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Racial variation in lipoprotein-associated phospholipase A_2 in older adults

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Abstract

Background: Lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) is a predictor of cardiovascular events that has been shown to vary with race. The objective of this study was to examine factors associated with this racial variation.

Methods: We measured Lp-PLA$_2$ mass and activity in 714 healthy older adults with no clinical coronary heart disease and not taking dyslipidemia medication. We evaluated the association between race and Lp-PLA$_2$ mass and activity levels after adjustment for various covariates using multivariable linear regression. These covariates included age, sex, diabetes, hypertension, body mass index, lipid measurements, C-reactive protein, smoking status, physical activity, diet, income, and education level. We further examined genetic covariates that included three single nucleotide polymorphisms shown to be associated with Lp-PLA$_2$ activity levels.

Results: The mean age was 66 years. Whites had the highest Lp-PLA$_2$ mass and activity levels, followed by Hispanics and Asians, and then African-Americans; in age and sex adjusted analyses, these differences were significant for each non-White race as compared to Whites ($p < 0.0001$). For example, African-Americans were predicted to have a 55.0 ng/ml lower Lp-PLA$_2$ mass and 24.7 nmol/ml-min lower activity, compared with Whites, independent of age and sex ($p < 0.0001$). After adjustment for all covariates, race remained significantly correlated with Lp-PLA$_2$ mass and activity levels ($p < 0.001$) with African-Americans having 44.8 ng/ml lower Lp-PLA$_2$ mass and 17.3 nmol/ml-min lower activity compared with Whites ($p < 0.0001$).

Conclusion: Biological, lifestyle, demographic, and select genetic factors do not appear to explain variations in Lp-PLA$_2$ mass and activity levels between Whites and non-Whites, suggesting that Lp-PLA$_2$ mass and activity levels may need to be interpreted differently for various races.

Background

Lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) circulates in the blood as an enzyme bound mainly to low-density lipoprotein (LDL) particles. Lp-PLA$_2$ has been found in multiple studies to be associated with incident and prevalent coronary heart disease (CHD) [1-6] and incident stroke,[5,7] independent of standard cardiovascular risk factors[8]. A collaborative meta-analysis of 32 prospective studies in 79,000 patients showed that both Lp-PLA$_2$ mass and activity added predictive value for vascular events and mortality

beyond traditional cardiovascular risk factors[9]. Currently, a direct Lp-PLA$_2$ inhibitor is being tested in a randomized trial for prevention of cardiovascular events in patients with CHD[10]. In a study of the general population, Lp-PLA$_2$ mass and activity levels were higher in Whites compared with African-Americans or Hispanics[11]. However, the degree to which genetic differences as opposed to lifestyle variations, including smoking status, diet and exercise, may explain racial differences remains unclear. The goals of this study were to confirm the racial variations in Lp-PLA2 mass and activity levels and to examine the factors that might explain these racial differences in a multi-racial cohort of healthy older individuals free of clinical CHD and not taking dyslipidemia medications.

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Methods

Study Sample
The participants in this study were recruited from Kaiser Permanente Northern California, a large integrated healthcare system that provides comprehensive care to more than 3 million people in San Francisco and the greater Bay Area. Details of participant recruitment have been described previously[12,13]. Briefly, we enrolled adults between 60 and 72 years old who lived within 50 miles of the research facility, and who did not have a diagnosis of cardiovascular disease, cancer, end-stage renal disease, liver failure, dementia, or human immuno-deficiency virus infection. By January 2001, 3,054 apparently eligible subjects were randomly chosen to be sent letters inviting participation. From these invitations, a total of 1,024 subjects were recruited, consisting of 639 men and 385 women. In the final year of recruitment, men, Hispanics, and African-Americans were selectively oversampled in order to better match the cases enrolled in the Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology study[14]. After excluding people who were taking dyslipidemia medications from this analysis, 714 subjects were included in the study. The study protocol was reviewed and approved annually by the institutional review boards at both Stanford University and the Division of Research at Kaiser Permanente Northern California. Written informed consent was obtained from all participants.

