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ORIGINAL RESEARCH

Discordance Between Very Low-Density Lipoprotein Cholesterol and Low-Density Lipoprotein Cholesterol Increases Cardiovascular Disease Risk in a Geographically Defined Cohort

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BACKGROUND: Clinical risk scores are used to identify those at high risk of atherosclerotic cardiovascular disease (ASCVD). Despite preventative efforts, residual risk remains for many individuals. Very low-density lipoprotein cholesterol (VLDL-C) and lipid discordance could be contributors to the residual risk of ASCVD.

METHODS AND RESULTS: Cardiovascular disease–free residents, aged ≥40 years, living in Olmsted County, Minnesota, were identified through the Rochester Epidemiology Project. Low-density lipoprotein cholesterol (LDL-C) and VLDL-C were estimated from clinically ordered lipid panels using the Sampson equation. Participants were categorized into concordant and discordant lipid pairings based on clinical cut points. Rates of incident ASCVD, including percutaneous coronary intervention, coronary artery bypass grafting, stroke, or myocardial infarction, were calculated during follow-up. The association of LDL-C and VLDL-C with ASCVD was assessed using Cox proportional hazards regression. Interaction between LDL-C and VLDL-C was assessed. The study population (n=39 098) was primarily White race (94%) and female sex (57%), with a mean age of 54 years. VLDL-C (per 10-mg/dL increase) was significantly associated with an increased risk of incident ASCVD (hazard ratio, 1.07 [95% CI, 1.05–1.09]; $P<0.001$]) after adjustment for traditional risk factors. The interaction between LDL-C and VLDL-C was not statistically significant ($P=0.11$). Discordant individuals with high VLDL-C and low LDL-C experienced the highest rate of incident ASCVD events, 16.9 per 1000 person-years, during follow-up.

CONCLUSIONS: VLDL-C and lipid discordance are associated with a greater risk of ASCVD and can be estimated from clinically ordered lipid panels to improve ASCVD risk assessment.

Key Words: atherosclerotic cardiovascular disease ■ lipid discordance ■ low-density lipoprotein cholesterol ■ very low-density lipoprotein cholesterol

Despite advances in atherosclerotic cardiovascular disease (ASCVD) risk prediction and preventive therapies over the past several decades, ASCVD remains the leading cause of death across the globe.[1] Several cardiovascular risk calculators, including the ASCVD pooled cohort risk equations (PCEs), have limitations in accurately quantifying individual risk.[2,3] The inaccuracies stem in part from omissions

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CLINICAL PERSPECTIVE

What Is New?

- Very low-density lipoprotein cholesterol (VLDL-C) was more strongly associated with an increased risk of atherosclerotic cardiovascular disease compared with low-density lipoprotein cholesterol, even after adjustment for traditional risk factors, and can be easily obtained from a standard lipid panel without an additional cost or clinical test.
- Lipid discordance, or disagreement between, VLDL-C and low-density lipoprotein cholesterol provides a novel indicator of residual atherosclerotic cardiovascular disease risk; those with discordantly high VLDL-C and low low-density lipoprotein cholesterol experienced the highest rates of atherosclerotic cardiovascular disease during study follow-up.

What Are the Clinical Implications?

- Those with elevated VLDL-C levels, and particularly those with discordantly high VLDL-C and low low-density lipoprotein cholesterol, may benefit from additional clinical assessments and screenings to evaluate signs of subclinical atherosclerotic cardiovascular disease and other important biomarkers.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
PCE	pooled cohort risk equation
VLDL-C	very low-density lipoprotein cholesterol

of key attributes of ASCVD, such as evidence of subclinical disease (eg, coronary artery calcium) and inflammatory biomarkers (eg, CRP [C-reactive protein]). Traditional risk factors, such as age, are overemphasized in comparison; this results in inflated estimates of risk in older populations and underestimations in certain at-risk younger individuals with signs of subclinical disease.[3–5] Furthermore, PCE does not directly consider low-density lipoprotein cholesterol (LDL-C) or very low-density lipoprotein cholesterol (VLDL-C), both of which have been previously identified as contributors to ASCVD risk.[3]

Recent evidence has indicated that VLDL-C is more strongly associated with ASCVD risk compared with LDL-C.[6–9] VLDL-C is a major component of remnant cholesterol or remnant lipoproteins, a compilation of partially lipolyzed remnant particles in the blood, including chylomicron remnants, intermediate-density lipoprotein, and VLDL-C.[10] VLDL-C is particularly atherogenic because of its ability to transport large amounts of lipids, ≈7 times more than LDL-C, to macrophages.[10] This process aids and accelerates the buildup of arterial plaque and subsequent development of ASCVD.[9–11]

In addition to the independent influences of LDL-C and VLDL-C on ASCVD risk, an increasing body of evidence suggests that discordance, or disagreement between, LDL-C and VLDL-C may further impact ASCVD risk. Lipid-lowering therapies have been a primary clinical strategy for reducing LDL-C and subsequent ASCVD risk for several decades. However, recent research has shown that individuals with optimal levels of LDL-C may sustain a residual risk of ASCVD because of discordantly high levels of remnant cholesterol, including VLDL-C.[3,7,8,10,12–14] Furthermore, the excess risk incurred from discordant lipid levels suggests the existence of a potentially complex nonlinear relationship between LDL-C and VLDL-C.[8]

Existing risk calculators capture only total cholesterol and high-density lipoprotein cholesterol (HDL-C) in their estimations. They do not separately take into account the independent effects of both LDL-C and VLDL-C, and they may overlook the effect of lipid discordance on ASCVD risk. Although the adverse effects of VLDL-C and remnant cholesterol have become more established in recent years, the challenge in measuring specific lipid subfractions has made it difficult to readily incorporate into risk assessment models.[3] In addition, the impacts of remnant cholesterol and analysis of discordance have only recently been introduced in large cohort studies, such as the ARIC (Atherosclerosis Risk in Communities) study.[8]

Historically, certain lipid subfractions have been estimated via the Friedewald equation. However, there are known challenges with using the Friedewald equation for lipoprotein calculations, particularly in individuals with high triglycerides.[10] The extended Martin-Hopkins and Sampson equations were developed to more accurately calculate LDL-C and VLDL-C and have both proven to be superior to the Friedewald equation.[10,15] Many clinical laboratories have adopted the use of the extended Martin-Hopkins or Sampson equations for lipid calculations in recent years for improved classification of dyslipidemia and subsequent ASCVD risk assessment. Notably, the Sampson equation has no intellectual property or cost restrictions, allowing for a simplified transition for many laboratories.[15] For this reason, only the Sampson and Friedewald equations are used for analysis and comparison purposes in this article.

