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Patient-Level Discordance in Population Percentiles of the TC/HDL-C Ratio Compared with LDL-C and Non-HDL-C: The Very Large Database of Lipids Study (*VLDL-2B*)

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Abstract

Background—The total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C) ratio, estimated low-density lipoprotein cholesterol (LDL-C), and non-HDL-C are routinely available from the standard lipid profile. We aimed to assess the extent of patient-level discordance of TC/HDL-C with LDL-C and non-HDL-C because discordance suggests the possibility of additional information.

Methods and Results—We compared population percentiles of TC/HDL-C, Friedewald-estimated LDL-C, and non-HDL-C in 1,310,432 U.S. adults from the Very Large Database of Lipids. Lipid testing was performed by ultracentrifugation (VAP, Atherotech, AL). One in three patients had ≥25 percentile units discordance between TC/HDL-C and LDL-C while one in four had ≥25 percentile units discordance between TC/HDL-C and non-HDL-C. The proportion of patients with TC/HDL-C > LDL-C by ≥25 percentile units increased from 3% at triglycerides <100 mg/dL to 51% at triglycerides 200–399 mg/dL. On a smaller scale, TC/HDL-C > non-HDL-C discordance by ≥25 percentile units increased from 6% to 21%. In those with <15th percentile levels of LDL-C (<70 mg/dL) or non-HDL-C (<93 mg/dL), a respective 58% and 46% were above the percentile-equivalent TC/HDL-C of 2.6. Age, sex, and directly measured components of the standard lipid profile explained >86% of the variance in percentile discordance between TC/HDL-C vs. LDL-C and non-HDL-C.

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Conclusions—In this contemporary, cross-sectional, big data analysis of U.S. adults who underwent advanced lipid testing, the extent of patient-level discordance suggests that TC/HDL-C may offer potential additional information to LDL-C and non-HDL-C. Future studies are required to determine the clinical implications of this observation.

Clinical Trial Registration Information—www.clinicaltrials.gov. Identifier: NCT01698489.

Keywords

Lipids; Lipoproteins; cholesterol; prevention

INTRODUCTION

Approximately 100 million cholesterol tests are performed annually in U.S. ambulatory clinics alone.[1] Controlling cholesterol is one of the American Heart Association's Life's Simple 7 and a central aspect of atherosclerotic cardiovascular disease (ASCVD) prevention in the U.S. and abroad.[2] Guidelines recommend using the standard lipid profile in several ways.[3–7] On initial patient evaluation, estimating a 10-year ASCVD risk score using the 2013 U.S. pooled cohort equations, the Framingham risk score or European systemic coronary risk estimation score is one of the components for eligibility for primary prevention statin therapy.[3–7] These risk scores include total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) as individual variables. Baseline LDL-C is also used to define treatment eligibility, and after intervention on-treatment LDL-C levels are compared to baseline and monitored over time, as are non-HDL-C and apolipoprotein B (apoB) levels in some guidelines.[4–7]

Current guidelines do not recommend using the TC/HDL-C ratio. It remains uncertain what information the ratio may add given that TC and HDL-C are already used in risk estimation, in estimating LDL-C by the Friedewald formula [LDL-C = TC – HDL-C – (triglycerides/5)],[8] and in calculating non-HDL-C. Moreover, Mendelian randomization and HDL-C raising trials argue against a causal role of HDL-C in ASCVD.[9–11] However, to some extent, it has been suggested that TC/HDL-C may be a marker of atherogenic particle burden.[12] Prior studies have shown TC/HDL-C's tracking with LDL particle concentration (LDL-P) and its association with risk for cardiovascular events.[13–16]

Before considering additional tests (e.g., LDL-P, apoB), it may be desirable to extract as much information as possible from the standard lipid profile. We have previously shown significant patient-level percentile discordance between LDL-C and non-HDL-C suggesting additional information carried by non-HDL-C.[17] Likewise, TC/HDL-C may offer potential additional clinical information to LDL-C and non-HDL-C if it is significantly discordant with them within individuals. Therefore, the primary aim of this study was to examine the extent of patient-level percentile TC/HDL-C discordance.

METHODS

Study population and lipid testing

We examined consecutive lipid profiles from 1,310,432 U.S. adults ≥18 years of age with triglycerides (TG) <400 mg/dL from the Very Large Database of Lipids (*VLDL*).[18] This study is part B of the *VLDL-2* study that specifically aims to assess discordance between lipid parameters. In *VLDL-2A*,[17] we examined discordance between LDL-C and non-HDL-C and in this study (*VLDL-2B*) we examine discordance between TC/HDL-C vs LDL-C and non-HDL-C. Lipid profiles were measured using direct ultracentrifugation by the Vertical Auto Profile (VAP) test (Atherotech Diagnostics Laboratory, Birmingham, Alabama).[18,19] The accuracy and precision of VAP lipid parameters have been validated, as previously described.[18,19] Lipid distributions in the *VLDL* population were nearly superimposable with lipid distributions from the National Health and Nutrition Examination Survey (NHANES) (Supplemental Figure 1).[18]

LDL-C in the main analyses was estimated by the Friedewald formula given its longstanding use in clinical practice worldwide.[8] In order to address bias associated with the Friedewald LDL-C estimation method, we performed supplemental analyses using LDL-C estimated by our recently described novel method[20] as well as VAP-measured direct LDL-C.

The Johns Hopkins Institutional Review Board declared our study exempt and further information regarding data extraction and management has been previously described.[18]

Statistical analysis

We assigned population percentiles to TC/HDL-C, LDL-C, and non-HDL-C, and also determined the TC/HDL-C percentiles corresponding to LDL-C and non-HDL-C cut-points still used in some current worldwide guidelines such as the Canadian Cardiovascular Society, European Society of Cardiology and European Atherosclerosis Society, National Lipid Association and International Society of Atherosclerosis cholesterol guidelines (Supplemental Table 1).[4–7]

We used pseudocolor-encoded density scatter plots to visually assess discordance between TC/HDL-C, LDL-C, and non-HDL-C percentiles in the whole population and across TG categories of <100, 100–149, 150–199, and 200–399 mg/dL. In order to quantify the magnitude of discordance, we calculated the difference between TC/HDL-C percentile, LDL-C percentile, and non-HDL-C percentile for every patient as follows: [TC/HDL-C percentile minus LDL-C percentile] and [TC/HDL-C percentile minus non-HDL-C percentile]. We calculated the median with 1st to 3rd quartiles (Q1–Q3) of discordance. In supplemental analyses, the same calculations were performed to study discordance of TC/HDL-C with direct LDL-C and LDL-C estimated by the novel method.[20]

After considering the heterogeneous definitions of discordance in the literature,[17,21–25] we quantified discordance at the 4 arbitrary thresholds of ≥5, ≥10, ≥25, and ≥50 percentile units discordance and chose the 10th and 25th percentile units cut-points for further analyses. For each percentile unit (x) cut-point, the population was divided into patients with TC/HDL-C percentile > LDL-C percentile by ≥(x) percentile units, patients with TC/HDL-C percentile

< LDL-C percentile by ≤(x) percentile units and patients with concordant TC/HDL-C and LDL-C percentiles within +/− (x) percentile units. The same method was used in all other discordance analyses.

