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Relation of Black Race between High Density Lipoprotein Cholesterol Content, High Density Lipoprotein Particles and Coronary Events (From the Dallas Heart Study)

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Abstract

Therapies targeting high density lipoprotein cholesterol content (HDL-C) have not improved coronary heart disease (CHD) outcomes. HDL particle concentration (HDL-P) may better predict CHD. However, the impact of race/ethnicity on the relations between HDL-P and subclinical atherosclerosis/ incident CHD events has not been described. Participants from the Dallas Heart Study, a multiethnic, probability-based, population cohort of Dallas County adults had the following baseline measurements: HDL-C, HDL-P by nuclear magnetic resonance imaging (NMR), and coronary artery calcium (CAC) by electron beam computed tomography. Participants were followed for a median of 9.3 years for incident CHD events (composite of first myocardial infarction, stroke, coronary revascularization, or cardiovascular death). The study comprised 1977 participants free from CHD (51% women, 46% Black). In adjusted models, HDL-C was not associated with prevalent CAC (p=0.13) or incident CHD overall (HR per 1SD: 0.89, 95% CI 0.76–1.05). However, HDL-C was inversely associated with incident CHD among non-Black (adjusted HR per 1SD 0.67, 95% CI 0.46–0.97) but not Black participants (HR 0.94, 95% CI 0.78–1.13, $p_{interaction} = 0.05$). Conversely, HDL-P, adjusted for risk factors and HDL-C, was inversely associated with prevalent CAC (p=0.009) and with incident CHD overall (adjusted HR per 1SD: 0.73, 95% CI 0.62–0.86) with no interaction by Black race/ethnicity ($p_{interaction} = 0.57$). In conclusion, in contrast to HDL-C, the inverse relationship between HDL-P and incident CHD

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events is consistent across ethnicities. These findings suggest that HDL-P is superior to HDL-C in predicting both prevalent atherosclerosis as well as incident CHD events across a diverse population and should be considered as a therapeutic target.

Keywords

high density lipoprotein cholesterol; high density lipoprotein particles; race and ethnicity; coronary heart disease; coronary calcium

HDL particle concentration (HDL-P) is an emerging marker that may better predict CHD and response to therapy than does high density lipoprotein cholesterol content (HDL-C). A population-based study from MESA (Multi-Ethnic Study of Atherosclerosis) revealed that HDL-P independently associates with reduced risk of incident CHD, even when adjusting for HDL-C, but the inverse association between HDL-C and CHD was attenuated after adjustment for HDL-P.[1] More recently, post-hoc analysis of the JUPITER (Justification for the Use of Statins in Prevention: Intervention Trial Evaluating Rosuvastatin) study showed that among individuals randomized to high potency statin therapy, on-treatment HDL-P was the only HDL composition marker that significantly associated with CHD events.[2] Although the variation in HDL-C across race/ethnicities is well-described, little is known about the race/ethnicity-specific cardiovascular epidemiology of HDL-P. The aim of this study is to compare the determinants of HDL-C and HDL-P and examine race/ethnicity-specific associations between HDL-P and sub-clinical and clinical atherosclerotic phenotypes.

Methods

The Dallas Heart Study (DHS) is a multiethnic, probability-based, population cohort study of Dallas County residents, with deliberate oversampling of Black participants. The study design has been extensively described previously.[3] Briefly, between 2000–2002, 2,971 participants completed a detailed in-home survey, laboratory testing, and imaging studies. For the current study, the study population comprised 1,977 participants who, at study entry, were not taking any lipid lowering medication or hormone replacement therapy, were free from malignancy, connective tissue disease, or HIV, and who survived at least 1 year since the baseline clinic visit. All participants provided written informed consent, and the protocol was approved by the institutional review board of the University of Texas Southwestern Medical Center.

Race/ethnicity, sex, smoking status, history of CHD, menopause status, exercise amount, and alcohol intake were self-reported. Blood pressure measurements were taken at rest, while seated. Five measurements were taken and the last three readings were averaged. Hypertension was defined as average systolic blood pressure ≥ 140 mmHg, average diastolic blood pressure ≥ 90 mmHg, or use of any anti-hypertensive medication. Diabetes was defined as fasting glucose level ≥ 126 mg/dL or use of any hypoglycemic medication. Smoking was defined as any current smoker.

