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Age-Modification of Lipoprotein, Lipid, and Lipoprotein Ratio-Associated Risk for Coronary Artery Calcium (From the Multi-Ethnic Study of Atherosclerosis [MESA])

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Abstract

Though abnormal lipoproteins and lipoprotein ratios are powerful risk factors for clinical cardiovascular (CV) events, these associations are stronger in younger compared to older age. Whether age modifies the relationships of lipoproteins and lipoprotein ratios to the relative risk for subclinical CV disease (CVD), as assessed by coronary artery calcium (CAC) scores, has not been examined in a contemporary, multi-ethnic cohort. We performed multivariate relative risk regression to determine the relative risks (RRs) for associations of lipoproteins and lipoprotein ratios with prevalent CAC in participants in MESA. Participants were community-dwelling adults ages 45–84 years without baseline clinically apparent CVD. We excluded those on lipid lowering therapy (15%), and stratified results by decades of age. 5,092 participants met inclusion criteria. In fully adjusted models, per standard deviation (SD) of low-density lipoprotein (LDL), age-stratified, adjusted relative risks (RRs) for CAC were 1.17 (95% Confidence Interval (CI) 1.07–1.28) for those aged 45–54 but 1.05 (95% CI 1.01–1.10) for those aged 75–84 (p -interaction = 0.12). The RR per SD of Total/HDL cholesterol ratio was 1.20 (95% CI 1.12–1.29) for those aged 45–54 but only 1.04 (1.00–1.09) for those aged 75–84 (p -interaction <0.001). Lipoproteins and lipoprotein ratios were associated with increased RRs for CAC across all age categories. However, these associations were markedly attenuated by age. In conclusion, abnormal lipoproteins in middle age are a powerful risk factor for early atherosclerosis as manifested by prevalent CAC.

Keywords

lipoproteins; age; coronary artery calcium

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INTRODUCTION

This study was undertaken to understand how age modifies the association of specific lipid parameters [total cholesterol, LDL cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol (Non HDL-C), triglycerides (TG), the ratio of total/HDL cholesterol (total/HDL-C), the ratio of LDL/HDL cholesterol (LDL/HDL-C), and the ratio of triglycerides/HDL cholesterol (TG/HDL-C)] with prevalent CAC in an asymptomatic, multi-ethnic cohort of contemporary, community-dwelling people without clinical CVD.

METHODS

The National Heart Lung Blood Institute (NHLBI) sponsored Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective evaluation of subclinical CVD in 6,814 men and women from 6 US communities. Participants included men and women aged 45–84 years and free of known CVD at the baseline exam (2000–2002), and were recruited through 6 field centers. Participants were classified as Caucasian, Chinese, Hispanic, or African-American. Further details regarding the design and objectives of the MESA study have been reported previously.¹

Those missing data for covariates and those using lipid lowering therapy were excluded (n=1,722). The final sample size for our analyses was 5,092 participants. Age, race/ethnicity, and highest level of education were self reported. Several CVD risk factors were measured or collected including waist circumference, medical history including presence of diabetes (DM defined using the 2003 ADA criteria of a fasting glucose ≥ 126 mg/dL or taking medications for DM), hypertension (defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg at baseline visit, or by a history of physician-diagnosed hypertension and taking medications for hypertension), family history of coronary heart disease (CAD) (first degree relative), medication use, and assessment of personal habits such as tobacco use. All biochemistry assays were performed on plasma drawn the morning of the baseline visit and stored at -70°C . Measurements were performed at a central location, the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT), using standardized methods and reagents.

Baseline coronary artery calcium (CAC) was measured twice, averaged, and quantified using the Agatston scoring method.² Depending on the field center CAC was measured either by electron-beam computed tomography (EBCT) or by multidetector row helical computed tomography (MDCT). Interobserver agreement ($k=0.93$) and intraobserver agreement ($k=0.90$) were very high.³ Careful quality control and standardized protocols were used at each clinical site. Further details regarding the protocol, acquisition and interpretation of CAC scans in MESA have been previously reported.⁴

