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Discordance between non-HDL-cholesterol and LDL-particle measurements: Results from the Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Cardiovascular risk assessment incorporates measurement of atherogenic lipids such as non-HDL cholesterol (non-HDL-C). It remains uncertain under which circumstances atherogenic lipoprotein enumeration such as LDL particle number (LDL-P) differs from simultaneously acquired non-HDL-C.

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Methods—Participants of the Multi-Ethnic Study of Atherosclerosis (MESA) were deemed LDL-P>non-HDL-C discordant if they exhibited higher LDL-P than expected for simultaneously measured non-HDL-C, given the observed distribution of both in MESA. Conversely, a lower LDL-P than would be suggested from non-HDL-C characterized LDL-P<non-HDL-C discordance. Regression models were used to estimate associations of demographics and comorbidities with discordance and of discordance with carotid intima-media thickness (CIMT) and detectable coronary artery calcium (CAC).

Results—Discordance was observed among 44% of subjects. LDL-P>non-HDL-C compared to LDL-P<non-HDL-C discordance was more common among Hispanics and smokers; among subjects with lower HDL-C, lower triglycerides, or greater insulin resistance by homeostatic model assessment of insulin resistance (HOMA-IR); and among subjects on lipid-lowering therapy, anti-hypertensive therapy, or hormone replacement therapy. In the setting of discordance, LDL-P exhibited a modestly greater association with CIMT than did non-HDL-C (+0.024−0.025 mm vs +0.018−0.021 mm per SD increase). In the presence of LDL-P<non-HDL-C discordance, LDL-P demonstrated a modestly greater association with detectable CAC than did non-HDL-C (OR 1.51 vs 1.46 per SD increase).

Conclusions—Our results demonstrated that disagreement between LDL-P and non-HDL-C was common and significantly associated with several clinical characteristics. In the setting of discordance, LDL-P was more closely associated with CIMT and CAC than non-HDL-C, though observed differences were small.

Keywords

cholesterol; lipoproteins; risk assessment; LDL-particle number; apolipoprotein B

1. Introduction

Measurement of non-HDL cholesterol (non-HDL-C) is one of the principal components of global cardiovascular risk assessment and a critical target for lipid-lowering therapy [1]. On the other hand, the value of lipoprotein particle enumeration—apolipoprotein B (apoB) and low-density lipoprotein particle number (LDL-P)—for atherogenic cardiovascular events remains a matter of debate. In 2006 a thirty-person, ten-country expert panel concluded that apoB was superior to any cholesterol measure [2], a sentiment shared by the 2009 Canadian Cardiovascular Society guidelines for dyslipidemia [3] as well as a 2008 American College of Cardiology/American Diabetes Association consensus statement [4]. A 2011 expert consensus panel of the National Lipid Association suggested that LDL-P measurement is “reasonable for many patients” at intermediate risk, with a family history of CHD, or in the setting of recurrent events [5]. In contradistinction, the 2010 American College of Cardiology/American Heart Association guidelines for risk assessment deemed any lipoprotein assessment unnecessary (Class III indication) [6]. Similarly, a recent review [7] concluded in favor of non-HDL-C, citing “established cutpoints with safe and achievable goals, no additional cost, and quick time to result with an easy mathematical calculation.”

Such divergent positions may obscure efforts to identify specific clinical scenarios in which readily available lipoprotein measures could yield insightful information above and beyond

cholesterol data. In particular, situations of discordance—circumstances in which cholesterol and lipoprotein values substantially disagree—may be most revealing [8]. To lend further clarity to this ongoing discussion in preventive cardiovascular medicine, we queried the Multi-Ethnic Study of Atherosclerosis (MESA) to: calculate the prevalence of discordance between non-HDL-C and total LDL-P, enumeration of LDL particles assessed by nuclear magnetic resonance (NMR) spectroscopy; identify clinical predictors of discordance between non-HDL-C and total LDL-P; and compare non-HDL-C and LDL-P with respect to their association with two validated surrogate endpoints for cardiovascular events—coronary artery calcium (CAC) and carotid intima-media thickness (CIMT)—within each discordance category. ApoB measurements were not performed in MESA; therefore our analysis was limited to a comparison of LDL-P and non-HDL-C.