The compound risks of LDL-C, VLDL-C, and lipid discordance have not been fully explored in the context of ASCVD risk assessment. This study aims to analyze

the ASCVD risk-inducing effects of these components in a large, geographically defined community cohort.

METHODS

Study Population

Participants were part of the Rochester Epidemiology Project, a comprehensive medical records–linkage system established in 1966 for individuals residing in Olmsted County, Minnesota, and surrounding counties.[16,17] The Rochester Epidemiology Project was used to identify a cohort of 51 965 cardiovascular disease–free Olmsted County residents aged ≥40 years on January 1, 2006 (baseline date). Individuals were included if they had a lipid panel measured within the baseline data collection period from January 1, 2001, to December 31, 2005 (n=39 098). The study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. The study was considered minimal risk by both Institutional Review Boards; thus, the requirement for informed consent was waived. However, patients who did not provide authorization to use their medicals records for research were excluded.

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to info@rochesterproject.org.

Measurements

Lipid measurements from clinical care were collected via the Rochester Epidemiology Project. The closest lipid measurements to the baseline date were used in the analysis. All lipid subfractions were estimated using both the Friedewald and Sampson equations for comparison purposes, and the Sampson calculations were used in primary regression analyses because of their improved accuracy in estimation.[15]

All other baseline demographic and clinical characteristics were extracted, and collection methods are detailed in a previous publication.[17] In summary, age, sex, race, and ethnicity were collected as demographic variables from patient records. Race and ethnicity were categorized per the US census. Clinical data were collected in the 5 years before baseline (2001–2005). All recorded heights and weights were used for body mass index calculation, and the median body mass index was computed for each patient. For all other clinical variables, the closest value to the baseline date was used. Extreme systolic and diastolic blood pressure measurements were excluded. Smoking status was ascertained via patient-provided information and coded as never or ever. Use of lipid-lowering and hypertension therapies was determined according to classification by the National Drug File Reference Terminology. Diabetes was defined by the presence of an *International Classification of Diseases, Ninth Revision* (*ICD-9*), code (ie, 249.xx–250.xx, 357.2, 362.01–362.06, 366.41, 790.21–790.22, 790.29, 791.5–791.6, V45.85, V53.91, and V65.46). ASCVD risk score was calculated using the American College of Cardiology and American Heart Association 10-year PCE.[18] Patients with missing data for quantitative traits used in the ASCVD risk score were assigned the midpoint of the normal range. For missing dichotomous variables, they were assigned the low-risk value (eg, nonsmoker).

The study cohort was categorized into concordant and discordant pairs using clinically standard optimal levels: <100 mg/dL for LDL-C and <30 mg/dL for VLDL-C.[7,8] Concordant individuals had VLDL-C and LDL-C levels that were both above optimal measures (high), or both within the optimal range (low). Discordant individuals had high LDL-C levels and low VLDL-C levels, or vice versa. Values of LDL-C and VLDL-C are reported using the Sampson equations unless otherwise noted.

Outcomes

The cohort was followed up through December 31, 2019, for incident ASCVD events. Incident ASCVD included any of the following diagnoses or procedures identified during follow-up: percutaneous coronary intervention, coronary artery bypass grafting, stroke, or myocardial infarction. Percutaneous coronary intervention was identified using the Mayo Clinic percutaneous coronary intervention registry; coronary artery bypass grafting was identified through the use of Current Procedural Terminology codes (33 503, 33 504, 33 510–33 514, 33 516–33 519, 33 521–33 523, 33 530, and 33 534–33 536); stroke was identified through a combination of clinical concepts[19] (transient ischemic attack), *ICD-9* codes (435.x9), and Current Procedural Terminology codes (70 553, 71 275, and 93 880); myocardial infarction was identified through inpatient hospitalization with primary diagnosis code *ICD-9* 410.xx (excluding 410.x2), or *International Classification of Diseases, Tenth Revision* (*ICD-10*), I21.xx. All-cause and ASCVD death information was collected through medical records, Minnesota death certificates, and National Death Index Plus records. Participants were followed up until the first incident ASCVD event, or through follow-up end date if they remained disease free.

Statistical Analysis

Baseline patient characteristics were summarized using median (interquartile range) for continuous variables and count (percentage) for categorical variables. Comparisons were made across groups using the

2-sample *t*-test (rank sum) or χ^2 (exact) test, as appropriate. The association of LDL-C and VLDL-C with time to ASCVD was evaluated using Cox proportional hazards regression, with adjustment for traditional risk factors used in the PCE. Total cholesterol was omitted from adjustment of traditional risk factors to reduce collinearity with the addition of LDL-C and VLDL-C. Associations are provided per 10-mg/dL unit increase in VLDL-C and LDL-C. Cumulative survival probabilities were estimated using the Kaplan-Meier method. To more flexibly investigate LDL-C and VLDL-C associations of ASCVD risk, tensor product smoothing was applied in a generalized additive model using the mgcv R package.[20–24] Marginal smooths and interactions were included in the model to individually evaluate main effects and the LDL-C and VLDL-C interaction. Significance testing was performed on the tensor product interaction term to investigate whether the values of one lipid measure impacted the estimated effect of the other on ASCVD risk. Visualizations of the smoothed effects were generated using contour plots via the itsadug R package.[25] In all cases, $P<0.05$ was considered statistically significant.

RESULTS

Study Population

Characteristics of the study population compared with the ineligible population (ie, no lipid panel) are provided in Table S1. The 39 098 individuals included in the study had a mean follow-up time of 11.8 years, with 4466 ASCVD events. Coronary heart disease events were the most common (n=2025), followed by stroke (n=1295) and death attributable to circulatory system diseases (n=1146). The comparison of baseline demographic and clinical characteristics of the study population, stratified by concordant-discordant pairs using clinical cut points, is summarized in Table 1. Nearly half (49.9%) of the study population had discordantly high LDL-C and low VLDL-C, and 4.8% had discordantly low LDL-C and high VLDL-C. Those with discordantly low LDL-C and high VLDL-C were more likely to be older, men, and ever smokers, compared with the other groups. Examining differences across racial and ethnic groups, there is a higher proportion of Asian participants (3.8%) and a lower proportion of White participants (92.1%) with discordantly low LDL-C and high VLDL-C compared with the other concordant-discordant pairings. Clinically, this group had an increased prevalence of diabetes (39.7%), higher use of hypertension and lipid-lowering therapies (53.6% and 53.1%, respectively), and higher triglycerides at baseline compared with all other groups ($P<0.001$).

