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Apolipoprotein B is associated with carotid atherosclerosis progression independent of individual cholesterol measures in a 9-year prospective study of Multi-Ethnic Study of Atherosclerosis participants

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Abstract

Background—High blood cholesterol contributes to atherosclerosis, yet reliance on the lipid panel alone may mischaracterize individuals with elevated lipoprotein particle numbers.

Objective—Determine whether elevated lipoprotein or apolipoprotein measures are associated with carotid atherosclerosis and plaque progression independent of cardiovascular (CV) risk

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COMPETING INTERESTS

The authors have no competing interests to disclose.

AUTHOR CONTRIBUTIONS

Brian T. Steffen: composed the manuscript text; contributed to study design, data interpretation, and critical revisions of the article

Weihua Guan: conducted the data analysis, interpreted results, and contributed to critical revisions of the article

Alan T. Remaley: contributed to data interpretation and critical revisions of the article

James H. Stein: contributed to study design, data acquisition, manuscript text, data analysis, interpreting results, and critical revisions of the article

Mathew C. Tattersall: contributed to study design, data acquisition, data analysis, data interpretation, and critical revisions of the article

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factors including standard lipids in a subcohort of 2,228 Multi-Ethnic Study of Atherosclerosis participants.

Methods—Ultrasonography assessed carotid artery plaque and common carotid intima media thickness (cIMT) at baseline and after a median period of 9.4 years. Nuclear magnetic resonance spectroscopy estimated lipoprotein particle concentrations. Apolipoprotein B (ApoB) and apolipoprotein A-I (ApoA-I) were measured using an automated immunoassay. Regression analysis determined associations of apolipoprotein and lipoprotein measurements with cIMT, and relative risk regression determined associations with carotid plaque progression.

Results—Following adjustment for typical CV risk factors, individuals in top quartiles of ApoB, ApoB/ApoA-I, LDL-P, small LDL-P, and total LDL-P/HDL-P showed similar risks of carotid plaque and cIMT progression as LDL-C non-HDL-C, total cholesterol (TC), and TC/HDL-C. A significant association with plaque progression remained in the top ApoB quartile following further adjustment for LDL-C ($p=0.02$) or TC+HDL-C ($p=0.04$), but was non-significant when adjusted for all lipid covariates ($p=0.086$). Those in the top quartile of small LDL-P concentrations showed greater cIMT progression than those in the referent following adjustment for LDL-C, but this was non-significant following adjustment for TC+HDL-C.

Conclusion—When coupled with evidence that apolipoprotein testing identifies lipid-lipoprotein discordance, these findings suggest that ApoB and small LDL-P provide atherosclerosis risk information that is not revealed by typical CV risk factors.

Keywords

atherosclerosis; carotid plaque; IMT; lipoproteins; ApoB; NMR

INTRODUCTION

Elevated blood lipids are well-established risk factors for atherosclerosis development, and clinical trials have shown that lipid-lowering therapy reduces low density lipoprotein-cholesterol (LDL-C) and results in the reversal or arrest of atherosclerotic disease.[1,2] And yet neither LDL-C nor the standard lipid panel accurately classifies all individuals. Indeed, those with normal total cholesterol and LDL-C may have a more substantial lipid-related risk of disease than is discerned by current risk assessment.[3–7] It has been proposed that other advanced metrics of lipids and lipoproteins offer a more tailored cardiovascular (CV) risk profile than traditional cholesterol measures alone.

A fundamental limitation of estimating atherogenic burden through lipid levels is that they are a measure of the cholesterol content within lipoprotein particles; however, lipoprotein particles are not a homogeneous population. Low-density lipoprotein populations are highly variable and are comprised of large to small particles—with smaller particles considered more atherogenic due to their greater susceptibility to oxidation and endothelial infiltration. [8,9] Moreover, small LDL particles do not have the cholesterol carrying capacity of larger particles. An individual may be within normal ranges of LDL-C and total cholesterol, yet have a high number of small LDL particles and therefore bear greater atherogenic burden than is discriminated by lipid testing.[10–14] We propose that lipoprotein particle concentrations and small lipoprotein subfraction levels will reveal atherosclerotic risk

independent of lipids and provide information that remains undefined in current CV risk assessment.

Numerous alternative techniques have been developed to quantify lipoprotein particles—among them, nuclear magnetic resonance (NMR) spectroscopy and apolipoprotein measurement. NMR spectroscopy estimates concentrations of total LDL particles (LDL-P) and high density lipoprotein particles (HDL-P) as well as discrete lipoprotein populations such as small LDL-P. In contrast, apolipoprotein A-I (ApoA-I) and apolipoprotein B-100 (ApoB) are proxies of HDL and LDL particles, respectively (though ApoB also quantifies the less-abundant intermediate and very-low density lipoproteins, comprising ~10% of total ApoB). The present analysis aims to determine whether total LDL-P, small LDL-P, ApoB, and ratios of ApoB/ApoA-I and LDL-P/HDL-P are associated with higher rates of common cIMT progression or risk of carotid plaque progression independent of typical CV risk factors including LDL-C, HDL-C, and total cholesterol in a subcohort of 2,228 Multi-Ethnic Study of Atherosclerosis (MESA) participants over a median 9.4 year follow-up period.