2. Methods

2.1 Study Population

Eligible participants included 6814 community-based men and women, 45–84 years of age and free of self-reported cardiovascular disease, recruited from 4 diverse ethnic groups (African American, Hispanic, White, Chinese American) at 6 centers in the United States. Participants with missing lipid or covariate data from the baseline visit were excluded (n=189, 2.8%). Total cholesterol and HDL-C were measured in fasting plasma using CDC-standardized methods. Non-HDL-C was calculated as total cholesterol minus HDL-C. Total LDL-P, hereafter referred to as LDL-P, was measured on frozen plasma specimens (−70°C) using proton NMR spectroscopy (LipoScience Inc., North Carolina) as described previously [9]. Total LDL-P includes small LDL (diameter 18–20.5 nm), large LDL (20.5–23 nm), and intermediate-density lipoproteins (IDL, 23–29 nm), and excludes very-low density lipoproteins (VLDL, >29 nm). Inter-assay reproducibility, determined from replicate analyses of plasma pools, is indicated by the following coefficients of variation: LDL-P, <4% [10]; total cholesterol, 2% [11]; HDL-C, 4.1% [11]. Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin measurements using updated, non-linear models [12]. CAC and maximum CIMT were measured at the baseline visit as previously described [13]. The MESA protocol for the measurement of CIMT was developed prior to the publication of the 2008 American Society of Echocardiography/Society of Vascular Medicine consensus statement [14] and did not incorporate assessment of mean common carotid artery CIMT.

2.2 Definitions of discordance

LDL-C thresholds defined by the 2004 National Cholesterol Education Program Adult Treatment Panel III update were 70 mg/dL, 100 mg/dL, 130 mg/dL, and 160 mg/dL, which approximated the 2^{nd}, 20^{th}, 50^{th}, and 80^{th} percentile for LDL-C in the Framingham cohort, respectively [15]. We applied the same percentile values to the MESA population to define five updated percentile categories each for non-HDL-C and LDL-P, consistent with the methodology of earlier reports [16–18]. Non-HDL-C thresholds were calculated to be 78 mg/dL (2^{nd} percentile), 113 mg/dL (20^{th} percentile), 141 mg/dL (50^{th} percentile), and 169 mg/dL (80^{th} percentile). LDL-P thresholds were calculated to be 644 nmol/L (2^{nd} percentile), 963 nmol/L (20^{th} percentile), 1222 nmol/L (50^{th} percentile), and 1514 nmol/L

(80th percentile). For reference, LDL-P and non-HDL-C values corresponding to 10 percentile increments in MESA are provided in Supplementary Table 1.

Individuals were deemed concordant if they exhibited LDL-P and non-HDL-C values within corresponding percentile categories, such as LDL-P and non-HDL-C measurements both between the 20th and 50th percentiles. Participants were defined as `LDL-P>non-HDL-C discordant' if they manifested LDL-P levels of a higher percentile category than simultaneously acquired non-HDL-C values, such as an LDL-P measurement between the 50th and 80th percentiles and a non-HDL-C value between the 20th and 50th percentiles. Conversely, participants were defined as `LDL-P<non-HDL-C discordant' if they manifested LDL-P levels of a lower percentile category than simultaneously obtained non-HDL-C values, such as an LDL-P measurement between the 2nd and 20th percentiles and a non-HDL-C value between the 20th and 50th percentiles.

We separately defined discordance based on the difference between LDL-P and non-HDL-C percentiles, with cutpoints of ±10 and ±20 percentile units (Supplementary Figure 1).

