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CME

Association of Combinations of Lipid Parameters With Carotid Intima-Media Thickness and Coronary Artery Calcium in the MESA (Multi-Ethnic Study of Atherosclerosis)

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CME Objective for this article: Upon the conclusion of this activity, the learner should be able to determine the association of combinations of lipid parameters with subclinical atherosclerosis.

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Association of Combinations of Lipid Parameters With Carotid Intima-Media Thickness and Coronary Artery Calcium in the MESA (Multi-Ethnic Study of Atherosclerosis)

Objectives The purpose of this study was to determine the association of combinations of lipid parameters with subclinical atherosclerosis.

Background Carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) are significantly associated with incident cardiovascular disease (CVD). The association between common dyslipidemias (combined hyperlipidemia, [simple] hypercholesterolemia, dyslipidemia of metabolic syndrome, isolated low high-density lipoprotein cholesterol, and isolated hypertriglyceridemia) compared with normolipemia, and CIMT and CAC has not been previously examined.

Methods The MESA (Multi-Ethnic Study of Atherosclerosis) participants were White, Chinese, African-American, or Hispanic adults without clinical CVD. Subjects with diabetes mellitus or who were receiving lipid-lowering therapy were excluded. Every participant was classified into only 1 of 6 groups defined by specific low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglyceride cut points. Multivariate linear and relative risk regressions evaluated the cross-sectional associations with CIMT and CAC after adjusting for CVD risk factors. Interactions with race, sex, and high-sensitivity C-reactive protein were evaluated for CIMT and CAC outcomes.

Results Among 4,792 participants, only those with combined hyperlipidemia and hypercholesterolemia demonstrated both increased common CIMT (combined hyperlipidemia 0.048 mm thicker, 95% confidence interval [CI]: 0.016 to 0.080 mm; hypercholesterolemia 0.048 mm thicker, 95% CI: 0.029 to 0.067 mm) and internal CIMT (combined hyperlipidemia 0.120 mm thicker, 95% CI: 0.032 to 0.208 mm; and hypercholesterolemia 0.161 mm thicker, 95% CI: 0.098 to 0.223 mm) as well as increased risk for prevalent CAC (combined hyperlipidemia relative risk: 1.22, 95% CI: 1.08 to 1.38; hypercholesterolemia relative risk: 1.22, 95% CI: 1.11 to 1.34) compared with normolipemia. The interactions between lipid parameters and race, sex, or high-sensitivity C-reactive protein were not significant for any outcomes.

Conclusions Combined hyperlipidemia and simple hypercholesterolemia were associated with increased CIMT and prevalent CAC in a relatively healthy multiethnic population. (J Am Coll Cardiol 2010;56:1034–41) © 2010 by the American College of Cardiology Foundation

Dyslipidemia is one of the most important risk factors for coronary heart disease (CHD) worldwide (1). Dyslipidemias vary in phenotypic expression because of the interaction of polygenic and environmental influences. Current guidelines are based on specific low-density lipoprotein cholesterol (LDL-C) cut points as primary targets (2).

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However, persons with dyslipidemia often also have abnormalities in high-density lipoprotein cholesterol (HDL-C) and/or triglycerides, which also have strong and independent associations with incident CHD (2–5). We have defined the 5 major dyslipidemias, combined hyperlipidemia, hypercholesterolemia, dyslipidemia of metabolic syndrome (MetS), low HDL-C, and hypertriglyceridemia (Table 1), using criteria based on current National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP)-III guidelines that define LDL-C, HDL-C, and triglyceride thresholds as abnormal (2). The biological rationale for classifying these lipid parameters is that these common combinations of lipid parameters capture the complexity of having more than 1 abnormal lipid parameter as often seen in patients at risk for cardiovascular disease (CVD).

We evaluated the relationship of these 5 dyslipidemias compared with normolipemia (NL) with carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) in a population free of clinically recognized CVD and diabetes mellitus. We sought to determine whether there is an independent association beyond other CVD risk factors of the combination of lipid parameters with subclinical atherosclerosis.

Beyond dyslipidemia, high-sensitivity C-reactive protein (hsCRP) has also been evaluated as a risk marker and is independently associated with incident CVD (6). Considering the recent JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study (7), which included subjects with LDL-C $<$130 mg/dl and hsCRP $\geq$2 mg/l, we also evaluated whether hsCRP at a cut point of 2 mg/l modified the association of combination of lipid parameters with CIMT and CAC. Finally, we evaluated whether race/ethnicity or sex modified the association of combination of lipid parameters with CIMT and CAC.