Baseline lipid levels stratified by use of lipid-lowering therapy are provided in Table S2. Of those using lipid-lowering therapy (26%), median total cholesterol and LDL-C levels were lower, but triglycerides and VLDL-C levels were higher, compared with those not using lipid-lowering therapy. As shown in Table S3, a greater proportion of participants were categorized as having discordantly high VLDL-C and low LDL-C when using the Friedewald versus Sampson equation (10.6% versus 4.8%). In those using lipid-lowering therapy at baseline, 10.0% had discordantly high VLDL-C and low LDL-C compared with only 3.0% of those not using lipid-lowering therapy (Table S4). Figure 1 illustrates the triglyceride distribution for each concordant-discordant pair based on clinical cut points.

Outcomes

On the basis of 4466 incident ASCVD events that occurred during follow-up, the crude ASCVD rate for the full cohort was 9.5 per 1000 person-years. Stratified by concordant-discordant pairs, the crude ASCVD rates during the follow-up period are provided in Table 1. Those with discordantly high LDL-C and low VLDL-C experienced the lowest crude ASCVD rate (7.7 per 1000 person-years); conversely, the group with discordantly low LDL-C and high VLDL-C experienced the highest crude ASCVD rate (16.9 per 1000 person-years). Survival curves by concordant-discordant pairs are shown in Figure 2. The group with discordantly high VLDL-C and low LDL-C levels experienced the lowest rate of ASCVD-free survival during follow-up; the discordantly high LDL-C and low VLDL-C group experienced the highest rate of ASCVD-free survival. Crude ASCVD rates for the concordant-discordant pairs estimated by the Friedewald equation are provided in Table S5.

The association of LDL-C and VLDL-C with ASCVD was investigated using a series of models independently assessing LDL-C and VLDL-C per 10 mg/dL, shown in Table 2. LDL-C was associated with a slight decrease in incident ASCVD within the full study population (hazard ratio [HR], 0.97 [95% CI, 0.97–0.98]). After adjusting for traditional ASCVD risk factors, the association between LDL-C and incident ASCVD was marginally significant (HR, 1.01 [95% CI, 1.00–1.02]). Additional adjustment for VLDL-C or triglycerides did not further modify the association. Stratified by concordant-discordant pairings, the unadjusted association between LDL-C and ASCVD was only significant in the concordantly low LDL-C and low VLDL-C group (HR, 0.92 [95% CI, 0.88–0.96]). In contrast, VLDL-C was associated with an increase in incident ASCVD (HR, 1.13 [95% CI, 1.11–1.14]) for the full cohort. This association remained significant after adjustment for traditional ASCVD risk factors (HR, 1.07 [95% CI, 1.05–1.09]). Additional adjustment for LDL-C did not modify the association, but VLDL-C was associated

Table 1. Comparison of Baseline Characteristics in the Study Cohort, Stratified by Concordant-Discordant Groups by Clinical Cut Points

Characteristic	Included cohort	Concordant-discordant groups				*P* value
		Concordant group (low LDL-C, low VLDL-C)	Concordant group (high LDL-C, high VLDL-C)	Discordant group (low LDL-C, high VLDL-C)	Discordant group (high LDL-C, low VLDL-C)	
Patients, n (%)	39098	10353 (26.5)	7343 (18.8)	1880 (4.8)	19522 (49.9)	
Age, mean (SD), y	56.7 (12.1)	57.4 (13.1)	56.7 (11.9)	58.9 (12.3)	56.2 (11.7)	<0.001
Age categories, y						
40–49	13490 (34.5)	3745 (36.2)	2483 (33.8)	497 (26.4)	6765 (34.7)	<0.001
50–59	11874 (30.4)	2667 (25.8)	2305 (31.4)	551 (29.3)	6351 (32.5)	
60–69	7181 (18.4)	1858 (18.0)	1364 (18.6)	426 (22.7)	3533 (18.1)	
70–79	4312 (11.0)	1326 (12.8)	784 (10.7)	278 (14.8)	1924 (9.9)	
≥80	2241 (5.7)	757 (7.3)	407 (5.5)	128 (6.8)	949 (4.9)	
Sex, female, n (%)	22341 (57.1)	6273 (60.6)	3710 (50.5)	860 (45.7)	11498 (58.9)	<0.001
Race, n (%)						
American Indian	70 (0.2)	18 (0.2)	19 (0.3)	9 (0.5)	24 (0.1)	<0.001
Asian	1034 (2.7)	274 (2.7)	225 (3.1)	71 (3.8)	464 (2.4)	
Black	714 (1.8)	192 (1.9)	96 (1.3)	27 (1.4)	399 (2.1)	
White	36295 (93.5)	9620 (93.6)	6800 (93.3)	1722 (92.1)	18153 (92.6)	
Hawaiian/Pacific Islander	43 (0.1)	10 (0.1)	10 (0.1)	3 (0.2)	20 (0.1)	
Other*/multiracial	678 (1.8)	165 (1.6)	141 (1.9)	38 (2.0)	334 (1.7)	
Unknown	264	74	52	10	128	
Hispanic ethnicity, n (%)	1044 (2.7)	250 (2.4)	222 (3.0)	59 (3.1)	513 (2.6)	0.049
BMI, median (IQR), kg/m^2	27.9 (24.6–31.9)	26.6 (23.5–30.9)	30.2 (27.0–34.1)	31.1 (27.8–35.2)	27.3 (24.4–31.0)	<0.001
Unknown, n	2301	466	576	121	1138	
Smoking status						
Ever, n (%)	12597 (40.1)	3473 (40.0)	2500 (43.7)	763 (48.8)	5861 (37.9)	<0.001
Unknown, n	7648	1673	1616	317	4042	
Systolic blood pressure, median (IQR), mm Hg	123 (112–134)	121 (110–132)	126 (118–138)	128 (118–138)	122 (112–134)	<0.001
Unknown	116	24	31	3	58	
Diastolic blood pressure, median (IQR), mm Hg	73.5 (66–80)	70 (64–79)	76 (70–82)	74 (68–80)	74 (68–80)	<0.001
Unknown, n	116	24	31	3	58	
Use of hypertension therapy, n (%)	12134 (31.0)	3574 (34.5)	2752 (37.5)	1007 (53.6)	4801 (24.6)	<0.001
Diabetic, n (%)	6462 (16.5)	3122 (20.6)	1525 (20.8)	746 (39.7)	2058 (10.5)	<0.001
Use of lipid-lowering therapy, n (%)	10041 (25.7)	3354 (32.4)	2233 (30.4)	999 (53.1)	3455 (17.7)	<0.001
Total cholesterol, median (IQR), mg/dL	196 (172–219)	161 (148–174)	224 (205–246)	173 (161–187)	204 (188–222)	<0.001
HDL cholesterol, median (IQR), mg/dL	54 (44–66)	58 (47–71)	46 (39–54)	42 (35–51)	56 (47–68)	<0.001
Triglyceride, median (IQR), mg/dL	118 (83–168)	92 (67–127)	212 (186–257)	249 (213–314)	105 (80–131)	<0.001
Values ≥400 mg/dL, n (%)	480 (1.2)	0	259 (3.5)	221 (11.8)	0	<0.001
LDL-C, median (IQR), mg/dL						
Friedewald	111.8 (91.8–133.0)	83.4 (73.0–91.4)	128.8 (112.0–150.4)	77.8 (64.3–85.8)	122.8 (110.2–138.8)	<0.001
Sampson	114.9 (95.0–135.9)	85.4 (74.7–92.5)	133.8 (118.0–154.3)	86.7 (75.1–94.2)	125.2 (112.4–141.4)	<0.001
VLDL-C, median (IQR), mg/dL						
Friedewald	23.6 (16.6–33.6)	18.4 (13.4–25.4)	42.4 (37.2–51.4)	49.8 (42.6–62.8)	21.0 (16.0–26.2)	<0.001
Sampson	20.1 (13.9–29.3)	14.3 (10.4–19.8)	38.4 (33.5–47.1)	39.0 (33.6–49.4)	18.5 (14.0–23.2)	<0.001
ASCVD risk score, n (%)						
Low risk (<5%)	21605 (55.3)	6143 (59.3)	3087 (42.0)	656 (34.9)	11719 (60.0)	<0.001
Borderline risk (5%–7.4%)	3631 (9.3)	652 (6.3)	927 (12.6)	211 (11.2)	1841 (9.4)	
Intermediate risk (7.5%–19.9%)	7567 (19.4)	1592 (15.4)	1972 (26.9)	520 (27.7)	3483 (17.8)	
High risk (≥20%)	6295 (16.1)	1966 (19.0)	1357 (18.5)	493 (26.2)	2479 (12.7)	