2.3 Statistical Analysis

To measure agreement between LDL-P and non-HDL-C levels, a weighted kappa statistic using Fleiss-Cohen weights was used. Summary statistics were calculated for demographic characteristics, lipid levels, and medication use for groups defined by discordance; differences across groups were evaluated using ANOVA, Kruskall-Wallace tests, or chi-squared tests, as appropriate. Discordance was treated as a nominal (unordered) outcome with three levels: LDL-P>non-HDL-C discordance, concordance, and LDL-P<non-HDL-C discordance. Multinomial logistic regression models were used to quantify the association between the odds of discordance and age, sex, ethnicity, smoking status, diabetes status, waist circumference, systolic blood pressure, TG, HDL-C, HOMA-IR, C-reactive protein (CRP), glomerular filtration rate estimated by the Modification of Diet in Renal Disease equation (eGFR), and use of selected pharmacologic therapies: lipid-lowering therapy, diabetes therapy, diuretic therapy, anti-hypertensive therapy, and hormone replacement therapy (HRT). Comparisons were made for LDL-P>non-HDL-C discordance versus concordance and LDL-P<non-HDL-C discordance versus concordance. Linear contrasts were used to evaluate equality of LDL-P>non-HDL-C discordance versus concordance and LDL-P<non-HDL-C discordance versus concordance odds ratios. We fit univariable and fully adjusted multivariable models; for brevity, only adjusted results are presented. We hypothesized that the association between the odds of discordance and HDL-C, TG, and HOMA-IR might vary across groups defined by ethnicity [19]. To evaluate effect modification we included interaction terms between ethnicity and these covariates in fully adjusted models. Likelihood ratio (LR) tests were used to evaluate the statistical significance of interaction effects.

Regression models were used to estimate the association of LDL-P and non-HDL-C with surrogate outcomes for cardiovascular disease in each discordant group: linear regression for CIMT; and logistic regression for detectable versus undetectable CAC. These cross-sectional analyses were restricted to study participants not taking lipid-lowering therapy (n=5557) so that measured LDL-P and non-HDL-C values would more closely reflect long-

term exposures. LDL-P and non-HDL-C were each standardized by their standard deviation to facilitate direct comparisons of their regression coefficients. Interaction terms between discordance and LDL-P or non-HDL-C were used to estimate associations for each discordance group. We fit unadjusted and fully adjusted models, which included age, sex, ethnicity, history of smoking, systolic blood pressure, HDL-C, HOMA-IR, anti-hypertensive therapy, and HRT. In the analysis of CIMT, a robust standard error estimator was used to provide valid inference in the presence of non-constant variance and non-normality (CIMT was positively skewed).

All hypothesis tests were two-sided and P values less than 0.05 were considered statistically significant, with the exception of interaction analyses, for which 0.10 was chosen as a threshold for significance. All statistical analyses were completed using R (R Development Core Team, Vienna, Austria) or SAS (SAS Institute, Cary, North Carolina).

3. Results

3.1 Prevalence of Discordance

The distribution of LDL-P and non-HDL-C values is shown for the overall study population and within ethnic subgroups in Figure 1. In the overall cohort (n=6625), concordance between LDL-P and non-HDL-C was observed among 56% of study participants (Table 1). 23% of individuals exhibited LDL-P>non-HDL-C discordance, while 21% demonstrated LDL-P<non-HDL-C discordance. Concordance was observed among 54% of African Americans, 57% of Hispanics, 56% of Whites, and 53% of Chinese Americans. Chinese Americans exhibited the highest rate of LDL-P<non-HDL-C discordance (29%), while African Americans exhibited the highest rate of LDL-P>non-HDL-C discordance (26%). Overall, the weighted kappa for LDL-P and non-HDL-C was 0.751 (95% CI 0.740–0.762); the correlation coefficient between LDL-P and non-HDL-C was 0.818.

We additionally defined discordance based on the difference between LDL-P and non-HDL-C percentiles. The distribution of LDL-P and non-HDL-C percentiles is shown for the overall study population in Supplementary Figure 1, along with a histogram of percentile differences between LDL-P and non-HDL-C. 52% and 24% of study participants exhibited absolute differences in LDL-P and non-HDL-C of at least 10 and 20 percentile units, respectively (Supplementary Table 2). Lower percentile values of non-HDL-C were exhibited among Chinese Americans (i.e., differences ≤ −10 percentile units) (34%). Higher percentile values of LDL-P were observed for African Americans (i.e., differences ≥ 10 percentile units) (29%).

