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TC/HDL-C Ratio Discordance with LDL-C and non-HDL-C and Incidence of Atherosclerotic Cardiovascular Disease in Primary Prevention: The ARIC Study

Renato Quispe, MD, MHS^{a,b,*}, Mohamed B. Elshazly, MD^{a,c,*}, Di Zhao, PhD^d, Peter P. Toth, MD, PhD^{a,e}, Rishi Puri, MBBS, PhD^f, Salim S. Virani, MD, PhD^g, Roger S. Blumenthal, MD^a, Seth S. Martin, MD, MHS^a, Steven R. Jones, MD^a, Erin D. Michos, MD, MHS^{a,d}

^aCiccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Baltimore, MD

^bDepartment of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY

^cDivision of Cardiology, Department of Medicine, Weill Cornell Medical College-Qatar, Education City, Doha, Qatar

^dDepartment of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

^eDepartment of Preventive Cardiology, CGH Medical Center, Sterling, IL, and University of Illinois College of Medicine, Peoria, IL

^fDepartment of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH

^gMichael E. DeBakey Veterans Affairs Medical Center and Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

Abstract

Aims: The TC/HDL-C ratio may carry additional information not available in more commonly used single cholesterol measures. Analysis of discordance between lipid parameters might help assess the impact of such additional information on risk of atherosclerotic cardiovascular diseases (ASCVD). We aimed to investigate the role of TC/HDL-C ratio in determining ASCVD risk when discordant with LDL-C and non-HDL-C.

Corresponding author and person to whom reprint requests should be addressed: Erin D. Michos, MD, MHS, FACC, FAHA, Associate Professor of Medicine, Ciccarone Center for the Prevention of Cardiovascular Disease, Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Blalock 524-B, 600 N. Wolfe Street, Baltimore, MD 21287, Office: 410-502-6813; Fax: 410-502-0231, edonnell@jhmi.edu.

AUTHOR'S CONTRIBUTIONS

RQ, MBE and EDM contributed to the conception or design of the work. RQ, MBE, DZ and EDM contributed to the acquisition, analysis, or interpretation of data for the work. RQ and MBE drafted the manuscript. RQ, MBE, DZ, PPT, RP, SSV, RSB, SSM, SRJ and EDM critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

*RQ and MBE are Co-first authors

CONFLICT OF INTEREST

Drs. Martin and Jones are listed as coinventors on a pending patent filed by Johns Hopkins University for LDLn-C estimation. Dr Jones has served as an advisor to Sano /Regeneron. Dr Martin has served as a consultant to Quest Diagnostics, Sano /Regeneron, Amgen, and the Pew Research Center. Dr Puri has received speakers' fees from Sanofi-Aventis and Amgen. Research honorarium from Cerenis (unrelated to the present work). The other authors report no conflicts.

Methods: We studied 14,403 ARIC participants who were ASCVD-free at baseline. TC/HDL-C discordance with LDL-C (estimated by our novel Martin/Hopkins method) and non-HDL-C was assessed at five visits and determined by being $\geq$ the median for each lipid parameter. We constructed Cox proportional hazard models to estimate risk for incident ASCVD events associated with each lipid concordance/discordance category using a time-varying approach.

Results: Mean age of participants was 54.1 years, 56% women, and 25% black. There were 2,634 ASCVD events over median (IQR) follow-up of 24.2 (16.0–25.4) years. Among individuals with LDL-C and non-HDL-C $<$ median, 26% and 21% had discordant TC/HDL-C median, respectively. These individuals had a 24% [HR 1.24 (95%CI 1.09, 1.41)] and 29% [1.29 (1.13, 1.46)] greater risk of incident ASCVD, respectively, compared to those with TC/HDL-C $<$ median after multivariable adjustment. In individuals with diabetes with LDL-C or non-HDL-C $<$ median, discordant TC/HDL-C median was more prevalent at 48% and 38%, respectively.

Conclusion: Clinically significant discordance exists between TC/HDL-C, available from the standard lipid profile, and the routinely used non-HDL-C and LDL-C. Such discordance may help inform ASCVD risk management, particularly in individuals with diabetes where discordance is more common.

