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Impact of Blood Lipids on 10-Year Cardiovascular Risk in Individuals Without Dyslipidemia and With Low Risk Factor Burden

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Abstract

Objective: To determine the association of plasma lipids with the prevalence of subclinical atherosclerosis and 10-year risk of incident cardiovascular (CV) events among healthy individuals without dyslipidemia and with low risk factor burden.

Patients and Methods: The analysis (June 24, 2020, through June 12, 2021) included 1204 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) study who were current nonsmokers and did not have CV disease, hypertension (blood pressure ≥130/80 mm Hg or

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

antihypertensive use), diabetes (fasting glucose ≥126 mg/dL or glucose-lowering medication use), and dyslipidemia (low-density-lipoprotein-cholesterol [LDL-C] ≥160 mg/dL, high-density-lipoprotein-cholesterol [HDL-C] <40 mg/dL, total cholesterol [TC] ≥240 mg/dL, triglycerides [TGs] ≥150 mg/dL, or lipid-lowering medication use) at baseline. Associations of lipids with baseline atherosclerosis (presence of carotid plaque and/or coronary calcification) and incident CV events over 10 years were examined using multivariable relative risk regression and Cox regression, respectively.

Results: At baseline, participants' median age was 54 (IQR, 49 to 62) years, and 10-year CV risk was 2.7% (IQR, 1.0% to 6.6%); 43.4% had subclinical atherosclerosis. A 1-SD higher LDL-C (23.4 mg/dL), TC (24.7 mg/dL), non–HDL-C (25.3 mg/dL), TC/HDL-C (0.75), and LDL-C/HDL-C (0.66) was associated with a higher prevalence of atherosclerosis of between 6% and 9% (P<.05). For every 1-SD higher LDL-C, non–HDL-C, TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C (0.49), the 10-year incidence of CV events was significantly increased by 40%, 44%, 51%, 49%, and 39%, respectively. For every 1-SD lower HDL-C (13.5 mg/dL), CV risk was increased by 37%. Triglycerides had no association with either outcome.

Conclusion: Except for TGs, all lipid variables were associated with atherosclerosis and future risk of CV disease among persons without dyslipidemia and with low risk factor burden.

Achieving and maintaining optimal lipid levels is one of the principal goals for both primary and secondary prevention of cardiovascular disease (CVD). Individuals at high and very high CVD risk are the main patient groups recommended for both nonpharmacologic and pharmacologic lipid managements and expected to obtain the greatest benefit.[1,2] However, among individuals at a low CVD risk, reduction in lipid levels is often under-emphasized in clinical practice, especially those whose lipid profiles may be considered normal. This has raised concerns because CVD risk has been shown to increase with increasing lipids[3] and blood pressure[4] levels below the thresholds that are used to define dyslipidemia and hypertension in clinical guidelines.

The 2018 American Heart Association/American College of Cardiology clinical guidelines recommend low-density lipoprotein cholesterol (LDL-C) greater than or equal to 160 mg/dL as one of the risk-enhancing factors to favor initiation of statin therapy in individuals at borderline to inter-mediate CVD risk (10-year risk of atherosclerotic cardiovascular disease [ASCVD] of 5% to less than 20% estimated by the Pooled Cohort Equations).[5] However, no recommendation has been made on whether and how aggressively LDL-C should be managed in low-risk populations. In this regard, data from two recent cohort studies showed a positive association between LDL-C levels less than 160 mg/dL and the presence and extent of subclinical atherosclerosis in individuals without marked dyslipidemia and with a low burden of traditional cardiovascular risk factors (CVRFs).[6,7] Although both studies suggest that stricter control of lipid levels could further improve cardiovascular health in populations without dyslipidemia and with a low CVD risk, they focused only on subclinical CVD and used a cross-sectional study design. Robust evidence from longitudinal studies in this population is needed to examine the association between lipids and incident CVD events.

Against this background, we conducted an analysis using prospective data from the Multi-Ethnic Study of Atherosclerosis (MESA)[8] with the aim of determining the association between multiple baseline lipid markers and incident CVD among apparently healthy participants without defined dyslipidemia and with a low burden of CVRFs. We also examined the cross-sectional associations of lipids with the presence of coronary artery calcium (CAC) and/or carotid plaque at baseline.[9]

PATIENTS AND METHODS

This study has been approved by the Tasmania Social Sciences Human Research Ethics Committee (H0023014).

