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HDL Cholesterol and Stroke Risk: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background and Purpose—Accurate identification of risk factors for stroke is important for public health promotion and disease prevention. HDL cholesterol is a potential risk factor, yet its role in stroke risk is unclear, as is whether HDL cholesterol content or particle number might be a better indicator of stroke risk. Furthermore, the degree to which ethnicity moderates the risk is unknown. As such, the current study examines the associations between incident stroke and both HDL cholesterol concentration and particle number, and assesses the moderating role of race and ethnicity.

Methods—The sample is a racially diverse cohort of US adults between the ages of 45 - 84 years enrolled in the Multi-Ethnic Study of Atherosclerosis between 2000 - 2002 and followed until December 2011. The associations among cholesterol content and stroke risk, particle number and stroke risk, and the interaction with race were explored.

Results—The incidence of stroke was 2.6%. HDL cholesterol concentration (mmol/L) (Hazard Ratio (HR) = 0.56; 95% Confidence Interval (CI): 0.312 - 0.988) and number of large HDL particles (μmol/L) (HR = 0.52, CI: 0.278 - 0.956) were associated with lower stroke risk. When interactions with race were evaluated, the relationship between both HDL variables and stroke were significant in Blacks, but not other races.

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Disclosures

None

Conclusions—Higher HDL cholesterol and a higher concentration of large particles are associated with lower risk of stroke in Blacks. Further research is needed to elucidate the mechanisms by which HDL subfractions may differentially affect stroke outcome in different races/ethnicities.

Keywords

Cholesterol; lipids; risk factors for stroke

High density lipoprotein (HDL) particles are heterogeneous in terms of size, shape, density, composition, and surface charge. HDL subclasses differ in their ability to promote cholesterol efflux, which is the first step in reverse cholesterol transport [1]. Furthermore, the effectiveness of the anti-atherogenic functionality of HDL may differ based on particle number and/or size [2]. Interestingly, HDL efflux varies between individuals and is independently associated with CVD events [3].

Previous literature supports an inverse relationship between HDL concentration (HDL-C) and cardiovascular disease (CVD) [4], but the specific relationship between stroke and both HDL-C and subclasses may be more complex. Some prospective studies have found higher HDL-C levels are associated with lower stroke risk [5, 6], while some studies have found no relation [7, 8] or even an increased risk [9]. For example, after a mean of 7.5 years follow up, researchers from both the Northern Manhattan Study (NOMAS) [10] and the Women's Health Initiative (WHI) Observational Study [11] found no significant relationships between baseline HDL-C or total cholesterol levels and stroke. However, baseline HDL size was significantly lower among control subjects versus cases in the WHI [11]. Other studies have also supported the finding that acute ischemic stroke patients had increased amounts of small-sized HDL particles [12]. These complex relationships are important when examining the association between HDL particles and stroke risk.

Given the complex nature of the HDL particles, it is unclear whether it is the cholesterol content, particle number, size, or functionality that may be the best marker of risk. It is particularly relevant to assess HDL composite measures, since previous trials have failed to show that increasing HDL-C leads to a decrease in cardiovascular risk [13]. Additionally, HDL cholesterol may uniquely affect the risk of stroke in different racial/ethnic groups. Specifically, compared to Blacks or non-Hispanic Whites, Hispanics tend to have lower levels of HDL cholesterol [14, 15], but higher triglycerides [14]. Conversely, Blacks tend to have lower prevalence of low HDL-C and high triglycerides [16]. These findings suggest that HDL cholesterol may differentially impact health outcomes for various racial/ethnic groups, highlighting the importance of the current study to address this gap in the literature. To our knowledge, no other study has examined racial/ethnic differences in HDL composite measures and how these differences may relate to stroke risk. Also, research on how particle number or size may influence risk in different races/ethnicities is lacking. Therefore, we tested the hypothesis that HDL-C, HDL particle number (HDL-P), and size uniquely predict stroke outcome across different racial and ethnic groups.

