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ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Impact of Social Determinants of Health and Lifestyle on Association Between Lipoprotein(a) and Cardiovascular Events

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ABSTRACT

BACKGROUND In European cohorts, healthier lifestyle either attenuated or associated with lower cardiovascular risk despite elevated lipoprotein(a) [Lp(a)].

OBJECTIVES The purpose of this study was to test if social determinants of health (SDOH) and Life's Simple 7 (LS7) scores impact the association of Lp(a) with cardiovascular events in U.S. cohorts.

METHODS We performed a sequential multivariable Cox proportional hazard analysis using the ARIC (Atherosclerosis Risk In Communities) and MESA (Multi-Ethnic Study of Atherosclerosis) cohorts. We first adjusted for age, gender, non-high-density lipoprotein-cholesterol, race, and ethnicity, then sequentially added SDOH and LS7 scores. The primary outcomes were time until first myocardial infarction (MI) or stroke.

RESULTS ARIC (n = 15,072; median Lp(a) = 17.3 mg/dL) had 16.2 years and MESA (n = 6,822; median Lp(a) = 18.3 mg/dL) had 12.3 years of average follow-up. In age, gender, race, and ethnicity, and non-high-density lipoprotein-cholesterol adjusted analyses, Lp(a) was associated with MI in ARIC (HR: 1.10, $P < 0.001$) and MESA (HR: 1.11, $P = 0.001$), and stroke in ARIC (HR: 1.07, $P < 0.001$) but not MESA (HR: 0.97, $P = 0.53$). In models with SDOH and LS7, associations of Lp(a) remained similar with MI (ARIC, HR: 1.08, $P < 0.001$; MESA, HR: 1.10, $P = 0.001$) and stroke (ARIC, HR: 1.06, $P = 0.002$; MESA, HR: 0.96, $P = 0.37$). Each additional SDOH correlated positively with MI (ARIC, HR: 1.04, $P = 0.01$; MESA, HR: 1.08, $P = 0.003$) and stroke in ARIC (HR: 1.08, $P = 0.00$) but not MESA (HR: 1.03, $P = 0.41$). Each additional LS7 point correlated negatively with MI (ARIC, HR: 0.88, $P < 0.001$; MESA, HR: 0.85, $P < 0.001$) and stroke (ARIC, HR: 0.91, $P < 0.001$; MESA, HR: 0.86, $P < 0.001$).

CONCLUSIONS SDOH and lifestyle factors associated with risk for MI and stroke but did not largely impact the association between Lp(a) and cardiovascular events. (JACC Adv 2024;3:101016) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CVD = cardiovascular disease

HDL-C = high-density lipoprotein-cholesterol

Lp(a) = lipoprotein(a)

LS7 = Life's Simple 7

MI = myocardial infarction

RERI = relative excess risk due to interaction

SDOH = social determinants of health

Lipoprotein(a) [Lp(a)] is an independent risk factor for the development of atherosclerotic cardiovascular diseases (ASCVD).[1,2] Aside from apheresis, there are no clinically available therapies that specifically target lowering of Lp(a), although agents are being developed (eg, pelacarsen, olpasiran, etc) and other Food and Drug Administration-approved therapies (eg, Proprotein convertase subtilisin/kexin type 9 inhibitors and niacin) have small impacts on Lp(a) levels. While awaiting therapeutic agents, patients with elevated Lp(a) can lower their risk for ASCVD with statins and other lipid-lowering therapies.[1] Additionally, lifestyle and social determinants of health (SDOH) have large impacts on cardiovascular outcomes and can be targets for risk modification.[3,4]

Findings from 2 European cohorts suggest that a healthy lifestyle can decrease the risk for ASCVD among those with elevated Lp(a). In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (n = 14,051 men and women from Norfolk, UK), those in the top vs the bottom tertile of Life's Simple 7 (LS7) score and Lp(a) ≥50 mg/dL had a HR of 0.33 (95% CI: 0.17-0.63) for death from coronary heart disease or stroke.[5] The risk of elevated Lp(a) was not completely abolished since those with Lp(a) <50 mg/dL in the top tertile of LS7 score had a HR of 0.17 (95% CI: 0.12-0.31). Second, in the ATTICA study (n = 3,042 Greek men and women without ASCVD), a higher Mediterranean diet score did not influence Lp(a) levels but did abolish (HR: 1.00; 95% CI: 0.98-1.01) the risk associated with Lp(a) for having an ASCVD event with a significant mediation effect (Sobel's test $P < 0.001$).[6]

SDOH are the conditions in which people are born, live, and work.[7] SDOH are associated with ASCVD events and may help to explain the differences in cardiovascular risk between different populations.[8-10] SDOH can impact risk for ASCVD via psychological, behavioral, and biologic mechanisms, which include chronic stress responses and systemic inflammation.[11] Given that Lp(a) is an acute phase reactant whose level is mediated by periods of inflammation and a preferential carrier of atherogenic oxidized phospholipids, it is plausible that SDOH could impact the association of Lp(a) on risk for CVD events.[12,13]

The impact of lifestyle factors on the association of Lp(a) with cardiovascular events has not been tested in U.S. cohorts. Furthermore, the impact of SDOH on the association of Lp(a) with cardiovascular outcomes is untested in any cohorts. We hypothesized that accounting for SDOH and lifestyle factors would greatly mitigate the risk associated with Lp(a) for myocardial infarction (MI) or stroke in U.S. cohorts.

METHODS

DATA. We performed a retrospective analysis of prospectively collected data from the ARIC (Atherosclerosis Risk In Communities) and the MESA (Multi-Ethnic Study of Atherosclerosis) cohorts. ARIC and MESA are prospective, longitudinal investigations into the cardiac risk factors, health outcomes, and demographic patterning of atherosclerosis. ARIC enrolled men and women aged 35 to 84 years, beginning in 1987, from 4 U.S. communities. MESA enrolled men and women aged 45 to 64 years, beginning in 2000, from 6 U.S. communities. Data were obtained via requests to the National Institute of Health's Biologic Specimen and Data Repository Information Coordinating Center. We used data from the first examination cycle and cohort surveillance data for cardiovascular events. The study was deemed exempt from review by the University of Michigan Institutional Review Board.

OUTCOMES. The primary outcomes were time until the first fatal or nonfatal MI or stroke. In ARIC, outcomes were tracked semiannually through 2006. In MESA, outcomes were tracked annually through 2015.

LP(a) ASSAYS. In ARIC, Lp(a) was measured as protein mass using a double-antibody enzyme-linked immunosorbent assay technique.[14,15] The protein mass represents about one-third of the total molecule mass,[16] thus the Lp(a) mass measured in ARIC visit 1 was tripled to be similar to the Lp(a) total mass measurement in MESA. This technique, although isoform sensitive, had excellent correlation (r = 0.88) with samples performed at visit 4 using an isoform insensitive turbidimetric immunoassay (Denka Seiken Co Ltd, Tokyo, Japan).[17] In MESA, Lp(a) was measured from cold storage 10 to 11 years after sample collection as mass content using an isoform insensitive latex-enhanced turbidimetric immunoassay (Denka Seiken, Tokyo, Japan) by Health Diagnostics Laboratory (Richmond, Virginia).[18,19]

STATISTICAL DESIGN AND ANALYSIS. Population characteristics were described as n, % for categorical variables (gender and race and ethnicity) or median (IQR) for non-normally distributed continuous variables (no continuous variables were normally distributed). Attempts to transform non-normally distributed to variables to normalcy did not lead to normal distribution.