(*Continued*)

Table 1. Continued

Type of ASCVD, events (rate per 1000 person-years)	Included cohort	Concordant-discordant groups				Log-rank *P* value
		Concordant group (low LDL-C, low VLDL-C)	Concordant group (high LDL-C, high VLDL-C)	Discordant group (low LDL-C, high VLDL-C)	Discordant group (high LDL-C, low VLDL-C)	
All ASCVD events	4466 (9.5)	1237 (10.2)	1037 (12.0)	355 (16.9)	1837 (7.7)	<0.001
Coronary heart disease (CHD) - MI, PCI, CABG	2025 (4.3)	464 (3.8)	525 (6.1)	180 (8.5)	856 (3.6)	<0.001
Death due to disease of circulatory system	1146 (2.4)	394 (3.2)	217 (2.5)	95 (4.5)	440 (1.8)	<0.001
Stroke	1295 (2.8)	379 (3.1)	295 (3.4)	80 (3.8)	541 (2.3)	<0.001

Data are given as number (percentage) or median (IQR), unless otherwise indicated. The VLDL-C cut point was 30 mg/dL and the LDL-C cut point was 100 mg/dL using the Sampson equation. ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CABG, coronary artery bypass grafting; CHD, coronary heart disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; and VLDL-C, very low-density lipoprotein cholesterol.

*The Rochester Epidemiology Project classifies race per the US Census: White, Black, Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, Other and mixed, or Unknown.

with an increased HR after adjustment for triglycerides (HR, 1.20 [95% CI, 1.10–1.31]). Stratified by concordant-discordant pairs, the association between VLDL-C and incident ASCVD was significant in the discordantly high LDL-C and low VLDL-C group and both concordant groups. The LDL-C and VLDL-C interaction was not statistically significant (*P*=0.11). Figure S1 displays a contour plot to visualize the relationship.

Further stratifying the study population into quartiles of VLDL-C and LDL-C levels based on the population distribution, those with increasingly discordant high VLDL-C and low LDL-C experienced the highest ASCVD rate during follow-up (17.0 per 1000 person-years), as shown in Table 3. Conversely, those with discordantly high LDL-C and low VLDL-C experienced the lowest ASCVD rate during follow-up, at only 5.4 per 1000 person-years. Cox regression results stratified by participant use of lipid-lowering therapy are provided in Table S6. Those using lipid-lowering therapy experienced higher ASCVD rates during follow-up, and