Risk Factor Measurement
All the study subjects attended a research clinic visit at Stanford University and completed a health survey about medical diagnoses, medication use, smoking history, family history, race and ethnicity, dietary intake, and physical activity. Subjects were asked to bring their medications, which were independently reviewed and recorded by the interviewer. Resting blood pressure was determined using standard sphygmomanometers. Weight, height, and waist circumference were measured by trained and certified staff using a stadiometer, balance scale, and tape. Blood tests were drawn for biomarker analysis, which included fasting lipid levels, glucose, C-reactive protein,[15] and $Lp-PLA_2$ mass and activity levels[16,17].

Stanford Seven-Day Physical Activity Recall
The Stanford Seven-Day Physical Activity Recall, a semi-structured interview, was used to estimate the amount of time that a person engaged in moderate-, hard-, and very hard-intensity activities during the previous seven days[18,19]. A trained interviewer guided the subject through the recall process, day-by-day, to determine the duration and intensity of physical activities performed, as well as time spent sleeping[19]. Time spent in light activity was estimated by subtracting the time included in sleep and moderate-, hard-, and very hard-intensity activities from the total hours in the recall period. Total energy expenditure was estimated by multiplying the hours spent in each level of activity with the estimated energy expenditure value for each intensity category.

Block Food Frequency Questionnaire
The Block Food Frequency Questionnaire was used to characterize dietary intake[20]. It queries average consumption of 106 foods by portion size and includes 13 questions on dietary supplementation, six questions on restaurant eating, five summary questions, eight questions on fat use or low-fat foods, and seven demographic and health-related questions.

Race Determination
Self-reported race was collected during the eligibility screening survey, on the baseline health survey and from the Kaiser Permanente data sources. In addition, birthplace, grandparents' race, and grandparents' country of origin were collected. The algorithm for assigning race was as follows: if self-reported race and grandparents' race were concordant, then subjects were coded to that race category (> 80% of subjects). In discordant cases, race was assigned by a hierarchy of grandparents' race, grandparents' country of origin, self reported race on the baseline health survey, and self-reported race on the screening survey. Only the major racial groups of White, African-American, Hispanic and Asian are used for this analysis. This method of classifying race has been validated in this cohort by high-throughput genotyping of more than 450,000 single nucleotide polymorphisms (SNPs) among African-Americans and Whites[21].

$Lp-PLA_2$ Measurement
Blood samples were collected at the baseline visit after an overnight fast and stored in aliquots frozen at -80 °C. $Lp-PLA_2$ mass (ng/ml) was measured using a dual enzyme linked immunoassay (PLAC test, diaDexus Inc., South San Francisco, CA)[16]. Intra- and inter-assay coefficients of variation were < 5% and < 8%, respectively, and sensitivity across the assay range was < 0.5 ng/mL. $Lp-PLA_2$ activity (nmol/ml-min) was measured by a colorimetric activity method (CAM test)[17]. Intra- and inter-assay coefficients of variation were < 4% and < 6%, respectively, and sensitivity across the assay range was < 5 nmol/ml-min.

Single Nucleotide Polymorphism Selection
A literature search for all of the documented SNPs related to $Lp-PLA_2$ mass and activity levels was conducted. Only those SNPs that were both documented in the literature to be related to $Lp-PLA_2$ and existed in our database were included in the analysis. The SNPs included in our database were selected for likely

association with atherosclerosis as determined *a priori* from literature review and by comparing up and down-regulated genes in diseased and non-diseased vascular endothelium. The genetic covariates included three SNPs in the PLA2G7 locus (Lp-PLA$_2$ gene) that have been documented to be associated with Lp-PLA$_2$ activity: Ala379Val (rs1051931), Arg92His (rs1805017), and Ile198Thr (rs1805017)[22]. The SNPs were coded as 0 for homozygous major, 1 for heterozygous, and 2 for homozygous minor.

