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# Discordance of Low-Density Lipoprotein and High-Density Lipoprotein Cholesterol Particle Versus Cholesterol Concentration for the Prediction of Cardiovascular Disease in Patients With Metabolic Syndrome and Diabetes Mellitus (from the Multi-Ethnic Study of Atherosclerosis [MESA])

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A stronger association for low-density lipoprotein particle (LDL-P) and high-density lipoprotein particle (HDL-P) versus cholesterol concentrations (LDL-C and HDL-C) in predicting coronary heart disease (CHD) has been noted. We evaluate the role of these factors and extent of particle-cholesterol discordance in those with diabetes mellitus (DM) and metabolic syndrome (MetS) for event prediction. In the Multi-Ethnic Study of Atherosclerosis, we examined discordance of LDL and HDL (defined as a subject's difference between baseline particle and cholesterol percentiles), LDL-C, LDL-P, HDL-C, and HDL-P in relation to incident CHD and cardiovascular disease (CVD) events in subjects with DM, MetS (without DM), or neither condition using Cox regression. Of the 6,417 subjects with 10-year follow-up, those with MetS (n = 1,596) and DM (n = 838) had significantly greater LDL and HDL discordance compared with those without these conditions. In discordance models, only LDL discordance (per SD) within the MetS group was positively associated with CHD events (adjusted hazard ratio [HR] = 1.22, 95% confidence interval [CI] 1.01 to 1.48, p < 0.05). In models with individual particle/cholesterol variables (per SD), within the DM group, HDL-P was inversely (HR 0.71, 95% CI 0.52 to 0.96, p < 0.05) and LDL-C positively (HR 1.47, 95% CI 1.07 to 2.03, p < 0.05) associated with CHD. In those with MetS, only LDL-P was positively associated with CHD (HR 1.34, 95% CI 1.00 to 1.78, p < 0.05). Similar findings were also seen for CVD. LDL discordance and higher LDL-P in MetS, and higher LDL-C and lower HDL-P in DM, predict CHD and CVD, supporting a potential role for examining lipoprotein particles and discordances in those with MetS and DM. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;■:■–■)

Current guidelines recommend statin therapy in patients with diabetes mellitus (DM) for prevention of cardiovascular disease (CVD).<sup>1</sup> Low-density lipoprotein cholesterol (LDL-C) concentration has been the primary focus of

treatment, but many with well-controlled LDL-C levels still have considerable residual CVD risk.<sup>2</sup> Although high-density lipoprotein cholesterol (HDL-C) is inversely associated with coronary heart disease (CHD),<sup>3</sup> it does not fully capture HDL-related CVD risk.<sup>4,5</sup> Both LDL and HDL particles range in size, densities, and composition. Although HDL particle number and size have been correlated to total HDL-C, the association is complex. HDL particle concentration (HDL-P), but not HDL cholesterol content, is inversely associated with CHD and subclinical disease,<sup>4</sup> and other studies have shown stronger associations of LDL particle concentration (LDL-P) than LDL-C with both subclinical disease<sup>6</sup> and CVD events.<sup>7</sup> Furthermore, studies show that in those with low LDL-C but discordantly high LDL-P or high LDL-C but discordantly low LDL-P, the risk of CVD events is related to LDL-P but not LDL-C.<sup>8,9</sup> There is, however, a lack of information on the relation of LDL-P and HDL-P on CVD risk prediction in patients with DM and metabolic syndrome (MetS). We hypothesize that the extent of discordance between LDL and HDL particle and cholesterol concentration at the patient level is related to CVD risk in MetS and DM.

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See page 6 for disclosure information.

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## Methods

The design of the Multiethnic Study of Atherosclerosis (MESA), a National Institutes of Health–sponsored prospective epidemiologic study of the prevalence, risk factors, and subclinical disease predictors of CVD has been previously published.<sup>10</sup> Briefly, 6,814 multiethnic participants aged 45 to 84 years were recruited from 6 US communities in 2000 to 2002 and were absent of known CVD. Recruitment was based on lists of residents, dwellings, telephone exchanges, lists of Medicare beneficiaries, and referrals by participants. The present study included 6,417 subjects with lipid concentration/particle and required covariates for CVD and CHD event analysis. Institutional review board approval was obtained from all MESA Field Centers.