3.2 Associations with Discordance

Participant characteristics for all discordance groups are shown in Supplementary Table 3. In the LDL-P>non-HDL-C discordant group, the mean LDL-P was 1324 nmol/L, corresponding to the 62nd percentile, and the mean non-HDL-C was 128 mg/dL, or 35th percentile. In the LDL-P<non-HDL-C discordant group, the mean LDL-P was 1103 nmol/L, corresponding to the 36th percentile, and the mean non-HDL-C was 152 mg/dL, or 63rd percentile. Multivariable-adjusted analysis of the association between covariates and LDL-

P>non-HDL-C and LDL-P<non-HDL-C discordance is shown in Table 2. LDL-P>non-HDL-C compared to LDL-P<non-HDL-C discordance was more common among Hispanics (compared to Whites) or smokers; among study participants with lower HDL-C, lower TG, higher HOMA-IR, or higher eGFR; and among subjects on lipid-lowering therapy, anti-hypertensive therapy, or hormone replacement therapy. Notably, CRP level, waist circumference, and diabetes medication use were not associated with discordance status in multivariable analysis.

Analysis of interaction effects revealed no influence of ethnicity on the association between HOMA-IR and discordance, but significant influences on HDL-C (LR $p<0.001$) and TG (LR $p=0.001$). The association between a decrement in HDL-C and LDL-P<non-HDL-C discordance was similar among all ethnicities, but the association with LDL-P>non-HDL-C discordance was strongest among Chinese Americans [OR=1.43, 95% CI (1.28, 1.61) per 5 mg/dL decrement]. Similarly, the association between an increment in TG and discordance was strongest among Chinese Americans [LDL-P>non-HDL-C discordance OR=0.75, 95% CI (0.68, 0.83); LDL-P<non-HDL-C discordance OR=1.25, 95% CI (1.16, 1.34) per 25 mg/dL increment].

Clinical predictors of discordance identified in multivariable analysis were subsequently used to define subgroups for further analysis of the prevalence of discordance (Figure 2). Among participants exhibiting any of the clinical predictors of LDL-P>non-HDL-C discordance (HDL-C<50 mg/dL, HOMA-IR≥0.7, lipid-lowering therapy, or HRT), the prevalence rates of any LDL-P>non-HDL-C discordance and discordance exceeding one percentile category were 26% and 2%, respectively. Among participants with none of these clinical predictors of LDL-P>non-HDL-C discordance, any LDL-P>non-HDL-C discordance and discordance exceeding one percentile category were observed in 10% and <1% of individuals.

3.3 Associations with Surrogate Cardiovascular Outcomes

Regarding the relationship to surrogate cardiovascular outcomes, both LDL-P and non-HDL-C were significantly associated with CIMT within each discordance category after adjustment for age, sex, ethnicity, history of smoking, systolic blood pressure, HDL-C, HOMA-IR, anti-hypertensive therapy, and HRT (Table 3). In the setting of any discordance, LDL-P exhibited a modestly greater association with CIMT than did non-HDL-C, with each standard-deviation (SD) increase in LDL-P associated with a 0.024–0.025 mm increase in mean CIMT, compared to 0.018–0.020 mm for non-HDL-C. Neither LDL-P nor non-HDL-C were significantly associated with the odds of detectable CAC in the setting of LDL-P>non-HDL-C discordance (Table 3). Among study participants with concordant levels of LDL-P and non-HDL-C, each SD increase in either measure was associated with 24–26% increase in the odds of detectable CAC. In the presence of LDL-P<non-HDL-C discordance, LDL-P demonstrated a modestly greater association with the odds of detectable CAC than did non-HDL-C, with each SD increase in LDL-P associated with a 51% increase in the odds of detectable CAC, compared to 46% for non-HDL-C. Similar results were obtained in analyses defining discordance as the difference between LDL-P and non-HDL-C percentiles, with cutpoints of ±10 (Supplementary Table 4) and ±20 (Supplementary Table 5) percentile

units. Namely, a modestly greater association with CIMT was observed with LDL-P compared to non-HDL-C in the setting of discordance but not concordance, although the confidence intervals for these estimates are broad and overlapping.

4. Discussion

In our analysis of the MESA cohort, LDL-P exhibited substantial disagreement with non-HDL-C. Discordance affected almost 1 out of 2 study participants. Lower HDL-C, lower TG, greater insulin resistance by HOMA-IR, lipid-lowering therapy, and HRT were associated with LDL-P>non-HDL-C discordance. Conversely, Chinese ethnicity, higher HDL-C, and higher TG were associated with LDL-P<non-HDL-C discordance.