Statistical methods

Baseline characteristics were presented as means and standard deviations for normally distributed continuous variables and as counts and proportions for categorical variables. Medians and interquartile ranges were used for non-normally distributed continuous variables. Differences in the baseline variables between racial groups were compared using a general linear model analysis of variance (ANOVA).

Linear regression was used to examine the association between race and Lp-PLA$_2$ mass and activity in separate models. The covariates for multivariable analysis were selected *a priori* and included biological, lifestyle, demographic, and genetic characteristics. The biological covariates included age, race, history of diabetes mellitus, history of hypertension, quantitative systolic blood pressure measurement, body mass index (BMI), waist circumference, LDL cholesterol level, high density lipoprotein (HDL) cholesterol level, asymmetric dimethylarginine (ADMA), and C-reactive protein (CRP); the lifestyle and demographic covariates were current smoking status, physical activity, percent of calories from saturated fat, percent of calories from carbohydrates, education level, and income.

A simple linear regression model was first used to analyze the relation between race and Lp-PLA$_2$ mass and activity adjusted for only sex. The biological, lifestyle, and genetic covariates were each included in separate multivariable models in addition to a single multivariable model with all the covariates. Data were analyzed using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Results

The study population consisted of 540 whites, 60 African-Americans, 62 Hispanics, and 52 Asians (Table 1). The average age was 66 years and women comprised 40% of the study cohort. The prevalence of hypertension (62%) was slightly higher and the prevalence of diabetes (13%) relatively lower than the general population[23,24]. Mean LDL levels were mildly elevated (128 mg/dL), while mean HDL levels were relatively high (54 mg/dL). The cohort was overweight (mean BMI of 28 kg/m^2) and only a small proportion were active smokers (7.3%).

Some baseline characteristics differed significantly among the racial groups (Table 1). The study had insufficient power to compare the non-White racial groups to each other, so all statistical comparisons are to Whites. Whites were the least likely to be diabetic, while in comparison, African-Americans were the most likely to be diabetic. Asians had the lowest mean BMI and smallest mean waist circumference. Asians and Hispanics were significantly less likely to be actively smoking as compared with Whites. Asians had a lower dietary intake of saturated fat and higher intake of from carbohydrates (both as percent of total energy). LDL and HDL levels were relatively similar comparing White with non-White groups. There were also significant differences in the SNP frequencies between White and non-White races. Compared with African-Americans and Hispanics, Whites were more likely to have the Ala379Val SNP. Hispanics were the most likely to have the Arg92His SNP, while African-Americans were the most likely to have the Ile198Thr SNP compared to Whites.

Men had significantly higher Lp-PLA$_2$ mass and activity levels than women, after adjusting for all covariates (p = 0.025). The mean Lp-PLA$_2$ mass for men was 246 ng/ml compared with 223 ng/ml for women. The mean Lp-PLA$_2$ activity for men was 142 nmol/ml-min compared with 114 nmol/ml-min for women. There was no evidence of an interaction between sex and racial variations in Lp-PLA$_2$ mass or activity in any model, so analyses were conducted in the combined cohort of men and women. A secondary analysis, which included subjects taking dyslipidemia medications, showed the same overall findings and confirmed that excluding these patients did not significantly change the final results.

Lp-PLA$_2$ mass and activity levels varied significantly between Whites and non-Whites in all linear regression models (Figures 1 and 2 and Tables 2 and 3). Whites had the highest Lp-PLA$_2$ mass and activity levels, followed by Hispanics. African-Americans and Asians had the lowest Lp-PLA$_2$ mass and activity levels. These differences between Whites and non-Whites remained highly significant even after adjusting for all covariates. In fact, the values of the β coefficients for non-White races were high, ranging from -25 to -55 ng/ml across models for predicting Lp-PLA$_2$ mass and -10 to -28 nmol/ml-min for predicting Lp-PLA$_2$ activity. The other covariates with strong associations with Lp-PLA$_2$ mass and activity levels included age, LDL, HDL, and ADMA levels. The Arg92His SNP in the PLA2G7 locus was associated with lower Lp-PLA$_2$ activity, but higher Lp-PLA$_2$ mass, whereas the other two SNPs had no significant associations.