In patients with Friedewald LDL-C or non-HDL-C <15th population percentile (Friedewald LDL-C <70 mg/dL, non-HDL-C <93 mg/dL), we examined the proportion of discordant patients above the percentile-equivalent TC/HDL-C of 2.6 across TG categories. Similarly in patients with direct and novel method LDL-C <12th percentile (70 mg/dL), we examined the proportion of discordant patients above the percentile-equivalent TC/HDL-C of 2.5.

Next, we compared age, sex, and multiple lipid parameters derived from the standard lipid profile between the 2 discordant (TC/HDL-C > LDL-C or non-HDL-C and TC/HDL-C < LDL-C or non-HDL-C) and concordant patient populations. This analysis was performed using a discordance definition of ≥10 and ≥25 percentile units. Subsequently, linear regression models of multiple variables were utilized to determine the strength of association (R^2) with discordance. TC/HDL-C – LDL-C percentile discordance and TC/HDL-C – non-HDL-C percentile discordance followed a normal distribution and were used as continuous outcomes. The natural log of TG (ln(TG)) was used in the model given that TG levels followed a log normal distribution. We initially forced in age, sex and ln(TG) since TG is not involved in calculating TC/HDL-C or non-HDL-C. We then sequentially added TC followed by HDL-C. Subsequently, we used various combinations of lipid parameters including HDL-C subfractions (HDL_2-C, HDL_3-C) and logarithmic LDL density ratio (LLDR).[26] Additionally, we standardized continuous predictor variables (per 1 standard deviation) in order to make them more comparable.

Statistical analyses and logarithmically scaled pseudocolor encoded density plots were generated using R Version 2.15.1 (Vienna, Austria), Stata Version 11.0 (College Station, TX) and Microsoft Excel 2010 (Redmond, WA).

RESULTS

TC/HDL-C discordance with LDL-C and non-HDL-C

We visually observed significant patient-level percentile discordance in TC/HDL-C vs. LDL-C (Figure 1A) and non-HDL-C (Figure 2A) in the whole population and across TG categories (Figures 1B and 2B). Correlation coefficients of TC/HDL-C with LDL-C were moderate (Spearman rho =0.56, r =0.55, $p < 10^{-15}$), and higher with non-HDL-C (Spearman rho = 0.72, r =0.70, $p < 10^{-15}$). At TG levels <100 mg/dL, discordance was largely characterized by TC/HDL-C < LDL-C or non-HDL-C percentiles. At higher TG levels ≥150 mg/dL, discordance shifted towards TC/HDL-C > LDL-C or non-HDL-C percentiles (Figures 1B and 2B).

In Figure 3, we observed that 67% and 34% of patients had ≥10 percentile units and ≥25 percentile units discordance between TC/HDL-C and LDL-C, respectively. On a smaller scale, 60% and 25% of patients had ≥10 percentile units and ≥25 percentile units discordance between TC/HDL-C and non-HDL-C, respectively. In contrast to TC/HDL-C

discordance, non-HDL-C vs. LDL-C percentile discordance was relatively small with only 3% having ≥25 percentile units discordance.

Discordance of ≥10 and ≥25 percentile units between TC/HDL-C and LDL-C estimated by the novel method was also significant, occurring in 64% and 30% of patients, respectively (Supplemental Table 2). Discordance of ≥10 and ≥25 percentile units between TC/HDL-C and direct LDL-C occurred in 65% and 31% of patients, respectively (Supplemental Table 2).

Examining TC/HDL-C – LDL-C percentile discordance, the median (Q1–Q3) discordance in percentile units was −13.3 (−29.8 to 0.1), 0.1 (−14.2 to14.9), 10.6 (−2.6 to 27.4), and 25.7 (7.2 to 46.1) in patients with TG levels <100, 100–149, 150–199, and 200–399 mg/dL, respectively (Table 1). To a smaller extent, TC/HDL-C – non-HDL-C percentile discordance was −5.1 (−20.3 to 6.2), 1.0 (−12.7 to 15.2), 4.9 (−6.5 to 19.4), and 7.2 (−1.5 to 22.0), respectively (Table 1).

The proportion of patients with TC/HDL-C > LDL-C by ≥25 percentile units increased gradually from 3% in the TG <100 mg/dL group to as high as 51% in the TG 200–399 mg/dL group (Table 1). This was much larger than TC/HDL-C > non-HDL-C discordance where the proportion of patients increased from 6% to 21% across the respective TG groups (Table 1). On the other hand, the proportion of patients with TC/HDL-C < LDL-C by ≥25 percentile units decreased gradually with increasing TG levels and was much larger than TC/HDL-C < non-HDL-C discordance (Table 1). TC/HDL-C discordance with direct LDL-C and LDL-C estimated by the novel method was less dramatic at higher TG levels compared to Friedewald LDL-C (Supplemental Table 2).

We also assessed TC/HDL-C discordance with LDL-C and non-HDL-C at the LDL-C goal <70 mg/dL recommended by multiple guidelines.[4–7] In our population, LDL-C of 70 mg/dL was the percentile-equivalent of non-HDL-C of 93 mg/dL and TC/HDL-C of 2.6 (15^{th} percentile) (Supplemental Table 1). In patients with <15^{th} percentile levels of Friedewald LDL-C or non-HDL-C, a respective 58% and 46% were at or above the percentile-equivalent TC/HDL-C of 2.6. When studied across TG categories, the percentage of patients with LDL-C <15^{th} percentile and TC/HDL-C ≥15^{th} percentile, increased from 29% at TG levels <100 mg/dL to 96% at TG levels 200–399 mg/dL (Figure 4A). A similar analysis showed that the percentage of discordant patients with non-HDL-C <15^{th} percentile and TC/HDL-C ≥15^{th} percentile increased from 33% at TG levels <100 mg/dL to 87% at TG levels 200–399 mg/dL (Figure 4B). Similar analyses revealed that 57% of patients with direct LDL-C <12^{th} percentile (70 mg/dL) and 56% with novel method LDL-C <12^{th} percentile (70 mg/dL) were above the percentile-equivalent TC/HDL-C ratio of 2.5 (Supplemental Figure 2).