Age, gender, race/ethnicity, and risk factor information were collected at the baseline MESA examination (2000 to 2002). Smoking was categorized as being either a former smoker (smoked  $\geq 100$  cigarettes in lifetime) or current (smoked cigarette in last 30 days). Family history of CHD was defined as a history of “heart attack” in parents, siblings, or child. Blood was drawn after a 12-hour fast and stored at  $-70^{\circ}\text{C}$ . Lipids and glucose were measured at a central laboratory. Lipids were assayed on thawed ethylenediaminetetraacetic acid plasma using Centers for Disease Control Prevention/National, Heart, Lung, and Blood Institute 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 was calculated using the Friedewald equation.<sup>11</sup> Plasma lipoprotein particle concentrations were measured at LipoScience, Inc. (Raleigh, North Carolina) by nuclear magnetic resonance spectroscopy. HDL-P and LDL-P (coefficient of variation  $<4\%$ ) are the sums of the particle concentrations of their respective subclasses, quantified from particle size using the amplitudes of their lipid methyl group nuclear magnetic resonance signals, and mean particle sizes are the weighted average of related subclasses.<sup>12</sup>

DM was defined as a fasting glucose  $\geq 7.0$  mmol/L (126 mg/dl) or if on insulin or oral DM medications. In those without DM, MetS was defined with  $\geq 3$  of the following: (1) waist circumference  $>88$  cm (35 in) for women and  $>102$  cm (40 in) for men, (2) HDL-C  $<1.0$  mmol/L (40 mg/dl) for men or  $<1.3$  mmol/L (50 mg/dl) for women, (3) fasting triglycerides  $\geq 1.7$  mmol/L (150 mg/dl), (4) blood pressure (BP)  $\geq 130$  mm Hg systolic or  $\geq 85$  mm Hg diastolic or on treatment, or (5) fasting glucose of 5.6 to 7.0 mmol/L (100 to 125 mg/dl), based on the American Heart Association/National Heart, Lung, and Blood Institute definition.<sup>13</sup> Those not defined as having DM or MetS were categorized into the neither disease group.

Incident CHD (myocardial infarction, CHD death, resuscitated cardiac arrest, definite angina or probable angina followed by revascularization) and CVD events (CHD, fatal or nonfatal stroke, or other atherosclerotic CVD death) were ascertained and adjudicated for MESA as previously described.<sup>14</sup> Follow-up time for those experiencing events was defined from the baseline examination date to the date of the first qualifying event. Those without an event were followed to death (from non-CVD causes), last follow-up, or the end of the study, after which they were censored.

Table 1

Baseline characteristics of study subjects with and without diabetes or metabolic syndrome by study group: Multi-Ethnic Study of Atherosclerosis

Characteristic	MetS without DM	DM	Neither DM nor MetS
	(N=1596)	(N=838)	(N=3983)
	Mean $\pm$ SD or N (%)		
Age (years)*	63.1 $\pm$ 10.0	64.7 $\pm$ 9.6	61.2 $\pm$ 10.3
Male	656 (41.1 %)	438 (52.3 %)	1957 (49.1 %)
Female	940 (58.9 %)	400 (47.7 %)	2026 (50.1 %)
White	644 (25.9 %)	157 (6.3 %)	1683 (67.8 %)
Black	150 (19.4 %)	102 (13.2 %)	522 (67.4 %)
Hispanic	407 (23.0 %)	325 (18.4 %)	1034 (58.6 %)
Chinese American	395 (28.4 %)	254 (18.2 %)	744 (53.4 %)
Systolic BP (mm Hg)*	133.6 $\pm$ 20.6	133.0 $\pm$ 22.2	122.2 $\pm$ 20.6
BP Medication*	760 (47.6 %)	472 (56.3 %)	862 (21.6 %)
BMI (kg/m <sup>2</sup> )*	30.8 $\pm$ 5.1	30.3 $\pm$ 5.8	26.7 $\pm$ 4.9
Cholesterol (mg/dL)*	195.8 $\pm$ 35.5	188.0 $\pm$ 37.5	193.8 $\pm$ 33.6
Triglycerides (mg/dL)*	172.5 $\pm$ 68.6	144.4 $\pm$ 73.6	102.9 $\pm$ 49.0
Smoker	790 (49.6 %)	422 (50.4 %)	1954 (49.2 %)
Family History of CHD <sup>†</sup>	688 (43.1 %)	320 (38.2 %)	1549 (38.9 %)
Statin Use*	259 (16.2 %)	208 (24.8 %)	470 (11.8 %)
HDL-C (mg/dl)*	43.2 $\pm$ 10.2	46.8 $\pm$ 13.2	55.2 $\pm$ 15.1
HDL-P ( $\mu\text{mol/l}$ )*	32.6 $\pm$ 6.4	32.7 $\pm$ 6.3	34.8 $\pm$ 6.7
LDL-C (mg/dl)*	118.1 $\pm$ 32.3	112.3 $\pm$ 33.4	118.0 $\pm$ 30.5
LDL-P ( $\mu\text{mol/l}$ )*	1354.3 $\pm$ 354.9	1264.8 $\pm$ 344.9	1199.2 $\pm$ 313.3