Venous blood was collected in a fasting state in ethylenediaminetetraacetic acid (EDTA) tubes. They were maintained at 4°C for ≤ 4 hours prior to centrifugation at 1430 x *g* for 15

minutes. Plasma was then extracted and frozen at −80°C until assays were performed by blinded individuals. High sensitivity C-reactive protein (hs-CRP) was analyzed by previously described technique.[4] HOMA-IR (homeostasis model assessment of insulin resistance index) was calculated by fasting insulin (μIU/mL) x fasting glucose (mmol/l)/ 22.5.[5] HDL particle sizes and concentrations were measured by LipoScience, Inc. (Raleigh, NC) using nuclear magnetic resonance (NMR) spectroscopy.

Coronary artery calcium (CAC) was measured by electron beam computed tomography (EBCT) in duplicates 1 – 2 minutes apart using an Imatron 150 XP scanner (Imatron Inc., San Bruno, CA).[6] CAC scores were expressed in Agatston units with the mean of two consecutive scans used as the final score.

All participants were followed for a median 9.3 years [IQR 8.8 – 9.8]. CHD events were adjudicated by two blinded cardiologists and defined as non-fatal myocardial infarction (MI), stroke, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), or CV death.[7]

HDL-C, HDL-P, and HDL size were expressed as medians with interquartile ranges. Levels of each parameter were compared across race/ethnicities among men and women separately using Wilcoxon rank-sum tests. Sex-specific linear regression models using multiple covariates were used to model HDL-C and HDL-P. Contribution of the models to the variance in HDL-C and HDL-P was assessed by the adjusted R^2 values. Individual covariates' contributions within these models were compared by their standardized beta coefficients (standard deviation unit change in HDL-C or HDL-P per 1 standard deviation change in the covariate). The independent associations of HDL-C and HDL-P with coronary calcium were assessed in models adjusted for age, sex, hypertension, diabetes, smoking, BMI, non-HDL, log triglyceride, menopause status, and alcohol (grams/week), and include both HDL-C and HDL-P. Cox proportional hazards models were used to determine hazard ratios for one standard deviation increases in HDL-C and HDL-P for time to first incident CHD events, adjusted for the same covariates above. In these models, participants with a history of lipid-lowering therapy, hormone replacement therapy, and history of CVD were also included and models were additionally adjusted for these covariates. Hazard ratios were then determined for non-fatal and fatal events separately. Interactions with sex and race/ ethnicity (Black vs. non-Black) were tested for all models. Two-sided p-values < 0.05 were considered significant. All analyses were performed using SAS 9.3 (Raleigh, NC, USA).

Results

The study comprised 1977 adult participants, 51% were women, and 46% were Black. Among men, Blacks had highest median HDL-C and HDL-P and largest median HDL particle size (Table 1). However, the magnitude of the differences in median HDL-P (2%) and HDL size (3%) were smaller than those in HDL-C (17%). Among women, White women had the highest median HDL-C and HDL-P (Table 1). Unlike Black men, Black women had discordant HDL composition compared to White women (similar median HDL-C but lowest median HDL-P and largest HDL particles). Black women, Hispanic women,

and White men had HDL-C levels ranging from 41 to 52 mg/dL despite all having the same median HDL-P level of 32 μmol/L.

Measured risk factors explained a larger proportion of the variance in HDL-C than HDL-P in both men and women. This difference was greater in men, where measured risk factors accounted for more than twice the variability in HDL-C compared with HDL-P (R^2=0.29 for HDL-C vs. 0.13 for HDL-P in men) (Table 2). Alcohol intake was the only risk factor associated with both HDL-C and HDL-P in both men and women.

Among men, factors positively associated with HDL-C included Black ethnicity, diabetes, exercise, and alcohol intake, and factors inversely associated with HDL-C included HOMA-IR, triglycerides, and hs-CRP (Table 2). In contrast, only HOMA-IR, alcohol intake, and hs-CRP were significantly associated with HDL-P in men. Among women, factors positively associated with HDL-C included age, exercise, and alcohol intake, whereas inverse associations included hypertension, smoking, HOMA-IR, triglycerides, and hs-CRP (Table 2). Factors associated with HDL-P included age, Black and Hispanic ethnicity, smoking, alcohol, and triglycerides. Notable sex-based differences in determinants of HDL composition included age and smoking (associated in women but not in men for both HDL-C and HDL-P) (Table 2). Interestingly, Black ethnicity was positively associated with HDL-C only in men and inversely associated with HDL-P only in women.

HDL-C was not associated with prevalent CAC in adjusted models (p=0.13). However serial adjustment for HDL-P resulted in a positive association between HDL-C and CAC (standardized beta = 0.07, p=0.008). HDL-P was inversely associated with prevalent CAC in fully adjusted models including HDL-C (standardized beta = −0.06, p=0.009). There were no statistically significant interactions by sex or ethnicity for associations between either HDL-C or HDL-P and prevalent CAC.