None of the other covariates were consistently associated with Lp-PLA$_2$ mass and activity levels. Hypertension and diabetes were weakly associated with Lp-PLA$_2$ activity and not associated with mass. Conversely,

Table 1 Baseline characteristics among older adults without clinical cardiovascular disease by major race subgroups; mean (s.d.) and N (%)

Variable	All subjects (n = 714)	White (n = 540)	African- American (n = 60)	Hispanic (n = 62)	Asian (n = 52)	P-value*
Age (years)	65.8 (2.9)	65.7 (2.9)	65.5 (3.0)	66.3 (2.8)	65.9 (2.5)	0.38
Female gender	284 (40%)	216 (40%)	20 (33%)	26 (42%)	22 (42%)	0.73
Diabetes mellitus	91 (13%)	58 (11%)	15 (25%)	10 (16%)	8 (15%)	0.011
History of hypertension	440 (62%)	321 (59%)	45 (75%)	39 (63%)	35 (67%)	0.095
Systolic blood pressure (mmHg)	131 (18)	130 (17)	136 (22)	133 (15)	136 (20)	0.0045
Body mass index (kg/m^2)	27.9 (5.0)	27.8 (5.0)	30.3 (5.8)	28.9 (3.9)	25.4 (3.6)	< 0.0001
Waist circumference (cm)	93.0 (14.6)	92.9 (14.4)	98.8 (16.9)	95.2 (12.9)	84.4 (11.4)	< 0.0001
Low density lipoprotein (mg/dL)	128 (32)	128 (30)	125 (38)	125 (32)	128 (36)	0.78
High density lipoprotein (mg/dL)	54 (16)	55 (17)	56 (17)	53 (15)	53 (13)	0.61
Triglycerides (mg/dL)[†]	116 (86)	118 (84)	97 (64)	138 (113)	121 (89)	0.12
ADMA[‡] (μmol/L)	0.63 (0.10)	0.64 (0.11)	0.61 (0.10)	0.64 (0.09)	0.62 (0.09)	0.20
C-reactive protein (mg/L)	3.4 (6.4)	3.4 (6.7)	4.4 (6.6)	3.5 (5.1)	1.9 (2.8)	0.22
LpPLA$_2$ mass (ng/mL)[†]	227 (71)	233 (75)	198 (63)	221 (59)	202 (73)	< 0.0001
LpPLA$_2$ activity (nmol/ml-min)[†]	130 (43)	134 (41)	108 (32)	124 (36)	124 (61)	< 0.0001
LpPLA$_2$ mass > 235 ng/mL	302 (42%)	260 (48%)	11 (18%)	19 (31%)	12 (24%)	< 0.0001
Current cigarette smoking	52 (7.3%)	42 (7.8%)	8 (13.3%)	1 (1.6%)	1 (1.9%)	0.035
Physical activity (kCal/kg-day)	34.8 (3.5)	34.9 (3.6)	34.4 (3.7)	35.0 (3.1)	34.6 (2.8)	0.76
Percent of calories from saturated fat	10.1 (2.7)	10.3 (2.7)	10.3 (2.9)	10.1 (2.5)	8.5 (1.7)	0.0001
Percent of calories from carbohydrates	46.6 (9.1)	46.0 (9.0)	46.3 (9.1)	49.1 (9.7)	49.8 (8.2)	0.0038
Annual income ≥ $50,000	452 (68%)	351 (70%)	37 (70%)	30 (54%)	34 (68%)	0.11
College graduate	173 (17%)	133 (25%)	10 (17%)	9 (15%)	21 (40%)	0.0059
Ala379Val						
Homozygous major	440 (63%)	340 (64%)	29 (49%)	32 (52%)	39 (75%)	0.011
Heterozygous	235 (33%)	170 (32%)	28 (47%)	25 (41%)	12 (23%)	0.021
Homozygous minor	28 (4%)	21 (4%)	2 (3%)	4 (7%)	1 (2%)	0.64
Arg92His						
Homozygous major	394 (56%)	291 (55%)	39 (66%)	27 (44%)	37 (71%)	0.011
Heterozygous	256 (36%)	198 (37%)	17 (29%)	28 (46%)	13 (25%)	0.075
Homozygous minor	55 (8%)	44 (8%)	3 (5%)	6 (10%)	2 (4%)	0.52
Ile198Thr						
Homozygous major	617 (87%)	479 (90%)	36 (61%)	59 (97%)	43 (83%)	< 0.0001
Heterozygous	85 (12%)	52 (10%)	22 (37%)	2 (3%)	9 (17%)	< 0.0001
Homozygous minor	4 (0.6%)	3 (0.6%)	1 (2%)	0 (0%)	0 (0%)	0.58

