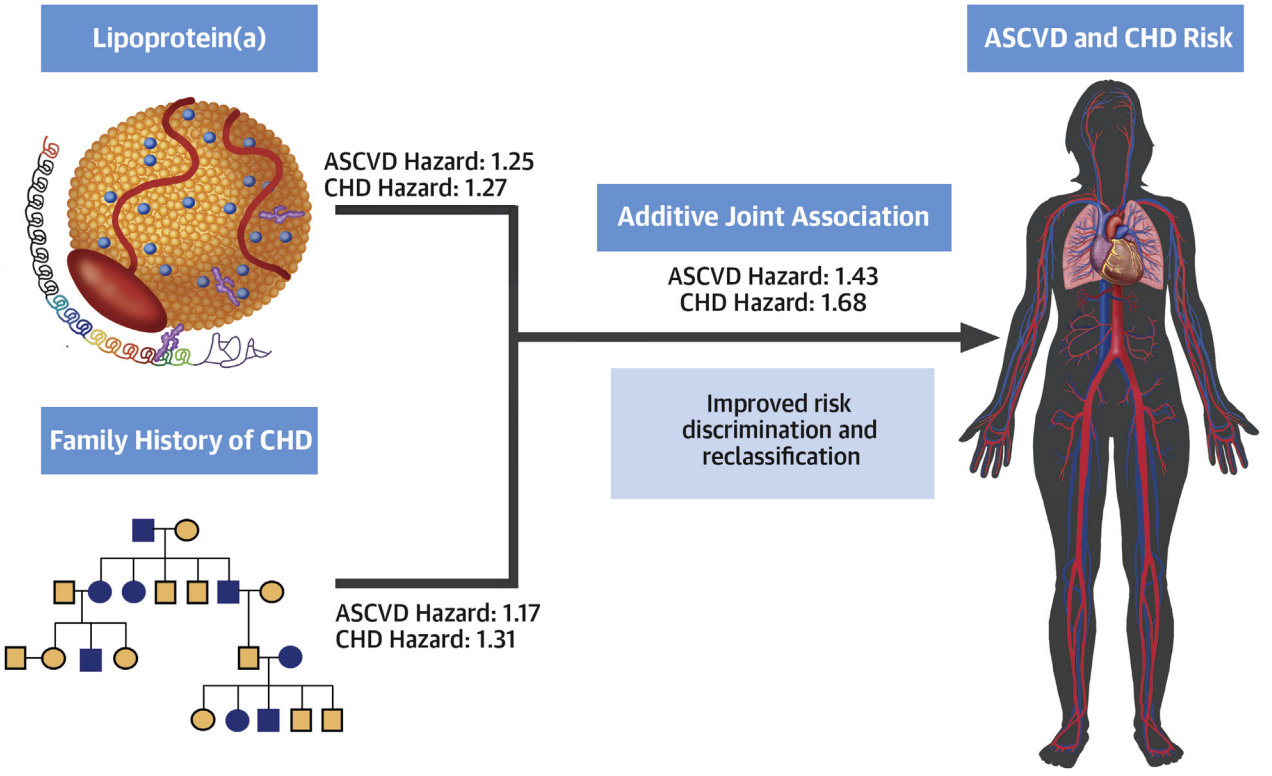
Fourth, the improvement in risk discrimination indexes (integrated discrimination index and C statistic) with the addition of elevated Lp(a) and FHx to the traditional risk factor model was small, suggesting limited clinical impact. However, there was a larger change in the net reclassification improvement, a measure of clinical risk reclassification, and this discrepancy in risk metrics has been seen with other risk markers (26).

Last, we did not explore the associations of Lp(a), FHx, and cardiovascular events in the context of apolipoprotein B level, a key driver of atherogenic risk (27), in our study.

CONCLUSIONS

Elevated plasma Lp(a) level and FHx of CHD (either premature or at any age) have an independent and additive joint association with long-term cardiovascular risk (**Central Illustration**). The presence of these 2 nontraditional cardiovascular risk markers can help identify asymptomatic subjects at elevated cardiovascular risk and may be useful for guiding primary

CENTRAL ILLUSTRATION **Independent and Joint Association of Lipoprotein(a) and Family History With Cardiovascular Risk**



Mehta, A. et al. J Am Coll Cardiol. 2020;76(7):781–93.