Study Population

The MESA study is a prospective, multiethnic cohort study that enrolled 6814 men and women (aged 45 to 84 years) who were free of manifest CVD from six US communities between 2000 and 2002.[8] Participants identified themselves as non-Hispanic White (38.6%), Chinese American (11.9%), African American (27.6%), or Hispanic American (21.9%).

For the current analysis, eligible participants were limited to those with a low burden of CVRFs. The included participants were not current smokers and did not have hypertension (blood pressure ≥130/80 mm Hg or antihypertensive agent use), diabetes (self-report, fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], or glucose-lowering agent use), or dyslipidemia (LDL-C ≥160 mg/dL [4.1 mmol/L], high-density-lipoprotein-cholesterol [HDL-C] <40 mg/dL [1.0 mmol/L], total cholesterol [TC] ≥240 mg/dL [6.2 mmol/L], triglycerides [TGs] ≥150 mg/dL [1.7 mmol/L], or lipid-lowering agent use) at baseline.

After excluding participants missing either baseline data on HDL-C and smoking status (n=48), or follow-up data on incident CVD events (n=28), as well as those who were current smokers and had dyslipidemia, hypertension or diabetes at baseline (n=5534), 1204 participants were considered to have a low CVRF burden and were included in the analysis.

Baseline Lipid Measurements

At baseline, levels of TC, HDL-C and TGs from blood samples obtained after a 12-hour overnight fast were measured at a central laboratory (University of Vermont, Burlington, VT, USA). The Hopkins/Martin formula was used to calculate LDL-C.[10] We also included the ratio of TC to HDL-C (TC/HDL-C), LDL-C/HDL-C, and TG/HDL-C, as these atherogenic indices may serve as better predictors of CVD by incorporating both atherogenic and protective lipid components.[11] Plasma lipoprotein particle concentrations were measured at LipoScience, Inc (Raleigh, NC, USA) by nuclear magnetic resonance spectroscopy using the LipoProfile-3 algorithm.[11]

Baseline Covariates

Baseline covariates were selected based on known associations with subclinical atherosclerosis and CVD (see Table 1).

Assessment of Subclinical Atherosclerosis

Subclinical atherosclerosis was defined as the presence of either any CAC or carotid plaque. Details of CAC and carotid artery plaque measurements and interpretation of results in MESA were previously described.[9] In brief, CAC was measured from cardiac noncontrast computed tomography scanning at baseline and was quantified using the Agatston scoring method.[12] Each participant was scanned twice and the average Agatston score of the two scans was used. In the present study, the presence of CAC was defined by a CAC score (CACS) of >0 Agatston units. Carotid plaque presence, measured using B-mode ultrasonography (data available in 986 participants), was defined as a focal abnormal wall thickness (intima media thickness >1.5 mm) or a focal thickening of >50% of the surrounding intima media thickness.[9]

Ascertainment of Incident CVD

Incident CVD was comprised of fatal and nonfatal myocardial infarction, resuscitated cardiac arrest, definite angina and probable angina associated with coronary revascularization, fatal or nonfatal stroke, and other atherosclerotic cardiovascular death. At 9- to 12-month intervals, MESA staff conducted phone interviews to ask about the participants' interim hospital admissions and CVD outpatient diagnoses. Copies of medical records from hospitalizations and outpatient diagnoses were collected, and two physicians independently classified end-points and assigned the incidence date.[13]

At the time of analyses, the study cohort had been followed for CVD events for a median of 16.1 years (up to 31 December 2017). We chose to use outcomes over 10 years after the baseline visit to align with most CVD risk prediction tools in which plasma lipid concentrations derived from one-off measurements are used to estimate 10-year risk for incident CVD events.

Statistical Analysis

Lipid metrics were modelled as continuous and categorical variables. Values for TG were log-transformed. Because frequencies of the presence of any CAC and carotid plaque is approximately 25% to 35%, their associations with lipid variables were evaluated with multivariable relative risk regression analyses (generalized linear model, specifying a log-link, binomial errors, and robust standard errors from the Huber-White sandwich estimator). Results are reported as prevalence ratios (PRs) and 95% CIs.

Multivariable Cox proportional hazards models were used to calculate HRs for incident CVD events up to 10 years associated with each baseline lipid variable modelled on a continuous scale (ie, 1-SD increment). The proportional hazards assumption was checked by using Schoenfeld residuals and no violation was found.[14] We repeated this analysis by stratifying our sample according to the tertiles of each lipid variable. Restricted cubic regression splines with three knots were plotted to further visualize a possible nonlinear relationship between each lipid variable and CVD. To investigate whether atherosclerotic plaques play a mediating role in the association between lipid and CVD, we repeated the analysis by further adjusting for the presence of CAC.