Methods

The MESA (Multi-Ethnic Study of Atherosclerosis) study is a prospective evaluation of subclinical CVD in 6,814 community-dwelling men and women sponsored by the National Heart, Lung, and Blood Institute. Participants

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Abbreviations and Acronyms

CAC = coronary artery calcium
CHD = coronary heart disease
CI = confidence interval
CIMT = carotid intima-media thickness
CVD = cardiovascular disease
HDL-C = high-density lipoprotein cholesterol
hsCRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein cholesterol
MetS = dyslipidemia of metabolic syndrome
NCEP = National Cholesterol Education Program
NL = normolipemia
RR = relative risk

were age 45 to 84 years and free of known CVD at the baseline examination (2000 to 2002). They belong to 4 racial/ethnic groups: white, Chinese, Hispanic, and African American. Participants participated through 6 field centers located in Forsyth County, North Carolina; St. Paul, Minnesota; Chicago, Illinois; New York, New York; Baltimore, Maryland; and Los Angeles County, California. At each study center, human subjects institutional review boards approved the study protocol. Every participant provided informed consent. Further details regarding the design and objectives of the MESA study can be found elsewhere (8).

Study population. Subjects with diabetes mellitus (confirmed baseline fasting glucose ≥126 mg/dl or receiving diabetes medication) or with missing data for diabetes were excluded from this analysis (n = 883) because diabetes is considered a CHD equivalent and because of the strong independent relationship of diabetes with low HDL-C and elevated triglycerides, CAC, and increased CIMT. Subjects receiving lipid-lowering therapy were excluded because lipid lowering has a substantial impact on all lipid parameters as well as on CIMT (n = 808). Finally, subjects with missing values for lipid parameters, CIMT measurements, or missing covariates were excluded (total n = 331). The final sample size for our analysis was 4,792 participants.

Baseline measurements. Age and race/ethnicity were self-reported. Cardiovascular risk factors were measured or collected, and included height, weight, and waist circumference, medical history including presence of diabetes (defined using the 2003 American Diabetes Association criteria of a fasting glucose ≥126 mg/dl or taking medications for diabetes), hypertension (defined as systolic blood pressure ≥140 mm Hg at baseline visit, or diastolic blood pressure ≥90 mm Hg, or by a history of physician-diagnosed hypertension and taking a medication for hypertension), and assessment of personal habits such as alcohol and tobacco use. Highest level of education completed as a measure of socioeconomic status was also captured.

Fasting triglycerides were measured in plasma using a glycerol blanked enzymatic method (Trig/GB, Roche Diagnostics, Indianapolis, Indiana). Cholesterol was measured in plasma on the Hitachi 911 using a cholesterol esterase, cholesterol oxidase reaction (Chol R1, Roche Diagnostics). The same reaction was also used to measure HDL-C after precipitation of non–HDL-C with magnesium/dextran. The LDL-C was calculated on specimens having a triglyceride of <400 mg/dl using the Friedewald formula (9). The LDL-C as determined by nuclear magnetic resonance spectroscopy was used instead of calculated LDL-C for subjects with triglycerides >400 mg/dl (10).

Serum glucose was measured using the glucose oxidase method on the Vitros analyzer (Johnson & Johnson, Rochester, New York). Insulin was measured in serum by an immunoenzymatic sandwich assay using Access Ultrasensitive insulin reagent on the Access immunoassay system (Beckman Instruments, Fullerton, California). The C-reactive protein was measured using the BNII nephelometer (High Sensitivity CRP, Dade Behring, Deerfield, Illinois). Creatinine was measured by rate reflectance spectrophotometry using thin film adaptation of the creatinine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson).

Definition of lipid parameters. Table 1 identifies the various HDL-C, LDL-C, and triglyceride cutoffs used to define each dyslipidemia. Categories are designed to be mutually exclusive. For example, if someone has low HDL and elevated triglycerides, they would be classified in the MetS dyslipidemia and not in the low HDL group. Participants are classified based on the most severe dyslipidemia. Thus, everyone is categorized into only 1 lipid group.