MATERIALS AND METHODS

Population

The primary aim of MESA is to investigate the development and progression of subclinical CV disease in an ethnically diverse cohort. The study design has been previously described, [15] and further information is available at www.mesa-nhlbi.org. Briefly, a population of 6,814 men and women without clinical evidence of CHD, between the ages of 45 and 84 years, and composed of 38.6% white, 27.6% black, 11.8% Chinese and 22.0% Hispanic were recruited from six communities in the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY; and St. Paul, MN). Institutional Review Board approval was obtained at all MESA sites, and all participants gave informed consent. Recruitment and Exam 1 examinations began in July 2000 and were conducted over a 24-month period. Information regarding age, sex, race/ethnicity, education, and lifestyle factors was obtained by questionnaires. Height (m) and weight (kg) were measured according to standard procedures.[15] Diabetes was defined as those clinically diagnosed or with fasting glucose of >6.94 nmol/L.

The current analysis consists of a subcohort of MESA participants and in whom all exposure and outcome variables as well as covariate measures were available. Common cIMT and carotid plaque score were evaluated at Exam 1 and Exam 5 in a subcohort of 3,441 MESA participants—their measurement is described below. Participants with Exam 1 measurements of both apolipoproteins and NMR lipoproteins were comprised of 4,679 MESA participants. Apolipoproteins were not measured in those taking lipid lowering medication at baseline or those in a subset of MESA 1000 participants for whom specimen volume was limited. The remaining overlap between MESA participants with apolipoprotein, NMR-derived lipoproteins, and carotid ultrasound measures resulted in a final study population of 1,925 individuals for cIMT progression and 2,228 individuals for plaque score progression. The 1,925 was nested within the 2,228.

Lipid and Lipoprotein Measurements

Fasting blood was drawn and serum and EDTA-anticoagulant tubes were collected and processed using a standardized protocol.[15] Lipids and glucose were measured at a central laboratory, the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center, Minneapolis, MN.[16] Lipids were assayed on thawed EDTA plasma within two weeks of the sample collection, and LDL-C was calculated using the Friedewald equation. ApoB was measured at Health Diagnostics Laboratory Inc (Richmond, Virginia) using Roche reagents and a modular-P analyzer (Roche Diagnostics; Indianapolis, IN). The laboratory of Dr. Alan T. Remaley (Bethesda, MD) carried out ApoA-I measurement using Diazyme reagents on the Siemens Dimension analyzer (Siemens AG, Munich, Germany).

NMR spectroscopy was conducted in MESA at Exam 1 as described previously.[11] Briefly, lipoprotein particle concentrations were measured from frozen EDTA plasma specimens (-70°C) and determined from the amplitude of their unique NMR signals. Small LDL particles (18.0–20.5) were defined as done by Otvos et al.[4] Inter-assay reproducibility of total LDL particles, total HDL particles, and small LDL were determined from replicate analyses of plasma pools and were found to be <4% for total LDL-P, <5% for HDL-P, and <8% small LDL-P.

Carotid Ultrasonography

B-mode ultrasonography was conducted at Exam 1 (2000–2002) and Exam 5 (2010–2012) on 3,441 MESA participants as previously described by Tattersall et al.[17] Images of the right and left common, bifurcation, and internal carotid arterial segments were obtained and converted into digital records. Certified sonographers used reference images from baseline to match the scanning conditions of the initial study—specifically, display depth, internal landmarks, angle of approach, degree of jugular venous distension, and ultrasound system settings. Ultrasound images were interpreted by the University of Wisconsin MESA Carotid Ultrasound Reading Center. The distal common carotid artery was defined as the distal 10-mm of the vessel. Common carotid IMT was defined as the mean of the left and right far wall distal common carotid artery wall thicknesses. When only one side was available, those participants were excluded to avoid any chance of an inappropriate comparison (e.g. comparing right side cIMT at baseline to left side cIMT at follow-up). Carotid plaque was defined as a discrete, focal wall thickening ≥ 1.5 mm or focal thickening at least 50% greater than the surrounding IMT. The carotid plaque score (0–12)—the number of carotid plaques present in the extracranial carotid arterial segments—was calculated. The intra-class correlation coefficients for intra- and inter-reader reproducibility for mean common cIMT were 0.99 and 0.95, respectively. To assess scan-rescan reproducibility, 44 scans were repeated by 3 sonographers (Pearson correlation of 0.94; mean (SD) differences of 0.006 (0.036–0.760) mm). Kappa values for intra- and inter-reader reproducibility of carotid plaque presence and score were 0.83 (95% confidence interval [CI] 0.70–0.96) and kappa=0.89 (95% CI 0.72–1.00), respectively.