Continuous variables were analyzed for significance using t-tests or analysis of variance (ANOVA) and categorical variables using chi-square tests. Cross-sectional analyses were performed using multivariate relative risk regression to evaluate the associations of specific lipids and lipoprotein ratios with CAC. Owens et al. previously reported that an age-independent association of Total/HDL-C with risk for prevalent aortic valve calcium (AVC) in MESA.⁵ We, therefore, also studied whether the Total/HDL-C (and LDL/HDL-C) might show a similar, age-independent association with prevalent CAC. In addition, we examined whether the TG/HDL-C, a validated marker of insulin resistance with better sensitivity for insulin resistance than the NCEP- ATP-III metabolic syndrome definition and a ROC score of 0.78 for insulin resistance in one study,^{6,7} was associated with risk of prevalent CAC. Associations of each lipoprotein or ratio with CAC were determined in both unadjusted and adjusted models using multivariate relative risk regression. Tests for interactions of age

(categorized as approximately decades of age: 45–54, 55–64, 65–74, 75–84) with lipoprotein-associated CAC risks were specified *a priori* and deemed significant at $p < 0.05$.

For the 1,016 (15%) participants on lipid lowering therapy and those with LDL-C that were unable to be calculated because TG were >400 , sensitivity analyses were performed using imputed lipid values. We used imputation to estimate the untreated levels of total, LDL, and HDL cholesterol and TG for these participants. Details regarding imputation methods can be found elsewhere.⁸

$P < 0.05$ was considered statistically significant for all major comparisons. All analyses were performed using STATA 10.0 for Windows, College Station, TX.

RESULTS

Demographic and metabolic variables for each age category are summarized in Table 1. There were no significant differences in gender or race/ethnicity among the age categories. As expected, the prevalence of hypertension and DM increased with age. The prevalence of smoking and proportion of participants with greater than a high-school education decreased with age. Family history of MI was lowest in the 45–54 age group category. ACEI/ARB use increased with age. Waist circumference generally increased with age but then decreased in the oldest age category (75–84 years). Glucose, IL-6 and creatinine increased with age. LDL-C, Non-HDL-C, TG, Total/HDL-C, LDL/HDL-C, and TG/HDL-C were highest in the 55–64 age group category. Regardless of age group, LDL-C, non-HDL-C, and TG were higher, HDL-C lower, and Total/HDL-C, LDL/HDL-C, and TG/HDL-C were higher in those with CAC vs. those without CAC (Table 2). The prevalence of CAC increased significantly with age ($p < 0.001$). The median CAC score for the entire cohort was 0 Agaston units, 0 aged 45–54, 0 aged 55–64, 19 aged 65–74, and 98 aged 75–84. The prevalence of CAC was 23% aged 45–54, 42% CAC aged 55–64, 62% CAC aged 65–74, and 80% CAC aged 75–84.

In age-stratified analyses adjusted for all co-variables studied there were significant interactions of age ($p < 0.05$) with relative risks (RRs) for the presence of CAC for all lipoprotein variables except LDL-C. Results are summarized in Figure 1. The associated RRs for CAC are highest in the youngest age group (45–54 years) for total cholesterol (Fig. 1A), LDL-C (Fig. 1B), TG (Fig. 1D) and non-HDL-C (Fig. 1E). Similarly, the apparent protective effect of HDL-C for decreased CAC risk is also strongest in the youngest age group (Fig. 1C). Similar results were observed in both unadjusted analyses and in demographically (age, gender and race/ethnicity)-adjusted analyses except that triglycerides had significantly increased RR for CAC in people ages 45–54 (data not shown) which was no longer significant in the fully adjusted analyses. Sensitivity analysis using imputed lipid and lipoprotein values demonstrated very similar age related attenuation of lipoproteins with prevalent CAC (Supplemental Figure 3).

Similar to findings for individual lipoproteins, risks for CAC associated with Total/HDL-C, LDL/HDL-C and TG/HDL were highest in the youngest MESA cohort (Figure 2). Moreover, significant interactions of age were found with risks for CAC associated with the Total/HDL-C (Fig. 2A), LDL/HDL-C, (Fig. 2B) and the TG/HDL (Fig. 2B). Similar results were observed in both unadjusted analyses and in demographically (age, gender and race/ethnicity)-adjusted analyses (data not shown). Sensitivity analysis using imputed lipid and lipoprotein values demonstrated very similar age related attenuation of lipoprotein ratios with prevalent CAC (Supplemental Figure 4).

DISCUSSION

To our knowledge, this is the first study to examine the interaction of age with lipoprotein- and lipoprotein ratio-associated risks for subclinical CAD, as assessed by CT-scan-derived CAC scores. The study demonstrates that the lipoprotein-associated RRs for CAC are markedly attenuated in older adults. Because study participants represent a contemporary cohort of relatively healthy, multi-ethnic men and women without baseline CVD, these findings may be widely generalizable to the US population.