\* $p < 0.001$ , <sup>†</sup> $p < 0.01$ . Denotes statistical significance between the three study groups (DM, MetS without DM, and Neither Disease).

BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HDL-P = high-density lipoprotein particle; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; MetS = metabolic syndrome.

Analyses were performed using SAS, version 9.3 (SAS Institute, Cary, North Carolina). For patients with DM, MetS without DM (MetS), and neither disease group, we compared baseline laboratory values and cardiovascular risk factors using the chi-square test for categorical variables and the Student's *t* test or ANOVA for continuous variables. Percentile distributions of LDL-P, LDL-C, HDL-P, and HDL-C were calculated from the study sample. LDL and HDL discordance was defined as a subject's difference between respective baseline lipoprotein particle and cholesterol percentiles (e.g., LDL-P% – LDL-C%). The Student's *t* test was used to calculate significance among groups (MetS, DM, or neither condition) for mean LDL and HDL discordance. Incident CHD and CVD event rates were calculated by quartile of discordance for both LDL and HDL discordance among the 3 groups.

Cox proportional hazards regression provided hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for CHD and CVD events. HDL-C, HDL-P, LDL-C, and LDL-P were each separately modeled with adjustments for baseline age, gender, race/ethnicity, family history, systolic BP, BP medication, smoking, body mass index, and statin use in each of the 3 groups and among all participants. Three separate models were conducted for all

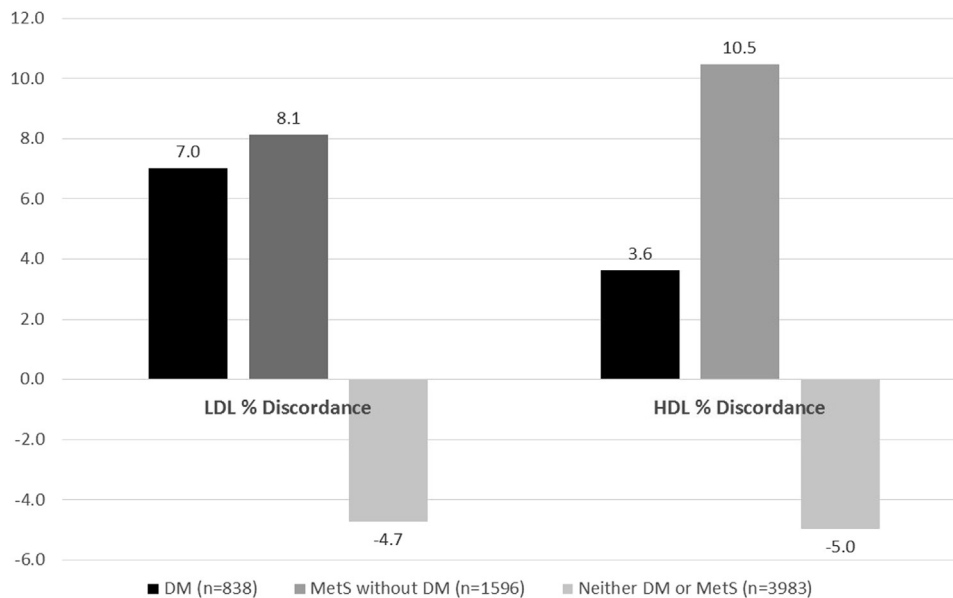


Figure 1. Percent discordance of particle versus cholesterol concentration for LDL and HDL. LDL % discordance and HDL % discordance is defined as a subject's difference between respective baseline lipoprotein particle and cholesterol percentiles. For LDL % discordance:  $p < 0.001$  among groups, except for DM versus MetS ( $p = 0.20$ ). For HDL % discordance:  $p < 0.001$  among groups.