We performed a sequential multivariable Cox proportional hazard analysis. In model 1, covariates were

age, gender, race, and ethnicity, non-high-density lipoprotein-cholesterol (HDL-C) (per 25 mg/dL increase), and Lp(a) (per 25 mg/dL increase). Model 2 included a SDOH score: an integer score ranging from 0 to 5 in ARIC and 0 to 11 in MESA. SDOH in ARIC included being unemployed, income <300% of the federal poverty level, <high school education, no regular site for health care access, and government or no health insurance. SDOH in MESA included these determinants and not being married or living with a partner, not owning a home, reports of loneliness/lack of social support, unsafe neighborhood residence, experience of discrimination in the last year, and somewhat or very serious food access problems. Model 3 included the LS7 score (smoking status, body mass index, physical activity, dietary score, total cholesterol, blood pressure, and fasting plasma glucose), which has been previously defined.[4] Each category received 0 to 2 points (range: 0-14 points). Non-HDL-C was calculated by subtracting HDL-C from total cholesterol and corrected for Lp(a) mass (non-HDL-C = total cholesterol-HDL-C-(Lp(a)× 0.3)).[20] We used interaction terms to test whether there is a modification of the effect on Lp(a) by SDOH or LS7 scores. We report HRs estimated at the mean of all covariates in the model by single point increase in SDOH or 25 mg/dL increase in Lp(a). We reported additive modification of the effect as relative excess risk due to interaction (RERI) and as well as measure of effect modification on multiplicative scale.[21] We used a generalized structural equation model to estimate if Lp(a) mediates the impact of SDOH or LS7 on outcomes and report indirect effects and total effects of SDOH or LS7 scores. An individual was censored if they died before a primary outcome event.

To test the proportional hazards assumption, we examined log-log plots of survival for parallel curves in all fully constructed models, which were acceptable for all outcomes. All Cox models considered competing risk for other causes of death (ie, non-MI death in the MI models). The generalized structural equation models were not adjusted for competing causes of death. All *P* values were 2-sided. Statistical significance was set at $P < 0.05$. Data were analyzed using Stata software, version 16 (StataCorp, LLC).

SENSITIVITY ANALYSES. To understand if correlations between SDOH and LS7 scores could impact outcomes, we tested whether SDOH or LS7 scores associated with Lp(a) level in age, gender, race and ethnicity, and non-HDL-C-adjusted models.

To understand the association between categorical Lp(a) level and cardiovascular outcomes, we use coarsened exact matching to match cases (Lp(a) >50 mg/dL) to controls (Lp(a) <50 mg/dL). In ARIC, matching covariates were coarsened to age (44-55 or 56-66 years), non-HDL-C (0-120.0, 120.1-160.0, 160.1-200.0, 200.1-240.0, and ≥240.1 mg/dL), SDOH score (integers: 0, 1-2, 3-5), and LS7 score (integers: 0-4, 5-9, 10-14). Non-coarsened variables included gender and race and ethnicity. In MESA, matching covariates were similar except age (44-57, 57-70, and 70-84 years) and SDOH score (integers: 0-1, 1-3, 3-5, >5). We repeated Cox proportional hazards regression in the same 3 models as described above except that we consider Lp(a) as a 3-level outcome (<50 mg/dL, ≥50 to <100 mg/dL, and ≥100 mg/dL).

RESULTS

POPULATION CHARACTERISTICS. In ARIC, the median age was 54 years, and in MESA, 62 years. Most were female (54.5% in ARIC and 52.9% in MESA, Table 1). Race and ethnicities represented were non-Hispanic White (73.9% in ARIC, 38.5% in MESA), non-Hispanic Black (26.1% in ARIC, 27.8% in MESA), and only MESA included Chinese (11.8%) and Hispanic (22.0%) individuals. Median Lp(a) was similar in both cohorts (18.3 mg/dL in ARIC and 17.3 mg/dL in MESA), whereas median non-HDL-C was higher in ARIC (152 mg/dL) than MESA (132 mg/dL). SDOH scores were lower in ARIC (median: 1 [IQR: 0-2]) than MESA (median: 2 [IQR: 1-3]). LS7 score was similar in ARIC (median: 8 [IQR: 6-10]) and MESA (median: 8 [IQR: 7-10]).

LP(a) ASSOCIATION WITH SDOH AND LS7 SCORES. In age, gender, and race and ethnicity adjusted models, SDOH score did not associate with Lp(a) level (increase in mg/dL Lp(a) per SDOH in either ARIC (0.50 [95% CI: −0.003 to 1.00]) or MESA (0.24 [95% CI: −0.27 to 0.74]). However, LS7 score did associate with lower Lp(a) level in both ARIC (−0.68 [95% CI: −0.90 to −0.45] and MESA (−0.46 [95% CI: −0.85 to −0.07]).

MYOCARDIAL INFARCTION. In all models, Lp(a) (per 25 mg/dL increase) was associated with MI (Table 2). The HR only slightly attenuated after adding SDOH and LS7 into the models (in ARIC from 1.10 (95% CI: 1.07-1.12) to 1.08 (95% CI: 1.05-1.11) and in MESA from 1.11 (95% CI: 1.05-1.18) to 1.10 (95% CI: 1.04-1.17). The association between non-HDL-C and MI in ARIC (1.15 [95% CI: 1.13-1.78]) and MESA (1.09 [95% CI: 1.03-1.16]) was similar when adding SDOH (1.15 [95% CI: 1.13-1.17] in ARIC and 1.09 [95% CI: 1.03-1.15] in MESA), then attenuated once LS7 score was added in ARIC (1.08 [95% CI: 1.06-1.10]) and nonsignificant in MESA (1.03 [95% CI: 0.97-1.09]).

TABLE 1 Population Characteristics (n = 15,027 for ARIC, n = 6,822 for MESA)

	ARIC	MESA
Age (y)	54 (49-59)	62 (53-70)
Female	8,196 (54.5%)	3,601 (52.9%)
Race and ethnicity	-	-
Non-Hispanic White	11,110 (73.9%)	2,622 (38.5%)
Non-Hispanic Black	3,917 (26.1%)	1,892 (27.8%)
Non-Hispanic Chinese	n/a	804 (11.8%)
Hispanic	n/a	1,496 (22.0%)
Lipoprotein(a) (mg/dL)	18.3 (6.9-43.8)	17.3 (7.5-40.6)
Non-HDL-C (mg/dL)	152 (124-182)	132 (109-155)
SDOH score	1 (0-2)	2 (1-3)
Life's Simple 7 score	8 (6-10)	8 (7-10)

Values are median (IQR) or n (%).

