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Lipoprotein(a) Levels and the Risk of Myocardial Infarction Among 7 Ethnic Groups

Editorial, see p 1493

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BACKGROUND: Lipoprotein(a) [Lp(a)] levels predict the risk of myocardial infarction (MI) in populations of European ancestry; however, few data are available for other ethnic groups. Furthermore, differences in isoform size distribution and the associated Lp(a) concentrations have not fully been characterized between ethnic groups.

METHODS: We studied 6086 cases of first MI and 6857 controls from the INTERHEART study that were stratified by ethnicity and adjusted for age and sex. A total of 775 Africans, 4443 Chinese, 1352 Arabs, 1856 Europeans, 1469 Latin Americans, 1829 South Asians, and 1221 Southeast Asians were included in the study. Lp(a) concentration was measured in each participant using an assay that was insensitive to isoform size, with isoform size being assessed by Western blot in a subset of 4219 participants.

RESULTS: Variations in Lp(a) concentrations and isoform size distributions were observed between populations, with Africans having the highest Lp(a) concentration (median=27.2 mg/dL) and smallest isoform size (median=24 kringle IV repeats). Chinese samples had the lowest concentration (median=7.8 mg/dL) and largest isoform sizes (median=28). Overall, high Lp(a) concentrations (>50 mg/dL) were associated with an increased risk of MI (odds ratio, 1.48; 95% CI, 1.32–1.67; $P<0.001$). The association was independent of established MI risk factors, including diabetes mellitus, smoking, high blood pressure, and apolipoprotein B and A ratio. An inverse association was observed between isoform size and Lp(a) concentration, which was consistent across ethnic groups. Larger isoforms tended to be associated with a lower risk of MI, but this relationship was not present after adjustment for concentration. Consistent with variations in Lp(a) concentration across populations, the population-attributable risk of high Lp(a) for MI varied from 0% in Africans to 9.5% in South Asians.

CONCLUSIONS: Lp(a) concentration and isoform size varied markedly between ethnic groups. Higher Lp(a) concentrations were associated with an increased risk of MI and carried an especially high population burden in South Asians and Latin Americans. Isoform size was inversely associated with Lp(a) concentration, but did not significantly contribute to risk.

Key Words: apolipoprotein(a) ■ biomarkers ■ lipoprotein(a) ■ myocardial infarction ■ risk assessment

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Clinical Perspective

What Is New?

- This study evaluated variations in lipoprotein(a) [Lp(a)] concentrations and isoform sizes across multiple ethnic groups, including African, Arab, Chinese, European, Latin American, South Asian, and Southeast Asian ancestries.
- High Lp(a) concentrations (>50 mg/dL) were associated with significantly increased risk of myocardial infarction in all populations except Arabs and Africans.
- The risk of myocardial infarction increased with increasing Lp(a) concentrations, independent of Lp(a) isoform size.
- This study confirmed the high population-attributable risk of myocardial infarction in the South Asian and Latin American populations, which had been previously hypothesized, but not confirmed.

What Are the Clinical Implications?

- This study supports the clinical use of Lp(a) concentrations, but not isoform size, as a marker of myocardial infarction risk in diverse populations, other than Africans and Arabs.
- The effects of clinical interventions that reduce Lp(a) in South Asians and Latin Americans should be investigated, given the high population-attributable risk.
- Therapeutic agents that target Lp(a) should continue to be evaluated for clinical use.
- Our results suggest the use of a single Lp(a) concentration threshold across ethnic groups might be adequate.

Associations of lipoprotein(a) [Lp(a)] levels with the risk of myocardial infarction (MI) have been demonstrated in populations of European ancestry.[1–7] Despite guidelines recommending its use for risk stratification,[8] Lp(a) is not routinely measured in clinical practice. Several factors explain the modest clinical uptake. First, marked differences in the mean Lp(a) levels between ethnic groups exist.[9–16] Second, heterogeneity in the strength of associations of elevated Lp(a) with MI have been suggested between populations.[4,7,16–24] Third, Lp(a) concentrations and isoform sizes vary, and the role of apolipoprotein (*apo*) *(a)* size polymorphisms on MI risk is unclear.[25–27] Fourth, the lack of assay standardization, and the sensitivity of most assays to Lp(a) size, make comparisons between studies challenging.[28] We address these issues by measuring Lp(a) concentrations using an isoform-insensitive assay concurrently with isoform size in participants enrolled in a large, case–control study of MI conducted in all continents of the world.

Plasma Lp(a) levels vary greatly across ethnic groups, and previous studies used different analytical methods, which hampered their ability to directly compare whether the association of Lp(a) with MI varied between ethnic groups. For instance, median Lp(a) concentrations have been reported to be up to 3 times higher in Africans compared with Europeans.[29–31] Such differences are also difficult to disentangle from differences in Lp(a) isoform size that stem from variations in *apo(a)* kringle IV (KIV) type 2 copy numbers, which in turn are strongly inversely correlated with Lp(a) concentration. Estimates of coronary artery disease risk associated with Lp(a) levels have similarly yielded inconsistent results between populations. Although higher Lp(a) levels correlate well with the rates of coronary artery disease in many populations, such as South Asians,[18–23] high Lp(a) levels in black Africans appear to confer a lesser coronary artery disease risk than in South Asians or Europeans.[24,32,33] These discrepancies are hypothesized to relate to the complex relationships between isoform size, Lp(a) levels, and coronary artery disease risk.