These results emphasize the profound association of lipoproteins with subclinical atherosclerosis in middle aged adults. In fact, the median CAC score among men and women aged 45–54 is 0 for all race/ethnic cohorts in MESA.³ One SD increase in LDL-C or non-HDL-C results in a 17% increased risk of CAC. As the presence of any CAC is abnormal in this age group, the study confirms that increased levels of “atherogenic” LDL-C and non-HDL-C, as well as decreased levels of “anti-atherogenic” HDL-C are important risk factors for subclinical atherosclerosis in middle age. LDL-C has been shown to be an important risk factor for CAC in young adults as well.⁹

Another key observation of this study is that, in the MESA cohort, the associations of all lipids with risk for CAC in older Americans, especially those over age 75, are far less robust. The meaning of CAC in older adults without clinically manifest CVD is not clear. In our study, the CAC prevalence was very high, at 80%, in the oldest age group. Furthermore, this analysis is cross-sectional and we do not know when CAC first developed in these participants. However, the presence of CAC is independently associated with incident CAD in asymptomatic populations in younger and older cohorts.^{10,11} The findings of this study are congruent with previous findings demonstrating the relationship of absolute lipid levels to CVD events was attenuated with increased age.¹² The most likely reasons we see an attenuation of the relationship of lipids and lipoproteins with age are that 1) the complicated interactions of risk factors over time result in variable rates of atherosclerosis progression and those who have lived to age 75 and developed CAC but have had no CVD events likely have a lower cumulative risk factor burden, may have accumulated CAC later, or may have a slower rate of CAC accumulation over time than those who have had events or those who are significantly younger with prevalent CAC 2) the presence of CAC in age >75 is very common and that any association of a risk factor with CAC will be decreased.

Because calcium is a prominent component of many atherosclerotic plaques, the presence of CAC signifies the presence of coronary atherosclerosis. However, CAC has limitations as a measure of subclinical atherosclerosis. First, while CAC scores do measure an important plaque component, calcium, they do not give any information about other structurally relevant plaque components, such as fibrous cap, lipid core or inflammation, or percent stenosis; one corollary of this is that a negative CAC score does not exclude clinically significant ischemia.¹³ In addition, the amount and distribution of CAC within a plaque may confer different properties in terms of plaque stability.^{14–17} This information is not captured by current CT analysis of CAC scores, which summarize total coronary calcium burden.¹⁴ Other CT technologies and recently magnetic resonance imaging have provided useful information regarding atherosclerotic plaque constituents including inflammation which may prove more useful in the future than CAC scoring for risk stratification of asymptomatic people.^{18,19} Finally, plaque calcification may result from a variety of osteogenic mediators and pathways,^{20–22} and CAC scores do not distinguish the relative contributions of these pathways to calcification.¹⁴ Nonetheless, CAC scores correlate strongly with histologically-assessed coronary plaque volume,²³ are strong predictors of risk for CVD events, are obtained by non-invasive means, and can be monitored serially.^{10,24–26}

Thus, CAC scores represent a practical, efficient and validated method for assessing the presence and severity of subclinical coronary disease in large, population-based studies.

Owens et al. recently reported an age-related attenuation for the association of total cholesterol and LDL-C for aortic valve calcium (AVC) in the MESA cohort. However, that study found no attenuation with age for the Total/HDL-C associated RR for AVC.⁵ In contrast, the present study, performed in the same cohort, demonstrates an age related attenuation of the Total/HDL-C associated risk for CAC. This differential effect of age on the Total/HDL-C associated risks for CAC as compared to AVC may reflect biological differences in the calcification processes of coronary arteries vs. cardiac valves.²¹

It is important to note that this was a cross-sectional analysis and thus we cannot definitively make recommendations regarding therapy based on our findings but it is reasonable to consider more aggressive screening and possibly lipid-altering strategies in middle aged people. Furthermore, statins have not been shown to decrease CAC progression in clinical trials arguing against the utility of serial CAC screening to monitor response to lipid lowering therapy.^{27,28} Also, although the relationship of lipids with CAC is less robust in older age, this does not argue against treating abnormal lipids in older age especially considering the positive benefit of statins in older people and that there is still an important relationship with lipids and CVD mortality.^{29,30}