To our knowledge, while prior publications have reported the relationship between LDL-P and LDL-C [10, 20–22], our study is the first to detail the prevalence of and characteristics associated with discordance between LDL-P and non-HDL-C. Our results support the concept that atherogenic lipoprotein particle enumeration and atherogenic cholesterol measurements are not equal in a substantial number of individuals [8], and provide guidance regarding clinical scenarios enriched for discrepant results. Additionally, our study revealed that in the setting of discordance, LDL-P was modestly superior to non-HDL-C in tracking with CIMT and detectable CAC even after adjustment for comorbidities. Analyses defining discordance as differences in LDL-P and non-HDL-C equal to or exceeding 10 or 20 percentile units revealed similar results.

Most [20, 21, 23–25] but not all [26–28] studies have demonstrated a stronger association between lipoprotein particle enumeration and cardiovascular risk compared to cholesterol measures in a variety of populations, with the exception of familial dysbetalipoproteinemia, a rare disease associated with remnant lipoprotein predominance. However, the majority of these analyses were performed without regard to discordance status. Limited data comparing LDL-C and LDL-P in the setting of discordance indicate a stronger association for the latter with cardiovascular events and surrogate imaging markers. In an analysis of the Framingham cohort, event-free survival directly tracked with LDL-P and not LDL-C when the two were discordant [20]. Similarly, in a prior examination of MESA, LDL-P proved a more reliable predictor of CIMT than LDL-C when the two values differed [21]. While limited by a cross-sectional approach and use of surrogate endpoints, our findings suggest an incremental prognostic value of LDL-P above and beyond non-HDL-C and highlight the importance of future analyses focusing on examining the relationship between lipoprotein particle count and cardiovascular outcomes specifically in the setting of discordance.

Our analysis has several limitations. We did not compare non-HDL-C with `non-HDL-P,' or more precisely, the sum total of LDL-P (which incorporates IDL-P) and VLDL-P quantified by NMR spectroscopy. It could be argued that non-HDL-P, a measure of total atherogenic lipoprotein concentration, provides a more appropriate comparator to non-HDL-C, a measure of total atherogenic lipoprotein cholesterol, than LDL-P alone. However, we chose not to include VLDL-P because: 1) the incremental prognostic value of VLDL-P above and beyond LDL-P remains uncertain [20] and 2) no clinical recommendation has suggested the use of VLDL-P [5, 16]. Of note, it is likely because of the exclusion of VLDL species that

LDL-P>non-HDL-C discordance *decreases* with increasing TG. This is the opposite of the relationship between LDL-P and LDL-C, for which LDL-P>LDL-C discordance *increases* with increasing TG [29].

In addition, the absence of apoB data from the MESA cohort was unfortunate. Applying a similar rationale as above, apoB may provide a more appropriate comparator to non-HDL-C than LDL-P. Although LDL-P incorporates IDL as well as LDL, it does not capture the contributions of larger lipoproteins including VLDL remnants that may promote plaque formation and instability. Additional advantages of apoB over LDL-P include its lower cost and a greater number of studies demonstrating an association with cardiovascular outcomes. In the Quebec Cardiovascular Study of 2,103 men free of coronary artery disease, discordance between apoB and non-HDL-C, defined as differing population quintiles, was prevalent, affecting 37% of study participants [30]. Future comparative analyses of apoB, LDL-P, non-HDL-P, and non-HDL-C are needed.

A second limitation of our work may be the timing of LDL-P and non-HDL-C measurement in relation to ascertainment of surrogate cardiovascular outcomes. A recent analysis of the Framingham Heart Study demonstrated a significantly greater association between CAC and LDL-C levels drawn >25 years prior to subclinical atherosclerosis assessment than between CAC and LDL-C levels drawn <5 years before imaging [32]. We suggest that future studies using the MESA cohort to examine the impact of discordance assess serial CAC and CIMT following the baseline examination of cholesterol and lipoproteins in addition to `hard' coronary endpoints.