participants together and then for each of the 3 groups using the above covariate adjustments. Model 1 examined the continuous HDL discordance variable, adjusted for LDL-C and LDL-P. Model 2 examined the continuous LDL discordance variable, adjusted for HDL-C and HDL-P. Model 3 examined the variables of HDL-C, HDL-P, LDL-C, and LDL-P separately but in the same model. All 3 models reflect adjustments for both particle and cholesterol concentration variables similar to previous studies.<sup>4</sup> All HRs were reported per SD to allow for direct comparison. Interaction between each LDL or HDL discordance, particle, and cholesterol variable with group variables were evaluated for significance. Interactions with gender and race/ethnicity were also examined. Sensitivity analyses were conducted for models 1 to 3 among all study groups, excluding patients with a history of statin use or hormone therapy at baseline and, separately, with the additional adjustment for excessive alcohol use (>14 drinks/week) and exercise (minutes/week).

Analysis involving dichotomous discordance (compared with continuous discordance analysis) as studied by others<sup>9</sup> involve categorizing individuals as  $<$  or  $\geq$  median levels of LDL-C. Discordance was defined as LDL-C greater than or equal to median and LDL-P less than the median level, or vice versa. This was also done for discordance groups between HDL-C and HDL-P. Risk factor-adjusted Cox regression was also used for discordantly high cholesterol/low particle groups versus high cholesterol/high particle groups.

## Results

Table 1 lists significant differences in baseline covariates among the 3 study groups. Both HDL-C and HDL-P were higher in participants without MetS or DM compared with neither disease ( $p < 0.001$ ). LDL-P was lower in those with

neither disease compared with both disease groups ( $p < 0.001$ ). Mean (SD) LDL discordance (LDL-P percentile – LDL-C percentile) among groups were 7.0 (21.3) for DM, 8.1 (19.3) for MetS alone, and  $-4.7$  (19.4) for those with neither disease. LDL discordance differed across all groups ( $p < 0.001$ ), except comparing DM and MetS ( $p = 0.20$ ) (Figure 1). Mean HDL discordance (HDL-P percentile – HDL-C percentile) among groups were 3.6 (22.7) for DM, 10.5 (19.4) for MetS alone and  $-5.0$  (19.5) for those with neither disease ( $p < 0.001$  between groups).

Of the 6,417 subjects, 462 subjects experienced CHD events and 659 subjects CVD events over an average 10-year follow-up. HDL discordance (model 1) was not predictive among the 3 study groups for either CHD or CVD (Table 2); however, in the entire sample, higher levels of HDL discordance were associated with decreased CHD (HR 0.90, 95% CI 0.81 to 1.00,  $p < 0.05$ ) and CVD (HR 0.90, 95% CI 0.83 to 0.99,  $p < 0.05$ ) events. Similar results were seen in sensitivity analyses in those without previous statin or hormone therapy use for CHD (HR 0.86, 95% CI 0.76 to 0.98,  $p < 0.05$ ) and CVD (HR 0.88, 95% CI 0.79 to 0.98,  $p < 0.05$ ); additionally, HDL discordance was associated with decreased CHD and CVD within the DM group. LDL discordance (model 2) was positively associated with CHD and CVD in the MetS group only but attenuated in sensitivity analyses excluding those with statin or hormone therapy use. When adjusting for the standard baseline covariates, interaction terms of HDL and LDL discordance variables with group, gender, and race/ethnicity variables were found to be insignificant.

Figure 2 shows with each increasing quartile of LDL discordance, there is a graded increase CHD and CVD event rates; this association with CHD was strongest in those with MetS (Figure 3) but is less clear within the DM or neither disease groups. In the overall sample, there was no

Table 2

Adjusted hazard ratio (95% confidence limits) for the likelihood of coronary heart disease (CHD) and cardiovascular disease (CVD) events by study groups