HDL-C was inversely associated with incident CHD in unadjusted models (HR per 1SD: 0.84, 95% CI 0.73–0.97) (Table 3). This association was partially attenuated in models adjusted for traditional risk factors and fully attenuated with further adjustment for HDL-P (fully adjusted HR per 1SD: 1.07, 95% CI 0.89–1.29) (Table 3). However, there was a significant interaction between HDL-C and ethnicity ($p_{interaction}$ = 0.05) such that HDL-C was inversely associated with incident CHD in non-Black participants (adjusted HR per 1SD: 0.67, 95%CI 0.46–0.97) but not among Black participants (adjusted HR per 1SD: 0.94, 95% CI 0.78–1.13) (Figure 1). This interaction between HDL-C and Black ethnicity was driven by non-fatal events (Figure 1).

HDL-P was inversely associated with incident CHD in unadjusted models (HR per 1SD: 0.76, 95% CI 0.66–0.87) (Table 3). This association was not attenuated in fully adjusted models including HDL-C (adjusted HR per 1SD: 0.73, 95% CI 0.62–0.86). HDL-P was inversely associated with both non-fatal and fatal events in fully adjusted models (Table 3). There was no statistically significant interaction between HDL-P and sex or ethnicity (Black vs. non-Black) for incident CHD events ($p_{interaction}$ >0.05) (Figure 1). Sensitivity analyses excluding participants with a history of CVD did not change the findings.

Discussion

In a large multi-ethnic population-based cohort, we describe for the first time that factors that associate with levels of HDL-P, a novel marker of HDL composition, vary significantly from those that associate with HDL-C in an ethnicity- and sex-specific manner. This is also the first report to show that HDL-P inversely associates with prevalent coronary calcium among the general population. In addition, we demonstrate that Black ethnicity modifies the association between HDL-C and incident CHD events whereas the inverse relationship between HDL-P and incident CHD events is consistent across sex and ethnicity categories. These findings support the concept that measurement of HDL-P is superior to HDL-C levels in predicting both prevalent sub-clinical coronary disease as well as incident CHD events across a diverse population.

Prior studies have established that low HDL-C is associated with incident CHD events, largely driven by its association with insulin resistance,[8] and is a major risk factor in current CHD risk score algorithms.[9] However, increases in HDL-C levels with various lipid-modifying therapies have not associated with improved CHD outcomes in prospective randomized controlled trials.[10–13] These discrepancies have prompted investigation into HDL particle composition as a novel CHD marker, mostly focusing on particle size. However, studies assessing large versus small HDL particles on therapy have also been inconsistent in their associations with CHD[2,14] in part due to the high correlation between HDL-C and HDL particle size. Recently, the Multi-Ethnic Study of Atherosclerosis (MESA) reported that, when adjusted for each other, total HDL-P measured by NMR but not HDL-C was inversely associated with both prevalent carotid intima media thickness and incident CHD events.[1] Subsequently, a post-hoc analysis of a randomized, placebo-controlled clinical trial of rosuvastatin (JUPITER) showed that on-treatment HDL-P was the only marker of HDL composition that was associated with a reduction in CHD events.[2] Of note, niacin and fenofibrate, therapies that have failed to improve cardiovascular outcomes when added to statins,[11,13,15] both significantly increase HDL-C and HDL size but have minimal to no effects on total HDL-P.[16,17] These studies suggest that HDL-P better predicts CHD and responses to therapy than HDL-C and markers of HDL size.

HDL-C levels vary by race/ethnicity but little is known about the impact of race/ethnicity on the association between HDL parameters and CHD.[18,19] Our study is the largest to date investigating differences in HDL composition as measured by NMR by ethnicity, including 593 non-White men and 702 non-White women. We found that race/ethnicity-specific differences in HDL composition were modified by sex. Black race/ethnicity was positively associated with HDL-C in men but inversely associated with HDL-P in women, highlighting the heterogeneous impact of race/ethnicity on HDL composition.