Methods

Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is comprised of 6,814 men and women between the ages of 45 – 84 who were enrolled between July 2000 and August 2002 from six field centers across the United States (Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University, and University of California at Los Angeles). The sample included White, Black, Hispanic, and Chinese participants. Individuals were excluded if they had prior diagnosis of a heart attack, stroke, transient ischemic attack, heart failure, angina, atrial fibrillation, or history of any cardiovascular procedure. Participants who had any existing medical condition that would prevent long-term participation, were pregnant, or weighed over 300 pounds were also excluded from the study. The MESA protocol has been approved by the Institutional Review Boards of all collaborating institutions, and all participants gave informed consent. The protocol for the current study has also been approved by the University of Miami Institutional Review Board.

Procedure

The objectives and design of MESA have been previously described in detail [see 17]. Participants arrived at the clinic fasting and completed an extensive battery of questionnaires and laboratory measurements. Participants are contacted every 9 – 12 months to assess morbidity and mortality. Baseline data and incident stroke are used in these analyses.

Lipid measurements

Blood samples were drawn after a 12-hour overnight fast and stored at -70°C. Lipids were measured at Collaborative Studies Clinical Laboratory at Fairview University Medical Center, Minneapolis, Minnesota. Lipids were assayed on thawed ethylenediaminetetraacetic acid (EDTA) plasma within two weeks of sample collection, using Centers for Disease Control Prevention/NHLBI standards. HDL-C was measured using the cholesterol oxidase method (Roche Diagnostics, Indianapolis, Indiana) after precipitation of non–HDL-C with magnesium/dextran (coefficient of variation 2.9%). LDL-C concentration was calculated using the Friedewald equation [18]. Plasma lipoprotein particle concentrations were measured at LipoScience, Inc. (Raleigh, North Carolina) by nuclear magnetic resonance (NMR) spectroscopy using the LipoProfile-3 algorithm. HDL-P and LDL particle number (LDL-P) (coefficient of variation <4%) are the sums of the particle concentrations of their respective subclasses, which are quantified based on particle size using the amplitudes of their lipid methyl group NMR signals, and mean particle sizes are the weighted average of related subclasses [19, 20]. Large particles were between 9.4 – 14 nm (μmol/L), medium particles were between 8.2 – 9.4 nm (μmol/L), and small particles were between 7.3 – 8.2 nm (μmol/L).

Covariates

Potential confounders that have a known relation and/or influence on HDL cholesterol and stroke risk were included. These included age, sex, race/ethnicity, systolic blood pressure,

educational attainment, medication usage (lipid lowering drugs, hypertensive medication, and hypoglycemic medication), BMI, cigarette status (Current, Former/Never), total cholesterol, triglycerides, and diabetes status at baseline (yes/no).

Endpoint

Endpoints were defined as stroke, both fatal and nonfatal. Stroke was defined as a rapid onset of neurologic deficit, headache, or meningismus, and neurologic deficits not secondary to brain trauma (closed head injury), tumor, infection (e.g., encephalitis or meningitis), or other non-vascular cause, and clinically relevant lesion on brain imaging OR duration greater than 24 hours OR death within 24 hours. Ischemic stroke events also included "unknown" (N = 8) and "other" responses (N = 1) by the reporter (.12% of the total sample), but excluded any type of hemorrhagic stroke event. Events were adjudicated by a review committee to ensure the validity of events and comparability between sites.

Statistical Analyses

All analyses were performed using SPSS Version 22.0. All variables were screened for outliers and univariate normality. Triglycerides were log transformed to achieve approximate normality. Continuous variables were centered on the variable mean to aid in interpretation of analysis.

Individuals with missing cholesterol data (N = 21) as well as individuals taking anticoagulant drugs (i.e. warfarin) were removed prior to analysis (N = 24), leaving a total sample size of 6,769. Cox proportional hazard regression models were constructed using HDL-C (mmol/L), HDL-P (μmol/L), and particle size (μmol/L) as continuous variables with incident stroke as the outcome over a 9.5 year follow-up period. All covariates were entered first (Model 1), and three subsequent models were constructed to examine the associations between HDL-C (Model 2), HDL-P (Model 3), and number of large, medium, and small HDL particles (Model 4) with stroke. Interactions between the HDL cholesterol variables and ethnicity were also examined (Models 5 – 7).