Variable	Hazard ratio (95% confidence interval) per standard deviation		
	MetS (without DM) (N= 1596)	DM (N= 838)	Neither DM nor MetS (N=3983)
CHD Events	139	105	218
Model 1 <sup>‡</sup> :	0.84 (0.68-1.04)	0.88 (0.72-1.08)	0.94 (0.80-1.10)
HDL Discordance			
Model 2 <sup>§</sup> :	1.21 (1.01-1.47)*	0.88 (0.71-1.10)	0.87 (0.74-1.02)
LDL Discordance			
Model 3 <sup>  </sup> :			
HDL-C	1.12 (0.73-1.73)	1.00 (0.70-1.43)	1.14 (0.90-1.45)
HDL-P	0.86 (0.63-1.17)	0.71 (0.52-0.96)*	0.82 (0.66-1.03)
LDL-C	0.80 (0.59-1.08)	1.47 (1.07-2.03)*	1.27 (1.01-1.59)*
LDL-P	1.34 (1.01-1.78)*	0.82 (0.58-1.17)	0.93 (0.71-1.22)
CVD Events	200	152	307
Model 1 <sup>‡</sup> :	0.95 (0.80-1.13)	0.90 (0.77-1.06)	0.88 (0.77-1.01)
HDL Discordance			
Model 2 <sup>§</sup> :	1.26 (1.07-1.47) †	0.88 (0.74-1.06)	0.91 (0.79-1.04)
LDL Discordance			
Model 3 <sup>  </sup> :			
HDL-C	1.05 (0.74-1.48)	0.98 (0.73-1.32)	1.12 (0.92-1.37)
HDL-P	0.97 (0.76-1.25)	0.75 (0.58-0.97)*	0.80 (0.66-0.96)*
LDL-C	0.77 (0.60-1.00)	1.41 (1.08-1.84)*	1.17 (0.96-1.42)
LDL-P	1.39 (1.09-1.75) †	0.76 (0.57-1.02)	0.99 (0.79-1.24)

\*p <0.05, †p <0.01.

All models were adjustments for age, sex, race/ethnicity, family history, systolic blood pressure, use of blood pressure medication, smoking, body mass index, statin use.

<sup>‡</sup> Model 1 additionally adjusted for LDL-C and LDL-P.

<sup>§</sup> Model 2 additionally adjusted for HDL-C and HDL-P.

<sup>||</sup> Model 3 include simultaneous adjustment with all four lipid variables.

association between HDL discordance quartiles and CHD and CVD events (Figure 2). However, when evaluated by group, those with DM had lower event rates with higher levels of HDL discordance (Figure 3).

When evaluating lipid parameters separately in all subjects (not reported in Table 2), both LDL-C (HR 1.17, 95% CI 1.06 to 1.28, p <0.01) and LDL-P (HR 1.16, 95% CI 1.05 to 1.28, p <0.01) were shown to be associated with CHD. Similar results were seen for CVD events. In the overall sample, HDL-C was not found to be significantly associated with CHD events but was modestly negatively associated with CVD events. HDL-P was more strongly negatively associated with CHD (HR 0.82, 95% CI 0.73 to 0.91, p <0.001) and CVD (HR 0.84, 95% CI 0.76 to 0.92, p <0.001) events.

When evaluating lipid parameters separately (not reported in Table 2), in those with neither DM nor MetS, LDL-C was predictive of CHD and CVD. Within the DM group, LDL-C predicted CHD and trended toward significance for CVD. LDL-C was not found to be significantly

associated with CHD or CVD in the MetS group. Only in those with neither condition was LDL-P predictive of CHD (HR 1.17, 95% CI 1.00 to 1.36, p <0.05) and CVD (HR 1.16, 95% CI 1.02 to 1.33, p <0.01). HDL-P was significantly protective of CHD (HR 0.72, 95% CI 0.56 to 0.92, p <0.01) and CVD (HR 0.77, 95% CI 0.63 to 0.95, p <0.05) events in DM. HDL-C did not predict CHD or CVD in any group.

When adjusted for baseline covariates and each lipoprotein particle and cholesterol variable in the same model (model 3), among all participants, HDL-P was the only variable that was significantly associated with CHD (HR 0.79, 95% CI 0.68 to 0.92, p <0.01) and CVD (HR 0.82, 95% CI 0.72 to 0.93, p <0.01). Within the DM group, HDL-P was negatively associated with CHD and CVD events (Table 2). HDL-C did not predict CHD or CVD events in any of the groups. Sensitivity analyses showed similar findings for HDL-P and HDL-C for CHD and CVD. LDL-C was positively associated with CHD and CVD events in the DM group (Table 2). Adjusting for the other lipid measures, LDL-P remained associated with CHD (HR 1.34, 95% CI 1.00 to 1.78, p <0.05) and CVD (HR 1.39, 95% CI 1.09 to 1.75, p <0.01) in the MetS group, but LDL-P did not predict CHD or CVD (despite a trend) for those with DM, the neither disease group, or the overall sample (Table 2). Similarly, LDL-P was not found to be significant within these groups in sensitivity analyses. All interaction terms between particle and cholesterol variables with group, gender, race/ethnicity variables were found to be insignificant. Additional adjustment for excessive alcohol use and exercise did not materially affect the results.