ARIC = Atherosclerosis Risk In Communities; HDL-C = high-density lipoprotein-cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; SDOH = social determinants of health.

Among demographic characteristics, there was no change in the association between age and MI and only a small change in association between gender and MI when adding SDOH and LS7 score (Table 2). There were changes in the association between race and ethnicity and MI when adding SDOH and LS7 into the models; the association of identifying as non-Hispanic Black compared to non-Hispanic White changed in ARIC from 1.13 (95% CI: 1.04-1.23) to 0.89 (95% CI: 0.82-0.98) and in MESA from 0.91 (95% CI: 0.74-1.11) to 0.70 (95% CI: 0.56-0.87). For those in MESA identifying as Hispanic-the association shifted from 1.00 (95% CI: 0.81-1.23) to 0.77 (95% CI: 0.61-0.98). There was no significant shift for those identifying as non-Hispanic Chinese. Given the large changes in association, we also tested for interactions between race and ethnicity with SDOH and LS7 scores, all of which were nonsignificant ($P > 0.05$).

EFFECT MODIFICATION AND MEDIATION OF LP(A) ON MI BY SDOH AND LS7 SCORE. There were no significant interactions between SDOH and Lp(a) on MI in ARIC (HR: 1.00, $P = 0.71$) or MESA (HR: 1.01, $P = 0.69$). Measures of effect modification on additive and multiplicative scale were also insignificant (Table 3). There was an interaction with a small effect size between LS7 and Lp(a) on MI in MESA (HR: 0.97, $P = 0.01$) but not ARIC (HR: 1.00, $P = 0.51$). Measure of effect modification on additive scale was not

TABLE 2 Sequential Multivariable Cox Proportional Hazards Regression for Myocardial Infarction in ARIC and MESA

	ARIC, (n = 14,302)								
	Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age (per year)	1.04	1.03-1.05	<0.001	1.04	1.03-1.04	<0.001	1.04	1.03-1.04	<0.001
Male	1.44	1.35-1.54	<0.001	1.44	1.35-1.54	<0.001	1.42	1.33-1.52	<0.001
Race and ethnicity	-	-	-	-	-	-	-	-	-
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.13	1.04-1.23	0.002	1.04	0.96-1.14	0.34	0.89	0.82-0.98	0.01
Non-HDL-C (per 25-mg/dL increase)	1.15	1.13-1.17	<0.001	1.15	1.13-1.17	<0.001	1.08	1.06-1.10	<0.001
Lipoprotein(a) (per 25-mg/dL increase)	1.10	1.07-1.12	<0.001	1.10	1.07-1.12	<0.001	1.08	1.05-1.11	<0.001
SDOH score (per 1-point increase)	-	-	-	1.09	1.06-1.13	<0.001	1.04	1.01-1.08	0.01
Life's Simple 7 score (per 1-point increase)	-	-	-	-	-	-	0.88	0.87-0.90	<0.001
	MESA (n = 6,668)								
	Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age (per year)	1.05	1.04. 1.06	<0.001	1.04	1.03-1.05	<0.001	1.04	1.03-1.05	<0.001
Male	2.07	1.76-2.44	<0.001	2.19	1.85-2.58	<0.001	2.19	1.86-2.60	<0.001
Race and ethnicity	-	-	-	-	-	-	-	-	-
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	0.91	0.74-1.11	0.35	0.83	0.67-1.03	0.09	0.70	0.56-0.87	0.002
Non-Hispanic Chinese	0.79	0.60-1.04	0.10	0.72	0.54-0.96	0.03	0.81	0.61-1.08	0.15
Hispanic	1.00	0.81-1.23	0.98	0.84	0.66-1.06	0.14	0.77	0.61-0.98	0.03
Non-HDL-C (per 25-mg/dL increase)	1.09	1.03-1.16	0.002	1.09	1.03-1.15	0.003	1.03	0.97-1.09	0.38
Lipoprotein(a) (per 25-mg/dL increase)	1.11	1.05-1.18	0.001	1.11	1.05-1.18	0.001	1.10	1.04-1.17	0.001
SDOH score (per 1-point increase)	-	-	-	1.11	1.05-1.17	0.001	1.08	1.03-1.14	0.003
Life's Simple 7 score (per 1-point increase)	-	-	-	-	-	-	0.85	0.82-0.89	<0.001

Abbreviations as in Table 1.

TABLE 3 Modification of the Effect of Lipoprotein(a) on Myocardial Infarction by SDOH Score[a]

	Lipoprotein(a) 30 mg/dL	Lipoprotein(a) 55 mg/dL	25 mg/dL Increase in LP(a) Within Strata of SDOH Score
ARIC			
SDOH score = 1.0	1.00	1.08 (1.05-1.11); $P < 0.001$	1.08 (1.05-1.11); $P < 0.001$
SDOH score = 2.0	1.04 (1.01-1.08); $P = 0.01$	1.13 (1.07-1.18); $P < 0.001$	1.08 (1.04-1.11); $P < 0.001$
Measure of effect modification on additive scale: RERI (95% CI) = −0.00 (−0.03 to 0.02), $P = 0.11$			
Measure of effect modification on multiplicative scale: ratio of HR (95% CI) = 1.00 (0.97-1.02); $P = 0.72$			
MESA			
SDOH score = 2.3	1.00	1.10 (1.03-1.16); $P = 0.005$	1.10 (1.03-1.16); $P = 0.005$
SDOH score = 3.3	1.08 (1.03-1.14); $P = 0.007$	1.20 (1.10-1.30); $P < 0.001$	1.11 (1.04-1.18); $P = 0.005$
Measure of effect modification on additive scale: RERI (95% CI) = 0.02 (−0.02 to 0.06); $P = 0.42$			
Measure of effect modification on multiplicative scale: ratio of HR (95% CI) = 1.01 (0.97-1.04); $P = 0.71$			

[a]Results are per 25 mg/dL increase in Lp(a) and per 1-point increase in SDOH score estimated as marginal outputs at the means of all covariates. HRs are adjusted for age, gender, race, and ethnicity, non-HDL-C, and Life's Simple 7 score.

RERI = relative excess risk due to interaction; other abbreviations as in Table 1.

significant in ARIC (RERI −0.01 [95% CI: −0.02 to −0.00], $P = 0.20$), but significant in MESA (−0.04 [95% CI: −0.06 to −0.02], $P < 0.001$, Table 4). Measure of effect modification on multiplicative scale was also not significant in ARIC (1.00 [95% CI: 0.99-1.01], $P = 0.52$), but significant in MESA (0.97 [95% CI: 0.95-0.99], $P = 0.008$).