These heterogeneous associations of race/ethnicity and HDL composition support stratified analyses of HDL composition and subclinical CHD phenotypes and clinical events. Indeed, we found an interaction between Black race/ethnicity and HDL-C with regard to incident CHD events, such that HDL-C was only associated with incident CHD among non-Blacks, driven mostly by the association between HDL-C and non-fatal CHD events. Similar findings were seen in the Jackson Heart Study with respect to HDL-C.[20] In contrast, the

inverse association between HDL-P and incident CHD was consistent across sex and ethnicity categories and was not attenuated by adjustment for risk factors or HDL-C, whereas any association between HDL-C and incident CHD was fully attenuated by adjustment for HDL-P. Our findings regarding race/ethnicity interactions for incident events were similar to those seen in a prior study with respect to HDL-P but were different with respect to HDL-C.[1] In our study, participants were much younger (44 vs. 61 years old) and had a higher proportion of Blacks (46% vs. 28%), which may have contributed to the differences. It may be that age and ethnicity impact HDL-C more than HDL-P and their associations with CHD. These findings contribute new information as to the heterogeneous impact of Black race/ethnicity on associations between HDL markers and outcomes, supporting the superiority of HDL-P over HDL-C in predicting incident CHD.

Our study is the first to report an inverse association between HDL-P and prevalent coronary calcium (CAC) in the general population. CAC is a noninvasive marker of coronary atherosclerosis and is robustly associated with incident CHD. Carotid intima media thickness, a measure of subclinical peripheral atherosclerosis, is also inversely associated with HDL-P levels.[1] Interestingly, the association between HDL-P and CHD is not attenuated by traditional CHD risk factors, suggesting that low HDL-P may reflect a novel pathway in the progression of arterial atherosclerosis and the development of subsequent CHD events.

Strengths of the study include large sample size, racially/ethnically diverse population, and subclinical atherosclerosis phenotyping. Limitations include inability to determine causation given the observational study design or to exclude the effect of unmeasured confounders. Apolipoprotein A-I concentration was not available in the Dallas Heart Study to correlate with other measures of HDL particle composition.

These findings support the concept that measurement of HDL-P is superior to HDL-C in predicting both prevalent subclinical coronary disease and incident CHD events across a diverse population. Given emerging evidence that on-treatment HDL-P numbers consistently predict CHD events better than on-treatment HDL-C or HDL particle size, the impact of ethnicity on the clinical benefits of various lipid-modifying therapies should be fully explored. Investigation of the effects across the spectrum of lipid-modifying therapies on HDL-P as they relate to outcomes are now warranted, and serious consideration should be given to focusing on raising HDL-P levels as a therapeutic target to reduce CHD risk.

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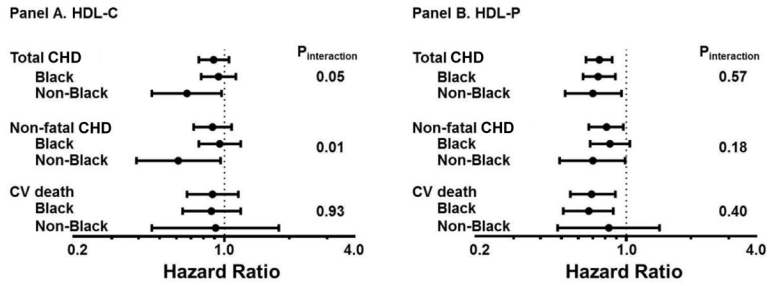

Figure 1. Hazard Ratios for High Density Lipoprotein Cholesterol (HDL-C) and High Density Lipoprotein Particle (HDL-P) and Incident Coronary Heart Disease (CHD) Stratified by Ethnicity

Hazard ratios and 95% confidence interval were calculated per 1 standard deviation (SD). All hazard ratios were adjusted for age, sex, ethnicity, hypertension, diabetes, smoking, body mass index (BMI), non-HDL, log Triglyceride, any lipid lowering drug, hormone replacement therapy, menopause status, alcohol (grams/week), and history of CHD at baseline. CHD events were defined as non-fatal myocardial infarction, stroke, coronary artery bypass grafting, percutaneous coronary intervention, and CV death (N=226: non-fatal =155; CV death = 81).

Table 1

High Density Lipoprotein Cholesterol Content (HDL-C), High Density Lipoprotein Particles (HDL-P), and High Density Lipoprotein (HDL) Size by Sex and Ethnicity

	N	HDL-C (mg/dL))	HDL-P (μmol/L)	HDL size (nm)
Men				
Black	425	48 (40 – 57)	33 (29 – 37)	8.9 (8.6 – 9.3)
White	337	41 (35 – 48)	32 (29 – 35)	8.7 (8.5 – 8.9)
Hispanic	168	41 (36 – 49)	30 (27 – 35)	8.7 (8.6 – 8.9)
p-value	<0.0001	0.0055	<0.0001	
Women				
Black	492	52 (45 – 62)	32 (29 – 37)	9.2 (8.9 – 9.5)
White	297	53 (44 – 63)	35 (31 – 39)	9.1 (8.8 – 9.4)
Hispanic	210	48 (40 – 55)	32 (28 – 36)	9.1 (8.9 – 9.3)
p-value	<0.0001	<0.0001	0.0053	

Median values reported with interquartile range. P-values derived from Wilcoxon rank-sum comparisons across ethnicity.