Using a dichotomous discordance measure, above-median LDL-C but below-median LDL-P trended toward overestimating CHD risk (adjusted HRs 0.30 to 0.82 among study groups) and CVD (adjusted HRs 0.52 to 0.88 among study groups) compared with particle/cholesterol concordant groups. For those with above-median HDL-C but below-median HDL-P, underestimation of CVD risk was present among the whole sample (HR 1.46, 95% CI 1.11 to 1.92, p <0.01) and those with neither DM nor MetS (HR 1.70, 95% CI 1.22 to 2.37, p <0.01) compared with particle/cholesterol concordant groups. Similar trends were seen with above-median HDL-C discordance in MetS and DM groups.

## Discussion

We show LDL- and HDL-positive discordance indicated by particle greater than concentration percentile in those with MetS and DM but a negative discordance in those without these conditions. Furthermore, in MetS, we show a greater magnitude of LDL particle to cholesterol concentration discordance predicts events. We show that LDL-P is predictive of CHD and CVD in those with MetS and HDL-P is protective of CHD and CVD in those with DM, even when adjusting for each other, HDL-C, and LDL-C. Our study is the first major prospective evaluation of these effects in those with MetS and DM in relation to future CHD and CVD events. Our findings indicate that LDL and HDL concentrations alone may not adequately capture CVD risk in those with MetS or DM. We show trends indicating overestimation of risk with discordantly high LDL-C to low



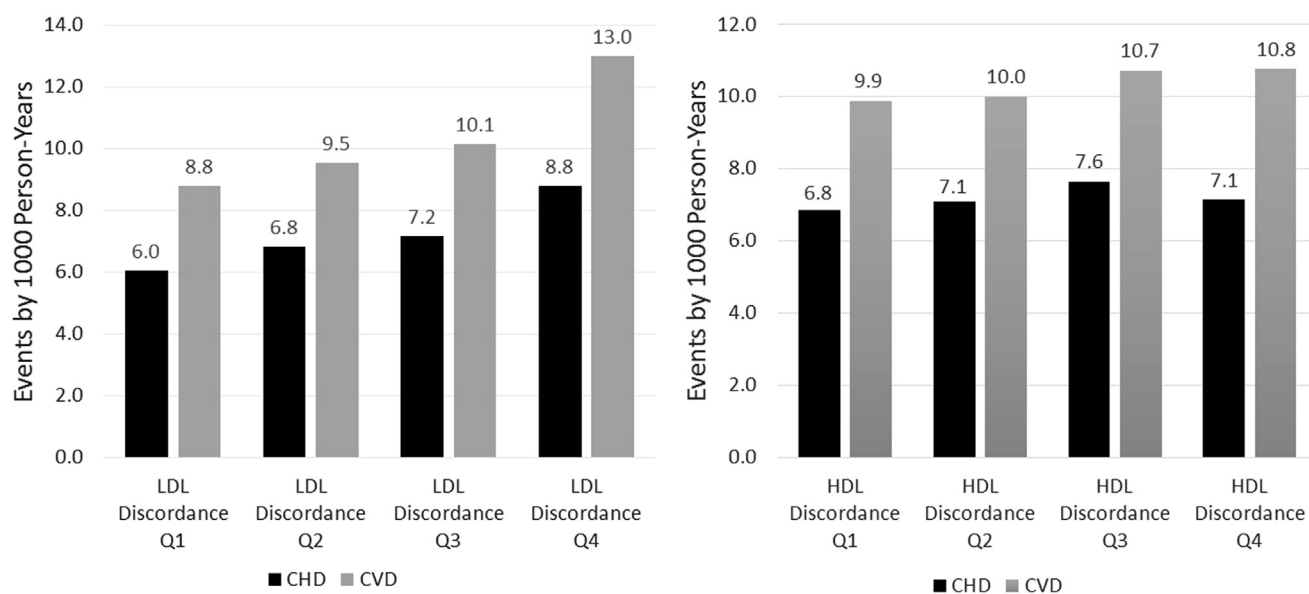


Figure 2. CHD and CVD events by LDL and HDL discordance quartiles. LDL discordance and HDL discordance is defined as a subject's difference between respective baseline lipoprotein particle and cholesterol percentiles. Increasing levels of quartile discordance is denoted moving from Q1 to Q4. LDL discordance ranges: Q1 (−86.7, −12.3); Q2 (−12.3, 0.0); Q3 (0.0, 11.9), Q4 (11.9, 78.7). HDL discordance ranges: Q1 (−96.9, −11.9), Q2 (−11.9, 0.4), Q3 (0.4, 12.3), and Q4 (12.3, 93.1). Q = quartile.