Statistical Analysis

Statistical analysis was conducted using Stata (version 14.1, Stata Corp, College Station, TX). Baseline characteristics are presented as means (SD) for continuous variables and

frequencies (%) for categorical variables. Common cIMT progression was defined as the change of cIMT measures between Exam 1 and 5 (Exam 5 – Exam 1), standardized by the follow-up time of each participant. Distribution of cIMT progression was examined using summary statistics and histograms. Linear regression analysis was performed to test for associations between lipid and lipoprotein measures and cIMT progression with minimal adjustments of age, sex, and ethnicity. Residual analyses were performed to examine the model assumptions. LDL-C, non-HDL-C, total cholesterol (TC)/HDL-C, ApoB, ApoB/ApoA1, and NMR-derived total LDL-P, small LDL-P, and LDL-P/HDL-P were divided into quartiles in the analysis. Each of the lipid and lipoprotein measures was analyzed separately. To determine whether apolipoprotein and NMR-derived lipoprotein measures were associated with cIMT progression independent of typical risk factors and common lipids, adjustments for systolic blood pressure, hypertension medication, lipid lowering medication as a time-dependent variable, diabetes, and lipid measures were made and separate linear regression analyses were performed for each of the measures in three models in which lipid covariates were examined as follows: model 1) LDL-C; 2) HDL-C and TC; and 3) LDL-C, HDL-C, and TC (shown in table 5). Notably, smoking status was not related to cIMT progression and was not included in the corresponding models. Carotid plaque progression was defined as a logistical variable. Regardless of their baseline score, if carotid plaque progression occurred, participants were assigned a (1); if carotid plaque progression did not occur, participants were assigned a (0). Risk of carotid plaque was analyzed using a relative risk regression model with the above covariates in the same multi-model approach. Smoking status was found to be related to carotid plaque progression and was included as a covariate.

RESULTS

Demographic and clinical characteristics of MESA participants stratified by carotid atherosclerosis outcomes are shown in Tables 1 and 2.

IMT and carotid plaque progression

Regression analysis determined associations of lipids and lipoproteins with rates of common cIMT progression ($\mu\text{m}/\text{year}$) following adjustment for age, sex, hypertension medication, systolic blood pressure, lipid lowering medication, diabetes, and race/ethnicity (Table 3). Individuals in top quartiles of LDL-C, non-HDL-C, TC, TC/HDL-C, ApoB, ApoB/ApoA-I, LDL-P or small LDL-P showed significantly greater cIMT progression than those in corresponding referent quartiles. Individuals in the top quartile of LDL-P/HDL-P showed a rate of progression that approached significance ($12.2 \mu\text{m}/\text{yr}$; $p=0.08$) compared to the referent. The strongest associations with cIMT progression were found in top quartiles of LDL-C ($12.9 \mu\text{m}/\text{yr}$ $p<0.001$), non-HDL-C ($13.1 \mu\text{m}/\text{yr}$ $p<0.001$), ApoB ($13.1 \mu\text{m}/\text{yr}$ $p=0.001$) and small LDL-P ($13.1 \mu\text{m}/\text{yr}$ $p=0.002$). These represent approximately 25% to 30% greater rates of cIMT progression than observed in individuals within referent quartiles. A minimal model adjusted for age, sex, race/ethnicity yielded similar results.

Relative risk regression determined associations of lipids and lipoproteins with carotid plaque progression (as a logistical variable, 0 or 1) over the median 9.4 year study period with adjustments for age, sex, hypertension medication, systolic blood pressure, lipid

lowering medication, diabetes, and race/ethnicity (Table 4). Only individuals in the top quartile of small LDL-P failed to show significantly greater risk of carotid plaque compared to the referent over the study period, although the association approached significance (RR=1.09; $p=0.07$). The strongest associations were observed in those in top quartiles of non-HDL-C (RR=1.18; $p=0.002$), LDL-P (RR=1.19; $p<0.001$), and ApoB (RR=1.23; $p<0.001$). A minimal model adjusted for age, sex, race/ethnicity yielded similar results.

To determine whether lipoprotein particle concentrations or apolipoproteins discern greater progression of cIMT independent of lipids, a multi-model approach was conducted with adjustments for typical CV risk factors as above and 1) LDL-C; 2) HDL-C and total cholesterol; and 3) LDL-C, HDL-C, and total cholesterol (shown in table 5). The addition of LDL-C to the baseline model rendered most associations of apolipoprotein and lipoprotein measures with cIMT progression non-significant except for small LDL-P ($p=0.02$). Further adjustment for TC+HDL-C or all lipid covariates rendered this relationship non-significant.

Risk of developing carotid plaque across quartiles of lipoprotein particle counts and apolipoproteins is shown in Table 6. As in table 5, a multi-model approach was conducted with adjustments for typical CV risk factors and 1) LDL-C; 2) TC and HDL-C; and 3) LDL-C, TC, and HDL-C. The addition of LDL-C or TC+HDL-C rendered most associations non-significant apart from ApoB. Individuals in the top quartile of ApoB showed significantly greater risk of carotid plaque progression than those in the referent quartile in model 1 (RR= 1.21; CI: 1.03–1.41; $p=0.02$) or model 2 (RR= 1.20; CI: 1.01–1.42; $p=0.04$). Adjusting for all lipid covariates rendered the association of ApoB and carotid plaque non-significant (RR= 1.17; CI: 0.98–1.41; $p=0.086$).