Keywords

Total cholesterol; HDL cholesterol; LDL cholesterol; non-HDL cholesterol; cardiovascular risk; primary prevention

INTRODUCTION

Cholesterol-related risk has been largely attributed to single lipid measures such as total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein cholesterol (non-HDL-C). For the primary prevention of atherosclerotic cardiovascular disease (ASCVD), the 2018 American Heart Association (AHA) /American College of Cardiology (ACC)/ Multi-Society Guidelines (1) recommend for those aged 40–75 without diabetes and with LDL-C 1.81–4.89 mmol/L, that an initial assessment of absolute ASCVD risk using the Pooled Cohorts Equations is performed. After this initial ASCVD risk assessment, consideration of clinical “risk enhancing factors” and coronary artery calcium, if performed, may further refine risk. Using a different approach, other medical societies such as the National Lipid Association (NLA) (2), International Atherosclerosis Society (3) and European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) (4) endorse specific LDL-C and non-HDL-C goals tailored to risk category. Nonetheless, cholesterol-related risk is more complex, and involves the interplay of several factors such as cholesterol particle concentration, reverse cholesterol transport and triglyceride-rich lipoproteins (TRL), to mention a few (5–6).

The TC to HDL-C ratio (TC/HDL-C), available from the standard lipid profile at no extra cost and highly correlated with levels of LDL particle (LDL-P) number (7,8), has been shown to be a strong cardiovascular risk marker by several studies (9–13). Recently, we showed that discordance between TC/HDL-C and LDL-C or non-HDL-C is common in 1.3 million individuals (14). TC/HDL-C reclassified atheroma progression and major adverse

cardiovascular event (MACE) rates in secondary prevention patients when discordant with LDL-C, non-HDL-C and apoB (15). Despite this, although apoB is considered a “risk enhancing factor” in the 2018 AHA/ACC/Multi-Society Cholesterol Guidelines (1), the TC/HDL-C ratio is not. However, TC/HDL-C ratio can easily be calculated from a standard lipid profile.

Using data from the Atherosclerosis Risk in Communities (ARIC) Study, a community-based predominantly biracial prospective cohort of middle-aged adults followed for over 20 years, we investigated the role of the TC/HDL-C ratio in determining ASCVD risk when discordant with LDL-C and non-HDL-C, among ARIC participants that were free of ASCVD at baseline.

METHODS

Study Population

The ARIC study is a multicenter, prospective cohort of 15,792 middle-aged men and women, established in 1987 from the following four communities in the United States: suburban Minneapolis, MN; Forsyth County, NC; Washington County, MD; and Jackson, MS. The ARIC Study design has been previously reported (16). Individuals aged 45 to 64 years were enrolled between 1987 and 1989 as part of the baseline (visit 1) clinic examination. Information from four subsequent clinic visits was included: 1990–1992 (visit 2), 1993–1995 (visit 3), 1996–1998 (visit 4), and 2011–2013 (visit 5).

For the present analysis, we had the following exclusion criteria: 1) those with prevalent ASCVD events at baseline (n=568); 2) those who were neither blacks or whites (n=46) or blacks from Minnesota and Maryland centers (n=55) given that small numbers did not allow for adjustment by race/center groups; 3) those missing values for lipid variables (n=442) or missing other key covariates at baseline (n=278) that were included in the Cox proportional models. Our final included sample was 14,403 participants.

Institutional review boards at all participating institutions approved the ARIC study. All participants provided written informed consent at each study visit.

Lipid variables

Fasting blood for lipids was collected at every visit and measured according to standard procedures (16). Plasma TC and triglycerides (TG) were determined by enzymatic methods, and HDL-C was measured after dextran-magnesium precipitation. Note that while dextran-Mg²⁺ precipitation methodology for HDL-C measurement was used at Visits 1, 2 and 3, HDL-C was measured using the Cobas-Fara II Analyzer (Roche) and the Monotest Cholesterol enzymatic assay at Visit 4, and the OLYMPUS HDL-C test (two reagent homogenous system for the selective measurement of serum or plasma HDL-C) at Visit 5.