As current recommendations for the clinical use of Lp(a) are based on data derived primarily from Europeans, we characterized the contribution of Lp(a) levels and isoform size to MI risk in 6 additional ethnic populations. We first established reference intervals for plasma Lp(a) concentrations and isoform size in healthy controls of African, Arab, Chinese, European, Latin American, South Asian, and Southeast Asian descent. We then determined the risk of MI conferred by elevated Lp(a) levels overall, and within each population using the clinically accepted threshold of 50 mg/dL. Finally, we assessed whether apo(a) isoform size contributed to MI risk after accounting for Lp(a) concentration.

METHODS

The data, analytic methods, and study materials will not be made publicly available to other researchers for purposes of reproducing the results or replicating the procedure because consent to participate in this study did not include public dissemination of patient data.

INTERHEART Study

The design and results of the INTERHEART study have been described previously.[34] The INTERHEART study was approved by the appropriate regulatory and ethics committees in all participating countries and centers. All participants provided informed consent before participation in the study.[34]

INTERHEART is a large, international, standardized, case–control study designed to determine the association between various risk factors and nonfatal acute MI in a total of 15 152 cases and 14 820 controls from 52 countries. Cases were defined as those who were admitted to a coronary care unit or equivalent cardiology ward within 24 hours of clinical characteristics of new MI. Controls were stratified by ethnicity and adjusted for age and sex, had no previous diagnosis of heart disease, and were recruited from hospital- or

Table 1. Patient Population Characteristics

	Africans		Arabs		Chinese	
	Controls	Cases	Controls	Cases	Controls	Cases
N	481	294	824	528	2407	2034
Age, y (SD)	52.52 (11.73)	54.44 (11.44)	51.2 (10.44)	52.94 (10.31)	59.81 (11.34)	61.34 (11.57)
Sex (male)*	63.0	63.0	88.0	87.0	69.0	71.0
Diabetes mellitus*	9.0	26.0	9.0	23.0	3.0	12.0
High blood pressure*	21.0	46.0	14.0	22.0	23.0	38.0
Current smoking*	41.0	54.0	32.0	54.0	29.0	44.0
Waist-to-hip ratio (SD)	0.91 (0.08)	0.94 (0.07)	0.93 (0.07)	0.95 (0.08)	0.87 (0.08)	0.88 (0.08)
Median apo B (5th and 95th percentile), g/L	0.86 (0.47–1.33)	0.97 (0.56–1.44)	0.98 (0.62–1.43)	1.04 (0.67–1.55)	0.83 (0.52–1.21)	0.83 (0.53–1.29)
Median apo A (5th and 95th percentile), g/L	1.19 (0.77–1.74)	1.10 (0.72–1.50)	1.15 (0.87–1.49)	1.03 (0.76–1.40)	1.23 (0.81–1.75)	1.14 (0.79–1.59)
Median Lp(a) (5th and 95th percentile), mg/dL	27.2 (3.3–102.4)	27.11 (4.1–110.6)	15.3 (2.0–66.8)	18.1 (2.0–82.6)	7.8 (1.9–39.9)	9.8 (2.3–53.4)
Median isoform size (5th and 95th percentile)	24 (14.8–30.0) N=200	24 (15–30.2) N=200	23 (14.0–30.0) N=200	23 (14.0–31.3) N=200	28 (15.0–32.0) N=918	28 (15.0–32.0) N=901
Lp(a) concentration >50 mg/dL*	27.0	26.0	12.0	15.0	3.0	6.0

(*Continued*)

community-based settings. Blood samples were obtained from all participants in the current analysis, centrifuged within 2 h, separated, and immediately frozen at –20°C or –70°C, dependent on the availability of specific freezers. Samples were periodically shipped in nitrogen vapor tanks for storage at –160°C in nitrogen vapor in Hamilton, Canada, except for samples from China, which were shipped, stored, and analyzed in Beijing, China. Immunoturbidimetric assays were used to measure apo concentrations (Roche/Hitachi 917 analyzer with Tina-quant apo B version 2 and apo A1 version 2 kits; Roche Diagnostics, Mannheim, Germany). All study participants consented to analysis of blood samples. Individuals with adequate biological samples were chosen to maximize representation of major ethnic groups (African, Arab, Chinese, European, Latin American, and South and Southeast Asian) while preserving the original case–control match as much as possible.

Lp(a) Plasma Measurement

Consistent with other similar studies,[35–37] Lp(a) concentration was measured in plasma using an immunoassay from Denka Seiken, which included a 5-point calibrator that minimizes the effects of apo(a) isoform size on corresponding measurements.[35] The analytic coefficient of variation for this assay was <4% at all 6 concentrations tested with control material or serum pools (>20 replicates at each level).