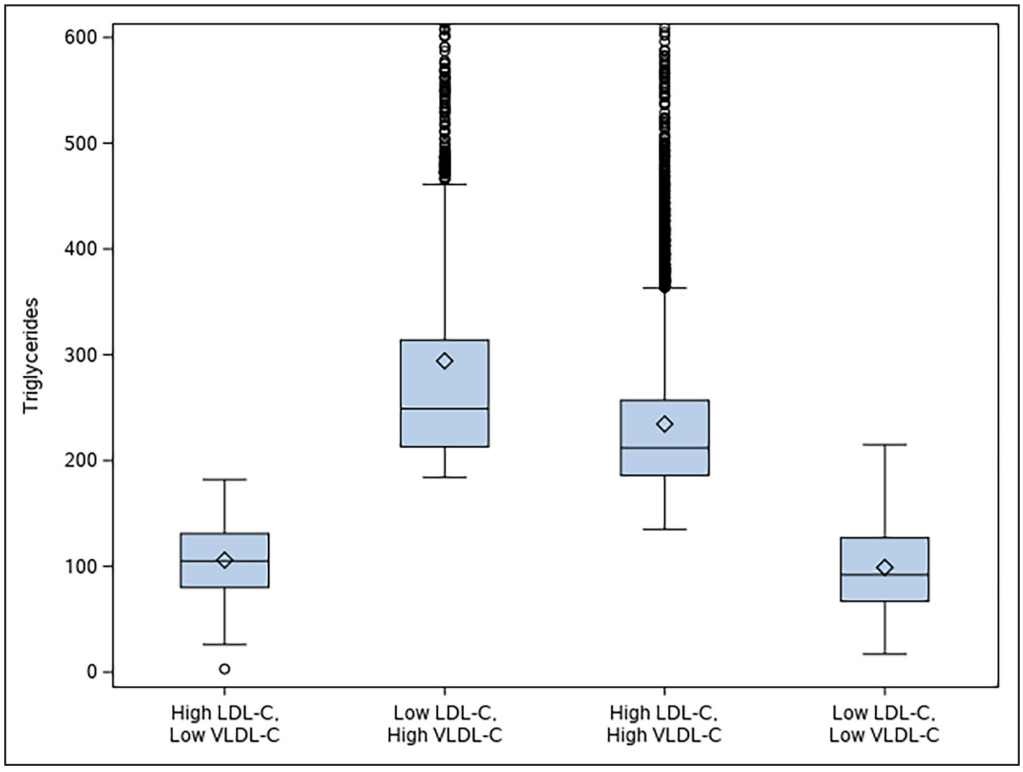

Figure 1. Box plots displaying triglyceride levels for the 4 concordant-discordant lipid groups.
LDL-C indicates low-density lipoprotein cholesterol; and VLDL-C, very low-density lipoprotein cholesterol.

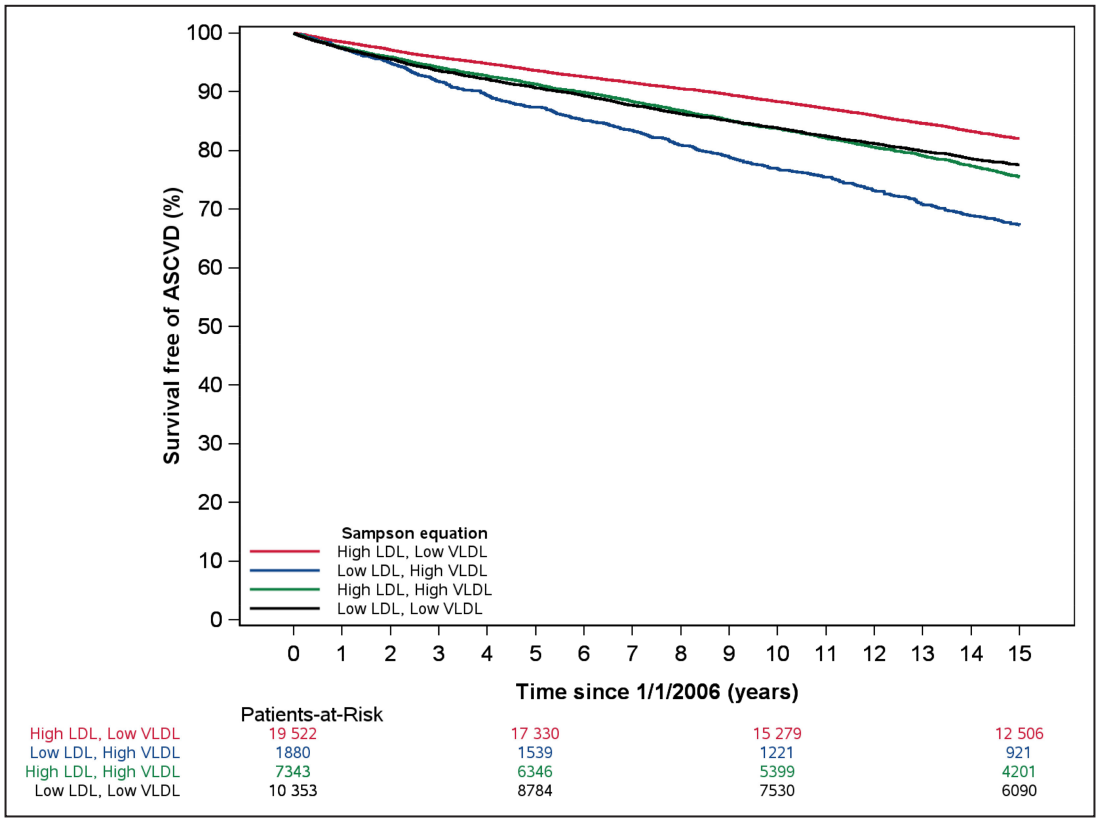

Figure 2. Atherosclerotic cardiovascular disease (ASCVD) survival curves, stratified by low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) concordant-discordant pairs.

the discordantly high VLDL-C and low LDL-C group again had the highest rates of ASCVD, regardless of lipid-lowering therapy use. Association results were consistent when lipid levels were estimated using the Friedewald equation (data not shown).

DISCUSSION

Overview of Findings

In this geographically defined study cohort of nearly 40 000 individuals, the complex association between VLDL-C and LDL-C with ASCVD was illustrated in several ways. The comparison of ASCVD rates by concordant-discordant pairs revealed trends consistent with published literature, albeit using differing subfractions.[7,8,26] On the basis of clinical cut points for LDL-C and VLDL-C, those with discordantly high VLDL-C and low LDL-C experienced the highest rates of ASCVD during follow-up, and over double the rate of those with discordantly high LDL-C and low VLDL-C. In addition, VLDL-C was more strongly associated with an increase in ASCVD compared with LDL-C in unadjusted models and those adjusted for traditional risk factors. However, the VLDL-C and LDL-C interaction was not statistically significant. Regardless, these results provide evidence that VLDL-C contributes to an increased residual risk of ASCVD in disease-free individuals, particularly in those with discordantly high VLDL-C and low LDL-C. Importantly, these lipid subfractions can be calculated using a standard lipid panel at no additional cost for use in optimizing ASCVD risk stratification.