Mediation testing found that SDOH indirectly mediated 3.6% of Lp(a)'s association with MI in ARIC (indirect HR: 1.01 [95% CI: 1.01-1.02], $P < 0.001$; total HR: 1.42 [95% CI: 1.36-1.49], $P < 0.001$) and 1.1% in MESA (indirect HR: 1.002 [95% CI: 1.000-1.005], $P = 0.04$; total HR: 1.25 [95% CI: 1.15-1.35], $P < 0.001$). LS7 score indirectly mediated 3.2% of Lp(a)'s association with MI in ARIC (indirect HR: 0.99 [95% CI: 0.99-1.00], $P = <0.001$; total HR 0.93 [95% CI: 0.80-0.86], $P < 0.001$) and 3.7% in MESA (indirect HR: 0.99 [95% CI: 0.99-1.00], $P = 0.004$; total effect HR 0.87 [95% CI: 0.81-0.94], $P < 0.001$).

STROKE. Lp(a) is associated with stroke in ARIC but not in MESA (Table 5). In ARIC, the association with stroke was similar before (HR: 1.07 [95% CI: 1.05-1.12]) and after including SDOH and LS7 scores (HR: 1.06 [95% CI: 1.02-1.10]). The association between non-HDL-C and stroke in ARIC (HR: 1.08 [95% CI: 1.05-1.10]) and MESA (HR: 1.10 [95% CI: 1.02-1.19] was unchanged when adding SDOH (HR: 1.08 [95% CI: 1.04-1.11] in ARIC and HR: 1.10 [95% CI: 1.02-1.18] in

TABLE 4 Modification of the Effect of Lipoprotein(a) on Myocardial Infarction by Life's Simple 7 Score[a]

	Lipoprotein(a) 30 mg/dL	Lipoprotein(a) 55 mg/dL	25 mg/dL Increase in LP(a) Within Strata of LS7 Score
ARIC			
LS7 score = 7.8	1.00	1.09 (1.06, 1.11); $P < 0.001$	1.09 (1.06, 1.11); $P < 0.001$
LS7 score = 8.8	0.88 (0.87-0.90); $P < 0.001$	0.96 (0.92, 1.00); $P = 0.03$	1.09 (1.05, 1.12); $P < 0.001$
Measure of effect modification on additive scale: RERI (95% CI) = −0.01 (−0.02 to −0.00), $P = 0.20$			
Measure of effect modification on multiplicative scale: ratio of HR (95% CI) = 1.00 (0.99-1.01), $P = 0.52$			
MESA			
LS7 score = 8.3	1.00	1.07 (1.00-1.13); $P = 0.06$	1.07 (1.00-1.13); $P = 0.06$
LS7 score = 9.3	0.86 (0.82-0.89); $P < 0.001$	0.88 (0.81-0.96); $P = 0.001$	1.03 (0.96-1.11); $P = 0.41$
Measure of effect modification on additive scale: RERI (95% CI) = −0.04 (−0.06 to −0.02), $P < 0.001$			
Measure of effect modification on multiplicative scale: ratio of HR (95% CI) = 0.97 (0.95-0.99); $P = 0.008$			

[a]Results are per 25 mg/dL increase in Lp(a) and per 1 point increase in LS7 score estimated as marginal outputs at the means of all covariates. HRs are adjusted for age, gender, race, and ethnicity, non-HDL-C, and Life's Simple 7 score.

LS7 = Life's Simple 7; other abbreviations as in Tables 1 and 3.

TABLE 5 Sequential Multivariable Cox Proportional Hazards Regression for Stroke in ARIC and MESA

	Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
ARIC (n = 14,282)									
Age (per year)	1.05	1.04-1.06	<0.001	1.05	1.04-1.06	<0.001	1.05	1.04-1.05	<0.001
Male	1.07	0.97-1.17	0.18	1.06	0.97-1.17	0.21	1.05	0.96-1.16	0.28
Race and ethnicity	-	-	-	-	-	-	-	-	-
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.61	1.45-1.79	<0.001	1.45	1.29-1.62	<0.001	1.28	1.14-1.44	<0.001
Non-HDL-C (per 25-mg/dL increase)	1.08	1.05-1.10	<0.001	1.07	1.04-1.11	<0.001	1.02	0.99-1.05	0.19
Lipoprotein(a) (per 25-mg/dL increase)	1.07	1.03-1.11	<0.001	1.07	1.03-1.10	<0.001	1.06	1.02-1.10	0.002
SDOH score (per 1-point increase)	-	-	-	1.12	1.08-1.18	<0.001	1.08	1.03-1.13	0.001
Life's Simple 7 score (per 1-point increase)	-	-	-	-	-	-	0.91	0.89-0.93	<0.001
MESA (n = 6,666)									
Age (per year)	1.06	1.05-1.07	<0.001	1.06	1.05-1.07	<0.001	1.06	1.04-1.07	<0.001
Male	1.16	0.92-1.47	0.20	1.20	0.95-1.53	0.13	1.20	0.95-1.53	0.13
Race and ethnicity	-	-	-	-	-	-	-	-	-
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.34	1.00-1.80	0.05	1.28	0.95-1.74	0.11	1.09	0.80-1.49	0.57
Non-Hispanic Chinese	0.65	0.40-1.05	0.08	0.62	0.38-1.00	0.05	0.69	0.43-1.13	0.14
Hispanic	1.50	1.12-2.01	0.007	1.36	0.99-1.88	0.06	1.26	0.92-1.73	0.16
Non-HDL-C (per 25-mg/dL increase)	1.10	1.02-1.19	0.01	1.10	1.02-1.18	0.01	1.04	0.96-1.12	0.33
Lipoprotein(a) (per 25-mg/dL increase)	0.97	0.89-1.06	0.53	0.97	0.89-1.06	0.52	0.96	0.88-1.05	0.37
SDOH score (per 1-point increase)	-	-	-	1.06	0.98-1.15	0.14	1.03	0.96-1.12	0.41
Life's Simple 7 score (per 1-point increase)	-	-	-	-	-	-	0.86	0.81-0.91	<0.001

Abbreviations as in Table 1.

MESA), then became nonsignificant once LS7 score was added (HR: 1.02 [95% CI: 0.99-1.05] in ARIC and HR: 1.04 [95% CI: 0.96-1.12] in MESA).

Among demographic characteristics, there was no change in association between age or gender and stroke when adding SDOH and LS7 score to the models (Table 5). Again there were shifts in associations for race and ethnicity and stroke; identifying as non-Hispanic Black compared to non-Hispanic White changed when adding SDOH and LS7 scores to the models in ARIC from HR 1.61 (95% CI: 1.45-1.79) to HR 1.28 (95% CI: 1.14-1.44) and in MESA from HR 1.34 (95% CI: 1.00-1.80) to HR 1.09 (95% CI: 0.80-1.49). For those in MESA identifying as Hispanic, the association also shifted from HR 1.50 (95% CI: 1.12-2.01) to 1.26 (95% CI: 0.92-1.73). There was no significant shift for those identifying as non-Hispanic Chinese. Given the large changes in association, we also tested for interactions between race and ethnicity with SDOH and LS7 scores, all of which were nonsignificant ($P > 0.05$).