Apo(a) KIV-2 Copy Number Measurements

The size of apo(a) isoforms, reported as the number of KIV domains in apo(a), was determined using high-resolution SDS-agarose gel electrophoresis on 1.0% gels followed by immunoblotting essentially as previously described.[38,39] Size standards for the gels were prepared using a mixture of purified recombinant apo(a) proteins ranging in number of KIV domains from 12 to 33.[40] For analyses, the isoform used was the predominant isoform.

Statistical Analysis

Differences in Lp(a) concentration and apo(a) isoform size in healthy controls were assessed using nonparametric Wilcoxon rank-sum tests. Age, sex, apo B, and apo A1 were included as covariates in regression models adjusting for risk factors. In particular, apo B was added as each apo(a) molecule is covalently bound to a single apo B molecule in blood. Associations with MI were tested using logistic regression. Power calculations were performed in R with 50 000 simulations and using logistic regression models, assuming a 2-sided *P*-value threshold of 0.05. Comparisons of the associations between Lp(a) with MI were first analyzed separately in each ethnic group (African, Arab, Chinese, European, Latin American, South Asian, and Southeast Asian), and these results were then combined using fixed-effects models. Performing separate analyses in each group followed by meta-analyses allowed us to more accurately model the effects of confounders in each group, compared with that which would have been achievable with a single analysis adjusting for ethnicity. For subgroup analyses of the associations between Lp(a) levels and MI, the data were adjusted for age, sex (except when stratifying for sex), ethnicity, apo A, and apo B.

We used splines to further explore the association of Lp(a) concentrations as a function of isoform size. Spline analyses were performed using the *gam* function of the *mccv* R package with default parameters. Within this algorithm, the degree of smoothness of model terms was estimated as part of the fitting process. Smooth terms were represented using penalized regression splines (or similar smoothers) with smoothing parameters selected by generalized cross-validation. Statistical

Table 1. Continued

Europeans		Latin Americans		South Asians		Southeast Asians	
Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases
905	951	738	731	881	948	621	600
60.37 (11.88)	60.63 (11.96)	59.13 (12.17)	59.37 (12.17)	50.44 (11.08)	51.24 (11.04)	57.23 (11.06)	57.56 (11.23)
71.0	70.0	75.0	75.0	90.0	90.0	81.0	83.0
7.0	15.0	11.0	19.0	8.0	20.0	9.0	24.0
34.0	43.0	29.0	50.0	13.0	29.0	17.0	42.0
27.0	42.0	18.0	40.0	31.0	49.0	29.0	49.0
0.92 (0.09)	0.94 (0.09)	0.93 (0.08)	0.96 (0.08)	0.3 (0.07)	0.95 (0.07)	0.9 (0.07)	0.94 (0.07)
0.95 (0.64–1.40)	1.01 (0.61–1.50)	0.95 (0.53–1.38)	0.99 (0.61–1.47)	0.92 (0.58–1.34)	0.97 (0.62–1.46)	0.96 (0.63–1.36)	1.03 (0.65–1.50)
1.26 (0.86–1.75)	1.19 (0.86–1.63)	1.18 (0.77–1.64)	1.07 (0.74–1.45)	1.07 (0.78–1.50)	1.02 (0.72–1.40)	1.29 (0.88–1.73)	1.10 (0.79–1.52)
9.6 (2.0–89.3)	11.5 (2.0–99.1)	11.5 (2.0–77.2)	14.7 (2.0–100.0)	13.8 (2.1–61.5)	18.9 (3.2–88.2)	10.2 (2.0–53.6)	12.9 (2.4–74.2)
25 (15.0–31.5) N=200	25 (16.0–31.0) N=200	27 (14.7–32.0) N=200	24 (15.0–32.0) N=200	26 (14.8–32.0) N=200	25 (15.8–31.3) N=200	28 (15.0–32.0) N=200	28 (15.0–33.0) N=200
14.0	18.0	14.0	21.0	9.0	18.0	7.0	13.0

Apo indicates apolipoprotein; and Lp(a), lipoprotein(a).
*Reported as a percentage.

details of the method have been reported previously.[41,42] Spline analyses (ie, generalized additive models) were adjusted for age, sex, apo B, apo A1, and ethnic group in all analyses.

The population-attributable risk (PAR) was used to estimate the risk of MI in 7 ethnic populations that can be attributed to high Lp(a) levels, adjusting for age, gender, apo B, and apo A1. To calculate PAR, the R (version 3.0.1) *attribrisk* function was used to enable modeling with any number of confounders/adjustors and exposures—which can be discrete or continuous—and allowed for flexibility in defining target values. PAR was truncated at zero in cases higher Lp(a) was associated to lower risk.

Not all analyses were performed with the same number of controls because some controls were removed from specific analyses due to their lack of necessary data. All analyses were performed in R, version 3.0.1.