DISCUSSION

In this subcohort of 2,228 MESA study participants, elevated levels of apolipoproteins and NMR-derived lipoproteins were associated with higher rates of carotid atherosclerosis and greater risks of carotid plaque progression over a median follow-up period of 9.4 years with adjustment for typical CV risk factors. Upon further adjustment for LDL-C or TC and HDL-C, ApoB remained a significant risk factor for carotid plaque progression in those with elevated levels. Adjusting for all cholesterol covariates rendered this association non-significant. Small LDL-P concentrations were associated with a greater rate of cIMT progression following adjustment for typical CV risk factors and LDL-C and further adjustment for other lipid covariates rendered this association non-significant.

CVD events vs subclinical outcomes

To date, numerous studies have examined whether measurement of ApoB and NMR-derived lipoproteins may replace or augment the existing standard lipid panel, yet their utility in assessing risk of CV disease for the majority of individuals remains unclear [13,18–21], and ApoB was given a ‘no recommendation’ by the 2013 AHA/ACC guidelines [22]. Much of the negative evidence relating to ApoB is based on cohort studies of hard clinical end-points such as myocardial infarction and stroke.[19, 21–25] It has been speculated that previous studies had too few events and/or abbreviated study timelines for differences between those with high and low lipoprotein levels to be discerned. In an attempt to circumvent these

issues, we relied on the intermediate outcome of subclinical carotid atherosclerosis over an approximate 10-year time course in two thousand individuals—providing greater statistical power to detect differences than reliance on event outcomes.

NMR-derived lipoprotein measures

Despite the dozens of studies on NMR lipoprotein testing and CV-related outcomes, there remains a paucity of research on carotid atherosclerosis and cIMT in prospective cohorts. Cross-sectional analyses in Atherosclerosis Risk in Communities,[26] Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (N=968), [27] Genetics of Coronary Artery Disease in Alaskan Natives (N=656),[28] and MESA cohorts[4] have reported significant associations between total LDL-P and cIMT or atherosclerosis. Of these, only the MESA study by Otvos et al. (4) examined the combination of lipoproteins and lipids as exposure variables. It was shown that those with high LDL-P but comparatively low LDL-C showed greater cIMT and higher risk of CVD incidence than those with high LDL-C but comparatively low LDL-P.[4] Our findings agree that NMR-derived lipoprotein measures are associated with carotid atherosclerosis outcomes. Our observation that adjusting for LDL-C or TC and HDL-C renders these associations non-significant suggests that NMR-derived lipoprotein measures provide no discernable advantage over standard lipids in assessing atherosclerosis risk. The approach used by Otvos et al (4), i.e. stratifying individuals by both LDL-C and NMR-derived LDL-P, may represent a more effective strategy for utilizing NMR measures.

Apolipoproteins

Apolipoproteins have been well-researched in the context of CV risk with mixed results, but only a limited number have examined carotid atherosclerosis outcomes. In 453 Women's Healthy Lifestyle Project participants, ApoB was found to significantly associate with internal cIMT ($p<0.001$), but not common cIMT over the 2.7 year follow-up period.[29] Similarly, ApoB/ApoA-I was related to 3-year progression of cIMT (common carotid + carotid bulb) in 313 male participants of the Atherosclerosis and Insulin Resistance study. [30] A follow up analysis of these participants confirmed that ApoB/ApoA-I directly associated with the progression of IMT over 8.9 years ($p=0.003$) independent of LDL-C, HDL-C, and non-HDL-C.[31] Although we observed the null finding for ApoB/ApoA-I after adjusting for standard lipids, it must be acknowledged that the Atherosclerosis and Insulin Resistance study included the carotid bulb in their cIMT measure. The carotid bulb is both thicker than the common carotid segment and is more prone to carotid plaque. It is therefore possible that this discrepancy in cIMT measurements may have contributed to result differences. Finally, in a subcohort of 472 Cardiovascular Risk in Young Finns study participants, ApoB and the ApoB/ApoA-I ratio measured at baseline were associated with common cIMT after a 21-year follow up period ($p<0.001$) independent of gender, age, and smoking.[6] Contrary to the above findings, a more recent study by Maki et al.[32] showed no association between ApoB and cIMT progression over 12 and 18 month time periods ($p=0.06$), but the abbreviated timelines may have contributed to the borderline result.

The present analysis shows MESA participants in the top ApoB quartiles have nominally higher common cIMT progression and greater risk of carotid plaque progression than

corresponding quartiles of LDL-C, non-HDL-C or total cholesterol. We are the first to show that the association of ApoB with carotid plaque progression remains significant following adjustment typical CV risk factors including LDL-C or TC and HDL-C—and approached significance in the fully adjusted model ($p=0.086$). Based on these results as well as previous studies [10–14,20,33–37], ApoB may be the more efficacious metric for classifying atherogenicity of an individual's lipid/lipoprotein profile compared to cholesterol measures—though not all studies agree.[23, 35–39]

Discordant cholesterol and lipoprotein measures

As proposed by other investigators [4,11,40], the benefit of NMR lipoprotein or apolipoprotein measurements may rely on identifying individuals with a discordant lipid-lipoprotein phenotype—particularly for those with normal cholesterol but comparatively high lipoprotein concentrations. These individuals' CV risks would be underestimated using current risk assessment tools without lipoprotein assessment. Further research is warranted to examine discordant lipid-lipoprotein phenotypes in MESA participants and whether race/ethnicity is an important modifying variable.

