JACC: ADVANCES VOL. 3, NO. 7, 2024

ORIGINAL RESEARCH

ISCHEMIC HEART DISEASE

Serum Lipoproteins Are Associated With Coronary Atherosclerosis in Asymptomatic U.S. Adults Without Traditional Risk Factors

Kamil F. Faridi, MD, MSc,[a] Shubham Lahan, MD,[b] Matthew J. Budoff, MD,[c] Ricardo C. Cury, MD, MBA,[d] Theodore Feldman, MD,[d] Alan P. Pan, MS,[e] Jonathan Fialkow, MD,[d] Khurram Nasir, MD, MPH, MSc[b]

ABSTRACT

BACKGROUND The relationship between atherogenic lipoproteins and subclinical coronary atherosclerosis has not been thoroughly evaluated in low-risk adults.

OBJECTIVES The purpose of this study was to assess the association of low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B (apoB) with coronary atherosclerosis in adults without traditional risk factors.

METHODS We assessed atherosclerosis on coronary computed tomography angiography among asymptomatic adults in the Miami Heart Study not taking lipid-lowering therapy and without hypertension, diabetes, or active tobacco use. Prevalence of atherosclerosis was evaluated based on serum LDL-C, non-HDL-C, and apoB, and multivariable logistic regression with forward selection was used to assess variables associated with coronary plaque.

RESULTS Among 1,033 adults 40 to 65 years of age, 55.0% were women and 86.3% had estimated 10-year atherosclerotic cardiovascular disease risk <5%. Coronary atherosclerosis prevalence was 35.9% (50.6% in men; 23.8% in women) and 3.4% had ≥1 high-risk plaque feature. Atherosclerosis prevalence increased with LDL-C, ranging from 13.2% in adults with LDL-C <70 mg/dL up to 48.2% with ≥160 mg/dL. Higher LDL-C (adjusted OR [aOR]: 1.13 [95% CI: 1.08-1.18] per 10 mg/dL), age (aOR: 1.43 [95% CI: 1.28-1.60] per 5 years), male sex (aOR: 3.81 [95% CI: 2.86-5.10]), and elevated lipoprotein(a) (aOR: 1.46 [95% CI: 1.01-2.09]) were associated with atherosclerosis. Higher serum non-HDL-C and apoB were similarly associated with atherosclerosis. In adults with optimal risk factors, 21.2% had atherosclerosis with greater prevalence at higher lipoprotein levels.

CONCLUSIONS Among asymptomatic middle-aged adults without traditional risk factors, coronary atherosclerosis is common and increasingly prevalent at higher levels of atherogenic lipoproteins. These findings emphasize the importance of lipid-lowering strategies to prevent development and progression of atherosclerosis regardless of risk factors. (JACC Adv 2024;3:101049) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Section of Cardiovascular Medicine, Department of Medicine, Yale School of Medicine, New Haven, Connecticut, USA; [b]Division of Cardiovascular Prevention and Wellness, Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas, USA; [c]Division of Cardiology, Harbor UCLA Medical Center, Torrance, California, USA; [d]Miami Cardiac and Vascular Institute, Baptist Health South Florida, Miami, Florida, USA; and the [e]Center for Health Data Science and Analytics, Houston Methodist Research Institute, Houston, Texas, USA.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2024.101049

ABBREVIATIONS AND ACRONYMS

apoB = apolipoprotein B

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcification

CCTA = coronary computed tomography angiography

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in the United States and globally, accounting for more than 15 million deaths worldwide every year.[1] The majority of ASCVD-related deaths are related to coronary atherosclerosis, which commonly develops early in life and progresses over time.[2-4] Elevated low-density lipoprotein cholesterol (LDL-C) is a primary cause of ASCVD including coronary atherosclerosis, and reducing LDL-C is fundamental to preventing ASCVD events.[5] Older guidelines have previously defined LDL-C ≥160 mg/dL as elevated for adults, and serum LDL-C levels <100 mg/dL have generally been considered optimal for individuals without clinical ASCVD.[6-8] However, serum LDL-C levels below either of these thresholds are likely insufficient to prevent atherosclerosis or clinical ASCVD.[9-11] Risk of clinical ASCVD is also better predicted by non-high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B (apoB),[7,12] which are rarely evaluated in studies assessing coronary atherosclerosis in asymptomatic populations. Additional evidence on the association between coronary atherosclerosis and measures of atherogenic lipoproteins (LDL-C, non-HDL-C, and apoB) in adults without clinical ASCVD or other risk factors is needed to better understand atherosclerosis development and tailor long-term primary prevention strategies.