The clinical utility of measuring lipoprotein subfractions in CVD risk prediction beyond routine lipid measures has been previously documented.[15,16] To investigate the prognostic value of novel lipid parameters, a separate analysis was conducted to assess the associations of LDL particle numbers (LDL-P: total, small, large) and HDL particle numbers (HDL-P: total, small, median, large) with baseline subclinical atherosclerosis and 10-year incident CVD events.

Sensitivity Analyses

In the MESA study, statin use was recorded at baseline and at each examination during the follow-up (from exam 1 [2000–2002] to exam 5 [2010–2011]). To remove the impact of interim statin use on the association between baseline lipid variables and CVD, we treated statin use during the follow-up as a time-varying covariate and repeated the analysis for CVD. We also repeated the analyses for subclinical atherosclerosis and incident CVD events in a subgroup with LDL-C and TC at desirable levels as recommended by the Adult Treatment Panel III guidelines (LDL-C <130 mg/dL and TC <200 mg/dL).[17] Similar analyses were also performed in a subgroup of participants with no obesity (body mass index [BMI] <30 kg/m^2), considering the impact of obesity on subclinical atherosclerosis.[6] We also estimated the association between baseline lipids and the risk of incident CVD events over 5 years, as well as over the entire follow-up period (16.1 years), with the data compared with the HRs over 10 years. Finally, we repeated the CAC analysis using an alternative definition of CAC presence (CACS >10)[18] and in participants with 10-year CVD risk lower than 5% (calculated by the Pooled Cohort Equations).

All models were adjusted for the baseline covariates listed previously, unless indicated, with risk estimates of outcomes reported as per 1-S.D. increment in each lipid measure to allow for direct comparisons of the strength of associations. All statistical tests were two-sided, and a *P* value less than 0.05 was considered statistically significant. Analyses were conducted with Stata/S.E. version 16 (StataCorp, College Station, TX, USA).

RESULTS

Baseline Characteristics

Baseline characteristics of the 1204 participants are shown in Table 1. The median age was 54.0 (IQR, 49 to 62) years and 63.4% (n=763) were female. Of the 1204 participants, 29.1% (n=350) had a CACS greater than 0, with the median CACS of 47.9 (IQR, 12.6 to 160.8) Agatston units. Overall, the median 10-year risk for ASCVD was 2.7% (IQR, 1.0% to 6.6%) and the mean levels of LDL-C, HDL-C, TC, TG (median), and non–HDL-C were 112.1, 57.9, 188.0, 83.0, and 130.1 mg/dL, respectively.

Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org) shows the proportion of participants with CAC, carotid plaque, and any subclinical atherosclerosis among the study sample. All proportions increased monotonically from the lowest to the highest tertile of baseline LDL-C, TC, and non–HDL-C. For HDL-C, the prevalence of subclinical atherosclerosis was highest in the lowest tertile (36.0%) and was similar between

the middle (31.6%) and highest tertile (32.4%). For TG, the prevalence of subclinical atherosclerosis was similar across tertiles (33.1% to 33.7%).

Associations of Lipid Markers With Subclinical Atherosclerosis at Baseline

Subclinical atherosclerosis was detected in 43.4% (n=522) of participants at baseline (CAC presence, n=350; carotid plaque presence, n=287). Significant associations were found between most lipid variables (except HDL-C and TG) and CAC presence (adjusted PR per 1-SD higher LDL-C, 1.11 [95% CI, 1.04 to 1.19]; TC, 1.10 [95% CI, 1.03 to 1.18]; non–HDL-C, 1.12 [95% CI, 1.05 to 1.19]; TC/HDL-C, 1.13 [95% CI, 1.06 to 1.20]; LDL-C/HDL-C, 1.12 [95% CI, 1.05 to 1.20]; and TG/HDL-C, 1.08 [95% CI, 1.01 to 1.15]). Higher LDL-C, TC, non–HDL-C, and LDL-C/HDL-C were also associated with an increased carotid plaque presence (adjusted PR per 1-SD higher was 1.13 [95% CI, 1.04 to 1.23], 1.12 [95% CI, 1.03 to 1.23], 1.13 [95% CI, 1.03 to 1.23], and 1.09 [95% CI, 1.09 to 1.20], respectively). Apart from HDL-C, TG, and TG/HDL-C, all lipid variables were significantly associated with the presence of subclinical atherosclerosis, with the strongest association observed for non–HDL-C (PR per 1-SD higher, 1.09 [95% CI, 1.02 to 1.14]) (Table 2).