CIMT. The intima-media layer of the carotid arterial wall was measured using high-resolution B-mode ultrasonography of the near and far walls of the left and right common and internal carotid arteries (11). The mean maximum value of the common and internal CIMT was evaluated separately. The intraclass correlation coefficients for intrareader and inter-reader reproducibility were 0.98 and 0.86, respectively, for common carotid measurements, and 0.99 and 0.94 for internal carotid measurements. A standardized protocol with quality control procedures was used and interpretation was done at a centralized reading station, New England Medical Center, Boston, Massachusetts (11,12). Analyses for the association of lipid parameters with common and internal CIMT were performed independently (13).

CAC. The Agatston scoring method was used to quantify baseline CAC, which was an average of 2 measurements (14). The CAC was measured either by electron-beam computed tomography or by multidetector row helical

Table 1 Definition of Lipid Parameter Combinations in MESA 2000 to 2002

	HDL-C (mg/dl)	LDL-C (mg/dl)	Triglycerides (mg/dl)
Normolipemia	>40 men, >50 women	<160	<150
Combined hyperlipidemia	No cutoff	≥160	≥150
Hypercholesterolemia	No cutoff	≥160	<150
MetS dyslipidemia	≤40 men, ≤50 women	<160	≥150
Low HDL-C	≤40 men, ≤50 women	<160	<150
Hypertriglyceridemia	>40 men, >50 women	<160	≥150

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MESA = Multi-Ethnic Study of Atherosclerosis; MetS = metabolic syndrome.

computed tomography, depending on the field center. Interobserver agreement (κ = 0.93) and intraobserver agreement (κ = 0.90) were very high (15). Careful quality control and standardized protocols were used at each clinical site, and biweekly phantom scans were performed to assure equivalence among sites (16). Detection of CAC was defined by a minimum of 130 Hounsfield units. Details regarding the protocol, acquisition, and interpretation of CAC scans in the MESA study have been reported previously (16).

Statistical analyses. We conducted a cross-sectional analysis to evaluate the association of combination of lipid parameters with CIMT and CAC. Skewed covariates such as insulin and CRP were log transformed. Important covariates that were identified a priori and included in the model were age, race/ethnicity, sex, clinical site, education, history of hypertension, current smoking status, alcohol use, estrogen use among women, waist circumference, fasting glucose, fasting insulin, CRP, and creatinine.

Multivariate linear regression was used in analyses of CIMT as a continuous outcome. We used multivariate linear regression methods with robust standard errors, which provide valid inference even when individual outcomes do not satisfy the standard assumptions of constant variance and normality (17). Multivariate relative risk regression was used in analyses when CAC was a dichotomous outcome, defined as subjects with CAC versus those without CAC. A p value <0.05 was considered significant. Interaction of race/ethnic group and lipid parameters on common and internal CIMT and prevalent CAC was assessed in separate models. Interaction of sex and lipid parameters on common and internal CIMT and prevalent CAC was assessed in separate models. The interaction of hsCRP dichotomized as <2 and ≥ 2 mg/l and lipid parameters on common and internal CIMT and prevalent CAC was assessed in separate models. A p value <0.05 was considered significant for interactions. All analyses were performed using STATA version 10.0 for Windows (StataCorp., College Station, Texas).

Results

Every subject was classified into only 1 lipid group. Table 2 describes the mean, minimum, and maximum values for LDL-C, HDL-C, and triglycerides to demonstrate accurate classification of combination of lipid parameters. Baseline characteristics of the total study population and by lipid parameters are shown in Table 3. Of 4,792 participants, more than one-half of the participants had dyslipidemia. Forty-eight percent were classified as NL, 4% as combined hyperlipidemia, 7% as hypercholesterolemia, 15% as MetS, 18% as low HDL, and 8% as hypertriglyceridemia. Fifty-three percent of all participants were women, and the mean age was 61 years. The racial/ethnic breakdown of the study population was 40% White, 12% Chinese, 26% African American, and 22% Hispanic. Participants who were NL were more likely to have completed high school. Participants who were NL or had hypertriglyceridemia were more likely to actively drink alcohol. Participants with MetS were more likely to smoke. Participants with MetS or hypertriglyceridemia were more likely to have hypertension. Women with hypertriglyceridemia were more likely to use estrogen. The NL participants had the lowest mean waist circumference, glucose, insulin, and hsCRP. Participants with combined hyperlipidemia and MetS had the highest Framingham/NCEP 10-year CHD risk scores. However, mean risk scores were rather low in all groups. (Comparisons of each dyslipidemia to another [pair-wise comparisons] are presented in Online Table 4.)