EFFECT MODIFICATION AND MEDIATION OF LP(a) ON STROKE BY SDOH AND LS7 SCORE. There were no significant interactions between SDOH and Lp(a) on stroke in ARIC (HR: 1.01, $P = 0.30$) or MESA (1.01, 0.65). For SDOH, measures of effect modification on additive and multiplicative scale were also insignificant (Table 6). For LS7 score and Lp(a) on stroke, there were also no significant interactions in ARIC (95% CI: 0.99-0.38) or MESA (95% CI: 0.98-0.25). For LS7 score, measure of effect modification on additive scale was small but significant in ARIC (95% CI: −0.01 to −0.02, $P = 0.02$), but not MESA (−0.01 [95% CI: −0.03 to 0.02], $P = 0.51$) (Table 7). Measure of effect modification on multiplicative scales was not significant.

Mediation testing found that SDOH indirectly mediated 5.1% of Lp(a)'s association with stroke in ARIC (indirect HR: 1.01 [95% CI: 1.00-1.01], $P = 0.004$; total HR: 1.17 [95% CI: 1.12-1.23], $P < 0.001$) and −2.4% in MESA (indirect HR: 0.999 [95% CI: 0.996-1.002], $P = 0.41$; total HR: 1.05 [95% CI: 0.92-1.18], $P = 0.50$). LS7 score indirectly mediated 2.0% of Lp(a)'s association with stroke in ARIC (indirect HR: 0.996 [95% CI: 0.993-0.999], $P = 0.004$; total HR: 0.82 [95% CI: 0.80-0.84], $P < 0.001$) and −0.9% in MESA (indirect HR: 1.002 [95% CI: 0.997-1.008], $P = 0.39$; total effect HR: 0.76 [95% CI: 0.68-0.85], $P < 0.001$).

COARSENED EXACT MATCHING. In ARIC, there were 214 (1.9% of those with Lp(a) <50 mg/dL) individuals

TABLE 6 Modification of the Effect of Lipoprotein(a) on Stroke by SDOH Score[a]

	Lipoprotein(a) 30 mg/dL	Lipoprotein(a) 55 mg/dL	25 mg/dL Increase in LP(a) Within Strata of SDOH Score
ARIC			
SDOH score = 1.0	1.00	1.08 (1.03-1.013); $P = 0.004$	1.08 (1.03-1.13); $P = 0.004$
SDOH score = 2.0	1.05 (1.01-1.09); $P = 0.01$	1.15 (1.08-1.22); $P < 0.001$	1.07 (1.03-1.11) $P = 0.003$
Measure of effect modification on additive scale: RERI (95% CI) = 0.02 (−0.01 to 0.05); $P = 0.18$			
Measure of effect modification on multiplicative scale: ratio of HR (95% CI) = 1.01 (0.99-1.04); $P = 0.31$			
MESA			
SDOH score = 2.3	1.00	0.96 (0.87, 1.04); $P = 0.31$	0.96 (0.87-1.04); $P = 0.31$
SDOH score = 3.3	1.03 (0.95-1.11); $P = 0.31$	1.00 (0.88-1.12); $P = 0.99$	0.97 (0.88-1.05); $P = 0.47$
Measure of effect modification on additive scale: RERI (95% CI) = 0.01 (−0.04 to 0.06); $P = 0.69$			
Measure of effect modification on multiplicative scale: ratio of HR (95% CI) = 1.01 (0.96-1.06); $P = 0.67$			

[a]Results are per 25 mg/dL increase in Lp(a) and per 1 point increase in SDOH score estimated as marginal outputs at the means of all covariates. HRs are adjusted for age, gender, race, and ethnicity, non-HDL-C, and Life's Simple 7 score.

Abbreviations as in Tables 1 and 3.

unmatched with Lp(a) < 50 mg/dL and 535 (14.8%) with Lp(a) ≥50 mg/dL. In MESA, there were 1,004 (18.7%) individuals unmatched with Lp(a) <50 mg/dL and 146 (10.0%) with Lp(a) >50 mg/dL. In ARIC, cases were similar to weighted controls in all factors except for Lp(a) (81.3 mg/dL vs 19.4 mg/dL, $P < 0.001$) (Table 8). In MESA, cases were similar to controls except for non-HDL-C (122.7 mg/dL vs 125.8 mg/dL, $P = 0.005$) and Lp(a) (86.0 mg/dL vs 18.8 mg/dL, $P < 0.001$).

In fully adjusted models that included SDOH score and LS7 score, Lp(a) ≥50 mg/dL to <100 mg/dL was associated with MI in ARIC (HR: 1.14, $P = 0.004$) and MESA (95% CI: 1.24-0.06) (Central Illustration shows coarsened exact matching weighted, but otherwise unadjusted survival curves by Lp(a) category). Lp(a) ≥100 mg/dL was also associated with MI in ARIC (HR: 1.37, $P < 0.001$) and MESA (95% CI: 1.57-0.008). Associations between other covariates and MI were similar, including similar shifts in association between race and ethnicity with MI after adding SDOH and LS7 scores to the model (Table 9).

In fully adjusted models that included SDOH score and LS7 score, Lp(a) >50 mg/dL to <100 mg/dL was associated with stroke in ARIC (95% CI: 1.16-0.01) but not in MESA (95% CI: 1.21-0.25) (Central Illustration). Lp(a) >100 mg/dL was also associated with stroke in ARIC (1.27, 0.02) but not in MESA (95% CI: 0.76-0.40). Associations between other covariates and MI were

TABLE 7 Modification of the Effect of Lipoprotein(a) on Stroke by Life's Simple 7 Score[a]

	Lipoprotein(a) 30 mg/dL	Lipoprotein(a) 55 mg/dL	25 mg/dL Increase in LP(a) Within Strata of LS7 Score
ARIC			
LS7 score = 7.8	1.00	1.05 (1.01-1.09); $P = 0.02$	1.05 (1.01-1.09); $P = 0.02$
LS7 score = 8.8	0.91 (0.89-0.93); $P < 0.001$	0.95 (0.890-1.00; $P = 0.04$	1.04 (0.99-1.09); $P = 0.09$
Measure of effect modification on additive scale: RERI (95% CI) = −0.01 (−0.02 to 0.00); $P = 0.02$			
Measure of effect modification on multiplicative scale: ratio of HR (95% CI) = 0.99 (0.98-1.01); $P = 0.38$			
MESA			
LS7 score = 8.3	1.00	0.94 (0.84-1.03); $P = 0.19$	0.94 (0.84-1.04); $P = 0.19$
LS7 score = 9.3	0.86 (0.80-0.91); $P < 0.001$	0.79 (0.68-0.89); $P < 0.001$	0.92 (0.80-1.03); $P = 0.14$
Measure of effect modification on additive scale: RERI (95% CI) = −0.01 (−0.03 to 0.02); $P = 0.51$			
Measure of effect modification on multiplicative scale: ratio of HR (95% CI) = 0.98 (0.94-1.01); $P = 0.24$			

[a]Results are per 25 mg/dL increase in Lp(a) and per 1 point increase in LS7 score estimated as marginal outputs at the means of all covariates. HRs are adjusted for age, gender, race, and ethnicity, non-HDL-C, and Life's Simple 7 score.