To investigate this further, we explored the association between atherogenic lipoproteins and subclinical coronary atherosclerosis detected by coronary computed tomography angiography (CCTA) in asymptomatic middle-aged U.S. adults without traditional ASCVD risk factors in the MiHeart (Miami Heart) Study. The MiHeart Study is the first large study using CCTA to comprehensively evaluate coronary atherosclerosis in asymptomatic U.S. adults and includes data on noncalcified and calcified coronary plaque, coronary stenosis, and high-risk plaque features.[13,14] We hypothesized that atherogenic lipoproteins would be associated with coronary atherosclerosis in otherwise healthy U.S. adults without traditional risk factors for ASCVD.

METHODS

DATA SOURCE-THE MIAMI HEART STUDY. This analysis used data from the MiHeart Study, a community-based cohort study conducted at Baptist Health South Florida (BHSF).[13,14] The study enrolled 2,459 volunteers from the general population between 2015 and 2018. All participants were employees of BHSF and/or residents of the Greater Miami area, aged 40 to 65 years at the time of initial enrollment, and free of clinically apparent cardiovascular disease including any known history of angina, coronary artery disease, stroke, transient ischemic attack, peripheral artery disease, abdominal aortic aneurysm, or heart failure. Potential volunteers with any of the following were also excluded from participation: weight ≥350 lbs; allergy to iodinated contrast agents; creatine >1.5 mg/dL or estimated creatinine clearance <50 ml/h; asthma or chronic obstructive pulmonary disease; active cancer; active systemic infection; use of steroids, immunosuppressive, or chemotherapeutic agents; and active pregnancy, breastfeeding, or planning to become pregnant. The study was approved by the BHSF Institutional Review Board and all participants provided written informed consent before enrollment.

As part of MiHeart Study data collection, information on demographics, clinical history, blood pressure, serum glucose, and lipids was obtained. Estimated 10-year ASCVD risk was based on the American College of Cardiology/American Heart Association pooled cohort risk equations for primary prevention.[15] Coronary CT assessments were performed on all participants using a 256-slice volumetric multidetector scanner (Revolution CT, GE Healthcare) allowing coverage of the entire heart in 1 heart beat with <1 second of image acquisition. A standard noncontrast coronary artery calcification (CAC) scan was performed first, followed by contrast-enhanced multidetector CCTA. CAC was quantified using the Agatson method by board-certified level III cardiac imagers blinded to participant information. Coronary arteries were evaluated based on the predominant plaque component in each segment using a modified American Heart Association 18-segment classification.[16] Each segment was assessed to

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 1, 2023; revised manuscript received March 27, 2024, accepted April 16, 2024.

quantify the maximal luminal stenosis and identify plaque vulnerability (positive remodeling, low CT attenuation, spotty calcifications, and napkin-ring sign). Further details on CT acquisition and image assessment have been previously described.[13,14] Participants were provided written reports for all study tests including CT results and were recommended to review results with their individual physicians. No direct therapeutic interventions were performed as part of study participation.

STUDY POPULATION. The current study was a cross-sectional analysis which included all participants of the MiHeart study without traditional ASCVD risk factors, defined for this investigation as stage II hypertension, diabetes, or active tobacco use. Individuals with any of the following were therefore excluded: self-reported hypertension, use of a blood pressure lowering medication, systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported diabetes, fasting plasma glucose ≥126 mg/dL, hemoglobin A1c ≥6.5%, use of a diabetes medication, and active tobacco use at the time of enrollment. All individuals using lipid-lowering medication were also excluded. Of those with CAC and CCTA data available (n = 2,359), 1,326 did not meet the specified risk factor criteria and were excluded. The final study cohort consisted of 1,033 participants.