The main lipid variables of interest for the present study were the TC/HDL-C ratio, non-HDL-C (TC minus HDL-C) and LDL-C estimated by the Martin/Hopkins equation. This novel-estimated LDL-C, which has been externally validated by groups inside and outside the US (17,18), uses 1 of 180 different factors for the TG to very low-density lipoprotein

cholesterol (VLDL-C) ratio according to non-HDL-C and TG levels (19). We created two categories for these three lipid variables at each visit: below (<) the median and at or above (≥) the median value. The median values at baseline were: LDL-C, 3.48 mmol/L, non-HDL-C, 4.09 mmol/L, TC/HDL-C, 4.2.

At baseline visit, four concordance-discordance categories were created for TC/HDL-C and LDL-C as follows: (1) concordant TC/HDL-C and LDL-C <median (n=5,486); (2) discordantly higher TC/HDL-C (if ≥median but LDL-C <median) (n=1,717); (3) discordantly lower TC/HDL-C (if <median but LDL-C ≥median) (n=1,720); (4) concordant TC/HDL-C and LDL-C ≥median (n=5,480). We created four similar concordant/discordant categories of TC/HDL-C with non-HDL-C (n= 5,743, 1,558, 1,463, and 5,639, respectively). For primary analyses, lipid measurements and these concordance groups were considered as time-dependent covariates and updated at each ARIC study visit making our analyses more accurate.

Other covariates

Demographics (age, sex, race/center, education, etc.) and cardiovascular risk factors (smoking status, physical activity, diabetes, hypertension) were obtained from history, physical examination and laboratory data at each study visit. Smoking status was categorized as never, former, and current smoker. Physical activity index was measured using a modified Baecke Physical Activity questionnaire (score range 1–5) (20). Body mass index (BMI) was calculated from measured height and weight. Diabetes mellitus was defined as a fasting (>8 hours) serum glucose ≥6.99 mmol/L, nonfasting glucose ≥11.10 mmol/L, self-reported physician diagnosis of diabetes mellitus or reported use of hypoglycemic agents. Blood pressure (BP) was measured 3 times, and the average of the second and third measurements was used. Hypertension was defined as systolic BP ≥140mmHg, diastolic BP ≥90mmHg, or reported use of antihypertensive medications. Use of any lipid-lowering medications was self-reported. Of note, all of these covariates (except physical activity) were also updated at every visit and considered time-dependent variables in the primary analyses.

Outcomes

The primary outcome was incident ASCVD determined from hospital discharge codes or death certificates. Incident ASCVD was defined as definite or probable myocardial infarction, definite coronary death, and definite or probable stroke (sudden or rapid onset of neurological symptoms that lasted for 24 hours or led to death in the absence of another cause) (21–23). Information on hospitalization was obtained from participants via yearly telephone calls, and vital records were examined for all deaths. Additionally, ARIC investigators conducted continuous surveillance for all cardiovascular disease-related hospitalizations and deaths. All ASCVD events were adjudicated by the ARIC study investigators. Study participants contributed follow-up time from the date of the participant's baseline visit until the date of incident ASCVD event, death, loss-to-follow-up, or the end of follow-up (December 31, 2013), whichever came first.

Statistical analysis

Concordance of TC/HDL-C with LDL-C and with non-HDL-C was shown graphically using scatter plots for each pairwise comparison. Baseline characteristics of the study population by lipid concordance categories were described using means and proportions, and were compared using ANOVA test and chi-square, respectively.

For our prospective analysis we used a time-varying approach Cox proportional hazard model, which has the advantage to control for covariates that changed over time. All variables were updated at each visit except for physical activity, sex, race/center and education. We designed three models: Model 1 was adjusted by age, sex and race/center groups. Model 2 was additionally adjusted by smoking status, education, physical activity, BMI, hypertension and diabetes. Model 3 was additionally adjusted by use of lipid-lowering medication.

Additionally, primary analyses were repeated by baseline diabetes status, and examined for evidence of effect modification (interaction). Three additional exploratory analyses were performed: 1) models were repeated using LDL-C estimated by the Friedewald equation rather than the Martin/Hopkins equation; 2) all covariates were considered as time-fixed variables (baseline values) rather than updated at each ARIC visit; and 3) discordance was defined using a continuous measure, presented as the ASCVD risk associated with each 10-percentile unit increment in discordance (TC/HDL-C percentile minus LDL-C and non-HDL-C percentile), updated at each ARIC visit.