LS7 = Life's Simple 7; other abbreviations as in Tables 1 and 3.

TABLE 8 Population Characteristics Cases With Lipoprotein(a) ≥50 mg/dL and Controls With Lipoprotein(a) <50 mg/dL After Coarsened Exact Matching Weights Applied

	Controls	Cases	*P* Value
		ARIC	
Age (y)	54.3 ± 5.8	54.3 ± 5.8	0.66
Female	6,826 (60.9%)	1,872 (60.9%)	1.00
Race and ethnicity	-	-	-
Non-Hispanic White	6,224 (44.5%)	1,366 (44.5%)	1.00
Non-Hispanic Black	4,981 (55.6%)	1,366 (55.6%)	1.00
Lipoprotein(a) (mg/dL)	19.4 ± 13.9	81.3 ± 30.1	<0.001
Non-HDL-C (mg/dL)	150 ± 45.0	149 ± 44.4	0.73
SDOH score	1.2 ± 1.2	1.2 ± 1.1	0.80
Life's Simple 7 score	7.5 ± 2.3	7.4 ± 2.3	0.07
		MESA	
Age (years)	62.3 ± 9.9	62.3 ± 10.0	0.83
Female	2,554 (5.87%)	773 (58.7%)	1.00
Race and ethnicity	-	-	-
Non-Hispanic White	1,364 (31.4%)	413 (31.4%)	1.00
Non-Hispanic Black	2,051 (47.2%)	621 (47.2%)	1.00
Non-Hispanic Chinese	248 (5.7%)	75 (5.7%)	1.00
Hispanic	683 (15.7%)	207 (15.7%)	1.00
Lipoprotein(a) (mg/dL)	18.8 ± 13.3	86.0 ± 34.6	<0.001
Non-HDL-C (mg/dL)	125.8 ± 33.3	122.7 ± 35.3	0.005
SDOH score	2.3 ± 1.7	2.3 ± 1.7	0.78
Life's Simple 7 score	8.2 ± 2.0	8.1 ± 2.0	0.38

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

similar, including similar shifts in association between race and ethnicity with stroke after adding SDOH and LS7 scores to the model (Table 10).

DISCUSSION

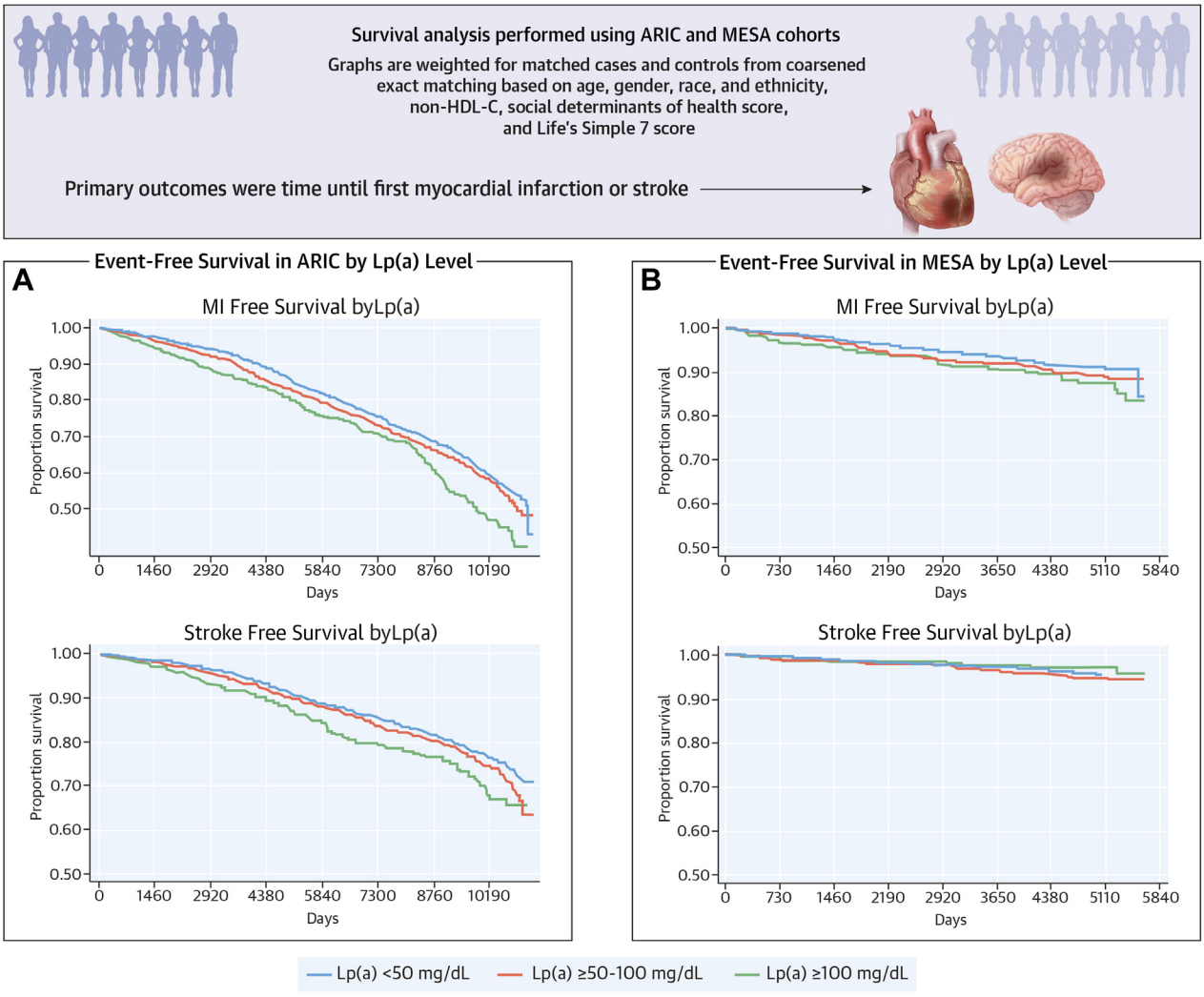
In this observational study of 2 well-characterized, multicenter U.S. cohorts, Lp(a) was associated with MI in both cohorts and stroke in ARIC but not MESA. Accounting for SDOH and lifestyle factors did not largely attenuate the association between Lp(a) and MI or stroke. There was only evidence for a small level of effect modification of the LS7 score on Lp(a)'s association with outcomes. There was also only a small amount of mediation of SDOH or LS7 scores through Lp(a). However, lifestyle factors and SDOH strongly associated with MI or stroke. The large impact of adding SDOH and LS7 scores on the association between race and ethnicity and non-HDL-C with cardiovascular events is intriguing and should be further explored.