CIMT findings. After adjustment for demographic and CVD risk factors, only combined hyperlipidemia and hypercholesterolemia had significantly higher mean maximum internal CIMT than NL (Fig. 1, blue lines). After adjustment for demographic and CVD risk factors, only combined hyperlipidemia, hypercholesterolemia, and low HDL had significantly higher mean maximum common CIMT compared with NL (Fig. 1, red lines).

CAC findings. After adjustment for demographic and CVD risk factors, only subjects with combined hyperlipidemia, hypercholesterolemia, and MetS had increased relative risk for prevalent CAC (Fig. 2).

Interaction by race/ethnicity. The p value for interaction between race and lipid parameters was not significant for common or internal CIMT (p = 0.3 and p = 0.1, respectively) or prevalent CAC (p = 0.6). However, an association of lipid parameters with CIMT and CAC stratifying by race/ethnicity (Online Table 5) shows hypothesis-generating trends.

Table 2 Mean, Minimum, and Maximum Values for HDL-C, LDL-C, and Triglycerides for Each Lipid Parameter Combination in MESA 2000 to 2002

	HDL-C (mg/dl)	LDL-C (mg/dl)	Triglycerides (mg/dl)
Normolipemia (n = 2,310)	60.9 (41.0, 142)	113 (26.0, 159)	85.8 (21.0, 149)
Combined hyperlipidemia (n = 171)	44.4 (24.0, 67.0)	179 (160, 274)	214 (151, 466)
Hypercholesterolemia (n = 331)	52.2 (30.0, 95.0)	177 (160, 284)	104 (39.0, 149)
MetS dyslipidemia (n = 736)	37.6 (15.0, 50.0)	114 (21.0, 159)	224 (150, 873)
Low HDL-C (n = 876)	40.3 (21.0, 50.0)	114 (28.0, 159)	103 (24.0, 149)
Hypertriglyceridemia (n = 368)	54.0 (40.1, 95.8)	122 (20.0, 159)	199 (150, 457)

Values are mean (minimum, maximum).
Abbreviations as in Table 1.

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Table 3 Subject Characteristics (MESA 2000 to 2002) as Classified by Combination of Lipid Parameters

	All	NL	Combined Hyperlipidemia	HC	MetS	Low HDL-C	HTG
n (%)	4,792	2,310 (48)	171 (4)	331 (7)	736 (15)	876 (18)	368 (8)
Age, yrs†	61 (10)	62 (11)	61 (10)	61 (10)	60 (10)	60 (11)	61 (10)
Women, %*	53	55	57	54	46	56	51
Race, %*							
White	40	42	42	41	41	32	47
Asian (Chinese)	12	12	11	9	16	13	12
African American	26	30	15	31	12	32	13
Hispanic	22	16	32	19	31	23	28
Framingham-NCEP CHD risk, %*	7.8 (7.1)	6.3 (5.9)	11.3 (8.1)	8.6 (6.8)	10.3 (7.8)	8.5 (8.3)	7.8 (6.5)
Completed high school, %*	84	88	80	83	79	80	79
Alcohol use, %*							
Never drank	20	17	25	20	21	24	21
Formerly drank	22	21	16	20	25	28	17
Currently drinks	58	62	59	60	54	48	62
Current smokers, %†	14	12	13	14	17	14	15
Hypertension, %†	39	37	36	36	43	37	44
Estrogen use, women, %*	28	32	17	15	23	14	62
Waist circumference, cm*	96 (14)	93 (14)	100 (13)	97 (13)	101 (13)	99 (13)	99 (13)
Glucose, mg/dl*	89 (9.5)	87 (9.2)	92 (9.3)	89 (9.1)	91 (9.5)	89 (9.7)	90 (9.9)
Insulin, mU/l*	5.0 (3.4–7.8)	4.0 (2.8–6.0)	6.2 (4.2–9.7)	4.9 (3.4–7.5)	7.5 (5.3–10.6)	6.1 (3.9–8.8)	5.7 (4.0–5.7)
CRP, mg/l*	1.8 (0.8–4.1)	1.5 (0.6–3.7)	2.3 (1.2–5.7)	1.9 (0.9–4.2)	2.3 (1.1–4.4)	2.1 (0.8–4.7)	2.4 (1.1–5.9)
Creatinine, mg/dl	0.94 (0.21)	0.94 (0.20)	0.96 (0.29)	0.96 (0.19)	0.96 (0.22)	0.94 (0.25)	0.94 (0.22)
TC, mg/dl*	197 (35)	190 (27)	267 (31)	250 (22)	197 (28)	175 (26)	211 (27)
LDL-C, mg/dl*	120 (31)	112 (24)	179 (22)	177 (19)	114 (26)	114 (24)	116 (25)
HDL-C, mg/dl*	52 (15)	61 (14)	44 (8.4)	52 (12)	38 (6.0)	40 (6.2)	55 (11)
Triglycerides, mg/dl*	107 (75–154)	82 (63–105)	189 (171–227)	106 (84–126)	201 (170–249)	105 (83–127)	181 (162–213)