Strengths and limitations

This study represents the largest and most comprehensive evaluation of NMR lipoprotein and apolipoprotein analytes, had an extended follow-up period, and included four races/ethnicities. The prospective study design allowed for the examination of temporality of associations between exposure variables and carotid atherosclerosis outcomes and is the first to show that elevated ApoB levels increase risk of carotid plaque independent of typical CV risk factors including lipid measures. With regard to atherosclerosis endpoints, high precision was achieved in ultrasound assessments with strong inter-reader and intra-reader reproducibility (0.95 and 0.99, respectively). In terms of limitations, apolipoproteins in MESA participants who were taking lipid-lowering medication at baseline were not measured, and this subcohort was comprised of participants that did not suffer a fatal event since they completed an Exam 5 visit. We therefore cannot discount the presence of a selection bias for healthier individuals with less carotid atherosclerosis compared to the entire MESA cohort. In addition, ultrasound assessments of the carotid arteries represent intermediate measures of CV health, although they have been shown to associate with incident CV events in MESA and improve Framingham risk prediction.[41–43] Adjustments for all lipid covariates were made in a fully adjusted model, but it is possible that including TC, LDL-C and HDL-C as covariates represents an over-adjustment and null findings should be interpreted with caution. Multiple demographic and clinical adjustments were made within the statistical model, but the possibility of residual confounding cannot be excluded. Finally, MESA is a U.S. cohort study and findings may not be generalizable to other populations.

Conclusions

These results suggest that elevated ApoB and small LDL-P add information to atherosclerotic disease that is not identified by typical CV risk factors including LDL-C or TC+HDL-C. Coupled with the evidence that lipoprotein or apolipoprotein testing is

instrumental in identifying lipid-lipoprotein discordance, ApoB appears to be a clinically useful marker in CV risk assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Lipoprotein metrics may provide risk information not covered by current risk factors
- We tested whether these metrics identify carotid atherosclerosis risk over 9.4 years
- Apolipoprotein B associated with plaque progression independent of cholesterol
- Small LDL particle counts were associated with intima media thickness progression
- ApoB and small LDL-P provide risk information not revealed by typical risk factors

Demographic and clinical characteristics in 1,946 MESA participants stratified by quartiles of common cIMT progression over the 9.4 year study period.

Table 1

	Quartiles of common cIMT progression (µm/year)				p-value
	1	2	3	4	
N	487	486	487	486	
cIMT progression, µm/yr	(-107–5.0)	(5.0–11.0)	(11.0–18.0)	(18.0–119)	
Age, mean (SD)	61.2 (9.6)	58.9 (9.3)	59.5 (9.4)	60.3 (9.3)	<0.001
Sex	232 (47.6)	210 (43.2)	230 (47.2)	239 (49.2)	0.28
Race					0.021
Black	152 (31.2)	120 (24.7)	134 (27.5)	145 (29.8)	
Caucasian	154 (31.6)	175 (36.0)	181 (37.2)	185 (38.1)	
Chinese American	59 (12.1)	86 (17.7)	71 (14.6)	53 (10.9)	
Hispanic	122 (25.1)	105 (21.6)	101 (20.7)	103 (21.2)	
Hypertension medication, n (%)	199 (40.9)	134 (27.6)	133 (27.3)	124 (25.5)	<0.001
Lipid lowering medication, n (%) *	181 (37.2)	134 (27.6)	147 (30.2)	130 (26.7)	0.001
BMI (kg/m ²), mean (SD)	28.1 (4.9)	27.2 (5.02)	27.3 (4.8)	28.0 (4.9)	0.006
Smoking status					0.11
Never, n(%)	251 (51.6)	279 (57.6)	255 (52.4)	239 (49.2)	
Former, n(%)	186 (38.3)	153 (31.6)	168 (34.5)	188 (38.7)	
Current, n(%)	49 (10.1)	52 (10.7)	64 (13.1)	59 (12.1)	
Total cholesterol (nmol/L), mean (SD)	5.06 (0.86)	5.09 (0.90)	5.06 (0.91)	5.13 (0.87)	0.53
LDL-C (nmol/L), mean (SD)	3.09 (0.76)	3.11 (0.81)	3.09 (0.80)	3.19 (0.80)	0.14
HDL-C (nmol/L), mean (SD)	1.32 (0.41)	1.38 (0.42)	1.34 (0.39)	1.31 (0.39)	0.05
Triglycerides (nmol/L), mean (SD)	1.44 (0.89)	1.34 (0.72)	1.38 (0.78)	1.38 (0.75)	0.25
Total LDL-P (nmol/L), mean (SD)	1265 (326)	1247 (346)	1258 (330)	1297 (341)	0.12
Small LDL-P (nmol/L), mean (SD)	546 (379)	489 (383)	516 (386)	564 (401)	0.01
LDL-P/HDL-P, mean (SD)	39.6 (14.8)	38.3 (14.8)	38.5 (14.4)	40.9 (16.6)	0.03
Apo-B (mg/dL), mean (SD)	108.4 (27.3)	107.5 (26.5)	108.0(25.9)	110.4 (25.2)	0.32
ApoB/ApoA-I, mean (SD)	0.91 (0.35)	0.88 (0.32)	0.91 (0.38)	0.95 (0.33)	0.04

* participants (%) were not taking lipid lowering medication at baseline, and began treatment over the study period

Table 2

Demographic and clinical characteristics in 2,228 MESA participants stratified by the occurrence of carotid plaque progression over the 9.4 year study period. Individuals who showed plaque progression were assigned to the case group while those in whom carotid plaque did not occur were assigned to the non-case group.