Additional analyses were performed on a study subgroup with optimal risk factors. This group included participants in the study cohort who met all of the following criteria: systolic blood pressure <120 mm Hg, diastolic blood pressure <80 mm Hg, fasting plasma glucose <100 mg/dL, hemoglobin A1c <5.7%, body mass index (BMI) <25 kg/m^2, HDL-C >40 mg/dL, triglycerides <150 mg/dL, and no former tobacco use.

STUDY VARIABLES AND OUTCOMES. The exposures of interest in this study were atherogenic lipoproteins as measured by LDL-C, non-HDL-C, and apoB. The primary outcome for this study was coronary atherosclerosis, defined as the presence of any coronary plaque on CCTA. Presence of CAC, coronary stenosis ≥50%, and high-risk plaque features (positive remodeling, low CT attenuation, spotty calcifications, and napkin-ring sign) were also evaluated. Data were analyzed with stratification by lipoprotein measures, age, and sex. Available demographic and clinical characteristics were considered in adjusted analyses assessing predictors of coronary atherosclerosis.

STATISTICAL ANALYSES. Characteristics of participants who met study criteria were reported, as were characteristics of excluded participants. Frequencies of coronary atherosclerosis, CAC, coronary stenosis ≥50%, and high-risk plaque features are described for the study cohort. Participant

TABLE 1 Characteristics of MiHeart Participants With and Without Traditional Risk Factors

	Study Cohort Without Traditional Risk Factors (n = 1,033)	Excluded Cohort With ≥1 Traditional Risk Factor (n = 1,326)	*P* Value
Age, y	51 (46-56)	56 (50-60)	<0.001
Women	568 (55.0)	602 (45.4)	<0.001
Race/ethnicity			0.44
Non-Hispanic White	435 (42.1)	582 (43.9)	
Non-Hispanic Black	28 (2.7)	54 (4.1)	
Non-Hispanic Asian	31 (3.0)	40 (3.0)	
Non-Hispanic other	1 (0.1)	1 (0.1)	
Non-Hispanic ≥1 race	12 (1.2)	20 (1.5)	
Hispanic/Latino	504 (48.8)	605 (45.6)	
Unknown/not disclosed	22 (2.1)	24 (1.8)	
Education			0.01
Less than high school	2 (0.2)	6 (0.5)	
High school	67 (6.5)	126 (9.5)	
Some college, no degree	105 (10.2)	170 (12.8)	
Bachelors degree	525 (50.8)	635 (47.9)	
Postgraduate studies	330 (31.9)	381 (28.7)	
Not disclosed	4 (0.4)	8 (0.6)	
Annual income, $			0.05
<25,000	19 (1.8)	30 (2.3)	
25,000 to <50,000	59 (5.7)	108 (8.1)	
50,000 to <75,000	75 (7.3)	126 (9.5)	
75,000 to <150,000	358 (34.7)	451 (34.0)	
≥150,000	417 (40.4)	488 (36.8)	
Not disclosed	105 (10.2)	123 (9.3)	
Family history of ASCVD			
Any MI	131 (12.7)	210 (15.8)	0.03
Premature MI	42 (4.1)	50 (3.8)	0.71
Any stroke	91 (8.8)	172 (13.0)	0.001
Premature stroke	13 (1.3)	24 (1.8)	0.29
Body mass index, kg/m^2	26.7 (23.7-29.4)	28.8 (25.8-32.5)	<0.001
Body mass index categories, kg/m^2			<0.001
Underweight (BMI <18.5)	8 (0.8)	1 (0.1)	
Normal weight (BMI 18.5-24.9)	353 (34.2)	246 (18.6)	
Overweight (BMI 25.0-29.9)	438 (42.4)	542 (40.9)	
Obese, class I (BMI 30-34.9)	176 (17.0)	337 (25.4)	
Obese, class II (BMI 35.0-39.9)	42 (4.1)	143 (10.8)	
Obese, class III (BMI ≥40)	16 (1.5)	56 (4.2)	
Tobacco use			<0.001
Current smoker	0 (0.0)	71 (5.4)	
Former smoker	232 (22.5)	342 (25.8)	
Prior hypertension	0 (0.0)	829 (62.5)	<0.001
Blood pressure, mm Hg			
Systolic blood pressure	118 (110-125)	128 (118-138)	<0.001
Diastolic blood pressure	75 (70-80)	81 (75-86)	<0.001
Prior diabetes mellitus	0 (0.0)	195 (14.7)	<0.001
Fasting glucose, mg/dL	91 (86-96)	95 (89-104)	<0.001
HbA1c, %	5.4 (5.2-5.6)	5.6 (5.4-5.9)	<0.001