Mean (SD) or median (interquartile range) reported. Across-group comparisons: *$p < 0.001$; †$p < 0.05$ chi-square for categorical variables, analysis of variance for continuous variables.
CHD = coronary heart disease; CRP = C-reactive protein; HC = hypercholesterolemia; HTG = hypertriglyceridemia; NCEP = National Cholesterol Education Program; NL = normolipemia; TC = total cholesterol; other abbreviations as in Table 1.

Interaction by sex. The p value for interaction between sex and lipid parameters was not significant for common or internal CIMT ($p = 0.5$ and $p = 0.07$, respectively) or prevalent CAC ($p = 0.5$). However, an association of lipid parameters with CIMT and CAC stratifying by sex (Online Table 6) shows hypothesis-generating trends.

Interaction by hsCRP. The p value for interaction of hsCRP dichotomized at the cut point of 2 mg/l with lipid parameters was not significant for internal or common CIMT ($p = 0.6$ and $p = 0.3$, respectively) or prevalent CAC ($p = 0.5$). However, an association of lipid parameters with CIMT and CAC stratifying by hsCRP (Online Table 7) shows hypothesis-generating trends.

Discussion

This is the first analysis examining the relationship between dyslipidemia as classified by combinations of lipid parameters with subclinical atherosclerosis as measured by CIMT and CAC within the same cohort. We demonstrate in a multiethnic U.S. population without diabetes or known clinical CVD that subjects with combined hyperlipidemia and hypercholesterolemia have increased internal and common CIMT and increased risk of prevalent CAC compared with NL subjects. Other dyslipidemias also demonstrate associations with CIMT or CAC, but not both.

Low HDL-C, which is independently associated with CHD (4), has an independent association with common CIMT only. Aging alone is a strong determinant of progression of CIMT. In the ARIC (Atherosclerosis Risk in Communities) study, the average progression of mean maximum common CIMT was 0.0065 to 0.010 mm/year (18). The cross-sectional difference in mean maximum common CIMT in low HDL compared with NL was approximately 0.02 mm, roughly equivalent to 2 to 3 years of aging. Combined hyperlipidemia and hypercholesterolemia each demonstrated a difference of 0.05 mm compared with normal, roughly equivalent to 5 to 8 years of aging. We evaluated common and internal CIMT separately because there may be differences in the initiation and progression of atherosclerosis in these sites due to differences in blood flow and lipid effects. The internal CIMT may be more strongly predictive of CVD events than the common CIMT (13). A recent meta-analysis, however, suggests that the specificity of CIMT measurement location (e.g., internal vs. common) is low in terms of clinical end points (19). Also, multiple different protocols which evaluate different carotid segments have been used in prospective cohort studies and random-

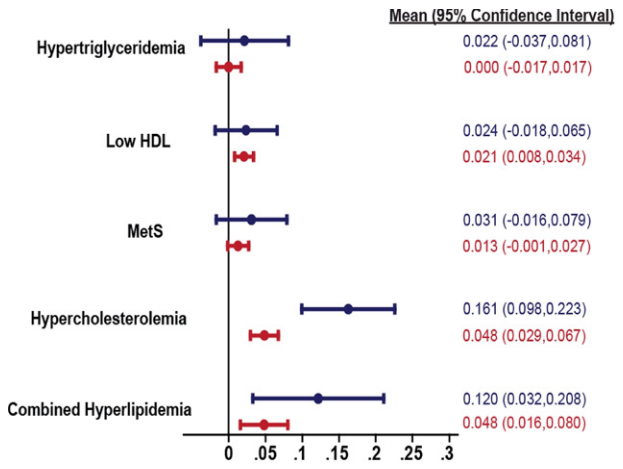

Figure 1 **Difference in Mean Maximum CIMT (mm) Compared With NL by Lipid Parameters**