RESULTS

Lp(a) Concentration and Isoform Size in Healthy Individuals

Differences in Lp(a) concentrations between healthy individuals from diverse ancestries were observed (Table 1 and Figure I in the online-only Data Supplement), with Africans having markedly higher concentrations in comparison with other populations ($P<10^{-15}$ for all pairwise comparisons). The median concentration was 27.2 mg/dL in Africans (95% percentile range, 2.2–128.5 mg/dL), compared with 7.8 mg/dL (95% percentile range, 1.5–55.4 mg/dL) in Chinese individuals, the population with lowest concentrations. Differences in isoform sizes were also observed, with Chinese and Southeast Asians having higher isoform sizes than other populations ($P<0.0001$ and $P\leq0.002$, respectively, for all pairwise comparisons). The median isoform size in Chinese and Southeast Asians was 28 (95% percentile, 15–32), whereas it was 23 (95% percentile, 14–30) and 24 (95% percentile, 14.8–30) in Arabs and Africans, respectively (populations with the smallest isoforms). A strong inverse relationship was observed between median isoform size and concentration (Figure IIa in the online-only Data Supplement). The inverse relationship between isoform size and concentration was also observed within each individual ethnic group (r^2 from 0.23–0.40 [rho from 0.48–0.63]; $P<10^{-15}$ in all populations; Figure IIb in the online-only Data Supplement). Lp(a) centile distributions for all ethnic groups are shown in Table I in the online-only Data Supplement.

Association of Lp(a) Concentrations With Myocardial Infarction

Using the clinically accepted Lp(a) concentration threshold of 50 mg/dL, we tested for associations with MI, after adjusting for age, sex, apo B, and apo A1 (Figure 1; refer to Figure III in the online-only Data Supplement for analyses where Lp(a) was treated as a continuous variable). The odds ratio for MI was 1.48 (95% CI, 1.32–1.67; $P=7.1\times10^{-11}$) for high versus low concentrations in the overall INTERHEART population. High Lp(a) concentrations were associated with a statistically significant increased risk of MI in all populations except Arabs and Africans, where a directionally inverse but nonsignificant association was observed (odds ratio [OR], 0.92;

95% CI, 0.65–1.32). However, those were also the 2 smallest groups tested and the confidence limits of the estimates within these subgroups overlap with the confidence limits of the overall estimate. To provide a comprehensive assessment of the effects of Lp(a) concentration on MI, we also tested for associations between Lp(a) and MI using Lp(a) cut-offs of 30, 40, 60, and 70 mg/dL (refer to Figure IV in the online-only Data Supplement). Consistent results were obtained regardless of Lp(a) cut-off, and all analyses were performed using a standard cut-off of 50 mg/dL. Similar associations with MI were also obtained after fully adjusting for INTERHEART factors, where high Lp(a) concentrations were associated with a statistically significant increased risk of MI in all populations except Arabs, Africans, and Europeans (Figure V in the online-only Data Supplement). To account for differences in the number of controls between analyses—which was attributable to missing data mainly for low-density lipoprotein cholesterol, body mass index, and smoking status variables (5% to 10%)—we replaced low-density lipoprotein cholesterol with apo B to include additional controls (5393–5867). Analyses under the revised conditions yielded comparable results, where high Lp(a) concentrations were associated with a statistically significant increased risk of MI in all populations except Arabs and Africans (Figure VI in the online-only Data Supplement). We also performed imputation strategies using the Multivariate Imputation by Chained Equations (MICE) method (performed in R), which also yielded consistent results with those observed in the previous analyses (Figure VII in the online-only Data Supplement).

We tested the statistical power to detect an association between Lp(a) concentration and risk of MI in African participants given our sample size and the effect size reported in the ARIC study at a *P*-value threshold of 0.05.[43] Regarding the effect size, a prospective study of 3467 African Americans reported a hazard ratio of 1.11 per 1 SD increase in log-transformed Lp(a) for incident coronary heart disease.[43] A total of 294 African MI cases and 474 controls were included in our study, which resulted in only a 17% power to detect an association.

Significant heterogeneity was observed in risk estimates ($P_{heterogeneity}$=0.007) across populations and was attributable to the inclusion of Africans. When African cases were removed from the analysis, heterogeneity was nonsignificant (*P*=0.08), with an OR of 1.58 (95% CI, 1.39–1.79; $P=1.44\times10^{-12}$) in the combined data from the other ethnic groups. Heterogeneity was also nonsignificant when African cases were removed for Lp(a) concentrations of 30, 40, 60, and 70 mg/dL as well (Table II in the online-only Data Supplement). Although effect size was homogeneous in non-African populations, the prevalence of high Lp(a) varied widely across ethnic groups (Table 1). This observation suggests that the PAR should also vary. To explore this possibility, we calculated the PAR for MI in each group, adjusting for age, sex, apo B, and apo A1. The PAR varied from 0 in Africans to 0.095 in South Asians (Table 2). Similarly, after fully adjusting for INTERHEART factors, the PAR for MI in each group ranged from 0 in Africans to 0.094 in South Asians, and 0.098 in Latin Americans (Table III in the online-only Data Supplement). We also tested for effect modifications by clinical risk factors when apo A and apo B were treated as dichotomous (Figure 2) or continuous variables. After adjusting for 8 clinical risk factors, no significant (ie, *P*<0.05/8=0.006) interaction was observed under either scenario with sex, diabetes mellitus, family history, premature MI, smoking status, high blood pressure, apo B, or apo A1. Similarly, Lp(a) concentration was also independent of age and sex in a previous study.[44]

A spline analysis for the risk of MI as a function of $\log_2$ Lp(a) concentration or isoform size is presented in Figure 3. The risk of MI increased with increasing concentrations of Lp(a), independent of isoform size (Figure 3A and 3C). Conversely, the risk of MI tended to be reduced with increasing Lp(a) isoform size; however, this relationship was attenuated after adjusting for Lp(a) concentration (Figure 3B and 3D).

