# 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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**Therapies targeting high-density lipoprotein cholesterol content (HDL-C) have not improved coronary heart disease (CHD) outcomes. High-density lipoprotein particle concentration (HDL-P) may better predict CHD. However, the impact of race/ethnicity on the relations between HDL-P and subclinical atherosclerosis and incident CHD events has not been described. Participants from the Dallas Heart Study (DHS), a multiethnic, probability-based, population cohort of Dallas County adults, underwent the following baseline measurements: HDL-C, HDL-P by nuclear magnetic resonance imaging, and coronary artery calcium 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 1,977 participants free of CHD (51% women, 46% black). In adjusted models, HDL-C was not associated with prevalent coronary artery calcium ($p = 0.13$) or incident CHD overall (hazard ratio [HR] per 1 SD 0.89, 95% confidence interval [CI] 0.76 to 1.05). However, HDL-C was inversely associated with incident CHD among nonblack (adjusted HR per 1 SD 0.67, 95% CI 0.46 to 0.97) but not black participants (HR 0.94, 95% CI 0.78 to 1.13, $p_{interaction} = 0.05$). Conversely, HDL-P, adjusted for risk factors and HDL-C, was inversely associated with prevalent coronary artery calcium ($p = 0.009$) and with incident CHD overall (adjusted HR per 1 SD 0.73, 95% CI 0.62 to 0.86), with no interaction by black race/ethnicity ($p_{interaction} = 0.57$). In conclusion, in contrast to HDL-C, the inverse relation between HDL-P and incident CHD events is consistent across ethnicities. These findings suggest that HDL-P is superior to HDL-C in predicting prevalent atherosclerosis as well as incident CHD events across a diverse population and should be considered as a therapeutic target.**  **(Am J Cardiol 2015;115:890−894)**

High-density lipoprotein (HDL) particle concentration (HDL-P) is an emerging marker that may better predict coronary heart disease (CHD) and response to therapy than does high-density lipoprotein cholesterol content (HDL-C). A population-based study from the Multi-Ethnic Study of Atherosclerosis (MESA) revealed that HDL-P was independently associated with reduced risk for 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 Justification for the Use of Statins in Prevention: Intervention Trial Evaluating Rosuvastatin (JUPITER) study showed that among subjects randomized to high-potency statin therapy, on-treatment HDL-P was the only HDL composition marker that was 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 aims of this study were to compare the determinants of HDL-C and HDL-P and to examine race/ethnicity-specific associations between HDL-P and subclinical 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, from 2000 to 2002, 2,971 participants completed a detailed in-home survey, laboratory testing, and imaging studies. For the present study, the study population comprised 1,977 participants who, at study entry, were not taking any lipid-lowering medications or hormone replacement therapy; were free of malignancy, connective tissue

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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

| Men | n = 848 | HDL-C | | HDL-P | |
|---|---|---|---|---|---|
| | | R2 = 0.29 | | R2 = 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 | R2 = 0.21 | | R2 = 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 |
| | 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.

The bold values identify those with significant P values < 0.05. The italics are for the HDL-P.

disease, and human immunodeficiency virus infection; and who survived ≥1 year after 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, gender, 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 3 readings were averaged. Hypertension was defined as average systolic blood pressure ≥140 mm Hg, average diastolic blood pressure ≥90 mm Hg, or use of any antihypertensive medication. Diabetes was defined as fasting glucose level ≥126 mg/dl or use of any hypoglycemic medication. Smoking was defined as any current smoking.

Venous blood was collected in a fasting state in ethylenediaminetetraacetic acid tubes. They were maintained at 4°C for ≤4 hours before centrifugation at 1,430g for 15 minutes. Plasma was then extracted and frozen at −80°C until assays were performed by blinded researchers. High-sensitivity C-reactive protein (hs-CRP) was analyzed using a previously described technique.[4] The homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated as fasting insulin (μIU/ml) × fasting glucose (mmol/L)/22.5.[5] HDL particle sizes and HDL-P were measured by LipoScience, Inc. (Raleigh, North Carolina) using nuclear magnetic resonance spectroscopy.

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

All participants were followed for a median of 9.3 years (interquartile range 8.8 to 9.8). CHD events were adjudicated by 2 blinded cardiologists and defined as nonfatal myocardial infarction, stroke, coronary artery bypass graft surgery, percutaneous coronary intervention, or cardiovascular death.[7]

HDL-C, HDL-P, and HDL particle size were expressed as medians with interquartile ranges. Levels of each parameter were compared across race/ethnicities in men and women separately using Wilcoxon rank sum tests. Gender-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 adjusted $R^2$ values. Individual covariates' contributions within these models were compared by their standardized β coefficients (SD unit change in HDL-C or HDL-P per 1 SD change in the covariate). The independent associations of HDL-C and HDL-P with coronary calcium were assessed in models adjusted for age, gender, hypertension, diabetes, smoking, body mass index, non-HDL, log-transformed triglyceride, menopause status, and alcohol (grams/week) and include HDL-C and HDL-P. Cox proportional hazards models were used to determine hazard ratios (HRs) for 1-SD increases in HDL-C and HDL-P for time to first incident CHD events, adjusted for the same covariates listed previously. In these models, participants with histories of lipid-lowering therapy, hormone replacement therapy, and cardiovascular disease were also included, and models were