	Carotid plaque progression		<i>p</i> -value
	Non-cases (0)	Cases (1)	
N	1007	1225	
Age, mean (SD)	57.8 (8.9)	62.2 (9.4)	<0.001
Sex, % female	447 (44.4)	603 (49.2)	0.02
Race			0.25
Black, n (%)	298 (29.6)	331 (27.0)	
Caucasian, n (%)	350 (34.8)	463 (37.8)	
Chinese, n (%)	143 (14.2)	154 (12.6)	
Hispanic, n (%)	216 (21.4)	277 (22.6)	
Hypertension medication, n (%)	272 (27.0)	422 (34.4)	<0.001
Lipid lowering medication, n (%)	263 (26.1)	435 (35.5)	<0.001
BMI (kg/m ²), mean (SD)	28.0 (5.3)	28.1 (5.0)	0.71
Smoking Status			<0.001
Never	591 (58.8)	588 (48.0)	
Former	330 (32.8)	469 (38.3)	
Current	84 (8.4)	167 (13.6)	
Total cholesterol (nmol/L), mean (SD)	5.01 (0.87)	5.14 (0.90)	<0.001
LDL-C (nmol/L), mean (SD)	3.04 (0.77)	3.17 (0.80)	<0.001
HDL-C (nmol/L), mean (SD)	1.34 (0.40)	1.31 (0.40)	0.07
Triglycerides (nmol/L), mean (SD)	1.37 (0.99)	1.46 (0.80)	0.02
Total LDL-P (nmol/L), mean (SD)	1233 (330)	1296 (343)	<0.001
Small LDL-P (nmol/L), mean (SD)	509 (373)	558 (400)	0.003
LDL-P/HDL-P, mean (SD)	38.0 (14.2)	40.3 (15.7)	<0.001
Apo-B (mg/dL), mean (SD)	105.9 (25.5)	110.9 (27.1)	<0.001
ApoB/ApoA-I, mean (SD)	0.90 (0.39)	0.93 (0.36)	0.03

Table 3

Mean levels of common cIMT progression are presented across quartiles of NMR-derived lipoprotein and apolipoprotein measures in a subcohort of 1,929 Multi-Ethnic Study of Atherosclerosis participants over a median follow-up period of 9.4 years. First quartiles serve as referents and [quartile ranges] are indicated. Adjustments were made for age, sex, hypertension medication, systolic blood pressure, lipid lowering medication, diabetes, and race/ethnicity. *Lipids were not included as covariates.*

	Quartile			
	1	2	3	4
LDL-C	[0.70–2.59]	[2.59–3.08]	[3.08–3.59]	[3.59–7.34]
	10.1 (0.58)	11.9 (0.58) p=0.02	11.6 (0.58) p=0.06	12.9 (0.60) p<0.001
TC	[2.04–4.50]	[4.50–5.04]	[5.04–5.61]	[5.61–9.21]
	10.5 (0.59)	11.5 (0.58) p=0.23	11.7 (0.58) p=0.16	12.6 (0.60) p=0.02
non-HDL-C	[1.06–3.15]	[3.15–3.71]	[3.71–4.27]	[4.27–8.28]
	10.1 (0.58)	11.7 (0.58) p=0.06	11.6 (0.57) p=0.08	13.1 (0.60) p<0.001
TC/HDL-C	[1.46–3.21]	[3.21–3.96]	[3.96–4.82]	[4.82–10.77]
	10.3 (0.59)	11.6 (0.58) p=0.14	12.0 (0.58) p=0.05	12.5 (0.61) p=0.02
ApoB	[11.4–91.3]	[91.3–106.7]	[106.7–123.5]	[123.5–358.1]
	10.3 (0.59)	11.9 (0.58) p=0.06	11.2 (0.58) p=0.30	13.1 (0.59) p=0.001
ApoB/ApoA-I	[0.10–0.69]	[0.69–0.86]	[0.86–1.06]	[1.06–5.39]
	10.1 (0.59)	11.7 (0.58) p=0.05	12.2 (0.58) p=0.01	12.4 (0.60) p=0.007
LDL-P	[238–1025]	[1025–1239]	[1239–1482]	[1482–3106]
	10.7 (0.58)	11.4 (0.58) p=0.33	11.8 (0.58) p=0.18	12.5 (0.58) p=0.03
small LDL-P	[12–108]	[108–518]	[518–802]	[802–2299]
	10.5 (0.59)	10.5 (0.58) p=0.96	12.4 (0.59) p=0.03	13.1 (0.61) p=0.002
LDL-P/HDL-P	[6.58–28.0]	[28.0–37.0];	[37.0–48.1]	[48.1–162.4]
	10.7 (0.59)	11.0 (0.58) p=0.67	12.4 (0.58) p=0.04	12.2 (0.60) p=0.08