Incident CVD

Over 10 years, 42 (3.5%) participants experienced an incident CVD event (myocardial infraction, n=17; stroke, n=10; CVD death, n=9; and other CVD events, n=6), of which 34 cases (81.0%) had any subclinical atherosclerosis at baseline. A 1-SD higher baseline LDL-C, non–HDL-C, TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C level was independently associated with an increased risk of incident CVD events by 40%, 44%, 51%, 49%, and 39%, respectively ($P<.05$). Higher baseline HDL-C was associated with a lower event risk (HR per 1-SD higher, 0.63; 95% CI, 0.41 to 0.96). A 1-SD higher TC and log TG was associated with 22% and 24% increased risk of incident CVD, respectively, although the associations did not reach statistical significance. There were 188 individuals who reported statin use during the follow-up. Adjusting for interim statin use as a time-varying covariate did not change the main results, except for a loss of significance for the HDL-C and CVD association (Table 3). After further adjustment for the presence of CAC, only the associations for HDL-C, TC/HDL-C, and LDL-C/HDL-C remained significant (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).

Figure 1 shows the risk of CVD across tertiles of each lipid variable. The risk of incident CVD increased in a stepwise manner with higher tertiles of LDL-C (P for trend=.04). Similar trends were also observed for TC/HDL-C, and LDL-C/HDL-C. An opposite trend was observed for HDL-C. Figure 2 shows restricted cubic regression splines of the association of individual lipid parameters with incident CVD events (data not shown for atherogenic indices). There was a monotonically increased risk of incident CVD events with increasing LDL-C and non–HDL-C levels, and with decreasing HDL-C levels.

Ancillary Analyses

In the analyses for lipoprotein particle variables (n=1204) adjusting for only nonlipid variables (model 1), a 1-SD higher total LDL-P was associated with an increased risk of subclinical atherosclerosis by 7% (95% CI, 1.02 to 1.13; $P=.008$) of incident CVD events

by 44% (95% CI, 1.04 to 2.00; *P*=.03); a 1-SD higher small LDL-P was associated with an increased risk of subclinical atherosclerosis by 6% (95% CI, 1.00 to 1.12; *P*=.04), and of incident CVD events by 59% (95% CI, 1.16 to 2.18; *P*=.004). By further adjusting for LDL-C and HDL-C (model 2), no significant associations were found for any lipoprotein particles (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).

Sensitivity Analyses

When repeating the main analyses in a subcohort of participants with desirable levels of LDL-C and TC (n=790), a 1-SD higher LDL-C, non-HDL-C, TC/HDL-C, and LDL-C/HDL-C at baseline was cross-sectionally associated with a higher prevalence of any subclinical atherosclerosis by 8%, whereas no associations were found for HDL-C, TC, TG, and TG/HDL-C. For a 1-SD higher HDL-C, TC/HDL-C, and LDL-C/HDL-C at baseline, the adjusted HR for incident CVD was 0.42 (95% CI, 0.22–0.80), 1.60 (95% CI, 1.02–2.50), and 1.61 (95% CI, 1.02–2.54), respectively. No associations with incident CVD were found for other lipid variables (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org).

The results when any subclinical atherosclerosis and incident CVD were the outcomes were similar to those provided above when limiting BMI less than 30 kg/m^2 at baseline, except for the loss of significance for the associations between LDL-C and non–HDL-C for incident CVD (Supplemental Table 4, available online at http://www.mayoclinicproceedings.org). The strength of the associations with LDL-C, TC, and non–HDL-C were modestly lowered with longer follow-up, indicating that the association of these lipid parameters with CVD may weaken over time (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org). Using CACS greater than 10 to define CAC presence did not materially change the main results (Supplemental Table 5, available online at http://www.mayoclinicproceedings.org). Among participants with 10-year ASCVD risk less than 5%, the significant association with atherosclerosis remains significant for LDL-C and TC (Supplemental Table 6, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

Within a multiethnic, middle-aged cohort of healthy adults without dyslipidemia and with a low CVRF burden, 43.4% of participants had atherosclerotic plaques and most lipid variables examined (except HDL-C and TG) had a significant cross-sectional association with the presence of CAC and or carotid plaques. Among those who experienced CVD events, 81.0% initially had any subclinical atherosclerosis. Less favorable levels of LDL-C, HDL-C, non–HDL-C, and all atherogenic indices at baseline were independently associated with a greater risk of incident CVD events, with the strongest association observed for TC/HDL-C and LDL-C/HDL-C. No associations with incident CVD events were found for TC or TG. These results collectively suggest that a further reduction in lipid levels, apart from TG, in those at low risk and with healthy lipid levels may confer additional cardiovascular benefits, especially among those with existing subclinical atherosclerosis.