We acknowledge that there is no universally accepted definition of disagreement between atherogenic lipoprotein particle enumeration and cholesterol. In our primary analysis, we chose to categorize non-HDL-C and LDL-P according to population percentiles because of their widespread clinical use, and we defined discordance as categorical differences, the predominant approach among the few previously published studies examining discordance [16, 17, 30, 31]. Recently, a publication by Otvos et al examined differences between LDL-P and LDL-C and defined discordance as values differing by ≥12 percentile units, a threshold chosen “so that approximately equal numbers of participants would be classified as concordant or discordant [21].” We believed that while such an approach was also reasonable, given prior precedent and widespread use of 2^{nd}, 20^{th}, 50^{th}, and 80^{th} percentile thresholds, our methodology was equally justified. Of note, among our LDL-P>non-HDL-C discordance, concordant, and LDL-P<non-HDL-C discordance groups, the prevalence of discordance as defined by LDL-P and non-HDL-C differing by ≥12 percentile units was 74%, 20%, and 77%, respectively. In analyses in which we defined discordance as a difference in LDL-P and non-HDL-C of at least 10 or 20 percentile units, we found similar associations with measures of subclinical atherosclerosis. Future analyses may benefit from further comparisons of definitions of discordance, such as differences of percentile units or, alternatively, differences in clinical risk categories that may be informed by the upcoming NCEP ATP IV guidelines.

In summary, to avoid underestimation of atherogenic lipoproteins, and potentially to avoid underestimation of cardiovascular risk, it may be particularly useful to assess LDL-P in the

setting of lower HDL-C, greater insulin resistance by HOMA-IR, lipid-lowering therapy, and hormone replacement therapy – circumstances associated with LDL-P>non-HDL-C discordance. Further research is needed to evaluate the incremental prognostic value of LDL-P in the setting of discordance for the prediction of cardiovascular events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- The value of lipoprotein particle enumeration remains a matter of debate
- We evaluated discordance between LDL-particle number and non-HDLc
- Discordance was defined as higher/lower LDL-P than predicted by non-HDLc
- 44% of subjects in the Multi-Ethnic Study of Atherosclerosis exhibited discordance
- Hispanic ethnicity, lower HDL-C were associated with LDL-P>non-HDLc discordance

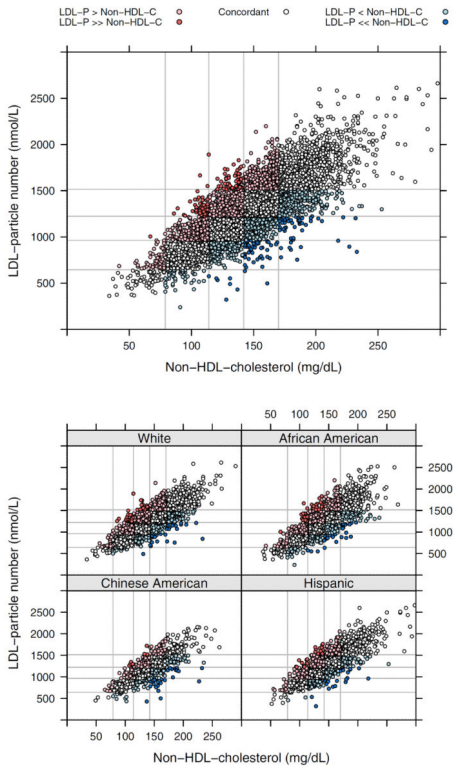

Figure 1.

Distribution of LDL-particle number and non-HDL-cholesterol in the overall cohort and by ethnicity. LDL-P>non-HDL-C discordant, LDL-P one risk category higher than expected for simultaneously measured non-HDL-C; LDL-P>>non-HDL-C discordant, LDL-P two or more risk categories higher than expected for simultaneously measured non-HDL-C; LDL-P<non-HDL-C discordant, LDL-P one risk category lower than expected for simultaneously measured non-HDL-C; LDL-P<<non-HDL-C discordant, LDL-P two or more risk categories lower than expected for simultaneously measured non-HDL-C. The numbers in each category are provided in Table 1.