Table 2

Correlates of High Density Lipoprotein Cholesterol Content (HDL-C) and High Density Lipoprotein Particles (HDL-P) by Sex

		HDL-C		HDL-P	
Men	**n = 848**	**R^2 = 0.29**		**R^2 = 0.13**	
		Std β	**p-value**	**Std β**	**p-value**
	Age	−0.0038	0.91	0.0069	0.85
	Black	**0.18**	**<0.00010**	0.056	0.15
	Hispanic	0.019	0.56	−0.036	0.34
	Hypertension	−0.018	0.57	0.020	0.58
	Diabetes mellitus	**0.10**	**0.0045**	0.051	0.19
	Smoking history	0.0063	0.84	−0.051	0.13
	HOMA-IR	**−0.095**	**0.0069**	***−0.14***	***0.0004***
	Exercise	**0.11**	**0.00020**	0.060	0.068
	Alcohol use	**0.20**	**<0.00010**	***0.24***	***<0.0001***
	Log triglyceride	**−0.35**	**<0.00010**	0.00079	0.98
	Family history	0.0020	0.95	−0.040	0.24
	hs-CRP	**−0.088**	**0.0037**	***−0.19***	***<0.0001***
Women	**n = 935**	R^2 = 0.21		R^2 = 0.13	
		Std β	**p-value**	**Std β**	**p-value**
	Age	**0.25**	**<0.00010**	***0.21***	***<.00010***
	Black	−0.012	0.74	***−0.13***	***0.0011***
	Hispanic	−0.066	0.072	***−0.15***	***0.00010***
	Hypertension	−0.064	0.059	0.020	0.56
	Diabetes mellitus	0.013	0.71	0.015	0.68
	Smoking history	**−0.085**	**0.0053**	***−0.078***	***0.014***
	HOMA-IR	**−0.079**	**0.026**	−0.073	0.052
	Exercise	**0.097**	**0.0013**	0.033	0.29
	Alcohol use	**0.16**	**<0.00010**	***0.11***	***0.00060***
	Menopause	0.018	0.55	0.027	0.38

		HDL-C		HDL-P	
Men	**n = 848**	**R^2 = 0.29**		**R^2 = 0.13**	
		Std β	**p-value**	**Std β**	**p-value**
	Log triglyceride	**−0.29**	**<0.00010**	***0.11***	***0.0024***
	Family history	−0.033	0.28	0.016	0.62
	hs-CRP	**−0.080**	**0.0098**	0.055	0.093

Standardized beta estimates derived from sex-stratified multivariate models adjusted for all listed variables. R2 values represent contribution of the model to the variance in HDL-C or HDL-P. HOMA-IR: homeostatic model assessment – insulin resistance; Alcohol: gram of alcohol intake/week.

Table 3

Hazard Ratios for High Density Lipoprotein Cholesterol Content (HDL-C) and High Density Lipoprotein Particles (HDL-P) and Incident Coronary Heart Disease (CHD)

	Total CHD	Non-fatal CHD	CV Death
HDL-C			
Unadjusted	0.84 (0.73–0.97)	0.84 (0.70–1.00)	0.85 (0.67–1.07)
Adjusted for TRFs	0.89 (0.76–1.05)	0.88 (0.72–1.08)	0.88 (0.67–1.16)
Adjusted for TRFs+HDL-P	1.07 (0.89–1.29)	1.00 (0.79–1.26)	1.12 (0.84–1.49)
HDL-P			
Unadjusted	0.76 (0.66–0.87)	0.81 (0.69–0.96)	0.69 (0.55–0.87)
Adjusted for TRFs	0.75 (0.65–0.86)	0.81 (0.68–0.97)	0.70 (0.55–0.89)
Adjusted for TRFs + HDL-C	0.73 (0.62–0.86)	0.81 (0.66–0.99)	0.67 (0.51–0.87)

Hazard ratios and 95% CIs derived from Cox-proportional hazards models for 1 SD increase in HDL-C or HDL-P. TRFs = age, sex, ethnicity, hypertension, diabetes, smoking, BMI, non-HDL-C, log triglyceride, any lipid-lowering therapy, hormone replacement therapy, menopause, alcohol intake, and history of CHD at baseline. Total CHD (N=226): non-fatal myocardial infarction and stroke, coronary artery bypass grafting, percutaneous coronary interventions, and cardiovascular (CV) death. Non-fatal CHD (N=155) excluded CV death. CV death (N=81).