Elevated plasma lipoprotein(a) level and family history of coronary heart disease have independent and additive joint associations with long-term atherosclerotic cardiovascular disease and coronary heart disease risk. ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease.

prevention therapy decisions. These results also support recent guideline recommendations for broader one-time assessment of Lp(a) levels.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In asymptomatic subjects, elevated plasma Lp(a) level and FHx of CHD are independent, additive risk factors for cardiovascular disease.

COMPETENCY IN PATIENT CARE: Further efforts are needed to integrate these risk factors in strategies that identify asymptomatic subjects at increased cardiovascular risk and enhance primary prevention of CHD.

REFERENCES

1. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol 2017;69:692–711.

2. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med 2009;361:2518–28.

3. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA 2009;302:412–23.

4. Virani SS, Brautbar A, Davis BC, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) study. Circulation 2012;125:241–9.

5. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. J Am Coll Cardiol 2013;61:1146–56.

6. Waldeyer C, Makarova N, Zeller T, et al. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur Heart J 2017;38:2490–8.

7. Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr., et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. JAMA 2004;291:2204–11.

8. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73:3168–209.

9. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111–88.

10. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. J Clin Lipidol 2015;9:S1–122.e1.

11. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. Am J Epidemiol 1989;129:687–702.

12. Victor RG, Haley RW, Willett DL, et al. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. Am J Cardiol 2004;93:1473–80.

13. Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond MG, Davis CE. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) study. Arterioscler Thromb 1994;14:1098–104.

14. Lackner C, Cohen JC, Hobbs HH. Molecular definition of the extreme size polymorphism in apolipoprotein(a). Hum Mol Genet 1993;2:933–40.

15. Marcovina SM, Hobbs HH, Albers JJ. Relation between number of apolipoprotein(a) kringle 4 repeats and mobility of isoforms in agarose gel: basis for a standardized isoform nomenclature. Clin Chem 1996;42:436–9.

16. Gaubatz JW, Heideman C, Gotto AM Jr., Morrisett JD, Dahlen GH. Human plasma lipoprotein [a]. Structural properties. J Biol Chem 1983;258:4582–9.

17. Marcovina SM, Albers JJ, Scanu AM, et al. Use of a reference material proposed by the International Federation of Clinical Chemistry and Laboratory Medicine to evaluate analytical methods for the determination of plasma lipoprotein(a). Clin Chem 2000;46:1956–67.

18. Guerra R, Yu Z, Marcovina S, Peshock R, Cohen JC, Hobbs HH. Lipoprotein(a) and apolipoprotein(a) isoforms: no association with coronary artery calcification in the Dallas Heart Study. Circulation 2005;111:1471–9.

19. Florido R, Zhao D, Ndumele CE, et al. Physical activity, parental history of premature coronary heart disease, and incident atherosclerotic cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study. J Am Heart Assoc 2016;5:e003505.

20. Philips B, de Lemos JA, Patel MJ, McGuire DK, Khera A. Relation of family history of myocardial infarction and the presence of coronary arterial calcium in various age and risk factor groups. Am J Cardiol 2007;99:825–9.

21. Kinpara K, Okada H, Yoneyama A, Okubo M, Murase T. Lipoprotein(a)-cholesterol: a significant component of serum cholesterol. Clin Chim Acta 2011;412:1783–7.

22. Langsted A, Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study. Lancet Diabetes Endocrinol 2016;4:577–87.

23. Ranthe MF, Carstensen L, Oyen N, et al. Family history of premature death and risk of early onset cardiovascular disease. J Am Coll Cardiol 2012;60:814–21.

24. Durrington PN, Ishola M, Hunt L, Arrol S, Bhatnagar D. Apolipoproteins (a), AI, and B and parental history in men with early onset ischaemic heart disease. Lancet 1988;1:1070–3.

25. Wilson DP, Jacobson TA, Jones PH, et al. Use of lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol 2019;13:374–92.

26. Pencina MJ, D'Agostino RB, Pencina KM, Janssens AC, Greenland P. Interpreting incremental value of markers added to risk prediction models. Am J Epidemiol 2012;176:473–81.

27. Sniderman AD, Thanassoulis G, Glavinovic T, et al. Apolipoprotein B particles and cardiovascular disease: a narrative review. JAMA Cardiol 2019;4:1287–95.

KEY WORDS atherosclerotic cardiovascular disease, cardiovascular risk, family history, lipoprotein(a), primary CVD prevention

APPENDIX For supplemental Methods and tables, please see the online version of this paper.