Continued on the next page

TABLE 1 Continued

	Study Cohort Without Traditional Risk Factors (n = 1,033)	Excluded Cohort With ≥1 Traditional Risk Factor (n = 1,326)	*P* Value
Lipids, mg/dL			
Total cholesterol	209 (186-234)	198 (171-228)	<0.001
Non-HDL cholesterol	144 (121-171)	139 (115-170)	<0.001
LDL cholesterol	125 (104-149)	117 (95-144)	<0.001
HDL cholesterol	61 (48-76)	53 (43-67)	<0.001
Triglycerides	85 (64-120)	106 (76-147)	<0.001
Apolipoprotein B	94 (80-111)	94 (79-111)	0.53
Lipoprotein(a) >125 nmol/L, %	174 (16.8)	245 (18.5)	0.25
Medication use			
Lipid-lowering medications	0 (0.0)	553 (41.7)	<0.001
Statins	0 (0.0)	527 (39.7)	<0.001
Aspirin	96 (9.3)	450 (33.9)	<0.001
10-y estimated ASCVD risk			<0.001
<5%	891 (86.3)	720 (54.3)	
5% to 7.4%	99 (9.6)	231 (17.4)	
7.5% to 19.9%	41 (4.0)	328 (24.7)	
≥20%	1 (0.1)	31 (2.3)	
Coronary plaque			
Any plaque	371 (35.9)	784 (59.1)	<0.001
≥50% stenosis	20 (1.9)	120 (9.0)	<0.001
CAC 0	771 (74.6)	604 (58.5)	<0.001
CAC 1-99	215 (20.8)	454 (34.2)	<0.001
CAC ≥100	47 (4.5)	268 (25.9)	<0.001
Any high-risk feature	35 (3.4)	130 (9.8)	<0.001

Values are median (IQR) or n (%). Traditional risk factors were defined as hypertension (self-reported hypertension, use of a blood pressure lowering medication, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg), diabetes (self-reported diabetes, fasting glucose ≥126 mg/dL, or HbA1c ≥6.5%), or active tobacco use. Participants on lipid-lowering therapy were also excluded.

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAC = coronary artery calcification; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; MiHeart = Miami Heart.

characteristics were compared using 2-sample *t*-test for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. To assess the association between coronary atherosclerosis and lipoprotein measures, frequency of any plaque and CAC were determined by strata of LDL-C, non-HDL-C, and apoB. Logistic regression models with forward stepwise variable selection based on significant reductions in Akaike information criterion were used to analyze the associations of multiple covariates with the presence of coronary plaque on CCTA in the study cohort and in those with an optimal risk factor profile. Models were developed separately for LDL-C, non-HDL-C, and apoB as continuous variables, with stepwise inclusion of other variables that resulted in statistically significant improvements in the model. There were no missing values for any of the variables included in adjusted analyses. Selected variables were also included in models that analyzed LDL-C, non-HDL-C, and apoB by quartiles across the study cohort. In secondary analyses, associations between lipoprotein measures and coronary atherosclerosis were further evaluated after excluding participants with LDL-C ≥160 mg/dL (n = 166 excluded), or with BMI ≥30 kg/m^2, history of former tobacco use, and/or family history of premature ASCVD (n = 442 excluded). Associations were presented as ORs with 95% CIs. *P* values <0.05 were considered statistically significant and all analyses were performed using R software, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