Table 4

Risks of carotid plaque progression are presented across quartiles of NMR-derived lipoprotein and apolipoprotein measures in a subcohort of 2,228 Multi-Ethnic Study of Atherosclerosis participants over a median follow-up period of 9.4 years. First quartiles serve as referents and [quartile ranges] are indicated. Adjustments were made for age, sex, hypertension medication, systolic blood pressure, lipid lowering medication, diabetes, smoking status, and race/ethnicity. *Lipids were not included as covariates*. Carotid plaque progression was treated as a logistical variable, and values are expressed as relative risk (95% confidence intervals) with accompanying *p*-values.

	Quartile			
	1	2	3	4
LDL-C	[0.65–2.59]	[2.59–3.08]	[3.08–3.59]	[3.59–7.34]
	ref	0.98 (0.88–1.08)	1.04 (0.95–1.15)	1.13 (1.03–1.25)
		p=0.66	p=0.41	p=0.01
TC	[2.04–4.50]	[4.50–5.04]	[5.04–5.61]	[5.61–9.23]
	ref	1.05 (0.95–1.16)	1.05 (0.94–1.16)	1.14 (1.03–1.27)
		p=0.36	p=0.40	p=0.01
non-HDL-C	[0.88–3.15]	[3.15–3.71]	[3.71–4.27]	[4.27–8.28]
	ref	1.04 (0.94–1.16)	1.09 (0.95–1.17)	1.18 (1.06–1.30)
		p=0.42	p=0.30	p=0.002
TC/HDL-C	[1.46–3.23]	[3.23–3.98]	[3.98–4.83]	[4.83–13.16]
	ref	1.01 (0.91–1.12)	1.07 (0.96–1.19)	1.15 (1.04–1.28)
		p=0.91	p=0.20	p=0.009
ApoB	[11.4–91.4]	[91.4–106.7]	[106.7–123.7]	[123.7–358.1]
	ref	1.11 (1.00–1.23)	1.07 (0.96–1.19)	1.23 (1.11–1.36)
		p=0.05	p=0.24	p<0.001
ApoB/ApoA-I	[0.10–0.70]	[0.70–0.87]	[0.87–1.07]	[1.07–7.25]
	ref	1.02 (0.92–1.13)	0.99 (0.89–1.09)	1.12 (1.02–1.24)
		p=0.73	p=0.78	p=0.02
LDL-P	[238–1028]	[1028–1243]	[1243–1482]	[1482–3106]
	ref	1.01 (0.91–1.12)	1.07 (0.96–1.18)	1.19 (1.07–1.31)
		p=0.80	p=0.22	p<0.001
small LDL-P	[0–111]	[111–529]	[529–807]	[807–2299]
	ref	0.98 (0.88–1.08)	0.99 (0.90–1.10)	1.09 (0.99–1.21)
		p=0.67	p=0.89	p=0.07
LDL-P/HDL-P	[6.58–28.1]	[28.1–36.9]	[36.9–47.9]	[47.9–162.4]
	ref	0.98 (0.89–1.09)	1.03 (0.93–1.14)	1.15 (1.04–1.27)
		p=0.81	p=0.60	p=0.006

Table 5

Mean levels of common cIMT progression [$\mu\text{m}/\text{year}$ (SE)] are presented across quartiles of NMR-derived lipoprotein and apolipoprotein measures in a subcohort of 1,929 Multi-Ethnic Study of Atherosclerosis participants over a median follow-up period of 9.4 years. First quartiles serve as referents and [quartile ranges] are indicated.

	Quartile			
	1	2	3	4
ApoB	[11.4–91.3]	[91.3–106.7]	[106.7–123.5]	[123.5–358.1]
Model 1	11.1 (0.78)	12.1 (0.59) p=0.29	11.1 (0.59) p=0.98	12.1 (0.81) p=0.46
Model 2	11.5 (0.85)	12.2 (0.60) p=0.49	10.9 (0.59) p=0.60	11.8 (0.89) p=0.87
Model 3	11.8 (0.86)	12.3 (0.60) p=0.57	11.0 (0.59) p=0.49	11.5 (0.90) p=0.88
ApoB/ApoA-I	[0.10–0.69]	[0.69–0.86]	[0.86–1.06]	[1.06–5.39]
Model 1	10.8 (0.67)	11.8 (0.58) p=0.24	12.1 (0.59) p=0.17	11.7 (0.67) p=0.40
Model 2	11.1 (0.79)	11.9 (0.59) p=0.40	11.9 (0.61) p=0.50	11.4 (0.75) p=0.82
Model 3	11.4 (0.80)	12.0 (0.59) p=0.53	11.9 (0.62) p=0.66	11.2 (0.76) p=0.90
LDL-P	[238–1025]	[1025–1239]	[1239–1482]	[1482–3106]
Model 1	11.6 (0.70)	11.7 (0.58) p=0.89	11.6 (0.59) p=0.99	11.6 (0.70) p=0.98
Model 2	11.9 (0.73)	11.8 (0.59) p=0.93	11.4 (0.59) p=0.66	11.3 (0.75) p=0.64
Model 3	12.2 (0.74)	11.9 (0.59) p=0.79	11.4 (0.59) p=0.44	11.0 (0.76) p=0.37
small LDL-P	[12–108]	[108–518]	[518–802]	[802–2299]
Model 1	10.8 (0.61)	10.5 (0.58) p=0.67	12.4 (0.59) p=0.08	12.9 (0.63) p=0.02
Model 2	10.9 (0.74)	10.6 (0.58) p=0.71	12.3 (0.61) p=0.18	12.7 (0.72) p=0.14
Model 3	10.9 (0.75)	10.5 (0.59) p=0.63	12.3 (0.62) p=0.19	12.9 (0.75) p=0.12
LDL-P/HDL-P	[6.58–28.0]	[28.0–37.0];	[37.0–48.1]	[48.1–162.4]
Model 1	11.6 (0.67)	11.2 (0.59) p=0.68	12.2 (0.58) p=0.51	11.4 (0.66) p=0.87
Model 2	12.1 (0.77)	11.3 (0.59) p=0.40	12.0 (0.60) p=0.98	10.9 (0.74) p=0.37
Model 3	12.5 (0.80)	11.5 (0.59) p=0.25	11.9 (0.60) p=0.56	10.6 (0.76) p=0.15