Isoform Size and Risk of Myocardial Infarction

We investigated whether the association between concentration and the risk of MI could be attributed to differ-

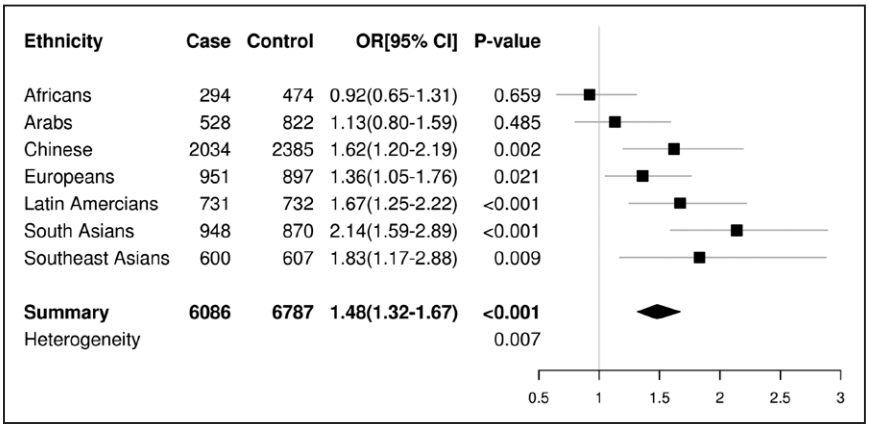

Figure 1. Association of high lipoprotein(a) [Lp(a)] concentrations with myocardial infarction.
Shown is a forest plot for association of high Lp(a) concentrations (defined as >50 mg/dL) and myocardial infarction in each ethnic group, after adjusting for age, sex, and apolipoprotein B and A. OR indicates odds ratio.

Table 2. Population-Attributable Risk of Myocardial Infarction in Individuals With High Lp(a) Concentrations (>50 mg/dL), for Each Ethnic Group

Ethnicity	Controls	Cases	PAR_1 [95% CI]*	PAR_2 [95% CI]†
Africans	474	294	0.000 [0.000–0.070]	0.000 [0.000–0.069]
Arabs	822	528	0.027 [0.000–0.076]	0.016 [0.000–0.061]
Chinese	2385	2034	0.027 [0.012–0.042]	0.023 [0.010–0.035]
Europeans	897	951	0.050 [0.020–0.079]	0.046 [0.007–0.086]
Latin Americans	732	731	0.087 [0.034–0.140]	0.084 [0.028–0.139]
South Asians	870	948	0.102 [0.070–0.134]	0.095 [0.051–0.138]
Southeast Asians	607	600	0.066 [0.036–0.097]	0.054 [0.028–0.080]

Apo indicates apolipoprotein; PAR, population-attributable risk; PAR_1, PAR model 1 (unadjusted); and PAR_2, PAR model 2 (adjusted for age, sex, apo A1, and apo B).

*Model unadjusted.

†Model adjusted for age, sex, apo A1, and apo B.

ences in isoform size. Depending on the number of KIV-2 repeats, we divided isoform size into 3 groups, including small (<22), medium (22–27), and large isoform size (22–27).[25,45] The association of log Lp(a) concentration (top versus the bottom two tertiles) with risk of MI remained unchanged before (odds ratio [OR]=1.22 per doubling of Lp(a) concentration; 95% CI, 1.07–1.40; *P*=0.004) and after (OR=1.20; 95% CI, 1.02–1.40; *P*=0.023) adjustment