Characteristics of discordant vs. concordant patient populations

Using discordance definitions of ≥10 and ≥25 percentile units, we compared three groups of patients as follows: TC/HDL-C > LDL-C percentile, concordant percentiles and TC/HDL-C < LDL-C percentile (Table 2). Age was similar between the three groups of patients at both levels of discordance (≥10 percentile units and ≥25 percentile units discordance). Patients

with TC/HDL-C > LDL-C, compared to concordant and TC/HDL-C < LDL-C, were more commonly male (approximately two thirds) with a more atherogenic lipid phenotype characterized by lower HDL-C and its subfractions, and higher TG, TG/HDL-C ratio, and LDL density (LLDR).[26] However, TC and LDL-C levels were lower in these patients. We observed similar results when comparing the 3 TC/HDL-C vs. non-HDL-C groups (Table 3).

Explaining discordance

In a linear regression model using TC/HDL-C – LDL-C percentile discordance as a continuous outcome, age, sex and ln(TG) (Model A) explained 40% of discordance (R^2 0.4). Adding TC to the model increased R^2 to 0.74 (Model B) and consecutively adding HDL-C increased R^2 to 0.88 (Model C). For each 1 standard deviation (SD) increment in ln(TG), discordance increased by 20 and 12 percentile units in models B and C, respectively (Table 4A). For TC/HDL-C – non-HDL-C percentile discordance, age, sex and ln(TG) explained 21% of discordance (R^2 0.21) which increased to 0.64 and 0.86 by adding TC then consecutively HDL-C in models B and C, respectively (Table 4B). For each 1 SD increment in ln(TG), discordance increased by 10 and 2 percentile units in models B and C, respectively, a smaller change compared to TC/HDL-C vs. LDL-C discordance.

More regression models using HDL subfractions and LLDR are shown in Supplemental Table 3. Models incorporating HDL_3-C were better at explaining discordance than HDL_2-C, while LLDR added minimally to the prediction of discordance.

DISCUSSION

Our cross-sectional study of 1.3 million patients shows the existence of significant patient-level TC/HDL-C discordance in relation to LDL-C and non-HDL-C. Patients with a disproportionately high TC/HDL-C do not differ in age, but tend to be male and have a more atherogenic lipid phenotype with lower HDL-C and higher TG while patients with disproportionately low TC/HDL-C have a less atherogenic phenotype. Discordance is largely explained by age, sex, and levels of standard lipid parameters, predominantly the latter. Overall, the finding of significant TC/HDL-C discordance may suggest potential additional information in TC/HDL-C not available in LDL-C or non-HDL-C alone.

Perhaps the most striking and original finding in our big data analysis is the sizable discordance between TC/HDL-C and non-HDL-C. TC/HDL-C is calculated from the same two data points as non-HDL-C, with the only difference being the mathematical operation of division, rather than subtraction. Although one might intuit that there is no additional information to extract from dividing rather than subtracting TC and HDL-C, this question requires careful attention and empirical evidence.

We document considerable TC/HDL-C discordance with non-HDL-C. We found only one previous study examining patient-level TC/HDL-C and non-HDL-C discordance. In 692 severely hypercholesterolemic patients, TC/HDL-C was only modestly correlated with non-HDL-C ($r = 0.39$),[27] compared with $r = 0.70$ in our study. The difference in correlation may be due to the relatively small size and high cholesterol levels in the prior study population

with mean non-HDL-C and TC/HDL-C of 192 mg/dL and 6.7, respectively, compared to our larger population with means of 136 mg/dL and 3.7, respectively. In the prior study, among low-risk patients with a non-HDL-C <190 mg/dL, only 8% had TC/HDL-C ≥6.0 but among high-risk patients with non-HDL-C <130 mg/dL, 58% had a TC/HDL-C ≥3.5 consistent with findings in our study.

Prior studies have shown that particle-based measures such as LDL-P or apoB are discordantly greater than LDL-C more frequently in patients with insulin resistance, lower HDL-C, lower LDL-C, higher TG, and those on statins.[22,25,28,29] To our knowledge, our study is the first and largest to evaluate characteristics of patients with TC/HDL-C discordance. We found that those with disproportionately high TC/HDL-C were most commonly men and had a generally more atherogenic lipid phenotype characterized by lower HDL-C and its subfractions, higher TG, and higher LDL density.[21,22,26,28] TG/HDL-C, an important marker associated with insulin resistance and inversely associated with LDL particle size,[30] was also higher. Our findings suggest that the lipid phenotype of these patients is, generally, comparable to those with obesity, diabetes and metabolic syndrome who have a prevalence of triglyceride-rich remnant lipoproteins and cholesterol-depleted apoB particles.[22,28] This phenotype may be associated with a higher risk of coronary events compared to patients with cholesterol-rich apoB particles.[31] Using linear regression, we have also shown that >86% of the variance in discordance is fundamentally explained by age, sex and the three directly measured standard lipid parameters, a finding that in the future may help clinicians focus attention on certain patient clusters, such as those with low TC and HDL-C, where significant discordance exists and risk may track more closely to TC/HDL-C.

By inversely integrating HDL-C, a higher TC/HDL-C ratio may reflect, to some extent, discordance between particle cholesterol content and concentration that tends to occur in patients with insulin resistance and low HDL-C levels.[28] This novel concept suggests that potential additional information contained in TC/HDL-C may not be due to the contentious conviction of an inverse relationship between HDL-C and CVD[9] but instead, TC/HDL-C might provide a partial gateway to lipoprotein particle concentration and size information from the standard lipid profile. A recent analysis showed that TC/HDL-C ratio of <3 was the standard lipid profile measure that was most correlated with a LDL-P of <1000 nmol/L.[12] In another study, the significant difference in LDL size between patients with coronary artery disease and controls became non-significant after adjusting for TC/HDL-C.[32] While more study is needed, this initial evidence indicates that TC/HDL-C may carry information related to particle concentration and size.

If viewed in this way, as a marker of atherogenic lipoprotein burden, TC/HDL-C may be more acceptable for clinical use with focus shifted away from the lack of proven HDL-C raising strategies. By such a view, lowering a discordantly elevated TC/HDL-C may be desirable, to achieve a further lowering in atherogenic lipoproteins. Retention of apoB containing lipoproteins is the fundamental event leading to subendothelial accumulation of cholesterol and atherosclerosis.[22,28,33] However, both non-HDL-C and LDL-C are inherently cholesterol, not particle, focused measures. When small, dense lipoproteins predominate, non-HDL-C and LDL-C may underestimate the burden of circulating

atherogenic particles. Particle burden can be measured with an added test, or, for no additional cost, perhaps TC/HDL-C could be first considered.