The overall findings have potential implications for primordial and primary prevention of CVD at a population level.[19]

Our findings for atherosclerosis are consistent with two previous observational studies. Fernandez-Friera et al.[7] reported a significant association of baseline LDL-C levels with the presence of subclinical atherosclerosis (detected in 49.7% of participants) in healthy middle-aged individuals who were not current smokers nor had hypertension, diabetes, or hypercholesterolemia at baseline (odds ratio for every 10-mg/dL increase in LDL-C, 1.18 [95% CI, 1.08 to 1.29]). Using similar selection criteria, another cohort study[6] found that LDL-C was an independent predictor for atherosclerosis in an Asian population (odds ratio for every 10-mg/dL increase in LDL-C, 1.08 [95% CI, 1.01 to 1.15]). Our analysis adds to these two studies by suggesting that all lipid variables except for TC and TG are linked to the risk of incident CVD events over a 10-year period.

The sensitivity analysis using different follow-up times suggested that the predictive value of most lipid parameters for risk of incident CVD events reduced over time. We also found that total and small LDL-Ps, but not other nuclear magnetic resonance–derived lipoprotein measures, were significant predictors of baseline subclinical atherosclerosis and incident CVD events, independent of nonlipid risk factors. However, the associations became nonsignificant by further adjusting for LDL-C and HDL-C.

Dyslipidemia has been shown to play a crucial role in the development and progression of atherosclerotic plaques in low-risk populations.[20,21] Low-density lipoprotein cholesterol is the dominant component of atherogenic cholesterol.[1] Unlike the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines in which a numeric goal for LDL-C was set at 116 mg/dL for low-risk populations (less than a 1% 10-year risk for fatal CVD),[22] the 2018 American Heart Association/American College of Cardiology multisociety guidelines[5] on lipid management made no such recommendation on the goal in low-risk groups, which has raised concerns.[23–25] Despite the endorsement of less strict lipid control in low-risk groups in both guidelines, our findings reveal a graded, positive association of LDL-C levels with risk of prevalent atherosclerosis and incident CVD among participants with LDL less than 160 mg/d and without other modifiable risk factors. This suggests that maximum tolerated reduction in lipids is likely to be associated with the best outcomes. Future randomized trials are needed to assess the efficacy of both pharmacological and nonpharmacological lipid-lowering strategies in preventing the development and progression of atherosclerosis, as well as incident cardiovascular disease over the long term.

We also found that a total of 81.0% of those who developed CVD events had initial subclinical atherosclerosis and the association between LDL-C and incident CVD events was weakened by further adjusting for CAC presence, indicating that calcified coronary plaques might mediate this association. These results support the conclusion that cardiac imaging could serve as a useful tool in helping reclassify some low-risk individuals into a higher risk group among whom more intensive lipid control may be needed. The imaging results would be expected to be most informative in those with enhancing risk factors such as a family history of premature coronary heart disease.

Study Limitations

Given the retrospective and observational study design, the analyses included in this study were exploratory. We were unable to rule out bias due to unmeasured factors and residual confounding. Second, single measurements of lipid panels at baseline may lead to an underestimation of risk associations due to random measurement error and resultant regression dilution bias.[26] In addition, the low number of CVD events in this study might have undermined the strength of results regarding CVD events. This has given rise to wide CIs around our effect estimates and may mean that some analyses have limited power to detect statistical significance.