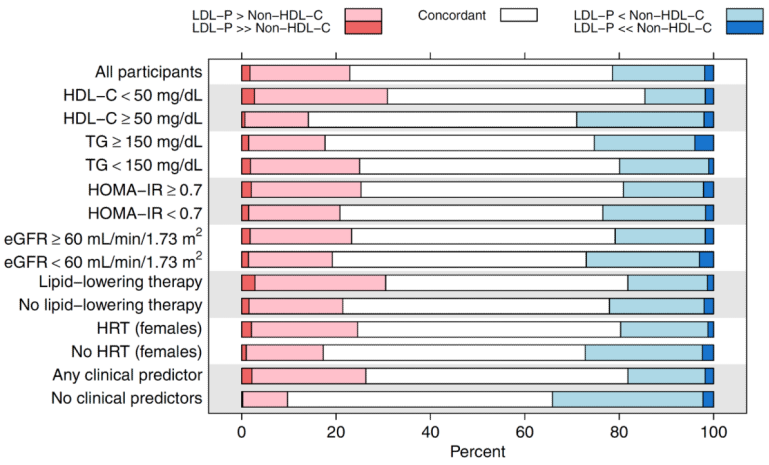

Figure 2.

Subgroup analysis of the prevalence of concordance and discordance between LDL-particle number and non-HDL-cholesterol. “Any clinical predictor” includes study participants with any of the following: HDL-C<50 mg/dL, HOMA-IR≥0.7, lipid-lowering therapy, or hormone replacement therapy (HRT). “No clinical predictor” excludes study participants with any of the four aforementioned characteristics.

Table 1

Discordance between LDL-particle number and non-HDL-cholesterol; summaries presented as *n* (row %); red shading indicates LDL-P>non-HDL-C discordance, blue shading indicates LDL-P<non-HDL-C discordance

Non-HDL-C (mg/dL and percentile)	LDL-P (nmol/L and percentile)					
	<644 <2nd	**644–962 2nd–<20th**	**963–1221 20th–<50th**	**1222–1513 50th–<80th**	**≥1514 ≥80th**	**Total**
<78 <2nd	69 (51.1)	65 (48.1)	1 (0.7)	0	0	135
78–112 2nd–<20th	55 (4.5)	711 (58.6)	390 (32.2)	55 (4.5)	2 (0.2)	1213
113–140 20th–<50th	7 (0.3)	353 (17.4)	1058 (52.2)	549 (27.1)	58 (2.9)	2025
141–168 50th–<80th	2 (0.1)	59 (3.0)	497 (25.7)	982 (50.7)	397 (20.5)	1937
≥169 ≥80th	0	10 (0.8)	48 (3.7)		867 (65.9)	1315

LDL-P and non-HDL-C percentiles derived from the Multi-Ethnic Study of Atherosclerosis cohort Weighted kappa: 0.751 (95% CI: 0.740, 0.762)

Table 2

Fully adjusted odds ratios comparing odds of LDL-P>non-HDL-C and LDL-P<non-HDL-C discordance versus concordance, defined by non-HDL-cholesterol and LDL-particle number