STUDY COHORT. The final cohort for this study included 1,033 individuals with a median (25th, 75th percentile; range) age of 51 years (46, 56; 40-65), and 55.0% (n = 568) were women. The median (25th, 75th percentile) serum LDL-C, non-HDL-C, and apo B levels were 125 (104, 149), 144 (121, 171), and 94 (80, 111) mg/dL, respectively. Compared to MiHeart participants who were excluded (n = 1,326), the study cohort was younger and had lower predicted ASCVD risk based on the pooled cohort risk equation, with more than 86% of participants having <5% estimated 10-year risk (**Table 1**). Men in the study cohort generally had higher BMI, atherogenic lipoprotein measures, and 10-year estimated ASCVD risk compared to women (**Table 2**).

CORONARY PLAQUE PREVALENCE AND ATHEROGENIC LIPOPROTEINS. Among MiHeart participants without traditional risk factors, 35.9% had coronary plaque, 25.3% had CAC >0 and 4.5% had CAC ≥100, 3.4% had at least 1 high-risk plaque feature and 1.9% had stenosis ≥50% on CCTA; prevalence of these features was less common compared with excluded participants with 1 or more traditional risk factors (**Table 1**). Among participants included in this study with CAC = 0, 14.1% had noncalcified plaque. Study cohort participants with coronary plaque were more commonly men and had higher levels of atherogenic lipoproteins (Supplemental Table 1). Prevalence of any coronary plaque and calcified plaque in the study cohort was progressively higher at increasing levels of LDL-C, non-HDL-C, and apoB (**Figure 1**). Coronary plaque was much more common in men than women across all lipoprotein strata except at the lowest levels (**Figure 2**, Supplemental Tables 2 and 3). Coronary plaque was increasingly prevalent with greater age among men and women (Supplemental Figure 1).

Among men, 3.0% had plaque with ≥50% stenosis and 5.8% had 1 or more high-risk plaque features, compared to 1.1% and 1.4% among women, respectively. Positive remodeling was the most common high-risk plaque feature and was present in 71.4% of those with at least 1 high-risk plaque. High-risk plaque generally appeared to be more frequent at higher serum lipoprotein levels, particularly among men, thought a definitive association was difficult to determine due to the relatively low occurrence of these plaques (Supplemental Tables 2 and 3).

COHORT WITH OPTIMAL RISK FACTORS. In the study cohort, 17.8% of participants (n = 184) had health metrics considered to be in the optimal range. A very large majority of participants with optimal risk factors were women (83.7%) and 98.4% had an estimated 10-year ASCVD risk of <5% (**Table 3**). Prevalence of coronary plaque was 21.2% in this subgroup, which was lower than the 39.3% of study participants without traditional risk factors but whose health metrics were not in the optimal ranges. In addition, 14.7% had CAC >0 but none had CAC ≥100. No participants in the optimal risk factor group had coronary stenosis ≥50%, only 2 (1.1%) had a high-risk plaque feature, and 7.6% of those with CAC = 0 had noncalcified plaque. Similar to the larger cohort, those with coronary plaque in the optimal risk factor group had higher average serum levels of atherogenic proteins and comparable blood pressure and serum glucose measurements (Supplemental Table 1). Only 30 men met criteria to be included in the optimal risk factor group but were observed to have a much higher prevalence of coronary plaque (53.3%) than women (14.9%). Prevalence of coronary plaque was generally higher at increased levels of atherogenic lipoproteins (Supplemental Figure 2, Supplemental Tables 4 and 5).