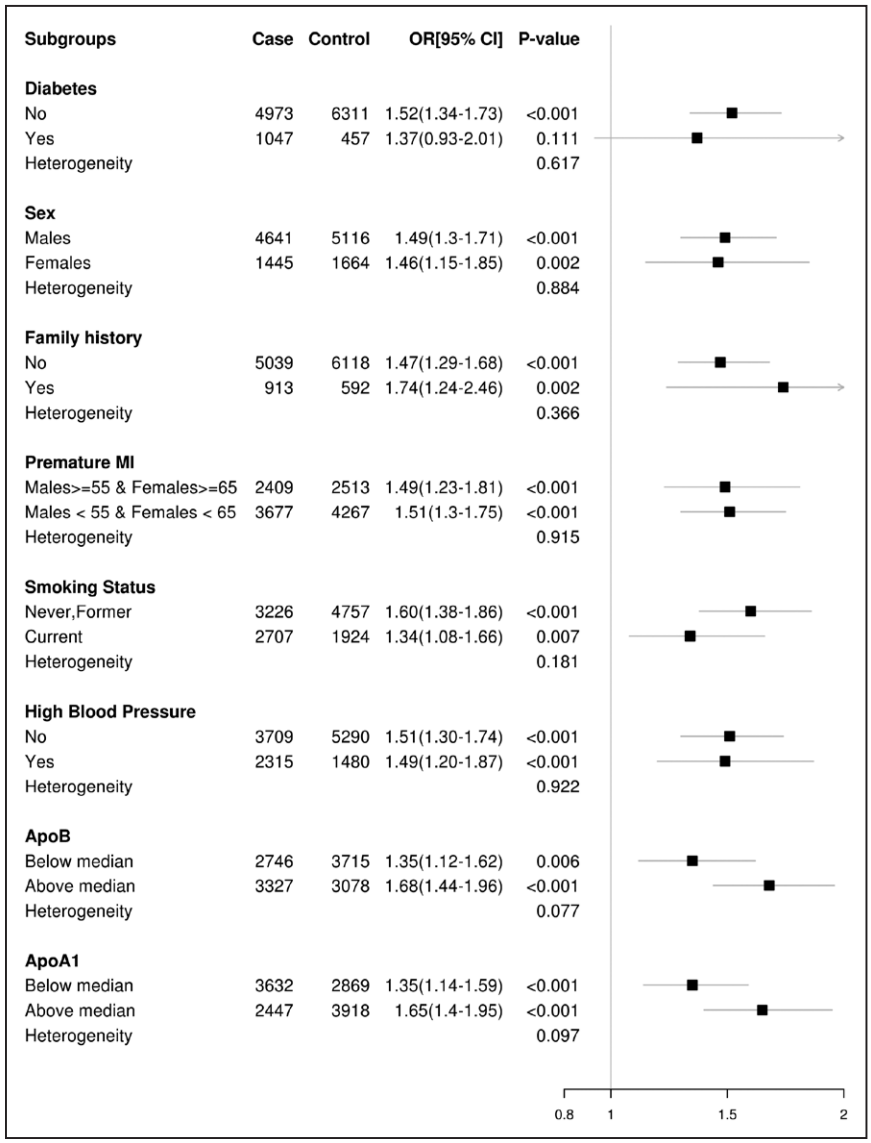

Figure 2. Subgroup analysis of associations between high lipoprotein(a) levels and myocardial infarction (MI), after adjusting for age, sex (except when stratifying for sex), ethnicity, and apolipoprotein (apo) B and A (as appropriate).
Ethnicity-specific medians were used for apo A and apo B. apo A and apo B were treated as dichotomous variables. OR indicates odds ratio.

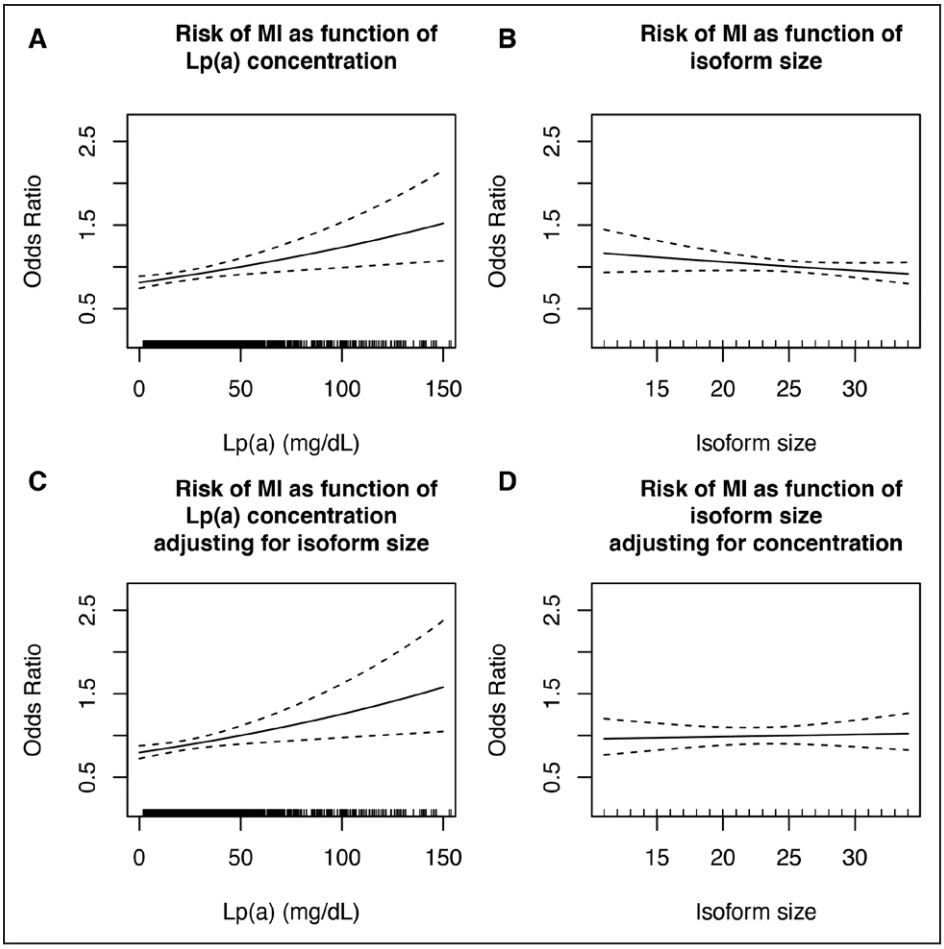

Figure 3. Spline analysis of myocardial infarction (MI) risk as a function of lipoprotein(a) [Lp(a)] concentration or isoform size (determined by Western blot). Lp(a) concentration (**A**), isoform size (**B**), or both (**C** and **D**) were included as independent variables in a spline logistic regression model using MI as the dependent variable. All analyses were adjusted for age, sex, apolipoprotein B and A, and ethnic group.

for isoform size tertiles (Figure 4). We also compared the first tertile and the upper 80th and 90th percentiles (Figures VIII and IX in the online-only Data Supplement, respectively) and found no difference in association, compared with that observed in Figure 4.