Results

Sample Characteristics

The mean age of participants included in this analysis was 62 years (SD = 10.24), and 53% were female. The sample was 38.4% White, 27.8% Black, 22.0% Hispanic, and 11.9% Chinese American. Sixteen percent were prescribed lipid-lowering drugs, 37.2% antihypertensive medications, and 8.6% hypoglycemic agents. Cigarette status was grouped into current users (13.0%) and former/non-users. Highest level of education completed varied from less than high school to college and beyond. Stroke events occurred in 2.6% of the sample (N = 176) with 85% being classified as ischemic.

Blacks had significantly higher systolic blood pressure than all other race/ethnic groups ($p < .001$) and significantly higher rates of blood pressure medication use (Table 1). Blacks had significantly fewer number of medium particles compared to other races/ethnicities ($p < .001$). Compared to all other races/ethnicities, Hispanics had the highest triglyceride, but

lowest HDL cholesterol levels, as well as significantly higher total cholesterol levels than Blacks and Chinese Americans, but not Whites ($p < .001$ for all). Hispanics had significantly fewer number of large particles compared to other races/ethnicities ($p < .001$). Whites had a greater number of HDL particles than all other races/ethnicities ($p < .001$). Chinese had significantly more small HDL particles compared to other races/ethnicities ($p < .001$).

Baseline HDL-C was significantly lower in those who experienced an incident stroke compared to those who did not have a stroke (Means: 48.2 vs. 51.0, $p = .02$). More current cigarette smokers were in the stroke group (17.0%) compared to the non-stroke group (12.9%) ($p < .01$). There were also more individuals taking oral hypoglycemic medication in the stroke group (17.6 vs 8.3%, $p < 0.01$) and on hypertension medication (57.4% vs. 36.7%, $p = .01$).

Covariate Correlations

HDL-C was strongly, positively correlated with total HDL-P ($\rho = .69$), number of large particles ($\rho = .91$), and number of medium particles ($\rho = .45$; ps $< .001$). HDL-C was strongly, negatively correlated with number of small HDL particles ($\rho = -.28$, $p < .001$). All other correlations are listed in Table 2.

HDL as a Predictor of Stroke Outcome

After multivariable adjustment, Model 2 shows that HDL-C was negatively inversely associated with incident stroke (Hazard Ratio (HR) = 0.56; 95% Confidence Interval (CI): 0.312 - 0.988). There was a trend between HDL -P and stroke (HR = 0.79; 95% CI: .613 - 1.027) (Model 3). Adjusting for number of medium and number of small HDL particles, the number of large particles was inversely associated with stroke events (HR = 0.52; 95% CI: 0.278 - 0.956) (Model 4). In a full model with HDL-C, HDL-P, and all three HDL sizes adjusted for one another, none was significant. Results from this full model are not shown. Results from all other models are listed in Table 3.

Interactions with Race/Ethnicity

The interaction between HDL-C and race/ethnicity for incident stroke was significant [Model 5: $\Delta\chi^2$ (3, N = 6769) = 6.990, p = .07]. The relationship was significant in Blacks ($p < .01$), but not in Chinese Americans ($p = .25$), Whites ($p = .27$) or Hispanics ($p = .48$).

There was no significant interaction between race/ethnicity and HDL-P (Model 6), number of medium, or number of small particles for incident stroke.

The interaction between number of large particles and race/ethnicity was also significant [Model 7: $\Delta\chi^2$ (3, N = 6769) = 7.560, $p = .06$]. Again, while the relationship was significant in Blacks (B = -1.640), it was not significant in Chinese Americans (B = .929), Whites (B = -.370), or Hispanics (B = -.508). Results from analyses that reached significance are shown in Table 4. Non-significant results are not shown.

Secondary Analyses: Ischemic Stroke Outcome Only

Given the significant findings for “total stroke” outcome, secondary analyses were run to determine if the significant finding was due primarily to associations with incident ischemic stroke (N = 147). After controlling for all covariates, HDL-C was inversely associated with incident ischemic stroke (HR = 0.52, 95% CI: 0.27 - 0.98). As before, there was a trend for HDL-P (HR = 0.76, 95% CI: 0.58 – 1.03). However, after controlling the covariates and both medium and small HDL particle numbers, the number of large HDL particles was inversely associated with ischemic stroke event (HR = 0.49, 95% CI: 0.25 - 0.98). Since the interactions from the primary analyses were not significant, interaction tests were not re-run with the smaller stroke outcome sample.