CONCLUSION

Among healthy individuals without dyslipidemia and with a low burden of CVRFs, less favorable lipid levels within the accepted healthy range, except for TG, were associated with a modestly increased risk of subclinical atherosclerosis at baseline and risk of incident CVD events over 10 years. These findings show a continuum of risk for subclinical atherosclerosis and CVD events among healthy persons with lipid levels that do not meet currently accepted criteria for dyslipidemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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POTENTIAL COMPETING INTERESTS

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Abbreviations and Acronyms:

CACS	coronary artery calcium score
CVRF	cardiovascular risk factor
HDL-C	high-density lipoprotein cholesterol

LDL-C	low-density lipoprotein cholesterol
MESA	Multi-Ethnic Study of Atherosclerosis
PR	prevalence ratio
TC	total cholesterol
TG	triglyceride

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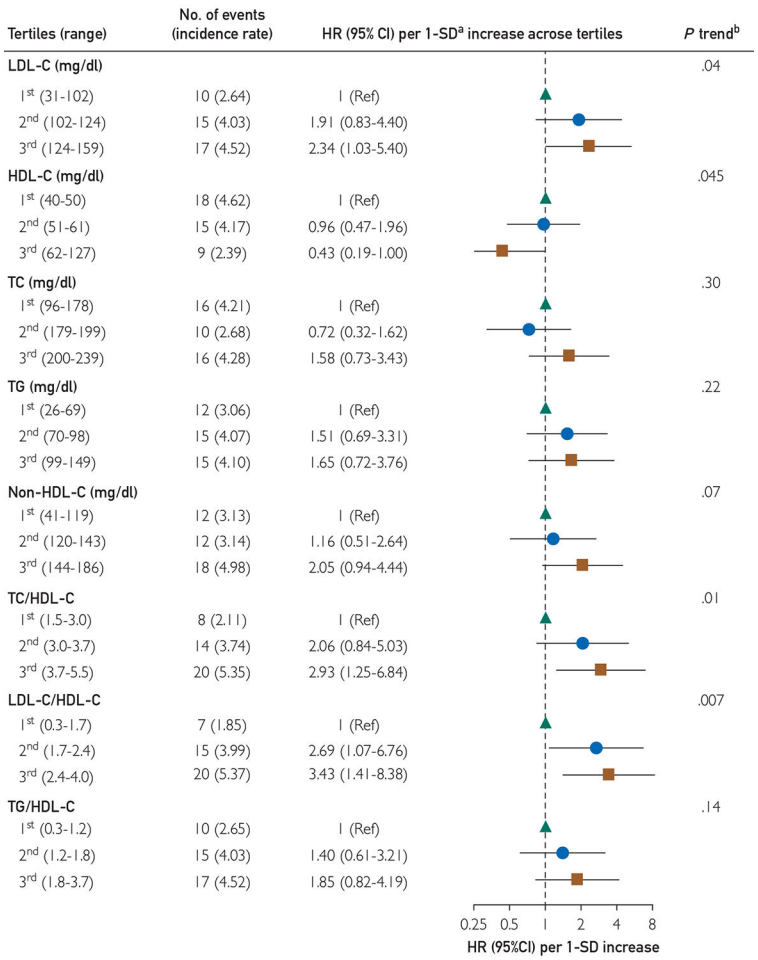

FIGURE 1.

Hazard ratios for incident cardiovascular disease (CVD) across tertiles of each lipid variable (first [lowest] tertile as reference group). Incidence rate was event rate per 1000 person-years. Hazard ratios for incident CVD were computed for the second and third tertiles, compared with the first tertile (lowest tertile). Superscript “a” (a) represents a 1-SD higher baseline LDL-C, HDL-C, TC, log TG, and non–HDL-C of 23.41, 13.51, 24.68, 0.37, and 25.31 mg/dL, respectively. One-SD higher baseline TC/HDL-C, LDL-C/HDL-C, and TG/HDL-C was 0.75, 0.66, and 0.48, respectively. Superscript “b” (b) indicates that *P* value for trend was calculated by assigning each tertile to the median value and treating the variable as a continuous variable. HDL-C = high-density cholesterol; lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total TG = triglyceride.