This analysis has important limitations. This is a cross-sectional analysis and thus understanding longitudinal changes in arterial calcification as related to age and lipoproteins are not possible. It is also subject to potential survivor bias in that those with prior CV events were excluded from MESA; however, these individuals likely had higher prevalence of both CAC and lipid disorders, so that the net effect on associations in this study is minimal. Also, the prevalence of lipid lowering therapy increases with age; thus, excluding those on lipid lowering therapy could introduce a bias by potentially excluding those with the worst lipid values. However, this bias is unlikely because our sensitivity analysis demonstrated very similar results to our main analysis. There also may be important residual confounders related to lipoproteins, age, and CAC that may not have been captured by our models. However, age was included as a continuous term in the model decreasing residual confounding by age that may not be captured if age was categorized.

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A. Total Cholesterol **B. LDL** **C. HDL** **D. Triglycerides** **E. Non-HDL**

Figure 1. 1A. Total cholesterol, 1B. LDL-C, 1C. HDL-C, 1D. Triglycerides, 1E. Non-HDL cholesterol

Relative Risk (RR) for lipoproteins and triglycerides (per standard deviation) for prevalent coronary artery calcium (CAC) as stratified by age. RR are adjusted for age, race/ethnicity, gender, highest level of education completed, site of enrollment, diabetes, hypertension, current smoking status, fasting glucose and insulin levels, adiposity as measured by waist circumference, education, family history of myocardial infarction (first degree relative), inflammation as determined by IL-6, ACEI or ARB use, and creatinine.

A. Total/HDL Ratio

B. LDL/HDL Ratio

C. Triglyceride/HDL Ratio

Figure 2. 2A. Total cholesterol/HDL-C ratio, 2B. LDL-C/HDL-C ratio, 2C. Triglycerides/HDL-C ratio

RR for lipoprotein and lipid ratios (per standard deviation) for prevalent CAC as stratified by age. RR are adjusted for age, race/ethnicity, gender, highest level of education completed, site of enrollment, diabetes, hypertension, current smoking status, fasting glucose and insulin levels, adiposity as measured by waist circumference, education, family history of myocardial infarction (first degree relative), inflammation as determined by IL-6, ACEI or ARB use, and creatinine.

Table 1

Mean and median demographic, metabolic, lipids, and CAC score in all participants included in analysis and stratified by age category in MESA 2000–2002

Variable	All (n=5,092)	45–54 (n=1,650)	55–64 (n=1,436)	65–74 (n=1,356)	75–84 (n=650)
Age (years)*	61 (10)	50 (3.4)	60 (3.2)	69 (3.3)	78 (3.2)
Women	53%	54%	54%	52%	52%
Race/Ethnicity					
Caucasian	38%	36%	37%	40%	41%
Chinese	12%	12%	12%	12%	12%
African-American	27%	27%	27%	28%	25%
Hispanic	23%	25%	24%	20%	21%
> High School					
Education*	65%	75%	64%	59%	54%
Hypertension*	44%	25%	42%	57%	67%
Diabetes Mellitus*	10%	7%	11%	12%	14%
Current smoker*	14%	19%	15%	10%	4%
Family History of MI*	41%	37%	43%	43%	42%
Ace Inhibitor/Angiotensin Receptor Blocker use*	15%	9%	14%	19%	21%
Waist circumference(cm2*)	98 (14)	96 (15)	98 (14)	99 (14)	98 (13)
Glucose (mg/dL)*	96 (29)	92 (28)	97 (32)	98 (25)	99 (31)
Insulin (mu/U*)	5.3 {3.4–8.2}	5.3 {3.5–8.4}	5.4 {3.6–8.8}	5.1 {3.3–8.1}	5.1 {3.2–7.3}
Creatinine (mg/dL*)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	1.0 (0.2)	1.0 (0.3)
Interleukin-6 (pg/mL*)	1.2 {0.8–1.9}	1.0 {0.6–1.7}	1.1 {0.7–1.8}	1.3 {0.9–2.1}	1.4 {1.0–2.1}
Total cholesterol (mg/dL*)	196 (35)	193 (34)	199 (36)	198 (34)	193 (34)
LDL cholesterol (mg/dL**)	120 (32)	119 (31)	122 (33)	120 (30)	117 (31)
HDL cholesterol (mg/dL*)	51 (15)	50 (14)	51 (15)	52 (16)	53 (15)
Non-HDL cholesterol (mg/dL*)	145 (35)	143 (35)	148 (36)	145 (34)	141 (34)
Triglycerides (mg/dL*)	109 {76–157}	105 {74–156}	114 {81–164}	109 {78–156}	106 {75–147}