At present, we can only comment on overall population-level risk signals for TC/HDL-C compared with non-HDL-C and LDL-C. The TC/HDL-C ratio has been strongly associated with cardiovascular risk.[14–16,34–36] In the Women's Health Study, TC/HDL-C was better than LDL-C and as good as or better than non-HDL-C and apolipoprotein fractions in the prediction of future cardiovascular events.[15] In another Women's Health Study, the net reclassification index for adding either apoB or LDL-P to TC/HDL-C was only 2%.[16] Similar results were demonstrated in the Framingham population,[35] Physicians Health Study,[37] and in statin-treated patients.[34] In a meta-analysis of approximately 900,000 patients with 55,000 vascular deaths, TC/HDL-C was suggested to provide 40% more risk information than non-HDL-C.[38]

Rather than the question of the general population risk information in a given lipid parameter, the most clinically-relevant question when considering additional parameters would seem to be: in those who have discordance, does discordance relate to greater atherosclerosis or greater risk of events? That is, related lipid parameters should be compared for risk signals when they disagree, not when they agree. This is a relatively new approach to epidemiologic analysis. Two studies have examined discordance between particle-based measures such as LDL-P and apoB vs. non-HDL-C in this way.[23,39] In these studies, discordance was sizeable and cardiovascular outcomes, including events, coronary artery calcium and carotid intimal medial thickness, tracked more closely with LDL-P and apoB. However, there is no conclusive outcome data to suggest that an advantage lies in the direction of the TC/HDL-C ratio in instances of discordance; thus, additional clinical studies using the patient-level discordance approach are warranted.

Study limitations

Our study limitations have been described in detail.[18] Although we lack important clinical characteristics, such as statin use, our population represents a contemporary population of 1.3 million patients with parallel age, sex, and lipid distributions to the NHANES population (Supplemental Figure 1). As a cross-sectional study, we cannot determine if TC/HDL-C discordance relates to risk for cardiovascular events, and if so, what magnitude of discordance is clinically significant. We note, however, that discordance between apoB and non-HDL-C of >5 percentiles was clinically significant[23] while another study showed that >12 percentile discordance between LDL-P and LDL-C was clinically significant.[25]

Conclusions

Our contemporary, big data analysis demonstrates that a substantial proportion of patients have significant discordance of TC/HDL-C with LDL-C and non-HDL-C. Therefore, the fundamental criterion for potential additional information – existence of discordance – is met. TC/HDL-C, available at no extra cost, warrants continued investigation of its potential clinical importance through discordance analyses in studies with longitudinal follow-up for clinical events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SSM and SRJ are listed as co-inventors on a pending patent filed by Johns Hopkins University for a method of low-density lipoprotein cholesterol estimation. PPT serves on the medical advisory board for Atherotech Diagnostic Lab; has received compensation for consultancy and lecturers from Abbvie, Aegerion, Amgen, AstraZeneca, Glaxo-SmithKline, Kowa, and Merck & Co, Novartis, and Regeneron. MB is a member of International Advisory Board of Amgen, and Sanofi and has given talks, attended conferences and participated in studies sponsored by MSD, Abbott, Sanofi and Amgen. KRK is an employee of Atherotech Diagnostics Laboratory and receives modest royalty from the University of Alabama in Birmingham, AL. SRJ serves on the medical advisory board for Atherotech Diagnostic Lab and as an advisor to Sanofi and Regeneron.

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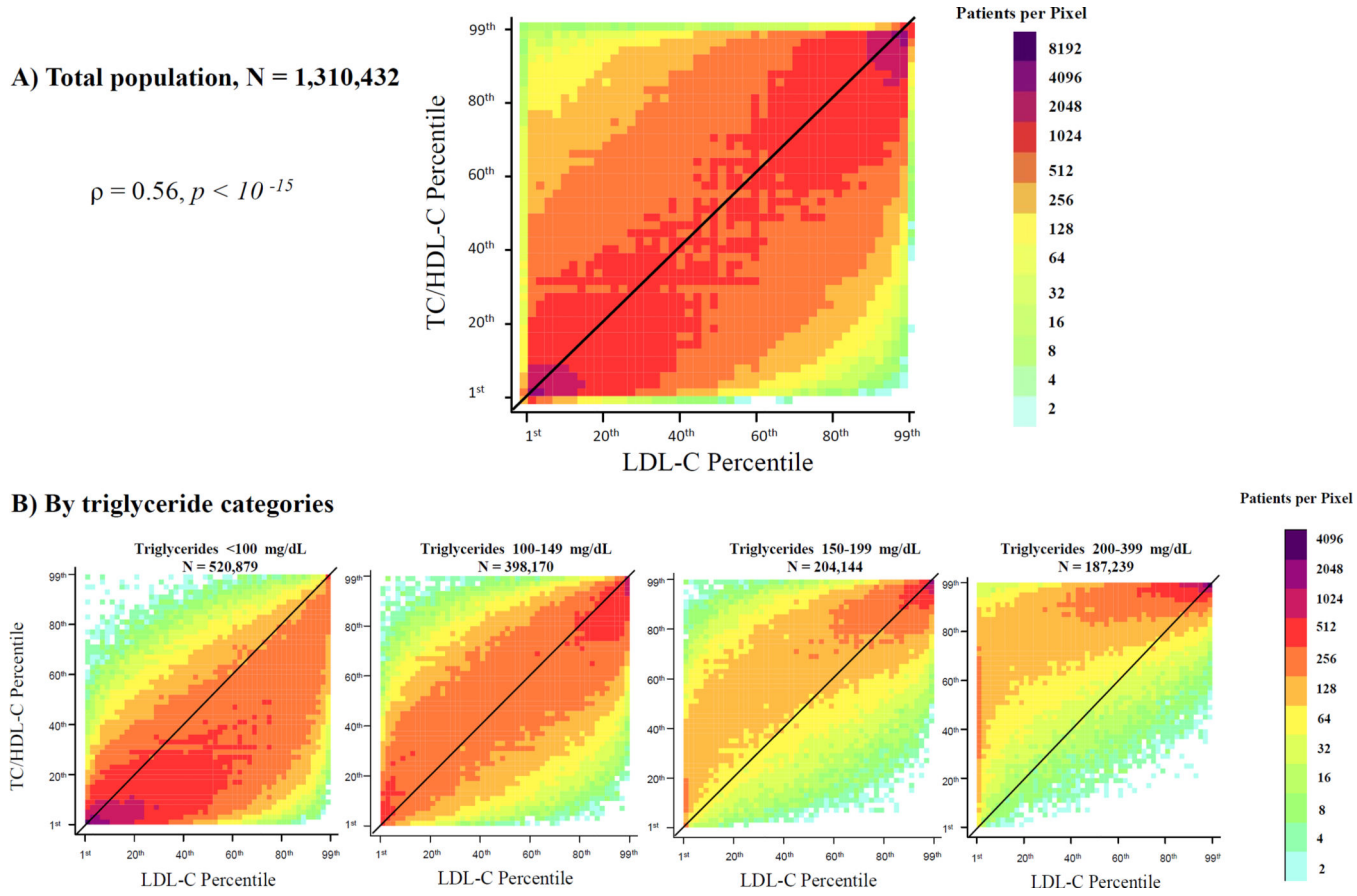


Figure 1.