RESULTS

Among the 14,403 included participants, the mean age at baseline was 54.1 years; 55.9% were women, and 25.3% were black. At the baseline visit, the cut-points for the median lipid values that defined the concordant/discordant groups were 4.2 for TC/HDL-C, 3.48 mmol/L for LDL-C, and 4.09 mmol/L for non-HDL-C. Supplemental Table 1 shows the baseline characteristics of study population by concordant/discordant TC/HDL-C and LDL-C groups. Those with discordantly higher TC/HDL-C (median but LDL-C <median) were more likely to be men, have higher average triglyceride levels, and more likely to have diabetes, hypertensive, and current smokers than the other groups. Supplemental Table 2 similarly shows the baseline characteristics of study population by concordant/discordant TC/HDL-C and non-HDL-C groups. The pair-wise distribution of lipid variables is shown in Figure S1 (TC/HDL-C vs. LDL-C) and Figure S2 (TC/HDL-C vs. non-HDL-C).

Over a median follow-up of 24.2 years (IQR 16.0 – 25.4), there were 2,634 incident ASCVD events. Table 1 shows the time-varying analysis for hazard of incident ASCVD by TC/HDL-C vs. LDL-C concordant/discordant groups. Among those with LDL-C <median, approximately 1 in 4 individuals (24%) had discordantly higher TC/HDL-C (median), and had a 24% greater risk of ASCVD (HR 1.24, 95% CI 1.09, 1.41) compared to those with concordantly lower TC/HDL-C <median after adjusting for demographics, ASCVD risk factors and use of lipid-lowering medications (Model 3). Conversely, among those with TC/HDL-C <median, those with discordantly higher LDL-C (27%) were not at significantly

elevated ASCVD risk (Table 1) compared to those with concordantly lower LDL-C (<median).

Table 2 shows the time-varying analysis for the hazard of incident ASCVD by TC/HDL-C vs. non-HDL-C concordant/discordant groups. Among individuals with non-HDL-C <median, 1 in 5 individuals (21%) had discordantly higher TC/HDL-C median and had a 29% greater risk of ASCVD (HR 1.29, 95% CI 1.13, 1.46) compared to those with concordantly lower TC/HDL-C (<median) (Model 3). Among those with TC/HDL-C <median, those with discordantly higher non-HDL-C (median) were at 18% increased risk of ASCVD compared with those with concordantly lower non-HDL-C (<median).

Table 3 examines impact of discordance by diabetes status. Among individuals with LDL-C <median, those with discordantly higher TC/HDL-C (median) had a significantly increased risk of ASCVD regardless of diabetes status (p-interaction=0.85).

When models were repeated using Friedewald equation instead of the Martin/Hopkins equation (Supplemental Table 3), and a time-fixed analysis for lipid concordance and covariates (baseline values for all) (Supplemental Table 4), results followed the same pattern as our main time-varying analysis. Finally, when assessing discordance as a continuous measure per 10-percentile unit increment in discordance, we observed a consistent pattern of increased ASCVD risk in Models 1–3 across all median LDL-C and non-HDL-C categories (Supplemental Table 5).

DISCUSSION

In this analysis from ARIC, a large biracial cohort of individuals free from ASCVD at baseline and followed for over 20 years, reinforcing our prior work, we demonstrated the existence of significant individual-level TC/HDL-C discordance with LDL-C and non-HDL-C. Amongst individuals with LDL-C or non-HDL-C <median, 1 in 4 and 1 in 5 individuals, respectively, had discordantly higher TC/HDL-C median. Individuals with such discordance had a more atherogenic clinical profile with higher levels of triglycerides, higher BMI, and greater prevalence of hypertension, diabetes and smoking compared to those with TC/HDL-C <median. Most importantly, we now show that those individuals with discordance had a significant increase in risk of incident ASCVD, independent of clinical risk factors and use of lipid-lowering medications. Among individuals with TC/HDL-C <median, those with an LDL-C median did not have a significantly increased ASCVD risk compared to those with LDL-C <median. Finally, discordance was twice as common among individuals with diabetes, where approximately 1 in every 2 or 3 individuals with LDL-C or non-HDL-C<median, respectively, had a TC/HDL-C level median and a higher risk of ASCVD.