The **blue lines** indicate mean maximum internal carotid intima-media thickness (CIMT) and 95% confidence interval; and the **red lines** indicate mean maximum common CIMT and 95% confidence interval (adjusted for age, race/ethnicity, sex, clinical site, education, history of hypertension, current smoking status, alcohol use, estrogen use among women, waist circumference, fasting glucose, fasting insulin, C-reactive protein, and creatinine). HDL = high-density lipoprotein; MetS = metabolic syndrome; NL = normolipemia.

ized controlled trials. This has made the standardization of CIMT in clinical practice very difficult.

Thus, combined hyperlipidemia, hypercholesterolemia, and low HDL were associated with increased CIMT. Isolated hypertriglyceridemia was not independently associated with CIMT or CAC. In fact, there is conflicting information regarding the association of isolated hypertriglyceridemia (fasting) with CHD risk after adjustment for other CVD risk factors. Our findings suggest that isolated fasting triglyceride elevations may be primarily a marker for other important CVD risk factors rather than a pathogenic risk factor for subclinical atherosclerosis.

Subjects with MetS dyslipidemia did not have significantly increased mean maximum common or internal CIMT compared with NL subjects. However, the relative risk of prevalent CAC was mildly but significantly increased among subjects with MetS (relative risk: 1.09; 95% confidence interval: 1.01 to 1.17) compared with NL subjects. CAC and CIMT share similar risk factors with each other and with CHD. However, plaque formation and subsequent calcium formation within the coronary arteries likely involves complex and different biological pathways than intima-media thickening of the carotid artery wall. In several studies, CIMT and CAC were correlated with each other, but only moderately (20–23).

More powerful than the isolated dyslipidemia of MetS is the aggregate of abnormalities that makes up the metabolic syndrome, and it is the aggregate that has powerful effects on subclinical atherosclerosis and CVD events (24,25). It is important to note that we are interested specifically in the question of whether, beyond all the associated features of metabolic syndrome, the dyslipidemia alone carries risk for subclinical atherosclerosis as defined by CIMT and CAC. Among participants classified with the dyslipidemia of MetS, 77% had the metabolic syndrome according to the current NCEP/ATP-III criteria (26).

C-reactive protein, an inflammatory marker strongly associated with metabolic syndrome, has recently been used to stratify participants in a clinical trial (7). We examined whether hsCRP dichotomized at 2 mg/l modified the association of combination of lipid parameters with CIMT or CAC. Overall, hsCRP did not modify these associations. This finding is congruent with the findings of others regarding the independent association of hsCRP with CAC in the MESA study (27).

Another issue of interest is whether race/ethnicity or sex contributes differentially to the relationships of combinations of lipid parameters and subclinical atherosclerosis. We did not find any significant interaction of race/ethnicity or sex with combinations of lipid parameters for subclinical atherosclerosis, suggesting that race/ethnicity as broadly defined or sex may not be important in assessing these relationships. However, it is important to consider inadequate power to detect interactions for race/ethnicity or sex or hsCRP. Also, race/ethnicity was self-identified and subject to misclassification and does not give any information about genetic differences. However, there still may be important environmental and social influences captured by race/ethnicity classification.

Our findings demonstrate the important impact of LDL-C on subclinical atherosclerosis, in combination with other lipid abnormalities or as the sole abnormality. However, we also demonstrate that other lipid abnormalities that are not defined by LDL-C demonstrate evidence of increased subclinical atherosclerosis, such as low HDL-C and MetS dyslipidemia. Current guidelines specify LDL cut