Patient-level discordance between population percentiles of TC/HDL-C and LDL-C. Population percentiles of TC/HDL-C and LDL-C are presented on this plot for the whole population **(A)** and for four different triglyceride categories **(B)**. Points to the left of the diagonal line represent individuals with TC/HDL-C percentile > LDL-C percentile and points to the right of the diagonal line represent individuals with TC/HDL-C percentile < LDL-C percentile. The density of data is expressed by different shades of color, which represent increasing densities of patients per pixel, from light blue to purple. The number next to each color on the color axis represents the maximum number of patients per pixel of this color. ρ is Spearman correlation coefficient. TC/HDL-C (Total Cholesterol to HDL-C ratio); LDL-C (Low-density Lipoprotein Cholesterol).

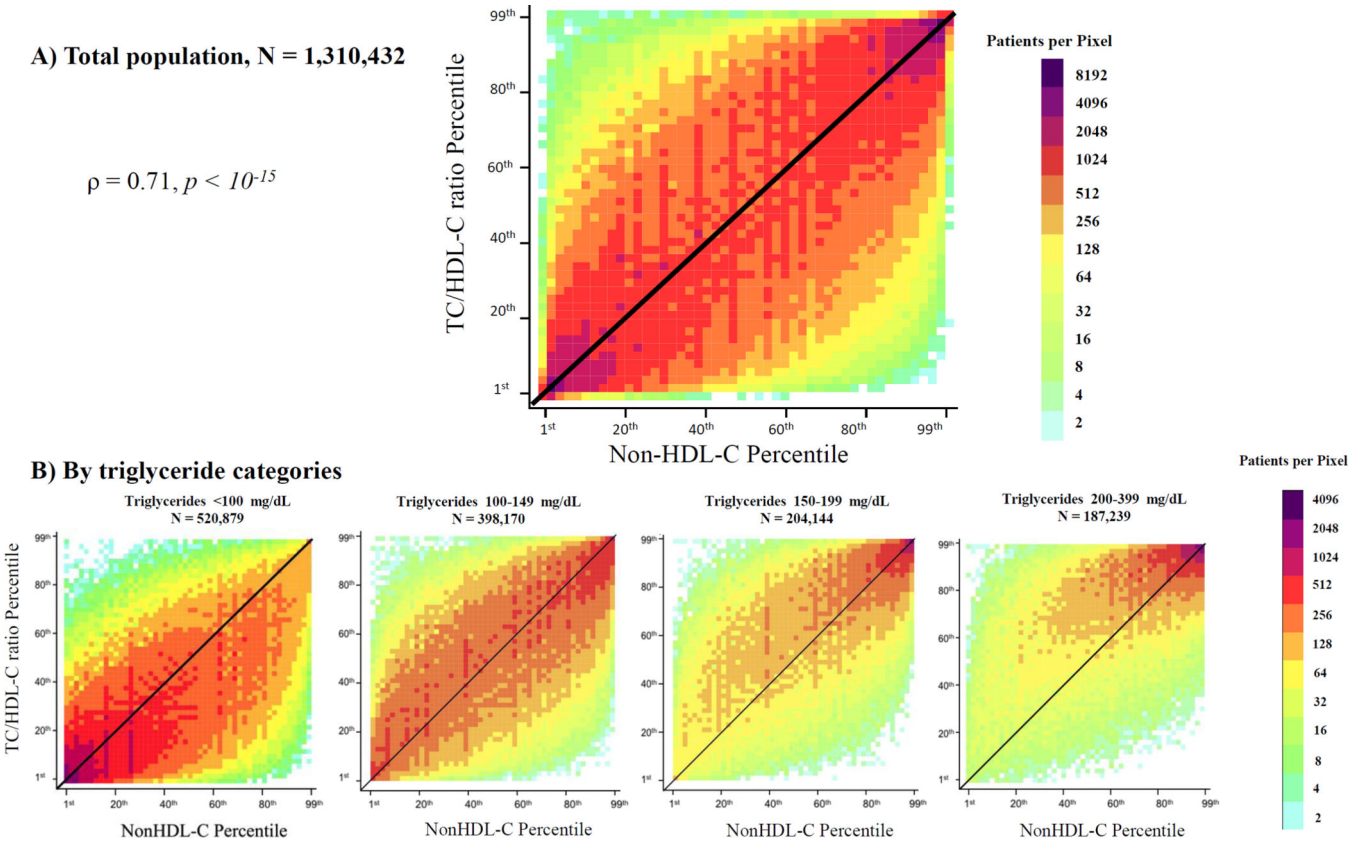
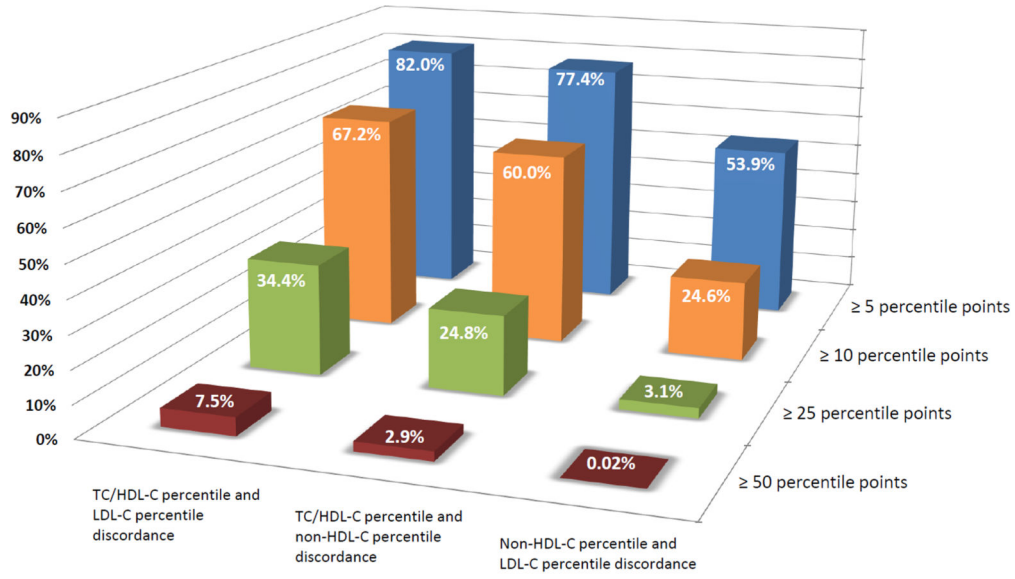


Figure 2.