* P-value indicates the comparison across racial groups by ANOVA
[†] Median (interquartile range), [‡] ADMA, asymmetric dimethylarginine

C-reactive protein was weakly associated with Lp-PLA$_2$ mass, but not activity. None of the lifestyle covariates were significantly associated with Lp-PLA$_2$ mass or activity levels.

Discussion

Our study confirms that Lp-PLA$_2$ mass and activity levels vary significantly between White and non-White races in healthy older adults without clinically diagnosed CHD and not taking dyslipidemia medications. Whites have the highest Lp-PLA$_2$ mass and activity levels, Hispanics have intermediate levels, and African-Americans and Asians have the lowest Lp-PLA$_2$ mass and activity levels. These relationships were not affected by statistical adjustment for lifestyle and demographic factors, standard biological risk factors, and three SNPs known to be associated with Lp-PLA$_2$ activity levels. These findings suggest that differences in Lp-PLA$_2$ mass and activity levels between Whites and non-Whites may be due to other genetic factors or perhaps to unmeasured lifestyle factors.

The differences between White, Hispanic, and African-American race and Lp-PLA2 mass and activity levels in our study were similar to the results from the Dallas Heart Study, the largest community-based study of Lp-PLA$_2$ levels[11]. One key difference was that our
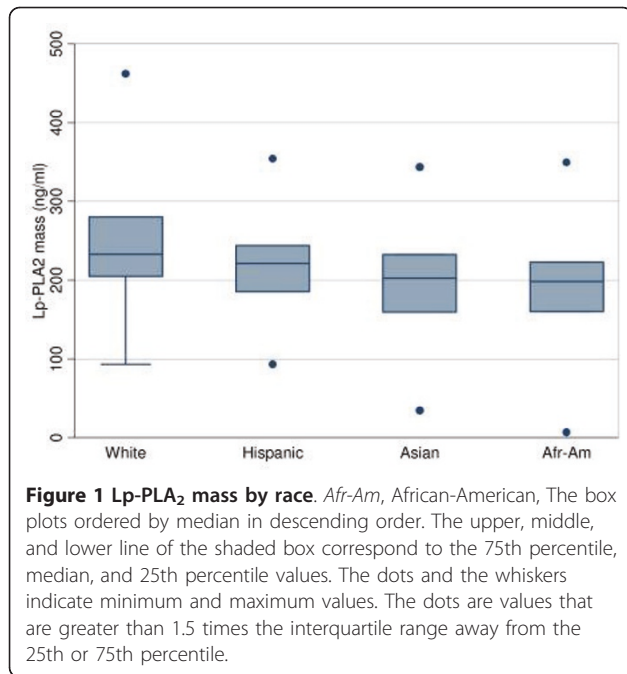
Figure 1 Lp-PLA$_2$ mass by race. *Afr-Am*, African-American, The box plots ordered by median in descending order. The upper, middle, and lower line of the shaded box correspond to the 75th percentile, median, and 25th percentile values. The dots and the whiskers indicate minimum and maximum values. The dots are values that are greater than 1.5 times the interquartile range away from the 25th or 75th percentile.