PREDICTORS OF CORONARY PLAQUE. In analyses without multivariable adjustment, most clinical characteristics were associated with the presence of coronary plaque (Supplemental Table 6). However, after multivariable adjustment, only higher atherogenic lipoproteins, increased age, male sex, and high lipoprotein(a) were significantly associated with coronary plaque in the study cohort; family history of premature ASCVD was also included in the model with apoB (**Table 4**). Participants in higher lipoprotein quartiles also had increased odds of having coronary atherosclerosis after multivariable adjustment (Supplemental Table 7). Results of multivariable analyses were similar when CAC >0 was evaluated as the outcome and after excluding participants with

TABLE 2 Characteristics of Men and Women Without Traditional Risk Factors

	Men (n = 465)	Women (n = 568)	*P* Value
Age, y	50 (45-55)	52 (47-57)	<0.001
Race/ethnicity			0.17
Non-Hispanic White	178 (38.3)	257 (45.2)	
Non-Hispanic Black	13 (2.8)	15 (2.6)	
Non-Hispanic Asian	13 (2.8)	18 (3.2)	
Non-Hispanic other	0 (0.0)	1 (0.2)	
Non-Hispanic ≥1 race	4 (0.9)	8 (1.4)	
Hispanic/Latino	244 (52.5)	260 (45.8)	
Unknown/not disclosed	13 (2.8)	9 (1.6)	
Education			0.28
Less than high school	2 (0.4)	0 (0.0)	
High school	32 (6.9)	35 (6.2)	
Some college, no degree	56 (12.0)	49 (8.6)	
Bachelors degree	230 (49.5)	295 (51.9)	
Postgraduate studies	143 (30.8)	187 (32.9)	
Not disclosed	2 (0.4)	2 (0.4)	
Annual income, $			<0.001
<25,000	8 (1.7)	11 (1.9)	
25,000 to <50,000	20 (4.3)	39 (6.9)	
50,000 to <75,000	21 (4.5)	54 (9.5)	
75,000 to <150,000	164 (35.3)	194 (34.2)	
≥150,000	214 (46.0)	203 (35.7)	
Not disclosed	38 (8.2)	67 (11.8)	
Family history of ASCVD			
Any MI	55 (11.8)	76 (13.4)	0.46
Premature MI	10 (2.2)	32 (5.6)	0.005
Any stroke	33 (7.1)	58 (10.2)	0.08
Premature stroke	5 (1.1)	8 (1.4)	0.63
Body mass index, kg/m^2	28.2 (26.0-30.8)	24.9 (22.4-28.1)	<0.001
Body mass index categories, kg/m^2			<0.001
Underweight (BMI <18.5)	0 (0.0)	8 (1.4)	
Normal weight (BMI 18.5-24.9)	74 (15.9)	279 (49.1)	
Overweight (BMI 25.0-29.9)	247 (53.1)	191 (33.6)	
Obese, class I (BMI 30-34.9)	110 (23.7)	66 (11.6)	
Obese, class II (BMI 35.0-39.9)	24 (5.2)	18 (3.2)	
Obese, class III (BMI ≥40)	10 (2.2)	6 (1.1)	
Tobacco use			
Current smoker	0 (0.0)	0 (0.0)	-
Former smoker	91 (19.6)	141 (24.8)	0.04
Prior hypertension	0 (0.0)	0 (0.0)	-
Blood pressure, mm Hg			
Systolic blood pressure	120 (114-126)	115 (106-124)	<0.001
Diastolic blood pressure	77 (73-82)	73 (68-79)	<0.001
Prior diabetes mellitus	0 (0.0)	0 (0.0)	-
Fasting glucose, mg/dL	92 (87-98)	90 (85-95)	<0.001
HbA1c, %	5.5 (5.3-5.6)	5.4 (5.2-5.6)	0.31
Lipids, mg/dL			
Total cholesterol	207 (183-231)	210 (189-236)	0.03
Non-HDL cholesterol	152 (130-181)	137 (116-163)	<0.001
LDL cholesterol	131 (110-154)	119 (99-142)	<0.001
HDL cholesterol	51 (42-61)	71 (58-85)	<0.001
Triglycerides	99 (70-138)	78 (61-107)	<0.001
Apolipoprotein B	100 (86-116)	89 (76-106)	<0.001
Lipoprotein(a) >125 nmol/L, %	71 (15.3)	103 (18.1)	0.22