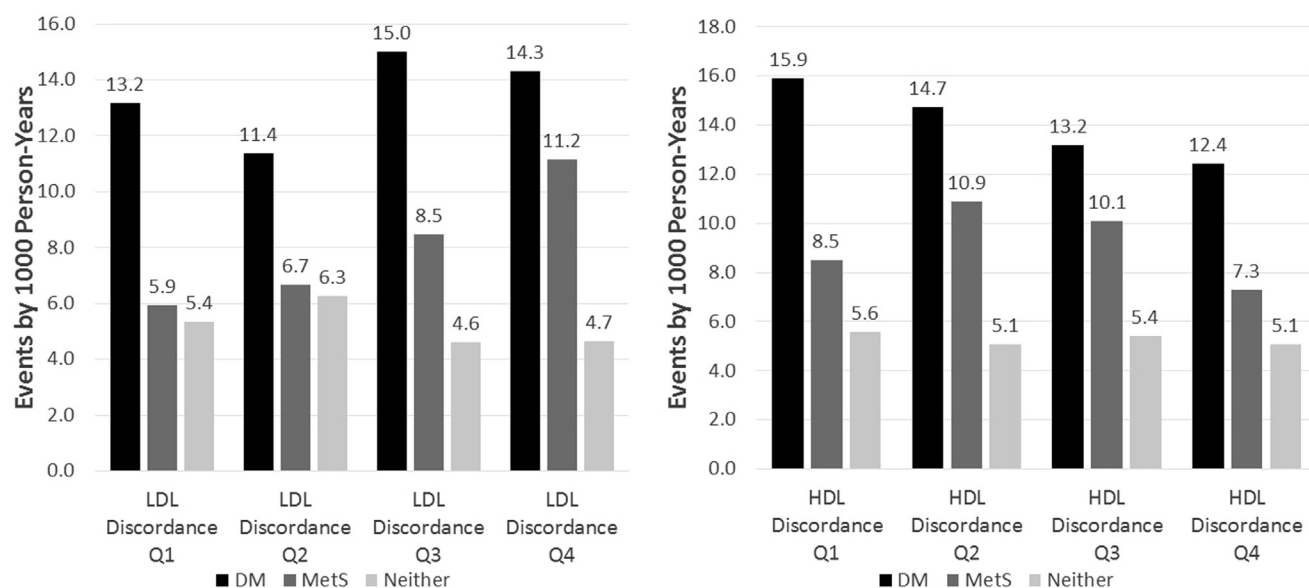


Figure 3. Disease group CHD events by LDL and HDL discordance quartiles. LDL discordance and HDL discordance is defined as a subject's difference between respective baseline lipoprotein particle and cholesterol percentiles. Increasing levels of quartile discordance is denoted moving from Q1 to Q4. LDL discordance ranges: Q1 (−86.7, −12.3); Q2 (−12.3, 0.0); Q3 (0.0, 11.9), Q4 (11.9, 78.7). HDL discordance ranges: Q1 (−96.9, −11.9); Q2 (−11.9, 0.4); Q3 (0.4, 12.3), Q4 (12.3, 93.1). Q = quartile.

LDL-P and underestimation of risk with discordantly high HDL-C to low HDL-P. This may reflect difficulty assessing CVD risk in rigid cholesterol to particle discordance groups based on subjective cutoffs. Rather, LDL-P and HDL-P may play a useful role in risk assessment specifically for patients with MetS and DM where individual discordance is greatest.

Although others have shown inverse relations between HDL-P with CHD and CVD,<sup>4,7</sup> we found this association to be primarily present in those with DM but not in those with or without MetS. The Multiple Risk Factor Intervention

Trial showed in a case-control study HDL-P (particularly medium sized) to predict CHD death in MetS.<sup>15</sup> This may be in part because of less robust adjustments or categorization of HDL-P into quartiles compared with our continuous analysis. There were also other more important predictors of risk in those with MetS (age, gender, family history, and systolic blood pressure) which may have prevented HDL-P to emerge as independently predictive of risk. Nonetheless, for those with DM, we show this association with CHD and CVD was not attenuated with the

additional adjustments of LDL-P, LDL-C, and HDL-C and that HDL-C was not associated with either CHD or CVD.