study also included Asians, who were found to have Lp-PLA$_2$ mass and activity levels that were similar to African-Americans, but lower than Whites. Our study also demonstrated that racial differences in Lp-PLA$_2$ mass and activity levels apply to older adults, given the fact that individuals in our study (mean age of 66 years) were substantially older than those in the Dallas Heart Study (mean age of 45 years). The Dallas Heart Study cohort included individuals taking statin medication,
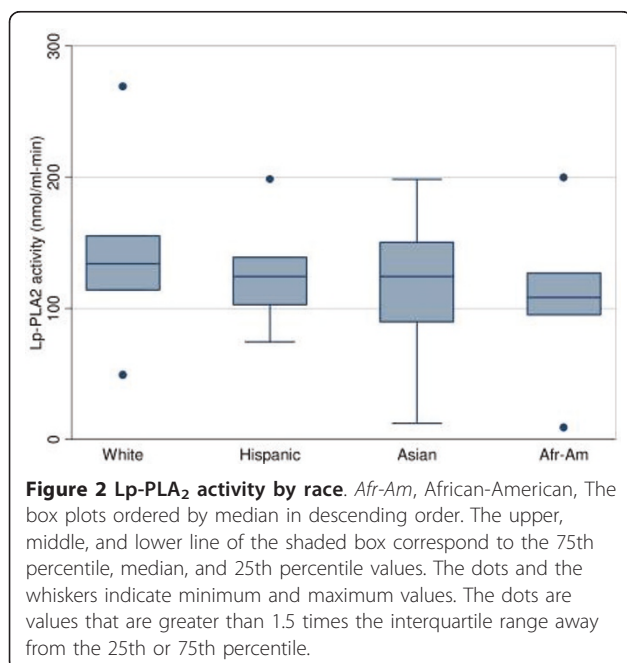

Figure 2 Lp-PLA$_2$ activity by race. *Afr-Am*, African-American, The box plots ordered by median in descending order. The upper, middle, and lower line of the shaded box correspond to the 75th percentile, median, and 25th percentile values. The dots and the whiskers indicate minimum and maximum values. The dots are values that are greater than 1.5 times the interquartile range away from the 25th or 75th percentile.

whereas our study excluded individuals taking any dyslipidemia medication, because such medications may reduce Lp-PLA$_2$ mass and activity levels[25]. Other studies that were in a small cohort[26] and in a selected population with vascular disease[27] also showed that Whites have higher Lp-PLA$_2$ mass and activity levels as compared with other races.

Because Lp-PLA$_2$ circulates bound to LDL particles, Lp-PLA$_2$ mass and activity levels depend greatly upon lipid metabolism and are strongly association with LDL and HDL levels[16]. Although we also found this association, adjustment for LDL and HDL levels did not alter the relation between race and Lp-PLA$_2$ mass and activity levels, suggesting that variations in LDL and HDL levels do not explain these racial differences. Diet and physical activity also affect lipid metabolism,[28] but adjustment for these lifestyle factors did not attenuate the association between race and Lp-PLA$_2$ mass and activity levels.