As expected from the inverse association between isoform size (smallest versus largest 2 tertiles) and concentration, larger isoform sizes showed a trend toward lower risk of MI (Figure 4; OR=0.91 per unit; 95% CI, 0.80–1.05; P>0.05). However, the trend became null after adjustment for log Lp(a) concentration (OR=1.00 per copy; 95% CI, 0.85–1.17). No significant heterogeneity across ethnic groups was observed either before or after adjustment for concentration ($P_{heterogeneity}$>0.05).

DISCUSSION

We conducted a comprehensive study of Lp(a), including measurements of concentrations and isoform size in 12 945 INTERHEART participants of African, Arab, Chinese, European, Latin American, South Asian, and Southeast Asian ancestry. Our results demonstrated significant differences in Lp(a) concentrations and isoform size between ethnic groups. Lp(a) concentrations were the lowest and isoform size the largest in Chinese and Southeast Asian cases, whereas concentrations were highest and isoform size the smallest in African and Arab cases. Despite the differences in Lp(a) concentrations between ethnic groups, high Lp(a) concentration (defined as >50 mg/dL) was associated with MI overall (OR=1.48), and in different ethnic subgroups with a range of mean Lp(a) levels, except Arabs (with relatively low mean levels) and Africans (with the highest levels). However, these 2 ethnic groups had the smallest sample size in this study. Collectively, these observations point toward a role for Lp(a) concentration in MI risk stratification, and to important differences with respect to population distribution in Lp(a) concentration. The prevalence of Lp(a) >50 mg/dL in healthy controls varied from 3.4% in Chinese samples to 26.6% in African samples, highlighting differences in the population burden of high Lp(a). The PAR correspondingly varied from 0% in Africans to 9.5% in South Asians.

Our results are consistent with previous studies conducted in Europeans. First, the risk of MI associated with high Lp(a) concentrations is consistent with previous reports.[31] Second, studies conducted in Europeans reported that isoform size did not contribute to MI risk after adjusting for Lp(a) concentrations.[4,25] Those data also agree with the results from INTERHEART Europeans, although