	LDL-P>non-HDL-C discordance vs. concordance	LDL-P<non-HDL-C discordance vs.concordance	P value*
Demographics			
Age (10 year increment)	0.97 (0.90, 1.04)	1.01 (0.94, 1.08)	0.32
Male (vs. female**)	0.85 (0.77, 0.94)	1.01 (0.90, 1.12)	0.012
Ethnicity			
African American (vs. White)	0.98 (0.87, 1.11)	1.02 (0.90, 1.15)	0.68
Chinese American (vs. White)	0.92 (0.78, 1.09)	1.29 (1.11, 1.49)	0.001
Hispanic (vs. White)	1.08 (0.96, 1.22)	0.80 (0.71, 0.90)	< 0.001
Comorbidities			
History of smoking (vs. none)	1.03 (0.96, 1.09)	0.91 (0.86, 0.98)	0.006
Waist circumference (5 cm increment)	0.98 (0.96, 1.01)	1.00 (0.97, 1.03)	0.31
Systolic blood pressure (10 mmHg increment)	1.02 (0.99, 1.06)	1.03 (1.00, 1.06)	0.70
Laboratory values			
HDL-cholesterol (5 mg/dL decrement)	1.28 (1.23, 1.32)	0.90 (0.88, 0.93)	< 0.001
Triglycerides (25 mg/dL increment)	0.79 (0.77, 0.82)	1.15 (1.12, 1.19)	< 0.001
CRP (multiplicative increment of 2)	1.02 (0.98, 1.07)	0.98 (0.94, 1.03)	0.13
HOMA-IR (multiplicative increment of 2)	1.09 (1.01, 1.19)	0.86 (0.79, 0.94)	< 0.001
eGFR (30 mL/min/1.73 m^2 decrement)	0.88 (0.79, 0.98)	1.16 (1.03, 1.32)	< 0.001
Medication use			
Lipid-lowering therapy (vs. none)	1.30 (1.19, 1.41)	0.92 (0.83, 1.00)	< 0.001
Diabetes therapy (vs. none)	1.09 (0.98, 1.21)	1.01 (0.90, 1.14)	0.29
Diuretic therapy (vs. none)	1.06 (0.96, 1.18)	1.06 (0.96, 1.18)	0.96
Anti-hypertensive therapy (vs. none)	1.05 (0.97, 1.14)	0.94 (0.86, 1.02)	0.028
Hormone replacement therapy*** (vs. none)	1.60 (1.41, 1.82)	0.74 (0.64, 0.84)	< 0.001

*Evaluating equality of LDL-P>non-HDL-C and LDL-P<non-HDL-C discordance odds ratios (vs. concordance)

**Among hormone replacement therapy non-users

***Among females

Table 3

Associations of LDL-particle number and non-HDL-cholesterol with surrogate endpoints for cardiovascular disease among participants with LDL-P/non-HDL-C discordance

	LDL-P SD = 338nmol/L	**Non-HDL-C SD = 34.7 mg/dL**
CIMT	Estimate* (95% CI); P value	Estimate* (95% CI); P value
Unadjusted model		
LDL-P>non-HDL-C discordance	0.030 (0.016, 0.044); < 0.001	0.021 (0.007, 0.035); 0.004
Concordance	0.021 (0.014, 0.027); < 0.001	0.019 (0.013, 0.026); < 0.001
LDL-P<non-HDL-C discordance	0.026 (0.012, 0.040); < 0.001	0.024 (0.012, 0.036); < 0.001
Adjusted model***		
LDL-P>non-HDL-C discordance	0.025 (0.012, 0.038); < 0.001	0.020 (0.008, 0.032); 0.002
Concordance	0.018 (0.012, 0.024); < 0.001	0.017(0.011, 0.023); < 0.001
LDL-P<non-HDL-C discordance	0.024 (0.011, 0.036); < 0.001	0.018 (0.008, 0.029); 0.001
Detectable CAC	Odds ratio** (95% CI); P value	Odds ratio** (95% CI); P value
Unadjusted model		
LDL-P>non-HDL-C discordance	1.15 (1.00, 1.33); 0.051	1.12 (0.96, 1.32); 0.16
Concordance	1.21 (1.14, 1.29); < 0.001	1.21 (1.14, 1.29); < 0.001
LDL-P<non-HDL-C discordance	1.40 (1.19, 1.65); < 0.001	1.39 (1.20, 1.60); < 0.001
Adjusted model***		
LDL-P>non-HDL-C discordance	1.15 (0.97, 1.36); 0.11	1.13 (0.93, 1.36); 0.21
Concordance	1.24 (0.15, 1.34); < 0.001	1.26 (1.16, 1.36); < 0.001
LDL-P<non-HDL-C discordance	1.51 (1.25, 1.83); < 0.001	1.46 (1.23, 1.72); < 0.001

* Estimate corresponds to the difference in mean CIMT, in mm, for each standard deviation increase in LDL-P and non-HDL-C

** Odds ratio corresponds to the ratio of odds of detectable CAC for each standard deviation increase in LDL-P and non-HDL-C

*** Adjusted for age, sex, ethnicity, history of smoking, systolic blood pressure, HDL-cholesterol, HOMA-IR, anti-hypertensive therapy, hormone replacement therapy