Based on the results of 2 prior studies,[5,6] we expected that social and lifestyle factors could mediate or moderate the risk for ASCVD events related to Lp(a). However, the risk associated with Lp(a) on MI and stroke did not greatly change when accounting for LS7 or SDOH scores. Furthermore, mediation testing and moderation testing were underwhelming. This differed from the ATTICA study since the addition of a Mediterranean diet score led to an abolishment of the risk from Lp(a) and a measurable mediation effect.[6] Our results were more similar to the EPIC-Norfolk study, wherein, despite better lifestyle associated with lower risk but did not abolish the risk among those with elevated Lp(a). This was also similar to EPIC-Norfolk since interaction tests were insignificant in this cohort and not sufficiently compelling in our study.[5] The most likely explanation for why we did not observe that SDOH and LS7 scores greatly attenuated risk from Lp(a) is that the mechanism of Lp(a)-induced atherosclerotic disease is less impacted by environment than genetics.[22] Potential mechanisms by which Lp(a) mediates atherosclerotic disease is as a preferential carrier of apolipoprotein B-associated oxidized phospholipids and autotaxins, which also may be driven by genetics.[22-26]

Lp(a) is an acute phase reactant that may increase in times of inflammation. Through this mechanism chronic stressors from SDOH could have been expected to impact Lp(a) levels.[12] However, we did not observe that SDOH score correlated with Lp(a) levels. There was, however, an observed, albeit small impact of LS7 score on Lp(a) levels, which is likely not clinically relevant. This could be because LS7 points are given for lower cholesterol levels, thus there could be collinearity (although post hoc testing (not shown) did not reveal high collinearity between LS7 or non-HDL-C and Lp(a)). Also, bariatric surgery or lower body mass index has correlated in some studies with lower Lp(a) level,[27,28] although this observation is inconsistent.[29,30] Lastly, increased healthy lifestyle may have anti-inflammatory impacts that could impact Lp(a) level.[31]

Even after accounting for many factors, Lp(a) remained associated with MI. This was observed when tested as a linear association and again after matching cases to controls based on Lp(a) as a categorical variable. Our matching analysis achieved excellent balance between cases and controls, with the only unbalanced factors as non-HDL-C, which differed by 3 mg/dL and we do not expect to account for a large difference in associated outcomes. In this matching analysis, our results were consistent with prior studies,[1] Lp(a) ≥50 mg/dL had a medium effect size on risk for MI, which was higher at levels ≥100 mg/dL. This was similar between cohorts. In a meta-analysis of studies, an Lp(a) of 48 mg/dL had a HR of about 1.1 to 1.2 and a level of 96 mg/dL or

CENTRAL ILLUSTRATION **Impact of Social Determinants of Health and Lifestyle on Association Between Lipoprotein(a) and Cardiovascular Events**



Brandt EJ, et al. JACC Adv. 2024;3(7):101016.

(A) Event-free survival in the ARIC study by lipoprotein(a) level. (Top graph) Compared to Lp(a) <50 mg/dL, final adjusted association with myocardial infarction After coarsened exact matching was HR: 1.14 ($P = 0.004$) for Lp(a) >50 mg/dL to <100 mg/dL and 1.37 ($P < 0.001$) for Lp(a) >100 mg/dL. (Bottom graph) Compared to Lp(a) <50 mg/dL, final adjusted association with stroke After coarsened exact matching was HR: 1.16 ($P = 0.01$) for Lp(a) >50 mg/dL to <100 mg/dL and 1.27 ($P = 0.02$) for Lp(a) >100 mg/dL. (B) Event-free survival in MESA by Lipoprotein(a) level. (Top graph) Compared to Lp(a) <50 mg/dL, final adjusted association with myocardial infarction After coarsened exact matching was HR 1.24 ($P = 0.06$) for Lp(a) >50 mg/dL to <100 mg/dL and 1.57 ($P = 0.008$) for Lp(a) >100 mg/dL. (Bottom graph) Compared to Lp(a) <50 mg/dL, final adjusted association with stroke After coarsened exact matching was HR: 1.21 ($P = 0.25$) for Lp(a) >50 mg/dL to <100 mg/dL and 0.76 ($P = 0.40$) for Lp(a) >100 mg/dL. HDL-C = high-density lipoprotein-cholesterol; Lp(a) = lipoprotein(a).

above a HR of about 1.3.[32] Increased risk at level of ≥50 mg/dL then ≥100 mg/dL were less consistent in the context of stroke wherein Lp(a) is associated with stroke in ARIC but not MESA. Similar to MI in ARIC, there was a stepwise increase in effect size at higher Lp(a) levels, which was a lower effect size than that observed in MI. However, the associations in MESA were absent. Prior studies testing the association between Lp(a) and stroke have been variable, with 1 meta-analysis suggesting that the impact of Lp(a) on increased risk for stroke may be more likely among cohorts ≤55 years old.[33]

TABLE 9 Sequential Multivariable Cox Proportional Hazards Regression for Myocardial Infarction in ARIC and MESA After Coarsened Exact Matching

	Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
ARIC (n = 14,010)									
Age (per year)	1.04	1.04–1.05	<0.001	1.04	1.03–1.05	<0.001	1.04	1.03–1.04	<0.001
Male	1.35	1.27–1.45	<0.001	1.34	1.26–1.44	<0.001	1.35	1.26–1.44	<0.001
Race and ethnicity	-	-	-	-	-	-	-	-	-
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.17	1.09–1.25	<0.001	1.08	1.01–1.17	0.03	0.93	0.86–1.00	0.06
Non-HDL-C (per 25-mg/dL increase)	1.14	1.12–1.16	<0.001	1.14	1.12–1.16	<0.001	1.08	1.05–1.10	<0.001
Lipoprotein(a)	-	-	-	-	-	-	-	-	-
0 to <50 mg/dL	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥50 to <100 mg/dL	1.14	1.05–1.25	0.003	1.14	1.05–1.25	0.002	1.14	1.04–1.24	0.004
≥100 mg/dL	1.43	1.23–1.66	<0.001	1.42	1.23–1.65	<0.001	1.37	1.18–1.59	<0.001
SDOH score (per 1-point increase)	-	-		1.08	1.04–1.11	<0.001	1.03	1.00–1.06	0.05
Life's Simple 7 score (per 1-point increase)	-	-		-	-		0.88	0.87–0.90	<0.001
MESA (n = 5,575)									
Age (per year)	1.04	1.03. 1.05	<0.001	1.03	1.03. 1.04	<0.001	1.03	1.02. 1.04	<0.001
Male	1.92	1.61–2.30	<0.001	2.05	1.71–2.45	<0.001	2.02	1.68–2.42	<0.001
Race and ethnicity	-	-	-	-	-	-	-	-	-
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	0.97	0.79–1.19	0.77	0.89	0.72–1.10	0.27	0.78	0.63–0.96	0.02
Non-Hispanic Chinese	0.64	0.40–1.04	0.07	0.58	0.36–0.95	0.03	0.66	0.40–1.07	0.09
Hispanic	0.93	0.71–1.22	0.60	0.74	0.55–1.00	0.05	0.71	0.52–0.96	0.03
Non-HDL-C (per 25-mg/dL increase)	1.06	0.98–1.14	0.14	1.06	0.98–1.14	0.14	1.01	0.93–1.09	0.84
Lipoprotein(a)	-	-	-	-	-	-	-	-	-
0 to <50 mg/dL	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥50 to <100 mg/dL	1.25	1.00–1.57	0.048	1.26	1.01–1.58	0.04	1.24	0.99–1.56	0.06
≥100 mg/dL	1.60	1.14–2.23	0.006	1.59	1.13 2.22	0.007	1.57	1.12 2.19	0.008
SDOH score (per 1-point increase)	-	-	-	1.13	1.06–1.20	<0.001	1.11	1.04–1.18	0.001
Life's Simple 7 score (per 1-point increase)	-	-	-	-	-	-	0.87	0.83–0.91	<0.001

Abbreviations as in Table 1.