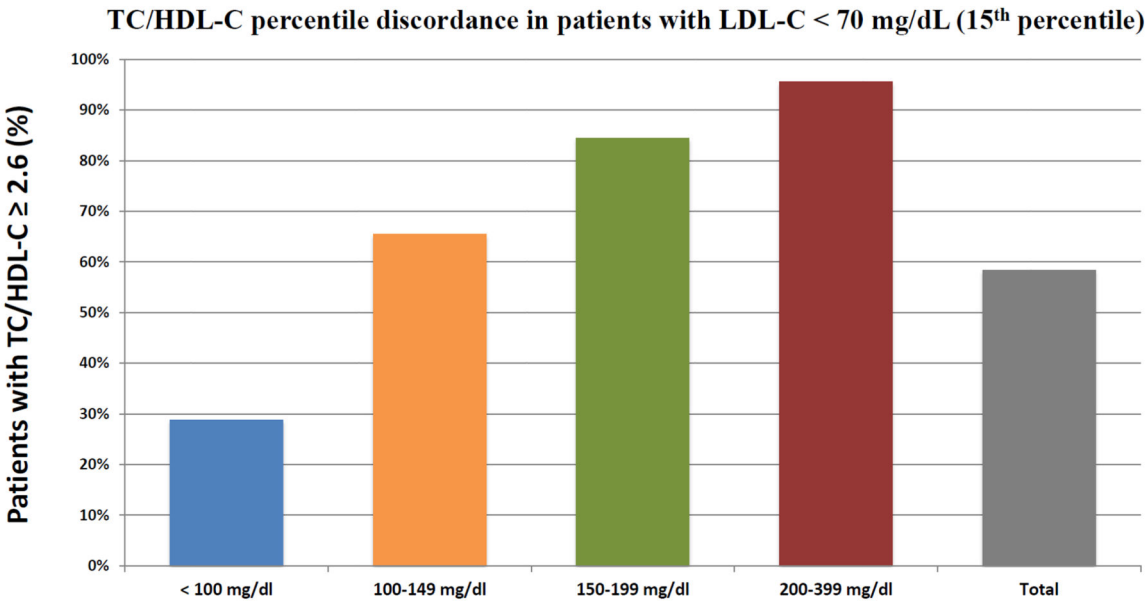
Patient-level discordance between population percentiles of TC/HDL-C and non-HDL-C. Population percentiles of TC/HDL-C and non-HDL-C are presented on this plot for the whole population **(A)** and for four different triglyceride categories **(B)**. Points to the left of the diagonal line represent individuals with TC/HDL-C percentile > non-HDL-C percentile and points to the right of the diagonal line represent individuals with TC/HDL-C percentile < non-HDL-C percentile. The density of data is expressed by different shades of color, which represent increasing densities of patients per pixel, from light blue to purple. The number next to each color on the color axis represents the maximum number of patients per pixel of this color. ρ is Spearman correlation coefficient. TC/HDL-C (Total Cholesterol to HDL-C ratio); non-HDL-C (Non-High-density Lipoprotein Cholesterol).



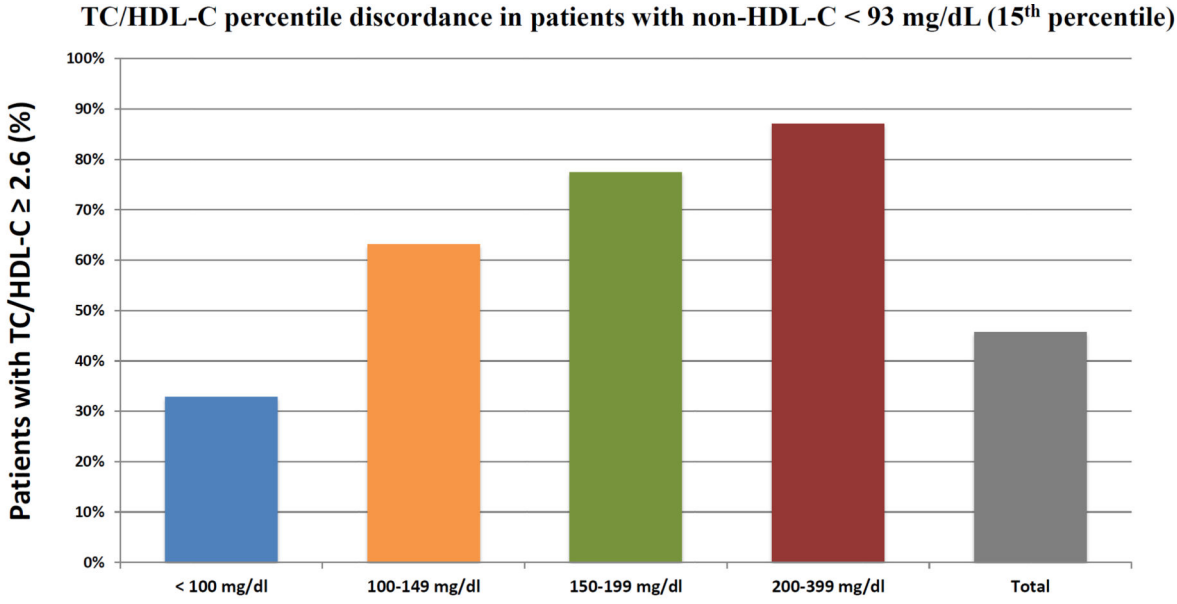
Absolute Percentile Unit Discordance Total population = 1,310,432	TC/HDL-C percentile and LDL-C percentile discordance n (%)	TC/HDL-C percentile and non-HDL-C percentile discordance n (%)	Non-HDL-C percentile and LDL-C percentile discordance n (%)
≥ 5 units	1,074,799 (82.0%)	1,014,051 (77.4%)	706,885 (53.9%)
≥ 10 units	880,581 (67.2%)	786,716 (60.0%)	322,331(24.6%)
≥ 25 units	450,578 (34.4%)	325,376 (24.8%)	41,045 (3.1%)
≥ 50 units	98,571 (7.5%)	38,016 (2.9%)	243 (0.02%)

Figure 3.