Discussion

In a large, racially and ethnically diverse sample of asymptomatic men and women at baseline, HDL-C and the number of large HDL particles were significantly, inversely associated with incident stroke after controlling for relevant covariates, which is consistent with prior studies linking stroke outcome and CVD to lower HDL-C [4-6] and larger HDL particles [21]. The associations were not significant after adjusting for other HDL composite variables. This suggests that above and beyond the variance shared by all of the different composite measures of HDL cholesterol, there is no single measure that adds additional unique information to the association with stroke risk. Finally, there were borderline significant interactions with race/ethnicity, which suggests that the relationship between HDL-C and number of large HDL particles may affect stroke outcome differently in Blacks compared to other races.

Results from another MESA study also found interesting racial/ethnic differences with regard to lipid profile and cardiovascular disease risk. More specifically, deGoma et al. [22] examined non-HDL cholesterol (non-HDL-C) and LDL particle number (LDL-P). Individuals were considered LDL-P > non-HDL-C discordant if LDL-P levels were higher than expected for the measured non-HDL-C. Results indicated that Blacks exhibited the highest rate of LDL-P > non-HDL-C discordance and higher percentile values of LDL-P, thus also identifying differences in cardiovascular disease risk factors in Blacks compared to other racial/ethnic groups.

While the current study supports the finding that HDL particle size adds little value in prediction of stroke risk beyond HDL-C alone, the question remains whether and why these subclasses are important to continue investigating. HDL particles are heterogeneous in terms of size, composition and function [23-25]. They are secreted from the liver as small, disc-shaped, lipid deficient particles containing apoA-I. These particles then acquire cholesterol and phospholipid from peripheral tissues through receptor (e.g., ABCA1) dependent and independent pathways increasing their size. These now spherical particles are further modified by the actions of cholesterol ester transfer protein (CETP), phosphatidylcholine-sterol O-acyltransferase (LCAT) and exchange of apolipoproteins from the surface of other lipoproteins (e.g., VLDL) resulting in the formation of large, fully mature HDL. Then, HDL particles are subject to further modification by the actions of phospholipid transfer proteins, hepatic lipase, endothelial lipase, SR-B1and CETP that then decrease HDL particle size.

These physiological steps form the so-called HDL cycle and reverse cholesterol transport pathways and regulate HDL particle number, size and cholesterol concentration.

A recent study [26] demonstrated an increase in of oxidative stress in HDL particles from patients after ischemic stroke and associated with a decrease in the anti-oxidant enzyme paraoxonase 1 activity. These authors suggested that under conditions of inflammation, oxidative stress and dyslipidemia, HDL becomes dysfunctional contributing to lower HDL-C and particle numbers. In the context of disease risk, a defect in any of the factors described above have the potential to alter HDL-concentration and particle size distribution. Understanding the relationships between the pathophysiology and HDL-particle size distribution may better aid in risk assessment.

While HDL-C may be a metabolic marker for increased risk for stroke rather than a causal factor [27], the major protein in HDL cholesterol, apolipoprotein A-1, has been found to be directly protective against atherosclerosis in several animal studies [28-34]. Whether subclasses of HDL differ in their anti-atherogenic functionality, the amount of apolipoprotein A-1, and ultimate efficiency in reverse cholesterol transport, remain important unanswered questions. Furthermore, certain genetic components that influence lipid level and stroke risk may be important to study at greater length. For example, the HMG-CoA reductase (HMGCR) is an enzyme involved in cholesterol synthesis that may affect response to statins differently across different races [35]. Ultimately, the pathophysiology of stroke with specific regard to the HDL cholesterol molecule is complicated by the presence of a number of influential factors and leaves room for future studies.

A major strength of this study is that it accounted for many of those influential factors, including hypertension, hypertensive medication, and triglycerides, strong predictors of stroke [36] . Additional strengths include its multiple-sites, longitudinal design, and inclusion of four different races/ethnicities, in addition to multiple validated measures of HDL cholesterol. Few other studies have examined the role of race/ethnicity in the relationship between HDL cholesterol and its subfractions with stroke outcome.