Various studies have shown associations between Lp-PLA$_2$ mass and activity levels and different genotypes of Lp-PLA$_2$, bolstering the hypothesis that there is a substantial genetic influence on Lp-PLA$_2$ levels. A study of the Framingham cohort, using 1943 SNPs, suggested that Lp-PLA$_2$ mass had a multivariable adjusted heritability of 25% and Lp-PLA$_2$ activity had 41% heritability[29]. Among Whites, the Ala379Val coding variant in the PLA2G7 locus was associated with increased Lp-PLA$_2$ activity, while the Arg92His coding variant was associated with decreased activity[22]. Among Japanese individuals, the Val279Phe SNP also in the PLA2G7 locus, which is much more prevalent in Japanese than in Whites, is associated with greatly decreased Lp-PLA$_2$ activity[30]. In fact, people who are homozygous for the Val279Phe polymorphism have almost no detectable Lp-PLA$_2$ activity[31,32]. Because of the probable strong genetic influence on Lp-PLA$_2$ mass and activity levels, one could hypothesize that the racial variations are due to genetic differences between races. Our study included only three SNPs, while the Framingham study revealed 12 SNPs linked with Lp-PLA$_2$ variability[29]. Therefore, adjusting for only three SNPs in our study was a limited test of genetic influence on the racial differences in Lp-PLA$_2$ and did not attenuate the strong association between race and Lp-PLA$_2$ mass and activity levels.

In addition to the limited number of Lp-PLA$_2$-related SNPs, another limitation of this analysis is that it is cross-sectional as we were unable to study whether Lp-PLA$_2$ level predicts subsequent risk of CHD events differentially by race. Before Lp-PLA$_2$ results can be added to existing CHD risk prediction equations, further evidence is needed to validate its incremental prognostic value in an ethnically-diverse cohort. Another limitation is the ability of questionnaires to accurately and fully

Table 2 Linear regression models predicting Lp-PLA2 mass (ng/mL)

Variables	Race & Sex (Model 1)		Model 1 + Biological Covariates		Model 1 + Lifestyle Covariates		Model 1 + SNPs*		All Covariates	
	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Race[†]										
African-American	-55.0	< 0.0001	-50.2	< 0.0001	-57.2	< 0.0001	-49.6	< 0.0001	-47.3	< 0.0001
Hispanic	-26.2	0.0016	-25.8	0.0008	-30.1	0.001	-27.7	0.0008	-30.0	0.0004
Asian	-47.1	< 0.0001	-45.7	< 0.0001	-45.4	< 0.0001	-43.1	< 0.0001	-42.0	< 0.0001
Female gender[‡]	-24.2	< 0.0001	-18.5	0.0045	-24.5	< 0.0001	-22.8	< 0.0001	-18.4	0.011
Biological Covariates										
Age (years)			2.4	0.0016					2.6	0.0019
Diabetes mellitus			-0.0042	0.95					-0.018	0.81
History of hypertension			-3.0	0.53					-3.76	0.49
Systolic blood pressure (mmHg)			0.16	0.23					0.14	0.33
Body mass index (kg/m2)			-0.46	0.63					-0.063	0.95
Waist circumference (cm)			0.092	0.81					-0.026	0.95
LDL (mg/dL)			0.75	< 0.0001					0.75	< 0.0001
HDL (mg/dL)			-0.26	0.094					-0.27	0.11
ADMA[§] (μmol/L)			38.8	0.06					33.2	0.14
C-reactive protein (mg/L)			1.1	0.0017					1.1	0.002
Lifestyle/Demographic Covariates										
Current smoking					0.012	0.90			0.0058	0.95
Exercise (kCal/kg-day)					0.63	0.40			0.76	0.28
% Calories from saturated fat					0.081	0.94			-0.96	0.38
% Calories from carbohydrates					-0.43	0.20			-0.60	0.058
Annual income ≥ $50,000					-0.019	0.74			0.051	0.32
College graduate					-0.091	0.086			-0.071	0.15
SNPs										
Ala379Val							2.2	0.60	2.5	0.55
Arg92His							11.8	0.0023	11.6	0.0025
Ile198Thr							-8.8	0.19	-6.1	0.37

* SNPs, single nucleotide polymorphisms
[†] Compared to White race
[‡] Compared to Male
[§]ADMA, asymmetric dimethylarginine

characterize all the lifestyle variations that could explain the racial differences of Lp-PLA$_2$ mass and activity levels. For example, there could be other lifestyle factors, such as diet choices unrelated to fat and carbohydrate intake, which influence Lp-PLA$_2$ mass and activity levels but are not captured by the survey. The relatively modest number of non-White participants may also limit our ability to detect the effects of lifestyle factors.