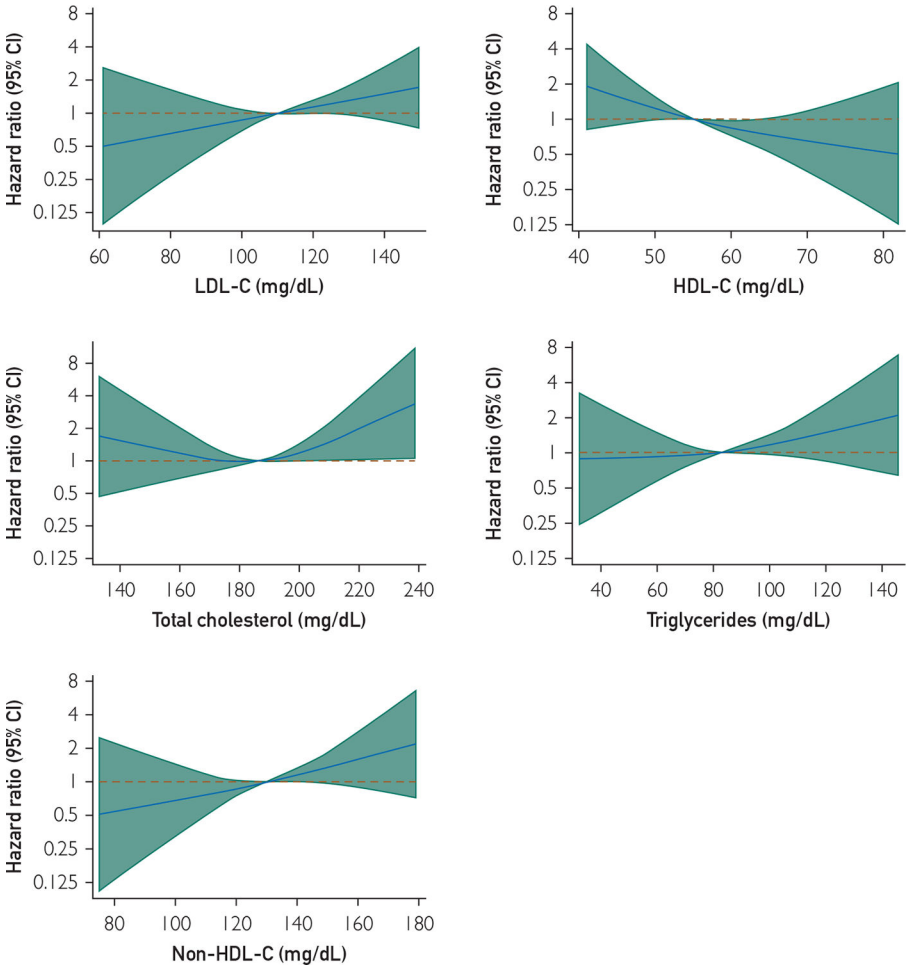

FIGURE 2.

Restricted cubic spline showing the association between baseline lipid parameter and incident cardiovascular disease (CVD) over a 10-year period. The solid blue line represents the adjusted hazard ratio for CVD associated with different levels of lipid variables and the light green shaded area represents 95% CI of the HR. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

TABLE 1.

Baseline Characteristics of Participants[a,b]

Characteristic	Total (n=1204)
Nonlipid variables	
Age, median (IQR), y	54 (49–62)
Women	763 (63.4)
Race/ethnicity	
White	546 (45.4)
Chinese	188 (15.6)
Black	235 (19.5)
Hispanic	235 (19.5)
BMI, mean (SD), kg/m^2	26.2 (4.9)
SBP, mean (SD), mm Hg	109.5 (10.8)
DBP, mean (SD), mm Hg	66.1 (7.7)
Fasting glucose, mean (SD), mg/dl	85.9 (9.3)
Ex-smoker	478 (39.7)
Total gross family income past year >$40,000	711 (59.1)
Education (college)	902 (74.9)
Total intentional exercise (≥1000 MET-min/wk)	589 (48.9)
Family history of myocardial infarction	
No	721 (59.9)
Yes	413 (34.3)
Uncertain	70 (5.8)
10-yr ASCVD risk (%), median (IQR)[c]	2.7 (1.0–6.6)
Lipid variables[d]	
LDL-C, mean (SD), mg/dL	112.1 (23.4)
HDL-C, mean (SD), mg/dL	57.9 (13.5)
TC, mean (SD), mg/dL	188.0 (24.7)
TG, median (IQR), mg/dL	83.0 (63–106)
Non-HDL-C, mean (SD), mg/dL	130.1 (25.3)
Subclinical atherosclerosis markers	
CACS >0	350 (29.1)
CACS (in participants with any CAC present) median (IQR), Agatston units	47.9 (12.6–160.8)
Carotid plaque (931 had available data)	287 (30.8)

[a]ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAC = coronary artery calcium; CACS = coronary artery calcium score; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MET = metabolic equivalent units; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

[b]Values are n (%) unless otherwise stated.

[c]A 10-year risk for ASCVD was calculated based on the Pooled Cohort Equation.