These important findings suggest that the TC/HDL-C ratio, available from the standard lipid profile at no extra cost, provides additional information that may potentially inform personalized ASCVD risk management. Thus, we may hypothesize that TC/HDL-C might be a “risk enhancer” factor for individuals without elevated LDL-C or non-HDL-C levels, in addition to those risk-enhancing factors such as elevated apoB already suggested by recent

guidelines (1). Having a discordantly higher TC/HDL-C is common, particularly in persons with diabetes, and might prompt consideration of more aggressive preventive therapies such as intensification of lipid management (through lifestyle and/or pharmacotherapy) even if LDL-C and non-HDL-C levels are not elevated.

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

Multiple population-based studies have shown that TC/HDL-C is one of the strongest markers of cardiovascular risk (9–13), and its individual components are included in commonly used risk scores such as Pooled Cohort Equations (1) or SCORE (4). In conditions associated with high TRL and low HDL-C levels, such as obesity and insulin resistance, evidence suggests that inversely integrating HDL-C with TC (in the TC/HDL-C ratio) can be a marker of discordance between lipoprotein particle number/size and cholesterol content (8, 24).

Discordance is a relatively novel and unique approach to epidemiological analyses that can help to more clearly assess the incremental risk prediction capacity of a given lipid measure over another (25, 26). Thus, the potential clinical utility of TC/HDL-C is most apparent among individuals in whom TC/HDL-C levels are inconsistent (discordant) with their other lipid parameters (i.e. LDL-C and non-HDL-C).

While several studies have previously examined discordance between LDL-C vs. non-HDL-C, LDL-P and apoB (11,25,27,28), studies examining TC/HDL-C discordance with alternative lipid parameters are scarce. In a prior study using a contemporary large database of more than 1.3 million U.S. adults, our group has previously shown that substantial discordance exists between TC/HDL-C vs. non-HDL-C and LDL-C (14). In patients with LDL-C <1.8 mmol/L, 58% had a TC/HDL-C above the population percentile-equivalent TC/HDL-C of 2.6. Discordance was more pronounced in those with high triglycerides and low HDL-C levels, characteristic of patients with insulin resistance, diabetes and metabolic syndrome who also have a higher prevalence of LDL and apoB-particles that are cholesterol depleted (24). A follow-up clinical outcomes study of patients with known coronary artery disease showed that TC/HDL-C reclassified atheroma progression and MACE rates at 2 years when discordant with LDL-C, non-HDL-C and even apoB (15). In those with apoB <59 mg/dL, patients with percentile equivalent TC/HDL-C of 2.5 had more atheroma progression and higher MACE compared to those with TC/HDL-C <2.5 (15). Another small non-clinical cross-sectional study showed that most high and intermediate-risk individuals that have already achieved non-HDL-C goals would require more aggressive treatment to reach suggested TC/HDL-C targets (29). However, there are no outcome data to our knowledge assessing the clinical impact of TC/HDL-C discordance with alternative lipid parameters in a primary prevention population such as ARIC.

Since TC and HDL-C are included in Pooled Cohort Equations, using the TC/HDL-C ratio for the sole purpose of risk assessment may not provide additional value in the general primary prevention population. However, it may offer value as a secondary treatment target beyond LDL-C or non-HDL-C, particularly in patients where discordance is common and lipid-lowering is recommended such as individuals with diabetes. We hypothesize that the use of TC/HDL-C ratio as a potential additional lipid target (after LDL-C and non-HDL-C)

for initiation or intensification of statin therapy can be of additional benefit to high-risk patients with low HDL-C, such as those with obesity, diabetes or metabolic syndrome. As one study has shown, a TC/HDL-C target of 3 was shown to effectively identify individuals meeting the secondary prevention target level of LDL-P <1000 nmol/L (8). However, pursuing secondary TC/HDL-C targets of percentile equivalence to non-HDL-C targets may be a more reasonable approach that applies to several levels of risk. As recent studies have shown no benefit to raising HDL-C levels, targeting TC/HDL-C (i.e. non-HDL-C/HDL-C) goals would involve lowering non-HDL-C more aggressively in patients with low HDL-C levels ("non-HDL-C sliding scale" hypothesis) (Figure S3). This approach needs further scrutiny in future randomized clinical trials.