Lipid Discordance and VLDL-C

Previous research has explored lipid discordance in a variety of ways, including based on lipid ratio of total cholesterol/HDL-C, remnant cholesterol/LDL-C, and low-density lipoprotein particle number/non–HDL-C.[8,27,28] Discordance remains a relatively novel concept in terms of assessing cardiovascular disease risk through lipid subfractions, and significant debate remains around the accuracy and superiority of risk assessment across these lipid subfractions. In addition, the clinical utility of subfractions varies based on individuals' lipid concordance-discordance.[29]

Our finding of varying ASCVD risk in discordant individuals emphasizes the possible clinical and biological importance of lipid discordance. Previous research

Table 2. Association of LDL-C and VLDL-C Estimated by the Sampson Equation With ASCVD, Stratified by Concordant-Discordant Pairs

Variable	Study population	Discordant group (high LDL-C, low VLDL-C)	Discordant group (low LDL-C, high VLDL-C)	Concordant group (high LDL-C, high VLDL-C)	Concordant group (low LDL-C, low VLDL-C)
Patients, n	39098	19522	1880	7343	10353
ASCVD events, n	4466	1837	355	1037	1237
Total person-years	468142	238946	21060	86699	121436
Crude ASCVD rate, per 1000 person-years	9.5	7.7	16.9	12.0	10.2

Time to ASCVD	HR (95% CI)*	*P* value	HR (95% CI)*	*P* value	HR (95% CI)*	*P* value	HR (95% CI)*	*P* value	HR (95% CI)*	*P* value
LDL-C (per 10 mg/dL)										
Unadjusted	0.97 (0.97–0.98)	<0.001	1.01 (0.99–1.04)	0.19	0.94 (0.88–1.01)	0.089	0.99 (0.97–1.01)	0.32	0.92 (0.88–0.96)	<0.001
Adjusted†	1.01 (1.00–1.02)	0.011	1.04 (1.02–1.06)	<0.001	1.00 (0.93–1.08)	0.96	1.04 (1.02–1.06)	0.001	0.97 (0.94–1.01)	0.19
Adjusted†+VLDL-C	1.01 (1.00–1.02)	0.25	1.04 (1.02–1.06)	<0.001	1.00 (0.93–1.08)	0.92	1.03 (1.01–1.05)	0.006	0.98 (0.94–1.02)	0.30
Adjusted†+triglycerides	1.01 (1.00–1.02)	0.022	1.04 (1.02–1.06)	<0.001	1.00 (0.93–1.09)	0.91	1.04 (1.02–1.06)	<0.001	0.98 (0.94–1.02)	0.23
VLDL-C (per 10 mg/dL)										
Unadjusted	1.13 (1.11–1.14)	<0.001	1.43 (1.32–1.55)	<0.001	0.97 (0.91–1.02)	0.20	1.11 (1.07–1.14)	<0.001	1.57 (1.44–1.72)	<0.001
Adjusted†	1.07 (1.05–1.09)	<0.001	1.07 (0.98–1.17)	0.11	1.01 (0.96–1.07)	0.74	1.11 (1.07–1.15)	<0.001	0.94 (0.85–1.04)	0.22
Adjusted†+LDL-C	1.07 (1.05–1.09)	<0.001	1.04 (0.95–1.14)	0.39	1.01 (0.96–1.07)	0.73	1.10 (1.07–1.14)	<0.001	0.95 (0.86–1.06)	0.35
Adjusted†+triglycerides	1.20 (1.10–1.31)	<0.001	2.02 (1.32–3.08)	0.001	1.04 (0.83–1.31)	0.72	1.29 (1.12–1.50)	<0.001	0.58 (0.27–1.25)	0.16

ASCVD indicates atherosclerotic cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; and VLDL-C, very low-density lipoprotein cholesterol.

*HR per 10 units of increase.

†Adjusted for ASCVD risk factors (age, sex, race, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, diabetes, smoking status, and hypertensive treatment use) included in the American College of Cardiology and American Heart Association 10-year pooled cohort risk equation.

Table 3. Comparison of the Quartiles of LDL-C and VLDL-C Estimated by the Sampson Equation and the ASCVD Rate

	VLDL-C, mg/dL			
LDL-C, mg/dL	Quartile 1 (<13.9)	Quartile 2 (13.9 to ≤20.1)	Quartile 3 (20.1 to ≤29.3)	Quartile 4 (≥29.3)
Quartile 1 (<95.0)	4148 (10.6) 379/49 384 (7.7)	2313 (5.9) 340/26 447 (12.9)	1766 (4.5) 280/20 071 (14.0)	1565 (4.0) 298/17 550 (17.0)
Quartile 2 (95.0 to ≤114.9)	2801 (7.2) 183/34 998 (5.2)	2635 (6.7) 263/32 309 (8.1)	2297 (5.9) 296/27 186 (10.9)	2040 (5.2) 339/23 589 (14.4)
Quartile 3 (114.9 to ≤135.9)	1878 (4.8) 120/23 566 (5.1)	2639 (6.8) 232/32 422 (7.2)	2723 (7.0) 322/32 848 (9.8)	2508 (6.4) 331/29 779 (11.1)
Quartile 4 (≥135.9)	905 (2.3) 61/11 248 (5.4)	2173 (5.6) 212/26 502 (8.0)	3070 (7.9) 323/37 114 (8.7)	3637 (9.3) 487/43 127 (11.3)

Data are given as number (percentage), number/person-years (rate per 1000 person-years). ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; and VLDL-C, very low-density lipoprotein cholesterol.

has indicated that measures including VLDL-C and remnant cholesterol are only clinically relevant for individuals discordant with LDL-C.[29] However, our study found that VLDL-C, independently and in addition to traditional ASCVD risk factors, was associated with an increase in ASCVD across the full study population and in individuals with concordantly high LDL-C and VLDL-C. Consistent with previous studies on lipid discordance using the Friedewald equation, we found that individuals with the greatest levels of discordance between LDL-C and VLDL-C using the Sampson equation also experienced significantly different ASCVD rates during follow-up. Those with discordantly high VLDL-C at baseline experienced a 2- to 3-fold increase in ASCVD rate compared with those with discordantly high LDL-C. As lipid-lowering therapies primarily target LDL-C levels, we hypothesize that those with concordantly high VLDL-C and LDL-C may be treated more aggressively than those with discordantly high VLDL-C and low LDL-C levels. Those with lower LDL-C levels are less likely to be treated by current clinical standards; as a result, this group may remain at a higher risk of ASCVD because of elevated VLDL-C.