Some limitations of the study are noted. In general, the incidence of stroke was low, particularly among Chinese-Americans. Future studies should seek to include a larger sample of minority participants. Furthermore, while the follow-up of this study extended to 9.5 years, increasing time duration of follow-up may capture other stroke events that occurred later in follow-up. These results do not indicate causality as HDL properties cannot be randomized. This study did not specifically assess HDL function, which warrants additional follow-up to the findings reported from these analyses. Additionally, HDL cholesterol may be influenced by a number of factors that were not included in analysis including diet, exercise, and alcohol intake. Despite these weaknesses, results are broadly adjusted for known risk factors for stroke and prospective cohort studies are the highest level of evidence for exposures that cannot be randomized.

Summary/Conclusions

In conclusion, lower levels of HDL cholesterol and large HDL particles are associated with elevated stroke risk, specifically in Blacks. These results have implications for risk assessment as well as treatment for individuals identified as at-risk for stroke event. More specifically, the way in which race/ethnicity may compound risk for stroke deserves greater attention. Further research is warranted to understand the mechanisms by which HDL functions to influence stroke risk in different races/ethnicities. More research is also needed to elucidate the relationship between HDL-P and stroke outcome, given that this has been identified as a significant predictor of cardiovascular events in other studies.

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- The degree to which ethnicity moderates the risk between HDL cholesterol and stroke is unknown.
- The associations among cholesterol content and stroke risk, particle number and stroke risk, and the interaction with race were explored.
- Higher HDL cholesterol and a higher concentration of large particles are associated with lower risk of stroke in Blacks.

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Table 1

Descriptive characteristics (mean and standard deviation) of the total sample and by race/ethnicity.

Variable	**Total Sample, N = 6769**	**Whites, N = 2601**	**Blacks, N = 1879**	**Hispanics, N = 1486**	**Chinese Americans, N = 803**
Age (years)	62.14 (10.24)	62.57	62.14	61.25	62.35
BMI (kg/m^2)	28.32 (5.47)	27.70 (5.04)	30.17 (5.87)	29.42 (5.09)	23.98 (3.30)
Seated systolic blood pressure (mmHg)	126.58 (21.50)	123.45 (20.43)	131.69 (21.62)	126.67 (21.93)	124.57 (21.63)
Total cholesterol (mmol/L)	5.02 (.92)	5.06 (.91)	4.90 (.94)	5.12 (.97)	4.98 (.82)
HDL cholesterol (mmol/L)	1.32 (.38)	1.35 (.40)	1.36 (.40)	1.23 (.34)	1.28 (.33)
Triglycerides (mmol/L)	3.40 (2.30)	3.43 (2.33)	2.71 (1.77)	4.06 (2.62)	3.69 (2.19)
HDL particles (total) (μmol/L)	34.04 (6.66)	35.00 (7.04)	33.47 (6.50)	33.23 (6.26)	33.72 (5.88)
Large HDL (9.4-14 nm) (μmol/L)	6.02 (3.46)	6.06 (3.57)	6.45 (3.65)	5.38 (3.04)	6.07 (3.18)
Medium HDL (8.2-9.4 nm) (μmol/L)	13.27 (6.84)	14.98 (7.43)	11.79 (5.98)	13.42 (6.50)	10.93 (5.77)
Small HDL (7.3-8.2 nm) (μmol/L)	14.74 (5.73)	13.97 (5.94)	15.23 (5.49)	14.43 (5.46)	16.72 (5.53)
Variable	N (% of Sample)	Whites, N = 2601	Blacks, N = 1879	Hispanics, N = 1486	Chinese Americans, N = 803
Stroke Outcome	176 (2.6)	67 (2.6)	53 (2.8)	45 (3.0)	11 (1.4)
Sex (Females)	3585 (53.0)	1358 (52.2)	1041 (55.4)	772 (52.0)	414 (51.6)
Cigarette Status (Users)	882 (13.0)	301 (11.6)	336 (17.9)	200 (13.5)	45 (5.6)
Medication Usage					
Lipid Lowering Drugs	1087 (16.1)	472 (18.1)	307 (16.3)	192 (12.9)	116 (14.4)
Hypertensive Meds	2520 (37.2)	860 (33.1)	948 (50.5)	481 (32.4)	231 (28.8)
Hypoglycemic Meds	581 (8.6)	98 (3.8)	220 (11.7)	184 (12.4)	79 (9.8)
Diabetes Status (Yes)	763 (11.3)	138 (5.3)	296 (15.8)	244 (16.4)	85 (10.6)
Education					
Less than HS	1216 (18.0)	126 (4.8)	228 (12.1)	663 (44.6)	199 (24.8)
HS/GED	1228 (18.1)	437 (16.8)	357 (19.0)	304 (20.5)	130 (16.2)
Some college	1921 (28.4)	740 (28.5)	648 (34.5)	371 (25.0)	162 (20.2)
College and above	2382 (35.2)	1291 (49.6)	632 (33.6)	148 (10.0)	311 (38.7)

Table 2

Correlations among all continuous covariates.