Our study has important clinical implications in the context that both SDOH and LS7 were consistent associated with risk for ASCVD. This consistency suggests that SDOH and lifestyle factors should continue to be the focus of clinicians. Health systems should continue to increase screening for SDOH and create pathways for managing SDOH when they are identified.[3,34,35]

Furthermore, when SDOH and LS7 were added to the model, the association between non-Hispanic Black or Hispanic participants and CVD events decreased or inverted. This suggests that non-Hispanic Black or Hispanic participants' SDOH and LS7 scores impact associations between race and ethnicity with MI or stroke. Addressing SDOH and lifestyle factors can therefore be seen as a chance for healthy equity in managing risk for ASCVD.[3,34,36] Future studies looking at associations between race and ethnicity and events should recognize our observations and that differences across race and ethnicity are driven by nonbiologic factors (eg, structural inequities).[9,37,38] These studies should specifically seek to understand whether SDOH and lifestyle factors have effect modification and mediating effects.

Lastly, we observed that when SDOH and lifestyle factors were included in the models, the effect size for the association between non-HDL-C and outcomes was reduced or eliminated. This emphasizes recent data that suggest Lp(a) may be more atherogenic than low-density lipoprotein-cholesterol.[39] The largest shift occurred when the LS7 score was added. This suggests that some of the association between atherogenic lipids and risk for ASCVD is driven by lifestyle factors. The LS7 score includes a lipid component, thus there could be collinearity of variables in the model. Lastly, the effect size of non-HDL-C on outcomes could have

TABLE 10 Sequential Multivariable Cox Proportional Hazards Regression for Stroke in ARIC and MESA After Coarsened Exact Matching

	Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
ARIC (n = 13,989)									
Age (per year)	1.04	1.03,1.05	<0.001	1.04	1.03-1.04	<0.001	1.03	1.03-1.04	<0.001
Male	1.05	0.96-1.16	0.27	1.04	0.95 1.14	0.414	1.04	0.95-1.15	0.38
Race and ethnicity	-	-	-	-	-	-	-	-	-
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.64	1.50-1.80	<0.001	1.43	1.30-1.48	<0.001	1.24	1.12-1.38	0.003
Non-HDL-C (per 25-mg/dL increase)	1.04	1.01-1.06	0.002	1.04	1.01-1.06	0.005	0.98	0.95-1.01	0.15
Lipoprotein(a)	-	-	-	-	-	-	-	-	-
0 to <50 mg/dL	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥50 to <100 mg/dL	1.17	1.04-1.31	0.01	1.17	1.04-1.32	0.008	1.16	1.04-1.31	0.01
≥100 mg/dL	1.33	1.09-1.62	0.005	1.31	1.07-1.60	0.008	1.27	1.04-1.55	0.02
SDOH score (per 1-point increase)	-	-	-	1.15	1.10-1.20	<0.001	1.10	1.05-1.15	<0.001
Life's Simple 7 score (per 1-point increase)	-	-	-	-	-	-	0.89	0.87-0.91	<0.001
MESA (n = 5,573)									
Age (per year)	1.06	1.04-1.07	<0.001	1.05	1.04-1.07	<0.001	1.05	1.04-1.07	<0.001
Male	1.14	0.88-1.49	0.33	1.19	0.91-1.56	0.20	1.18	0.90-1.55	0.24
Race and ethnicity	-	-	-	-	-	-	-	-	-
Non-Hispanic White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-Hispanic Black	1.17	0.86-1.60	0.31	1.11	0.81-1.52	0.51	0.96	0.70-1.31	0.78
Non-Hispanic Chinese	0.77	0.38-1.58	0.48	0.72	0.35-1.49	0.38	0.82	0.40-1.71	0.60
Hispanic	1.49	1.02-2.17	0.04	1.28	0.84-1.94	0.25	1.21	0.80-1.84	0.37
Non-HDL-C (per 25-mg/dL increase)	1.11	1.01-1.21	0.04	1.10	1.01-1.21	0.04	1.05	0.95-1.16	0.32
Lipoprotein(a)	-	-	-	-	-	-	-	-	-
0 to <50 mg/dL	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
≥50 to <100 mg/dL	1.23	0.89-1.70	0.22	1.23	0.89-1.70	0.21	1.21	0.88-1.67	0.25
≥100 mg/dL	0.78	0.41-1.48	0.45	0.78	0.41-1.48	0.44	0.76	0.40-1.44	0.40
SDOH score (per 1-point increase)	-	-	-	1.08	0.99-1.15	0.09	1.05	0.96-1.16	0.26
Life's Simple 7 score (per 1-point increase)	-	-	-	-	-	-	0.86	0.80-0.92	<0.001

Abbreviations as in Table 1.

been reduced in the context that we were unable to track therapies introduced over time. If those with higher non-HDL-C were more likely to be treated with lipid-lowering therapies then this could confound this association.

STUDY STRENGTHS. A strength of this study is that we used 2 large cohorts with long follow-up periods and many of the observations were similar between cohorts. Additionally, we used multiple methods and yielded similar results, including matching cases of Lp(a) ≥50 mg/dL to controls that were similar on many factors.

STUDY LIMITATIONS. There may be additional SDOH that were not measured in either cohort. Several of the items are self-reported, which could be subject to social desirability bias and incomplete data collection. The generalized structural equation model to determine mediation was unable to consider competing risk, although all other models did consider competing risk. Lastly, these data are observational, and further work needs to be done to understand the mechanisms by which SDOH and lifestyle alter the biochemistry of Lp(a).

CONCLUSIONS

Our findings support that Lp(a) is an independent risk factor for cardiovascular events and that this associated risk is not greatly impacted by SDOH or lifestyle factors. In addition, SDOH and lifestyle factors strongly associate with risk for ASCVD, which may explain some of the association between race and ethnicity or non-HDL-C with MI or stroke. This impact of SDOH and LS7 should be considered when

designing and interpreting observational and clinical studies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Lp(a) is an independent risk factor for cardiovascular disease. In addition, SDOH and lifestyle are strongly associated with cardiovascular risk. However, the risk associated with Lp(a) and cardiovascular outcomes is not significantly attenuated after considering SDOH and lifestyle factors.

TRANSLATIONAL OUTLOOK: Additional work is need to understand the mechanisms by which Lp(a) leads to atherosclerosis. Understand more mechanism by which Lp(a) leads to atherosclerosis may increase understanding if the risk associated with Lp(a) risk might be mitigated through changes to environmental exposures.

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