Strengths and Limitations

There are a number of strengths of the present analysis including the use of a well-characterized bi-ethnic cohort of middle-aged individuals with a remarkably long-term follow-up (over 20 years). ASCVD events were adjudicated by an expert panel. Lipid values are well known to change over time (time-dependent), but we were able to update concordance/discordance status at multiple time points during follow-up, allowing us to perform time-varying analysis, which provided more accurate lipid status classification. We defined discordance by dichotomizing at median values, but the impact of TC/HDL discordance showed consistent results when using a continuous discordance measure of difference in percentile units (25). Finally, we used the novel Martin/Hopkins method of LDL-C estimation to eliminate any misclassification that may be related to LDL-C estimation errors seen with Friedewald equation (30), but results were consistent when Friedewald-estimated LDL-C was used.

However, our study findings should be considered in the context of several limitations. First, although we carefully adjusted for numerous lifestyle and ASCVD risk factors, as with all observational studies, there is potential for residual confounding. Second, apoB and LDL-P were not available at all ARIC visits, so we could not compare time-varying discordance with those parameters; however, those parameters are not part of the standard lipid profile that is used most often in a clinical setting. Third, HDL-C was measured using different methodologies in Visit 4–5 compared to 1–3, as described in our methods section. Nevertheless, time-fixed and time-varying analyses showed consistent findings, and HDL-C is used for the calculation of LDL-C, non-HDL-C and TC/HDL-C, for which any potential measuring bias/error would not have a significant impact on the results. Finally, although we adjusted for use of lipid lowering medications, which was updated at each study visit, we were not able to account for statin intensity or change in intensity dosing over follow-up.

CONCLUSIONS

In summary, the TC/HDL-C ratio provides additional clinical information to routinely used cholesterol measures, such as non-HDL-C and LDL-C, and should be considered for additional risk assessment in primary prevention population, particularly high-risk patients such as individuals with diabetes. Individuals who reach low levels of LDL-C or non-HDL-C may still be at high risk of ASCVD if TC/HDL-C is discordantly higher. Using TC/HDL-

C targets to provide alterable non-HDL-C targets scaled to individualized HDL-C levels in a 'non-HDL-C sliding scale' approach needs to be further scrutinized in future studies and clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATION LIST

ACC	American College of Cardiology
AHA	American Heart Association
NLA	National Lipid Association
ESC	European Society of Cardiology
ASCVD	Atherosclerotic Cardiovascular Diseases
ARIC	Atherosclerosis Risk in Communities
TC/HDL-C	Total to high-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
Non-HDL-C	Non-high-density lipoprotein cholesterol

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Table 1.

Hazard ratios (95% CI) for ASCVD events across TC/HDL-C and LDL-C* groups from visit 1 and visit 5 (time-varying analysis): the Atherosclerosis Risk in Communities Study (1987–2013)

	IR*	N events /n visits	Model 1	Model 2	Model 3
Concordantly low TC/HDL-C ratio and low LDL-C	6.5	704 /20448	Reference (1)	Reference (1)	Reference (1)
Discordantly high TC/HDL-C ratio and low LDL-C	11.5	435 /7292	1.49 (1.32, 1.69)	1.24 (1.09, 1.40)	1.24 (1.09, 1.41)
Discordantly low TC/HDL-C ratio and high LDL-C	6.2	247 /7287	0.96 (0.83, 1.11)	1.03 (0.89, 1.20)	1.04 (0.90, 1.21)
Concordantly high TC/HDL-C ratio and high LDL-C	11.6	1248 /20737	1.67 (1.52, 1.83)	1.54 (1.40, 1.69)	1.54 (1.40, 1.70)

* LDL-C was calculated using Martin/Hopkins equation (<https://jamanetwork.com/journals/jama/fullarticle/1779534>)

Model 1: adjusted by age, sex and race/center

Model 2: Model 1 + smoking status, alcohol drinking, education, physical activity, body mass index, hypertension, and diabetes

Model 3: Model 2 + use of lipid-lowering medication (time-varying)

Incidence rate, per 1000 person-years

Bolded results are statistically significant.