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. HDL Cholesterol conc (mmol/L)	1								
2. HDL Particle Number (µmol/L)	.692**	1							
3. HDL Large Particles (µmol/L)	.909**	.567**	1						
4. HDL Med Particles (µmol/L)	.451**	.628**	.279**	1					
5. HDL Small Particles (µmol/L)	-.284**	.066**	-.279**	-.633**	1				
6. BMI (kg/m2)	-.211**	-.086**	-.226**	-.076**	.128**	1			
7. Systolic Blood Pressure (mmHg)	.005	.074**	.016	-.018	.097**	.154**	1		
8. Total cholesterol (mmol/L)	.192**	.162**	.115**	.106**	-.008	-.008	.036**	1	
9. Triglycerides (mmol/L)	-.374**	.030*	-.343**	-.083**	.272**	.109**	.061**	.288**	1

** $p < .01$,

* $p < .05$

Table 3

Results from survival models with HDL composite measures, adjusted for all covariates.

Variable	B	SE	Hazard ratio	95% CI
Model 1				
Age	.056**	.009	1.06	1.039 – 1.077
Sex (M/F)	.147	.160	1.16	.846 – 1.586
Race/Ethnicity:			1.00	
Whites	REF			
Blacks	-.016	.224	.98	.634 – 1.528
Hispanics	-.157	.242	.86	.532 – 1.373
Chinese Americans	-.200	.241	.82	.511 – 1.313
Education				
Less than HS	REF		1.00	
HS/GED	-.200	.241	.82	.511 – 1.313
Some college	-.016	.224	.98	.634 – 1.528
College and above	-.157	.242	.86	.532 – 1.373
Cigarette status	.685**	.215	1.98	1.302 – 3.022
Medication:				
Lipid Lowering Drugs	-.183	.203	.83	.559 – 1.240
Hypertensive medication	.342*	.170	1.41	1.009 – 1.962
Hypoglycemic medication	.484*	.211	1.62	1.073 – 2.456
BMI (kg/m2)	.018	.016	1.02	.988 – 1.049
Systolic Blood Pressure	.018**	.003	1.02	1.011 – 1.025
Total cholesterol	.077	.088	1.08	.909 – 1.283
Triglycerides	.326*	.159	1.39	1.014 – 1.894
Diabetes status	.065	.234	1.07	.674 – 1.689
Model 2				
HDL-C	-.589*	.294	.56	.312 – .988
Model 3				
HDL-P	-.231	.132	.79	.613 – 1.027
Model 4				
HDL Large Particles	-.663*	.315	.52	.278 – .956
HDL Medium Particles	-.102	.161	.90	.659 – 1.237
HDL Small Particles	-.134	.186	.87	.607 – 1.259

** $p < .01$,

* $p < .05$

Model 1 included all covariates without any HDL composite measures.

Model 2 included all covariates plus HDL-C.

Model 3 included all covariates plus HDL-P.

Model 4 included all covariates plus all three HDL size composites.

Table 4

Simple effects from the race/ethnicity interactions with HDL composite measures.

Interaction	B	Hazard Ratio	95% CI
HDL-C			
Whites	-.417	.66	.313 – 1.388
Blacks	-1.378**	.25	.097 - .658
Hispanics	-.348	.71	.267 – 1.865
Chinese Americans	.913	2.49	.522 – 11.893
HDL Large particles			
Whites	-.370	.69	.306 – 1.560
Blacks	-1.640**	.19	.066 - .568
Hispanics	-.508	.60	.202 – 1.790
Chinese Americans	.929	2.53	.482 – 13.283

Adjusted for all relevant covariates.

** $p < .01$