In this study, we chose to focus specifically on VLDL-C to examine the role of discordance with LDL-C. Although remnant cholesterol, non–HDL-C, and apolipoprotein B have been previously used to estimate residual ASCVD risk, VLDL-C remained our focus for 3 primary reasons. First, remnant cholesterol contains biologically differing components, such as chylomicron remnants, intermediate-density lipoprotein, and VLDL-C. Remnant cholesterol is often used as a rough estimation of VLDL-C, although VLDL-C alone provides increased precision in analyzing the cholesterol subfraction of interest. Second, non–HDL-C is a sum of all atherogenic lipid components, including LDL-C. Because subfraction discordance has previously been shown to be clinically relevant in the development of cardiovascular disease, it was important to describe the lipid components discretely from one another rather than as a cumulative sum of all non–HDL-C particles. Last, in contrast to apolipoprotein B, VLDL-C is an easily obtained component of a standard lipid panel and can be estimated without an additional cost or clinical test.

As previously noted, VLDL-C may be particularly atherogenic because of its increased cholesterol content per particle compared with LDL-C.[10] This increased cholesterol content may even make VLDL-C more potent within the arterial intima compared with LDL-C because of its increased size.[11,30] Conversely, larger remnant lipid components may be less atherogenic than VLDL-C because of their inability to enter the arterial intima because of their size. Because lipid-lowering therapy primarily targets the reduction of LDL-C, VLDL-C and other lipoproteins may remain elevated and contribute to residual risk.[30,31] Within our study population, a greater proportion of those on lipid-lowering therapy had discordantly high VLDL-C levels, and had, on average, lower LDL-C levels and higher VLDL-C and triglyceride levels compared with those not on lipid-lowering therapy. Lipid-lowering therapy may be masking the residual risk of ASCVD as discordance was increasingly prevalent in this subgroup compared with those not on lipid-lowering therapy.

Limitations and Strengths

A notable limitation of our study includes the lack of racial and ethnic diversity of this geographically defined cohort. We are also lacking participant information related to socioeconomic status, which is strongly linked to ASCVD.[32,33] As a result, we are unable to adjust for known risk factors and predictors that may be prevalent in those with high VLDL-C levels. Notably, the discordantly low LDL-C and high VLDL-C group had a slightly higher proportion of non-White, specifically Asian, individuals compared with the other groups, and experienced the highest rates of ASCVD for all outcomes. Although the study population was overwhelming White race and non-Hispanic ethnicity, these differences may warrant additional investigation with more representative population sizes for all racial and ethnic groups. Furthermore, socioeconomic variables, including income and education, are not currently considered in the PCE, and these components may provide valuable insight into risk estimation in the future. In addition, the stratification into concordant-discordant pairings used in regression analysis was based on clinical cut points

for VLDL-C and LDL-C rather than population median levels. Although categorization based on population distributions would have yielded additional uniformity across groups during regression analysis, the use of concordant-discordant pairings based on clinical cut points did not introduce external bias of the sample data, and provided clinically relevant groupings.

Notable strengths of the study include the inclusion of nearly 40 000 individuals with a median follow-up of nearly 12 years, the use of an improved lipid equation (Sampson versus Friedewald), and the availability of robust electronic health record data for participants. The greatest strength of using VLDL-C in discordance identification and risk estimation is that it is available as part of a standard lipid panel with no additional testing and can be readily implemented to better identify patients at a heightened risk of ASCVD who remain undetected by current clinical standards.

Summary and Recommendations

Our findings illustrate the importance of identifying individuals with discordant lipid levels, particularly those with low LDL-C and discordantly high VLDL-C. ASCVD events increased with increasing VLDL-C regardless of LDL-C. However, patients with the lowest LDL-C and highest VLDL-C went on to experience the highest rates of ASCVD. Thus, the use of VLDL-C could potentially identify patients with misclassified risk using the current version of the PCE. Measures of total cholesterol and non–HDL-C fail to accurately assess and identify discordance in lipid ratio, particle number, and cholesterol amount, yet each of these has been previously identified as clinically relevant.[27–30,34] Beyond the PCE, current clinical guidelines do not yet recognize lipid discordance, VLDL-C, or broader remnant cholesterol as risk enhancers to inform individual risk discussions.

Our results suggest that lipid discordance is an additional factor to consider for ASCVD risk assessment, particularly in the presence of elevated VLDL-C. Discordant patients can then be triaged for follow-up clinical assessments as appropriate, including screening for biomarkers, such as CRP, anemia, or creatinine, to better quantify and reduce individual ASCVD risk. Future research should investigate the association between PCE estimated risk and actual ASCVD outcomes as a function of VLDL-C discordance, both in the presence and the absence of lipid-lowering therapy. Furthermore, discordant individuals with low LDL-C and high VLDL-C require additional analysis to better understand the features of lipid discordance and to determine if there are unique predictors for events in this group, such as those related to socioeconomic status, additional illness burden, or prevalent biomarkers.

In summary, the importance of lipid discordance as a consideration of ASCVD risk was illustrated in this large, geographically defined cohort. We described the clinical utility of identifying individuals with discordantly high VLDL-C and low LDL-C levels and reported a significant association between VLDL-C and incident ASCVD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S6
Figure S1

REFERENCES

1. Balakumar P, Maung UK, Jagadeesh G. Prevalence and prevention of cardiovascular disease and diabetes mellitus. *Pharmacol Res*. 2016;113:600–609. doi: 10.1016/j.phrs.2016.09.040
2. Paquette M, Bernard S, Cariou B, Hegele RA, Genest J, Trinder M, Brunham LR, Beliard S, Baass A. Familial hypercholesterolemia-risk-score: a new score predicting cardiovascular events and cardiovascular mortality in familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol*. 2021;41:2632–2640. doi: 10.1161/ATVBAHA.121.316106
3. Carr SS, Hooper AJ, Sullivan DR, Burnett JR. Non-HDL-cholesterol and apolipoprotein B compared with LDL-cholesterol in atherosclerotic cardiovascular disease risk assessment. *Pathology*. 2019;51:148–154. doi: 10.1016/j.pathol.2018.11.006
4. Fu Y, Wu Y, Liu E. C-reactive protein and cardiovascular disease: from animal studies to the clinic (review). *Exp Ther Med*. 2020;20:1211–1219. doi: 10.3892/etm.2020.8840
5. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol*. 2018;72:434–447. doi: 10.1016/j.jacc.2018.05.027
6. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol*. 2006;98:1363–1368. doi: 10.1016/j.amjcard.2006.06.032
7. Quispe R, Elshazly MB, Zhao D, Toth PP, Puri R, Virani SS, Blumenthal RS, Martin SS, Jones SR, Michos ED. Total cholesterol/HDL-cholesterol ratio discordance with LDL-cholesterol and non-HDL-cholesterol and incidence of atherosclerotic cardiovascular disease in primary prevention: the ARIC study. *Eur J Prev Cardiol*. 2020;27:1597–1605. doi: 10.1177/2047487319862401