Our data show HDL-C is inferior to HDL-P for prediction of clinical events among those with DM. Although HDL-C is correlated to HDL-P, the relation of HDL-C with CVD is complex, influenced by atherogenic lipoproteins, inflammation, and insulin resistance, making it a poorer marker in those with DM.<sup>16</sup> In fact, in those with DM, HDL-P but not HDL-C is associated with cholesterol efflux<sup>17</sup> and that prediction of CHD by HDL-C may be explained by markers associated with MetS.<sup>18</sup> This was not the case for HDL-P, which was also predictive of CHD and remained predictive after additional adjustments for apolipoprotein B and triglycerides. Given this, it should be no surprise that in those with DM, HDL-C may reflect metabolic risk and not add to event prediction and possibly why recent clinical trials that increased HDL-C but had minimal effects on HDL-P<sup>19</sup> failed to show CVD protection.<sup>20,21</sup>

Persons with DM carry significant residual risk that inadequately explained by LDL-C.<sup>2</sup> We continue to show that LDL-C plays an important role in predicting CHD and CVD events in those with DM. However, in those with MetS, we show LDL-C may underestimate CHD and CVD risk compared with LDL-P and the magnitude of discrepancy between particle and cholesterol concentration in itself is predictive of CHD and CVD events. This indicates that simply having low LDL-C (as commonly measured in clinical practice), either from therapy or naturally, can underestimate LDL's predictive power for clinical events. Although we did not show LDL discordance to predict CVD in the DM group, this could be related to a bias of high-intensity statin treatment attenuating the relation of LDL with events. In addition, the continued dominant relation of LDL-C (in addition to risk factors of age, gender, and systolic blood pressure) with CHD and CVD events in DM may have made it more difficult for LDL discordance or particle number to emerge as independently predictive. Nonetheless, LDL-P was clearly found to be a better predictor for clinical events in those with MetS. Markers of overall LDL-P (as in this study) rather than size have been shown to be a more important determinant for CVD events.<sup>6,22</sup>

Strengths of MESA include its ethnic diversity and community-based recruitment; however, with any non-randomized design, there is the possibility of bias from unmeasured cofounders. Not all variables that are known to predict CVD events (such as Apo A-I and apo B) could be included given their unavailability in the MESA data set. Also, although statin use was adjusted for and sensitivity analyses performed, we could not adjust for changes in statin use and their possible effects on CVD events.

As recent guidelines have suggested aggressive statin use in DM for preventing CVD,<sup>1</sup> the extent to which statin use affects the relation between CVD and lipid profile discordance is also of interest. It is clear that statin treatment changes the cholesterol and triglyceride content of LDL particles.<sup>23</sup> Studies using different statins have shown that the percentage decrease in LDL-C exceeds the percentage reduction in LDL-P,<sup>24,25</sup> which is concerning given the closer relation of LDL-P with CVD events.<sup>8</sup> In addition, secondary analysis of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

(JUPITER) study has shown that in patients without diabetes, potent rosuvastatin treatment leads to increase in HDL-P and HDL-C. However, HDL-P, not HDL-C, was shown to be inversely associated with CVD events when adjusting for each other and other CVD risk factors.<sup>26</sup>

There has been increasing evidence documenting the value of HDL-P and LDL-P in predicting CVD events and as a marker for successful lipid-lowering therapy. The American Association of Clinical Endocrinologists recently specified an LDL-P target of <1,200 nmol/L for moderate CVD risk and LDL-P target of <1,000 nmol/L for high CVD risk,<sup>27</sup> supported by evidence that high-risk patients who achieve LDL-P <1,000 nmol/L compared with an LDL-C <100 mg/dl had a greater reduction in CVD events.<sup>28</sup>

Our study shows that in subjects with MetS greater LDL discordance is associated with future CVD events. We show that HDL-P, not HDL-C, is inversely related to CVD events. Although this study and others have shown the benefit of examining lipoprotein particles in patients free of baseline CVD, our results further support a potential role for examining lipoprotein particles and their magnitude of discordance with cholesterol concentration for risk assessment and evaluation of therapeutic goals in patients with MetS and DM.

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## Disclosures

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