[d]To convert mg/dL to mmol/L, multiply LDL-C, HDL-C, TC, and non–HDL-C values by 0.02586 and TG by 0.011.

TABLE 2.

Cross-sectional Associations of Individual Lipid Variables at Baseline With Presence of CAC, Carotid Plaque, or Either[a]

		Presence of CAC (CACS>0) (n=350 of 1204, 29.1%)		Presence of carotid plaque (n=287 of 931, 30.8%)		Presence of either (athero-sclerosis)(n=522 of 1204, 43.4%)	
	1 SD	PR per 1-SD increment[b] (95% CI)	*P*	PR per 1-SD increment[b] (95% CI)	*P*	PR per 1-SD increment[b] (95% CI)	*P*
Lipid parameters, mg/dL							
LDL-C	23.41	1.11 (1.04–1.19)	.001	1.13 (1.04–1.23)	.005	1.08 (1.02–1.14)	.005
HDL-C	13.51	0.94 (0.86–1.01)	.11	0.99 (0.91–1.09)	.85	1.00 (0.94–1.06)	.90
TC	24.68	1.10 (1.03–1.18)	.004	1.12 (1.03–1.23)	.008	1.08 (1.03–1.14)	.004
Log TG	0.37	1.07 (1.00–1.15)	.06	1.02 (0.94–1.12)	.62	1.03 (0.97–1.09)	.35
Non-HDL-C	25.31	1.12 (1.05–1.19)	.001	1.13 (1.03–1.23)	.007	1.09 (1.02–1.14)	.005
Atherogenic indices							
TC/HDL-C	0.75	1.13 (1.06–1.20)	<.001	1.09 (1.00–1.19)	.06	1.06 (1.01–1.12)	.03
LDL-C/HDL-C	0.66	1.12 (1.05–1.20)	<.001	1.09 (1.01–1.20)	.04	1.07 (1.01–1.12)	.02
TG/HDL-C	0.49	1.08 (1.01–1.15)	.02	1.01 (0.93–1.10)	.81	1.02 (0.96–1.08)	.51

[a]CAC = coronary artery calcium; CACS = coronary artery calcium score; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PR = prevalence ratio; TC = total cholesterol; TG = triglyceride.

[b]Individual lipid variables were modelled in separate relative risk regression analyses, with an adjustment for age, sex, race/ethnicity, body mass index, smoking status (former, never), systolic and diastolic blood pressure, fasting plasma glucose, annual family income, education level, family history of myocardial infarction, and total intentional exercise. Prevalence ratios of the presence of CAC, carotid plaque, and subclinical atherosclerosis are for a 1-SD higher lipid level.

TABLE 3.

Association Between Lipid Markers at Baseline and Incident CVD Over a 10-year Period With and Without Treating Interim Statin Use as a Time-Varying Variable[a,b]

		Model 1		Model 2	
	1-SD	Adjusted HR per 1-SD increment[c] (95% CI)	*P*	Adjusted HR per 1-SD increment[c] (95% CI)	*P*
Lipid parameters (mg/dL)					
LDL-C	23.41	1.40 (1.01–1.96)	.046	1.41 (1.01–1.96)	.04
HDL-C	13.51	0.63 (0.41–0.96)	.03	0.62 (0.37–1.04)	.07
TC	24.68	1.22 (0.86–1.72)	.26	1.22 (0.81–1.83)	.35
Log TG	0.37	1.24 (0.87–1.77)	.24	1.24 (0.82–1.87)	.31
Non-HDL-C	25.31	1.44 (1.02–2.02)	.04	1.44 (1.03–2.02)	.03
Atherogenic indices					
TC/HDL-C	0.75	1.51 (1.09–2.10)	.01	1.51 (1.12–2.05)	.007
LDL-C/HDL-C	0.66	1.49 (1.08–2.07)	.02	1.49 (1.11–1.99)	.007
TG/HDL-C	0.49	1.39 (1.02–1.89)	.04	1.39 (1.00–1.95)	.049

[a]HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride.

[c]Values are HRs for a 1-SD higher lipid level, adjusted for age, sex, race/ethnicity, body mass index, smoking status (former, never), systolic and diastolic blood pressure, fasting plasma glucose, annual family income, education level, family history of myocardial infarction, and total intentional exercise.

[b]Model 1 analyzed the association between each lipid marker at baseline and incident cardiovascular events over a 10-year period, which did not consider interim statin use. Model 2 additionally treated statin use at each visit after baseline as a time-varying variable.