Baseline model: Adjustment for age, sex, systolic blood pressure, hypertension medication, lipid lowering medication, diabetes, smoking status, race/ethnicity

Model 1: baseline model + LDL-C

Model 2: baseline model + HDL-C, total cholesterol

Model 3: baseline model + LDL-C, HDL-C, and total cholesterol

Table 6

Risk of carotid plaque progression is presented across quartiles of NMR-derived lipoprotein and apolipoprotein measures in a subcohort of 2,228 Multi-Ethnic Study of Atherosclerosis participants over a median follow-up period of 9.4 years. First quartiles serve as referents and [quartile ranges] are indicated. Carotid plaque progression was treated as a logistical variable, and values are expressed as relative risk (95% confidence intervals).

	Quartile			
	1	2	3	4
ApoB	[11.4–91.4]	[91.4–106.7]	[106.7–123.7]	[123.7–358.1]
<i>Model 1</i>	ref	1.10 (0.98–1.23)	1.06 (0.93–1.20)	1.21 (1.03–1.41)
<i>Model 2</i>	ref	1.10 (0.98–1.24)	1.05 (1.05–1.20)	1.20 (1.01–1.42)
<i>Model 3</i>	ref	1.09 (0.97–1.23)	1.04 (0.90–1.20)	1.17 (0.98–1.41)
ApoB/ApoA-I	[0.10–0.70]	[0.70–0.87]	[0.87–1.07]	[1.07–7.25]
<i>Model 1</i>	ref	0.98 (0.88–1.09)	0.93 (0.83–1.04)	1.04 (0.92–1.17)
<i>Model 2</i>	ref	0.98 (0.88–1.09)	0.91 (0.80–1.04)	1.00 (0.87–1.16)
<i>Model 3</i>	ref	0.96 (0.85–1.07)	0.89 (0.78–1.02)	0.98 (0.84–1.14)
LDL-P	[238–1028]	[1028–1243]	[1243–1482]	[1482–3106]
<i>Model 1</i>	ref	1.00 (0.89–1.12)	1.05 (0.93–1.18)	1.14 (1.00–1.31)
<i>Model 2</i>	ref	0.99 (0.90–1.11)	1.04 (0.92–1.17)	1.12 (0.97–1.29)
<i>Model 3</i>	ref	0.99 (0.89–1.12)	1.04 (0.92–1.18)	1.13 (0.97–1.31)
small LDL-P	[0–111]	[111–529]	[529–807]	[807–2299]
<i>Model 1</i>	ref	0.97 (0.88–1.07)	0.98 (0.88–1.08)	1.06 (0.95–1.18)
<i>Model 2</i>	ref	0.96 (0.86–1.07)	0.95 (0.84–1.07)	1.01 (0.87–1.16)
<i>Model 3</i>	ref	0.96 (0.86–1.07)	0.95 (0.84–1.08)	1.02 (0.88–1.17)
LDL-P/HDL-P	[6.58–28.1]	[28.1–36.9]	[36.9–47.9]	[47.9–162.4]
<i>Model 1</i>	ref	0.96 (0.86–1.07)	0.99 (0.88–1.11)	1.09 (0.96–1.23)
<i>Model 2</i>	ref	0.96 (0.86–1.07)	0.98 (0.87–1.11)	1.07 (0.93–1.24)
<i>Model 3</i>	ref	0.96 (0.86–1.08)	0.99 (0.87–1.13)	1.08 (0.93–1.26)

Baseline model: Adjustment for age, sex, systolic blood pressure, hypertension medication, lipid lowering medication, diabetes, smoking status, race/ethnicity

Model 1: baseline model + LDL-C

Model 2: baseline model + HDL-C, total cholesterol

Model 3: baseline model + LDL-C, HDL-C, and total cholesterol