Variable	All (n=5,092)	45–54 (n=1,650)	55–64 (n=1,436)	65–74 (n=1,356)	75–84 (n=650)
Total cholesterol/HDL cholesterol ratio *	4.1 (1.2)	4.1 (1.3)	4.2 (1.2)	4.0 (1.2)	3.9 (1.1)
LDL/HDL cholesterol ratio *	2.5 (1.0)	2.6 (1.0)	2.6 (1.0)	2.5 (0.9)	2.4 (0.9)
Triglycerides/HDL cholesterol ratio *	2.8 (2.0)	2.8 (2.1)	2.9 (2.0)	2.7 (1.9)	2.6 (1.7)
Median (50%) Coronary Artery Calcium score *	0 {0,63}	0 {0,0}	0 {0,33}	19 {0,166}	98 {8,366}

Mean and (SD) or median and {interquartile range} reported

* p<0.001,

** p<0.05 by chi-square for categorical variables and ANOVA for continuous variables across group comparisons

Table 2

Mean/Median lipid, lipoprotein, and lipoprotein ratio values as stratified by Age Category and Presence Vs. Absence of Coronary Artery Calcium (CAC)* in MESA 2000–2002

Variable	Age 45–54 (n=1650)		Age 55–64 (n=1436)		Age 65–74 (n=1356)		Age 75–84 (n=650)	
	No CAC	+ CAC	No CAC	+ CAC	No CAC	+ CAC	No CAC	+ CAC
	n=1273 (77%)	n=377 (23%)	n=830 (58%)	n=606 (42%)	n=518 (38%)	n=838 (62%)	n=131 (20%)	n=519 (80%)
Total Cholesterol	191 (34)	199 (34)	199 (35)	199 (37)	197 (33)	198 (34)	188 (34)	195 (35)
P value No CAC Vs. +CAC**	<0.001		0.08		0.69		0.06	
LDL Cholesterol	117 (31)	125 (32)	120 (32)	124 (34)	118 (30)	122 (30)	112 (29)	119 (31)
P value No CAC Vs. +CAC**	<0.001		0.015		0.007		0.017	
HDL Cholesterol	51(14)	46 (13)	53 (16)	49 (14)	56 (16)	50 (15)	54 (15)	52 (15)
P value No CAC Vs. +CAC**	<0.001		<0.001		<0.001		0.18	
Non-HDL Cholesterol	140 (35)	153 (35)	146 (35)	151 (37)	141 (34)	148 (34)	134 (32)	142 (34)
P value No CAC Vs. +CAC**	<0.001		0.006		<0.001		0.01	
Triglycerides	100 {71, 147}	124 {85, 179}	111 {78, 162}	119 {84, 165}	104 {73, 148}	114 {82, 159}	102 {72, 142}	107 {76, 150}
P value No CAC Vs. +CAC***†	<0.001		0.07		0.001		0.24	
Total/HDL cholesterol ratio	4.0 (1.2)	4.7 (1.4)	4.0 (1.2)	4.4 (1.7)	3.8 (1.1)	4.2 (1.2)	3.7 (1.0)	4.0 (1.1)
P value No CAC Vs. +CAC**	<0.001		<0.001		<0.001		0.005	
LDL/HDL cholesterol ratio	2.5 (0.9)	3.0 (1.1)	2.4 (0.9)	2.8 (1.0)	2.3 (0.9)	2.6 (0.9)	2.2 (0.8)	2.5 (0.9)
P value No CAC Vs. +CAC**	<0.001		<0.001		<0.001		0.003	
Triglycerides/HDL cholesterol ratio	2.6 (1.9)	3.5 (2.5)	2.7 (2.0)	3.1 (2.1)	2.4 (1.8)	2.9 (2.0)	2.4 (1.6)	2.6 (1.7)
P value No CAC Vs. +CAC**	<0.001		<0.001		<0.001		0.15	

Mean and (SD) or median and (interquartile range) reported

* P <0.001 for No CAC vs. CAC and age category using chi-squared analyses

** P value comparing No CAC vs. + CAC for each lipid variable in preceding row within each age category using ANOVA

† Testing performed on log transformed triglycerides