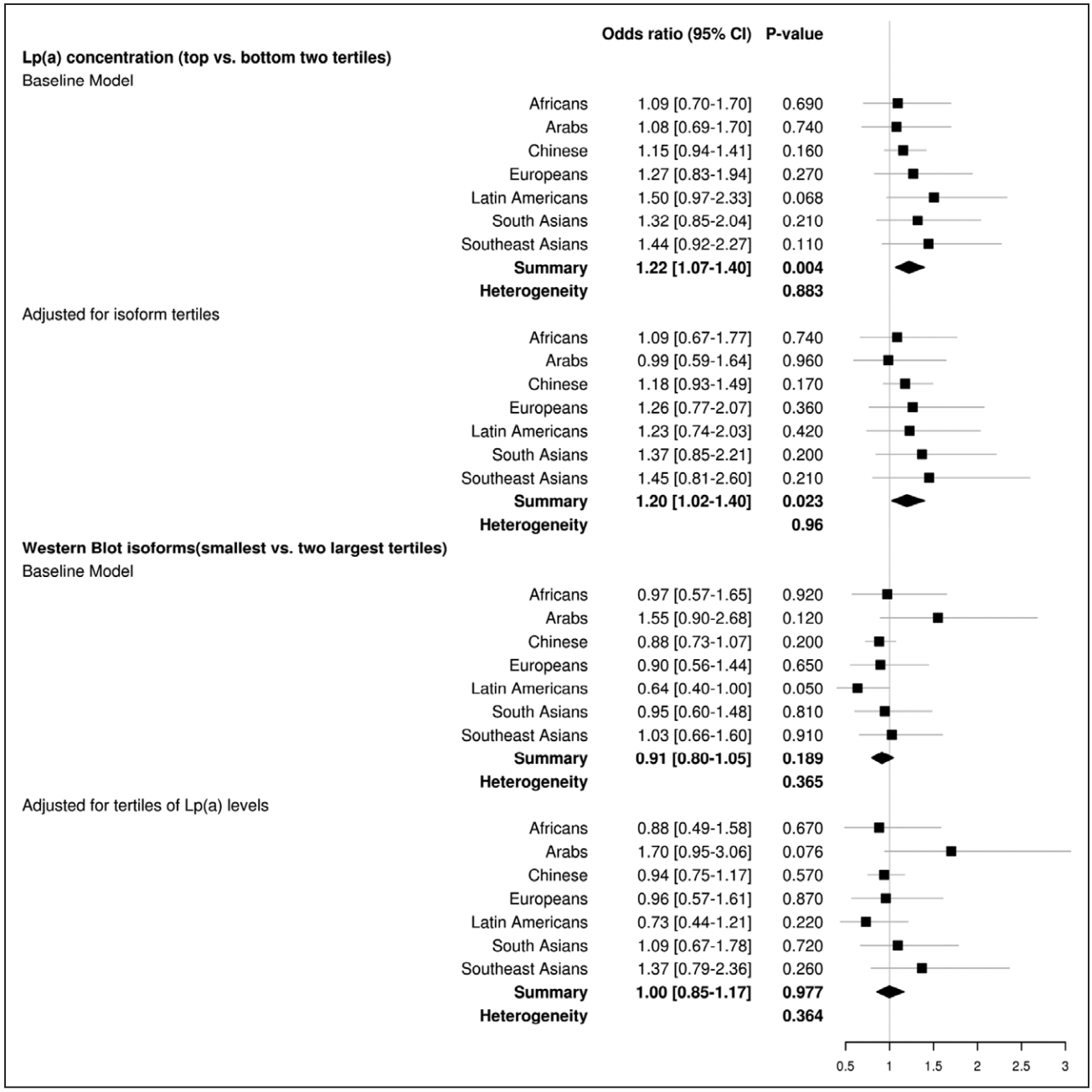

Figure 4. Association of lipoprotein(a) [Lp(a)] concentration (top) and isoform size (bottom) with myocardial infarction (MI).
Association of log Lp(a) concentration (**top** vs **bottom** 2 tertiles) and isoform size (smallest vs largest 2 tertiles), as determined by Western blot (smallest [<22] vs largest [>27]), with MI stratified by ethnic group and adjusted for age, sex, and apolipoprotein B and A.

our sample size with isoform determination was small. A recent report observed an independent contribution of concentration and isoform size in South Asians.[27] We did not replicate this observation; however, the number of South Asian participants with both isoform and concentration measurements was limited in our study. Nonetheless, no such effect was observed in the larger (n=1819) Chinese population included in our study.

Neither Lp(a) concentrations nor isoform size was associated with MI in Africans. Although these results are consistent with previous studies in African Americans,[24,46] others have reported conflicting results.[9,43] In particular, a prospective study of 3467 African Americans reported a hazard ratio of 1.11 per 1 SD increase in log-transformed Lp(a) for incident coronary heart disease.[43] The power to detect such an association was only 17% in our study, given the limited number of African participants compared with other INTERHEART populations. Genetic differences between Africans and African Americans could also explain these results, where 30% of African Americans are expected to carry at least 1 *LPA* allele of European origin.[47]

Our study has several strengths. The use of standardized questionnaires and the central collection of biolog-

ical specimens enabled the comparison of results across populations. Furthermore, the plasma Lp(a) assay used has minimal bias to isoform size,[35] an important confounder in Lp(a) studies and a requirement to delineate the respective roles of Lp(a) concentrations and isoform size. Some limitations to this study also warrant discussion. First, despite the large overall size of this study, power was limited in some ethnic groups, including Africans and Arabs, which had 294 and 528 cases, respectively. Similarly, the lower proportion of women in most ethnic groups is also a limitation. Thus, larger studies are required to assess Lp(a) risk in Africans and to more precisely define risk in other populations included in our study. Second, the number of participants with both concentration and isoform size measurements was limited, which may have skewed relationships attributable to power.

Our results support the clinical use of Lp(a) concentrations, but not isoform size, as a marker of MI risk in diverse populations, other than Africans and Arabs. The PAR was particularly strong in South Asians and Latin Americans and indicates that the current clinical thresholds of 50 mg/dL are applicable to these populations. Notably, this level of ethnic diversity has not previously been observed within the context of a single study and is a substantial benefit of this study. Our findings also suggest that interventions that reduce Lp(a) in South Asians and Latin Americans should be investigated, as they may be particularly beneficial.

As anti-Lp(a) therapies become increasingly more advanced, studies such as this will assist in providing the necessary foundations for potential therapeutic efficacies and decision making. Burgeoning therapeutic agents that target Lp(a), including antisense oligonucleotides (ASOs), are in advanced stages of development, and our findings suggest that such agents may have different effects in different ethnic groups. ASOs targeting apo(a) are injected subcutaneously, bind plasma proteins, and accumulate in the liver. There, they bind their mRNA target, which is then cleaved by ribonuclease H1. Following this, the ASO is then free to bind additional targets and repeat the process.[48] Studies testing ASOs reduced apo(a) by 30.0% in 8K-apo(a) mice and 86% in 12K-apo(a) mice.[49] Subsequent phase I and II clinical trials found that ASO therapies (ISIS-APO(a)Rx, IONIS-APO(a)-LRx, ISIS 681257) resulted in a dose-dependent decreases in plasma Lp(a) concentrations in healthy individuals,[50,51] patients with elevated Lp(a) levels,[51] and patients with hyperlipoproteinemia(a) and established cardiovascular disease (ClinicalTrials.gov Identifier: NCT03070782). Thus, the efficacy of ASO therapies should continue to be evaluated for clinical use, and our findings suggest that such agents may have different impacts on coronary artery disease risk in different ethnic groups, as evidenced by the wide range of PAR observed.

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Disclosures

None.

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