8. Quispe R, Martin SS, Michos ED, Lamba I, Blumenthal RS, Saeed A, Lima J, Puri R, Nomura S, Tsai M, et al. Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study. *Eur Heart J*. 2021;42:4324–4332. doi: 10.1093/eurheartj/ehab432
9. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. *Endocr Rev*. 2019;40:537–557. doi: 10.1210/er.2018-00184
10. Krauss RM, King SM. Remnant lipoprotein particles and cardiovascular disease risk. *Best Pract Res Clin Endocrinol Metab*. 2023;37:101682. doi: 10.1016/j.beem.2022.101682
11. Doi T, Langsted A, Nordestgaard BG. Elevated remnant cholesterol reclassifies risk of ischemic heart disease and myocardial infarction. *J Am Coll Cardiol*. 2022;79:2383–2397. doi: 10.1016/j.jacc.2022.03.384
12. Ruscica M, Ferri N, Santos RD, Sirtori CR, Corsini A. Lipid lowering drugs: present status and future developments. *Curr Atheroscler Rep*. 2021;23:17. doi: 10.1007/s11883-021-00918-3
13. Blaha MJ, Blumenthal RS, Brinton EA, Jacobson TA; National Lipid Association Taskforce on Non HDLC. The importance of non-HDL cholesterol reporting in lipid management. *J Clin Lipidol*. 2008;2:267–273. doi: 10.1016/j.jacl.2008.06.013
14. Heidemann BE, Koopal C, Bots ML, Asselbergs FW, Westerink J, Visseren FLJ. The relation between VLDL-cholesterol and risk of cardiovascular events in patients with manifest cardiovascular disease. *Int J Cardiol*. 2021;322:251–257. doi: 10.1016/j.ijcard.2020.08.030
15. Sampson M, Ling C, Sun Q, Harb R, Ashmaig M, Warnick R, Sethi A, Fleming JK, Otvos JD, Meeusen JW, et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. *JAMA Cardiol*. 2020;5:540–548. doi: 10.1001/jamacardio.2020.0013
16. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ 3rd. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. *Mayo Clin Proc*. 2012;87:1202–1213. doi: 10.1016/j.mayocp.2012.08.012
17. Manemann SM, St Sauver JL, Liu H, Larson NB, Moon S, Takahashi PY, Olson JE, Rocca WA, Miller VM, Therneau TM, et al. Longitudinal cohorts for harnessing the electronic health record for disease prediction in a US population. *BMJ Open*. 2021;11:e044353. doi: 10.1136/bmjopen-2020-044353
18. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49–S73. doi: 10.1161/01.cir.0000437741.48606.98
19. Zhao Y, Fu S, Bielinski SJ, Decker PA, Chamberlain AM, Roger VL, Liu H, Larson NB. Natural language processing and machine learning for identifying incident stroke from electronic health records: algorithm development and validation. *J Med Internet Res*. 2021;23:e22951. doi: 10.2196/22951
20. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *J R Stat Soc Ser B Stat Methodol*. 2011;73:3–36. doi: 10.1111/j.1467-9868.2010.00749.x
21. Wood SN, Pya N, Säfken B. Smoothing parameter and model selection for general smooth models. *J Am Stat Assoc*. 2016;111:1548–1563. doi: 10.1080/01621459.2016.1180986
22. Wood SN. Stable and efficient multiple smoothing parameter estimation for generalized additive models. *J Am Stat Assoc*. 2004;99:673–686. doi: 10.1198/016214504000000980
23. Wood SN. *Generalized Additive Models: an Introduction with R, Second Edition*. 2nd ed. New York: Chapman and Hall/CRC; 2017. doi: 10.1201/9781315370279
24. Wood SN. Thin-plate regression splines. *J R Stat Soc B*. 2003;65:95–114. doi: 10.1111/1467-9868.00374
25. van Rij J, Wieling M, Baayen R, van Rijn H. Itsadug: interpreting time series and autocorrelated data using GAMMs. R Package version 2.4.12022.
26. Sampson M, Wolska A, Warnick R, Lucero D, Remaley AT. A new equation based on the standard lipid panel for calculating small dense low-density lipoprotein-cholesterol and its use as a risk-enhancer test. *Clin Chem*. 2021;67:987–997. doi: 10.1093/clinchem/hvab048
27. Elshazly MB, Quispe R, Michos ED, Sniderman AD, Toth PP, Banach M, Kulkarni KR, Coresh J, Blumenthal RS, Jones SR, et al. Patient-level discordance in population percentiles of the total cholesterol to high-density lipoprotein cholesterol ratio in comparison with low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol: the very large database of lipids study (VLDL-2B). *Circulation*. 2015;132:667–676. doi: 10.1161/CIRCULATIONAHA.115.016163
28. Degoma EM, Davis MD, Dunbar RL, Mohler ER 3rd, Greenland P, French B. Discordance between non-HDL-cholesterol and LDL-particle measurements: results from the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2013;229:517–523. doi: 10.1016/j.atherosclerosis.2013.03.012
29. Mora S, Buring JE, Ridker PM. Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. *Circulation*. 2014;129:553–561. doi: 10.1161/CIRCULATIONAHA.113.005873
30. Varbo A, Benn M, Tybjaerg-Hansen A, Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;61:427–436. doi: 10.1016/j.jacc.2012.08.1026
31. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;384:626–635. doi: 10.1016/S0140-6736(14)61177-6
32. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, Quyyumi AA, Taylor HA, Gulati M, Harold JG, et al. Socioeconomic status and cardiovascular outcomes: challenges and interventions. *Circulation*. 2018;137:2166–2178. doi: 10.1161/CIRCULATIONAHA.117.029652
33. Shen R, Zhao N, Wang J, Guo P, Shen S, Liu D, Liu D, Zou T. Association between socioeconomic status and arteriosclerotic cardiovascular disease risk and cause-specific and all-cause mortality: data from the 2005-2018 National Health and Nutrition Examination Survey. *Front Public Health*. 2022;10:1017271. doi: 10.3389/fpubh.2022.1017271
34. Mazidi M, Webb RJ, George ES, Shekoohi N, Lovegrove JA, Davies IG. Nutrient patterns are associated with discordant apoB and LDL: a population-based analysis. *Br J Nutr*. 2022;128:712–720. doi: 10.1017/S000711452100369X