3-D plot of the extent of discordance between TC/HDL-C, LDL-C and non-HDL-C percentiles across different percentile units thresholds. On the X-axis, we present discordance between TC/HDL-C and LDL-C percentiles, TC/HDL-C and non-HDL-C percentiles and LDL-C and non-HDL-C percentiles from left to right, respectively. On the Y-axis, we represent the magnitude (%) of patient-level discordance at thresholds of ≥5, ≥10, ≥25, and ≥50 percentile units. TC/HDL-C (Total Cholesterol to HDL-C ratio); LDL-C (Low-density Lipoprotein Cholesterol); non-HDL-C (Non-High-density Lipoprotein Cholesterol).



Triglyceride category	< 100 mg/dl N = 78,578	100-149 mg/dl N = 51,893	150-199 mg/dl N = 27, 757	200-399 mg/dl N = 33,105	Total N = 191,333
TC/HDL-C ≥ 2.6, N	22,672	34,010	23,467	31,645	111,794
%	28.9%	65.5%	84.5%	95.6%	58.4%



Triglyceride category	< 100 mg/dl N = 119,159	100-149 mg/dl N = 47,189	150-199 mg/dl N = 13,812	200-399 mg/dl N = 6,446	Total N = 186,606
TC/HDL-C ≥ 2.6, N	39,147	29,793	10,701	5,616	85,257
%	32.9%	63.1%	77.5%	87.1%	45.7%

Figure 4.

Proportions with LDL-C or non-HDL-C <15th population percentile but discordantly high TC/HDL-C. **A)** The proportion of patients with LDL-C < 70 mg/dL and TC/HDL-C ≥ 2.6 (15th percentile equivalent cut-points) across various triglyceride categories **B)** The proportion of patients with non-HDL-C < 93 mg/dL and TC/HDL-C ≥ 2.6 (15th percentile equivalent cut-points) across various triglyceride categories. TC/HDL-C (Total Cholesterol to HDL-C ratio); LDL-C (Low-density Lipoprotein Cholesterol); non-HDL-C (Non-High-density Lipoprotein Cholesterol).

Table 1

Patient-level percentile discordance between TC/HDL-C compared to LDL-C and non-HDL-C across triglyceride categories.

	Triglyceride categories (mg/dL)				
	<100 N = 520,879	**100–149 N = 398,170**	**150–199 N = 204,144**	**200–399 N = 187,239**	**Total N = 1,310,432**
A) TC/HDL-C and LDL-C percentile discordance					
TC/HLD-C percentile minus LDL-C percentile median (Q1–Q3)	−13.3 (−29.8, 0.1)	0.1 (−14.2, 14.9)	10.6 (−2.6, 27.4)	25.7 (7.2, 46.1)	−0.73 (−17.5, 16.5)
≥10 percentile units discordance					
TC/HDL-C < LDL-C, n (%)	290,999 (55.9)	124,294 (31.2)	29,621 (14.5)	8,158 (4.4)	453,072 (34.6)
Concordant, n (%)	167,655 (32.2)	145,922 (36.7)	70,338 (34.5)	45,936 (24.5)	429,851 (32.8)
TC/HDL-C > LDL-C, n (%)	62,225 (11.9)	127,954 (32.1)	104,185 (51.0)	133,145 (71.1)	427,509 (32.6)
≥25 percentile units discordance					
TC/HDL-C < LDL-C, n (%)	164,103 (31.5)	51,827 (13.0)	9,008 (4.4)	1,879 (1.0)	226,727 (17.3)
Concordant, n (%)	339,495 (65.2)	293,620 (73.5)	137,744 (67.5)	89,995 (48.1)	859,854 (65.6)
TC/HDL-C > LDL-C, n (%)	17,371 (3.3)	53,723 (13.5)	57,392 (28.1)	95,365 (50.9)	223,851 (17.1)
B) TC/HDL-C and Non-HDL-C percentile discordance					
TC/HDL-C percentile minus non-HDL-C percentile median (Q1–Q3)	−5.1 (−20.3, 6.2)	1.0 (−12.7, 15.2)	4.9 (−6.5, 19.4)	7.2 (−1.5, 22.0)	0.17 (−13.2, 13.6)
≥10 percentile units discordance					
TC/HDL-C < non-HDL-C, n (%)	212,270 (40.8)	115,724 (29.0)	40,003 (19.6)	21,191 (11.3)	398,188 (29.7)
Concordant, n (%)	207,514 (39.8)	150,783 (37.9)	82,340 (40.3)	83,079 (44.4)	523,716 (40.0)
TC/HDL-C > non-HDL-C, n (%)	101,095 (19.4)	131,663 (33.1)	81,801 (40.1)	82,969 (44.3)	397,528 (30.3)
≥25 percentile units discordance					
TC/HDL-C < non-HDL-C, n (%)	100,396 (19.3)	45,139 (11.3)	12,766 (6.3)	5,559 (3.0)	163,860 (12.5)
Concordant, n (%)	389,154 (74.7)	299,857 (75.3)	154,397 (75.6)	141,648 (75.6)	985,056 (75.2)
TC/HDL-C > non-HDL-C, n (%)	31,329 (6.0)	53,174 (13.4)	36,981(18.1)	40,032 (21.4)	161,516 (12.3)

TC/HDL-C (Total Cholesterol to HDL-C ratio); LDL-C (Low-density Lipoprotein Cholesterol); non-HDL-C (Non-High-density Lipoprotein Cholesterol); Q1–Q3 (1st to 3rd quartile)

Table 2

Characteristics of patients with TC/HDL-C > LDL-C percentile discordance and TC/HDL-C < LDL-C percentile discordance versus percentile concordance.