Lp-PLA$_2$ is viewed as a novel CHD risk marker that could be used to risk stratify individuals when considering primary prevention strategies, such as initiating statin therapy or setting lipid treatment goals. Various authors have suggested using a uniform threshold for Lp-PLA$_2$ mass, regardless of sex and race, for categorizing risk[1,33]. However, the results from this study confirm that Lp-PLA$_2$ mass and activity levels vary significantly between Whites and non-Whites, independent of known biological and lifestyle factors. These racial variations could affect the

performance of Lp-PLA$_2$ as a prognostic risk marker. For example, African-Americans may have lower Lp-PLA$_2$ mass and activity levels than Whites despite having similar degrees of atherosclerosis and vascular inflammation or they may simply have less underlying atherosclerotic disease. In light of the high cardiovascular event rates in African-Americans, the former possibility seems more likely. As a result, using the same Lp-PLA$_2$ threshold in Whites and African-Americans may underestimate risk in African-Americans compared with Whites.

Conclusions

If Lp-PLA$_2$ mass and activity levels are inherently different between races, then these levels may need to be interpreted differently for various races. Before incorporating information on Lp-PLA$_2$ mass and activity levels in assessing cardiovascular risk for individual patients, additional larger, multi-racial prospective studies are

Table 3 Linear regression models predicting Lp-PLA2 activity (nmol/mL-min)

Variables	Race & Sex (Model1) β	P-value	Model1 + Biological Covariates β	P-value	Model 1 + Lifestyle Covariates β	P-value	Model1 + SNPs* β	P-value	All Covariates β	P-value
Race[†]										
African-American	-24.7	< 0.0001	-18.5	< 0.0001	-27.0	< 0.0001	-22.8	< 0.0001	-18.0	< 0.0001
Hispanic	-10.1	0.009	-10.6	0.0006	-14.4	0.0006	-10.2	0.009	-13.1	0.0001
Asian	-12.1	0.003	-14.2	< 0.0001	-10.4	0.018	-11.9	0.004	-13.9	0.0001
Female gender[‡]	-28.1	< 0.0001	-18.2	< 0.0001	-28.3	< 0.0001	-27.6	< 0.0001	-17.4	< 0.0001
Biological Covariates										
Age (years)			1.05	0.0006					1.13	0.0006
Diabetes mellitus			-0.057	0.038					-0.067	0.024
History of hypertension			-2.38	0.23					-3.65	0.094
Systolic blood pressure (mmHg)			-0.0034	0.95					0.0012	0.98
Body mass index (kg/m2)			-0.41	0.29					-0.34	0.39
Waist circumference (cm)			0.041	0.79					-0.0066	0.97
LDL (mg/dL)			0.44	< 0.0001					0.45	< 0.0001
HDL (mg/dL)			-0.69	< 0.0001					-0.72	< 0.0001
ADMA[§] (μmol/L)			23.4	0.0048					23.1	0.012
C-reactive protein (mg/L)			-0.23	0.10					-0.22	0.13
Lifestyle/Demographic Covariates										
Current smoking					0.035	0.43			0.025	0.49
Exercise (kCal/kg-day)					0.36	0.30			0.38	0.17
% Calories from saturated fat					1.09	0.038			0.047	0.91
% Calories from carbohydrates					0.31	0.045			-0.055	0.66
Annual income ≥ $50,000					-0.023	0.38			0.011	0.60
College graduate					-0.0095	0.70			0.014	0.48
SNPs										
Ala379Val							1.20	0.55	1.45	0.40
Arg92His							-2.06	0.26	-3.75	0.015
Ile198Thr							-6.03	0.056	-4.38	0.11

* SNPs, single nucleotide polymorphisms
[†] Compared to White race
[‡] Compared to Male
[§]ADMA, asymmetric dimethylarginine

needed to delineate the specific risk associated with different Lp-PLA$_2$ levels within individual racial groups.

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