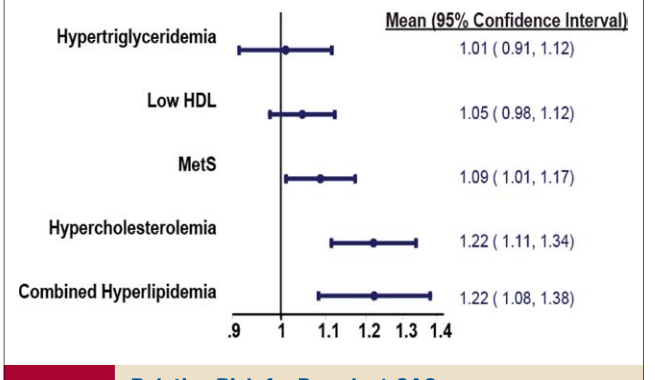

Figure 2 **Relative Risk for Prevalent CAC Compared With NL by Lipid Parameters**

The **blue lines** indicate coronary artery calcium (CAC) mean and 95% confidence interval (adjusted for age, race/ethnicity, sex, clinical site, education, history of hypertension, current smoking status, alcohol use, estrogen use among women, waist circumference, fasting glucose, fasting insulin, C-reactive protein, and creatinine). RR = relative risk; other abbreviations as in Figure 1.

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points as primary therapeutic targets for initiating lifestyle or pharmaceutical therapy on the basis of various risk scores, the most common being the Framingham risk score or NCEP variation of the Framingham risk score (2). There are many people for whom lipid-lowering therapies would not be recommended based on Framingham/NCEP risk score and current guidelines despite having dyslipidemias and/or subclinical atherosclerosis, including those specified in this analysis.

Importantly, risk estimation has progressed beyond 10-year risk estimates. Analyses of life-time risk have been created to determine risks in younger cohorts (28). Recently, adults ≤50 years of age with low 10-year CHD risk but high lifetime CHD risk demonstrated higher baseline burden of subclinical disease and progression of subclinical disease (29). Large prospective longitudinal studies have demonstrated consistent and significant associations of increased CIMT and CAC with incident risk of myocardial infarction and/or stroke (13,19,21,30). Both CIMT and CAC contribute to CVD prediction, although receiver operator curves for incident CVD (CHD, stroke, and fatal CVD) were higher with CAC than CIMT in the MESA study cohort (21).

In support of causal associations of lipids with subclinical atherosclerosis and CVD events, clinical trials of lipid-lowering therapy, especially statins, have demonstrated decreased progression of CIMT (31,32). Furthermore, statin therapy decreases CVD events in both primary and secondary prevention of CVD without significant cost, considering generic statins, or significant risk following appropriate guidelines for monitoring (33,34).

This study is observational, and we may not have controlled for all possible confounders. However, our model includes important covariates, and the appropriate functional form for each covariate was evaluated. We defined MetS dyslipidemia as HDL ≤40 mg/dl for men and ≤50 mg/dl for women to construct mutually exclusive categories. The actual definition of low HDL when defining MetS is <40 mg/dl for men (<50 mg/dl for women) (2). Only 5.4% of men and women with MetS had an HDL-C equal to 40 or 50 mg/dl, respectively. Also, the definition of MetS dyslipidemia does not include the other nonlipid features of the metabolic syndrome, so we could focus on the impact of the dyslipidemia of MetS in isolation on subclinical atherosclerosis. We appropriately excluded subjects receiving lipid-lowering therapy because lipid-lowering therapy and its duration can significantly confound the relationship between lipids and CIMT. Finally, these are cross-sectional associations, and therefore causality cannot be proved.

Conclusions

Dyslipidemias, defined by combinations of lipid parameters that are commonly seen in clinical practice, were associated with increased subclinical atherosclerosis. Combined hyperlipidemia and simple hypercholesterolemia, in which the primary abnormality was elevated LDL-C, were associated with increased subclinical atherosclerosis in both carotid and coronary arteries in a nondiabetic population without CVD. Race/ethnicity, sex, and hsCRP did not modify the associations between combinations of lipid parameters and CIMT or CAC. These findings are widely generalizable, as the MESA study participants were multiethnic persons who were free living in their respective communities spanning the U.S. Furthermore, subclinical atherosclerosis was significantly associated with combinations of lipid parameters independent of other CVD risk factors in otherwise low-risk populations. Greater efforts are needed to detect dyslipidemia in primary prevention and consider appropriate treatment.

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Key Words: carotid intima media thickness ■ coronary calcium ■ dyslipidemia ■ multiethnic.

APPENDIX

For supplementary tables, please see the online version of this article.