	≥10 percentile units discordance			≥25 percentile units discordance		
Variables	**TC/HDL-C > LDL-C**	**Concordant**	**TC/HDL-C < LDL-C**	**TC/HDL-C > LDL-C**	**Concordant**	**TC/HDL-C < LDL-C**
N (%)	427,509 (32.6%)	429,851 (32.8%)	453,072 (34.6%)	223,851 (17.1%)	859,854 (65.6%)	226,727 (17.3%)
Age	60 (49–70)	60 (49–70)	59 (50–69)	60 (49–70)	59 (49–70)	59 (51–68)
Male, n (%)	283,680 (66.4%)	214,974 (50.0%)	121,479 (26.8%)	157,428 (70.3%)	417,561 (48.6%)	45,144 (19.9%)
HDL-C	40 (36–44)	51 (47–56)	68 (61–78)	37 (33–41)	52 (46–59)	75 (69–85)
TG	159 (118–217)	113 (83–154)	86 (67–113)	184 (137–246)	112 (83–153)	80 (64–103)
TG/HDL-C	3.92 (2.88–5.54)	2.19 (1.59–3.04)	1.26 (0.91–1.71)	4.9 (3.71–6.66)	2.17 (1.53–3.07)	1.06 (0.80–1.39)
TC	163 (141–187)	182 (153–221)	212 (190–238)	158 (139–178)	185 (159–215)	224 (205–246)
LDL-C	89 (70–109)	108 (77–143)	123 (102–146)	83 (67–99)	107 (81–136)	129 (112–148)
Non-HDL-C	122 (101–146)	131 (96–173)	142 (119–167)	120 (102–140)	130 (101–166)	146 (127–167)
TC/HDL-C	4.02 (3.41–4.80)	3.52 (2.73–4.64)	3.05 (2.61–3.57)	4.2 (3.67–4.90)	3.49 (2.82–4.37)	2.93 (2.58–3.31)
HDL_2-C	9 (7–10)	12 (10–15)	19 (15–23)	8 (6–9)	12 (10–15)	22 (18–26)
HDL_3-C	31 (28–35)	39 (36–42)	50 (45–56)	29 (26–32)	39 (35–44)	54 (50–60)
LLDR	1.0 (0.56 – 1.41)	0.66 (0.24 – 1.08)	0.25 (−0.17 – 0.69)	1.11 (0.68 – 1.50)	0.64 (0.19 – 1.08)	0.13 (−0.83 – 1.24)

All values reported other than n (%) are median (Q1–Q3)

HDL-C (high-density lipoprotein cholesterol); TG (triglycerides); TC (total cholesterol); LDL-C (low-density lipoprotein cholesterol); non-HDL-C (Non-High-density Lipoprotein Cholesterol); LLDR (logarithmic LDL-C density ratio); Q1–Q3 (1^{st} to 3^{rd} quartile)

Table 3

Characteristics of patients with TC/HDL-C > non-HDL-C percentile discordance and TC/HDL-C < non-HDL-C percentile discordance versus percentile concordance.

	≥10 percentile units discordance			≥25 percentile units discordance		
Variables	**TC/HDL-C > Non-HDL-C**	**Concordant**	**TC/HDL-C < Non-HDL-C**	**TC/HDL-C > Non-HDL-C**	**Concordant**	**TC/HDL-C < Non-HDL-C**
N (%)	397,528 (30.3)	523,716 (40.0%)	389,188 (29.7%)	161,516 (12.3%)	985,056 (75.2%)	163,860 (12.5%)
Age	60 (49–70)	59 (48–70)	59 (51–69)	61 (50–71)	59 (49–70)	60 (52–69)
Male, n (%)	277,138 (69.7%)	252,153 (48.1%)	90,842 (23.3%)	122,789 (76.0%)	470,354 (47.7%)	26,990 (16.5%)
HDL-C	40 (36–44)	52 (48–57)	69 (62–79)	36 (32–39)	52 (45–60)	78 (72–88)
TG	135 (99–186)	115 (80–167)	95 (72–128)	146 (108–199)	114 (81–162)	89 (69–117)
TG/HDL-C	3.40 (2.39–5.00)	2.19 (1.44–3.43)	1.34 (0.95–1.92)	4.13 (2.97–5.90)	2.18 (1.44–3.36)	1.12 (0.82–1.54)
TC	157 (138–177)	186 (161–219)	219 (199–243)	147 (131–162)	188 (163–213)	234 (218–254)
LDL-C	87 (69–105)	108 (79–140)	127 (107–149)	79 (64–93)	106 (83–134)	134 (118–153)
Non-HDL-C	116 (97–137)	133 (99–173)	148 (126–172)	111 (96–126)	132 (104–164)	154 (137–174)
TC/HDL-C	3.89 (3.33–4.62)	3.53 (2.70–4.68)	3.10 (2.66–3.62)	4.06 (3.60–4.68)	3.50 (2.83–4.40)	2.96 (2.62–3.33)
HDL_2-C	8 (7–10)	12 (10–15)	19 (16–24)	7 (6–9)	12 (10–16)	23 (19–28)
HDL_3-C	31 (28–34)	40 (36–43)	50 (46–56)	28 (26–31)	39 (35–45)	56 (52–61)
LLDR	0.99 (0.54 – 1.42)	0.67 (0.23 – 1.09)	0.22 (−0.19 – 0.66)	1.12 (0.67 – 1.54)	0.65 (0.19 – 1.10)	0.07 (−0.33 – 0.49)

All values reported other than n (%) are median (Q1–Q3)

HDL-C (high-density lipoprotein cholesterol); TG (triglycerides); TC (total cholesterol); LDL-C (low-density lipoprotein cholesterol); non-HDL-C (Non-High-density Lipoprotein Cholesterol); LLDR (logarithmic LDL-C density ratio); Q1–Q3 (1^{st} to 3^{rd} quartile)

Table 4

Multivariable linear regression analysis to predict percentile discordance between TC/HDL-C versus LDL-C and non-HDL-C.

	A) TC/HDL-C – LDL-C percentile discordance			B) TC/HDL-C – non-HDL-C percentile discordance		
	A	**B**	**C**	**A**	**B**	**C**
Constant	−7.66 (0.03); −301.07	−3.83 (0.02); −234.36	−0.91 (0.01); −76.48	−7.32 (0.02); −312.3	−3.96 (0.02); −246.56	−0.78 (0.01); −76.11
ln(TG)*	16.07 (0.02); 787.95	20.03 (0.01); 1513.74	12.46 (0.01); 1086.47	6.39 (0.02); 339.97	9.87 (0.01); 759.52	1.64 (0.01); 165.56
Age	0.17 (0.02); 9.01	−1.76 (0.01); −150.99	−0.32 (0.01); −38.23	−0.04 (0.02); −2.09	−1.73 (0.01); −150.83	−0.16 (0.01); −22.27
Gender (male)	16.41 (0.04); 446.19	8.38 (0.02); 349.42	2.03 (0.02); 113.89	15.65 (0.03); 461.78	8.60 (0.02); 364.92	1.70 (0.02); 110.00
HDL-C			−13.24 (0.01); −1140.88			−14.39 (0.01); −1434.58
TC		−17.27 (0.01); −1393.68	−11.52 (0.01); −1142.03		−15.18 (0.01); −1247.17	−8.94 (0.01); −1022.61
R^2	0.4025	0.7601	0.8801	0.2138	0.6417	0.8611

* Natural log of triglycerides due to log normal distribution of triglycerides

Results shown are: coefficient (Standard Error); T statistic

All covariates, except gender, were standardized by their standard deviations.

All values are statistically significant ($p<0.0001$)

HDL-C (high-density lipoprotein cholesterol); TG (triglycerides); TC (total cholesterol); LDL-C (low-density lipoprotein cholesterol); non-HDL-C (Non-High-density Lipoprotein Cholesterol)