Abbreviations: CI = confidence intervals; ASCVD = atherosclerotic cardiovascular disease; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol

Table 2.

Hazard ratios (95% CI) for ASCVD events across TC/HDL-C and non-HDL-C groups from visit 1 and visit 5 (time-varying analysis): the Atherosclerosis Risk in Communities Study (1987–2013)

	IR*	N events /n visits	Model 1 Reference (1)	Model 2 Reference (1)	Model 3 Reference (1)
Concordantly low TC/HDL-C ratio, low non-HDL-C	6.3	724 /21487	1.50 (1.32, 1.70)	1.28 (1.13, 1.46)	1.29 (1.13, 1.46)
Discordantly high TC/HDL-C ratio, low non-HDL-C	11.4	392 / 6545	1.10 (0.95, 1.28)	1.17 (1.01, 1.36)	1.18 (1.01, 1.37)
Discordantly low TC/HDL-C ratio, high non-HDL-C	6.7	227 / 6248	1.73 (1.57, 1.89)	1.56 (1.42, 1.72)	1.57 (1.42, 1.72)
Concordantly high TC/HDL-C ratio, high non-HDL-C	11.7	1291/21484			

Model 1: adjusted by age, sex and race/center

Model 2: Model 1 + smoking status, alcohol drinking, education, physical activity, body mass index, hypertension, and diabetes

Model 3: Model 2 + use of lipid-lowering medication (time-varying)

Incidence rate, per 1000 person-years

Bolded results are statistically significant.

Abbreviations: CI = confidence intervals; ASCVD = atherosclerotic cardiovascular disease; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol

Hazard ratios (95% CI) for ASCVD events across TC/HDL-C, non-HDL-C and LDL-C groups from visit 1 and visit 5, stratified by diabetes status at baseline the Atherosclerosis Risk in Communities Study (1987–2013)

	No diabetes (n = 12879)		Diabetes (n = 1524)		P-interaction by diabetes status
	Model 1	Model 2	Model 1	Model 2	
Concordantly low TC/HDL-C ratio and low LDL-C	Reference (1)	Reference (1)	Reference (1)	Reference (1)	0.85
Discordantly high TC/HDL-C ratio and low LDL-C	1.27 (1.10, 1.46)	1.27 (1.10, 1.46)	1.31 (1.00, 1.71)	1.32 (1.00, 1.72)	
Discordantly low TC/HDL-C ratio and high LDL-C	0.99 (0.85, 1.17)	1.00 (0.85, 1.18)	1.07 (0.74, 1.53)	1.11 (0.78, 1.60)	
Concordantly high TC/HDL-C ratio and high LDL-C	1.53 (1.37, 1.70)	1.53 (1.38, 1.70)	1.57 (1.26, 1.95)	1.57 (1.26, 1.96)	
Concordantly low TC/HDL-C ratio, low non-HDL-C	Reference (1)	Reference (1)	Reference (1)	Reference (1)	0.94
Discordantly high TC/HDL-C ratio, low non-HDL-C	1.31 (1.13, 1.51)	1.31 (1.13, 1.51)	1.35 (1.02, 1.79)	1.35 (1.02, 1.79)	
Discordantly low TC/HDL-C ratio, high non-HDL-C	1.13 (0.95, 1.34)	1.13 (0.96, 1.34)	1.19 (0.83, 1.72)	1.22 (0.85, 1.75)	
Concordantly high TC/HDL-C ratio, high non-HDL-C	1.56 (1.40, 1.73)	1.56 (1.41, 1.74)	1.59 (1.28, 1.97)	1.58 (1.27, 1.97)	

Model 1: adjusted by age, sex, race/center, smoking status, education, physical activity, body mass index, hypertension

Model 2: model 1 +use of lipid-lowering medication (time-varying)