Continued on the next page

TABLE 2 Continued

	Men (n = 465)	Women (n = 568)	*P* Value
Medication use			
Lipid-lowering medications	0 (0.0)	0 (0.0)	-
Statins	0 (0.0)	0 (0.0)	-
Aspirin	54 (11.6)	42 (7.4)	0.02
10-y estimated ASCVD Risk			<0.001
<5%	335 (72.0)	556 (97.9)	
5% to 7.4%	88 (18.9)	11 (1.9)	
7.5% to 19.9%	40 (8.6)	1 (0.2)	
≥20%	1 (0.2)	0 (0.0)	

Values are median (IQR) or n (%). Traditional risk factors were defined as hypertension (self-reported hypertension, use of a blood pressure lowering medication, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg), diabetes (self-reported diabetes, fasting glucose ≥126 mg/dL, or HbA1c ≥6.5%), or active tobacco use. Participants on lipid-lowering therapy were also excluded. Abbreviations as in Table 1.

LDL-C ≥160 mg/dL (Supplemental Table 8). Associations between atherogenic lipoproteins and coronary plaque were also similar after excluding participants with BMI ≥30, former history of tobacco use, and/or family history of premature ASCVD (Supplemental Tables 9 and 10).

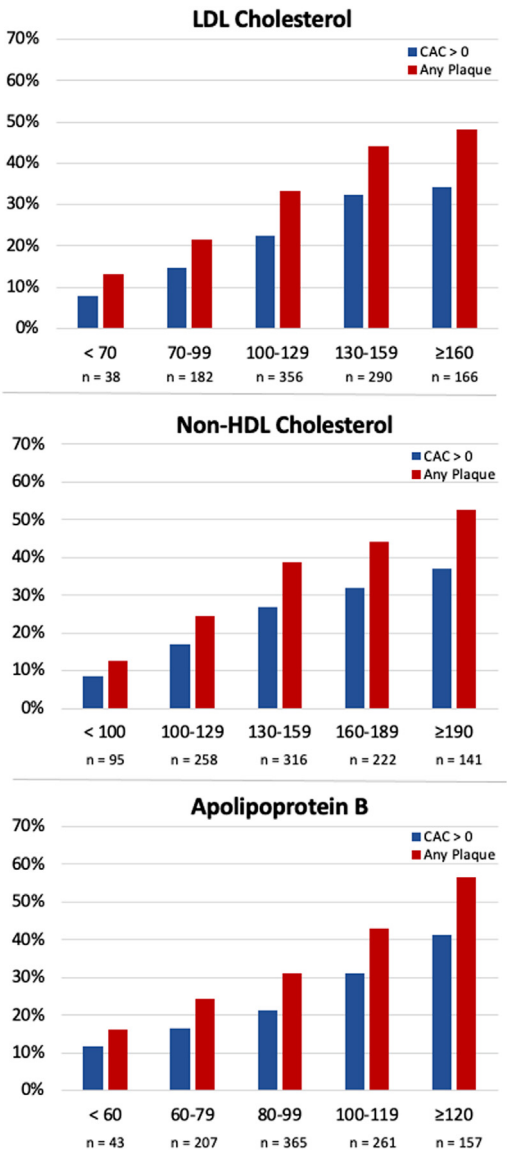
In the subgroup with optimal risk factors, increased age and male sex were the most significant predictors of coronary atherosclerosis (**Table 4**). Higher serum LDL-C, non-HDL-C, and apoB appeared to be positively associated with coronary plaque after multivariable adjustment, though findings were not statistically significant in this smaller subgroup (**Table 4**, Supplemental Table 7).

DISCUSSION

In this study of asymptomatic middle-aged U.S. adults without hypertension, diabetes, or active tobacco use, we found that coronary atherosclerosis detected by CCTA is present in more than one-third of individuals and is increasingly prevalent at higher levels of LDL-C, non-HDL-C, and apoB. Coronary plaque was much more common in men and frequently found even at lower serum levels of atherogenic lipoproteins (**Central Illustration**), though high-risk coronary plaque features were relatively uncommon. These findings emphasize the importance of atherogenic lipoproteins even in low-risk adults without traditional risk factors for ASCVD.

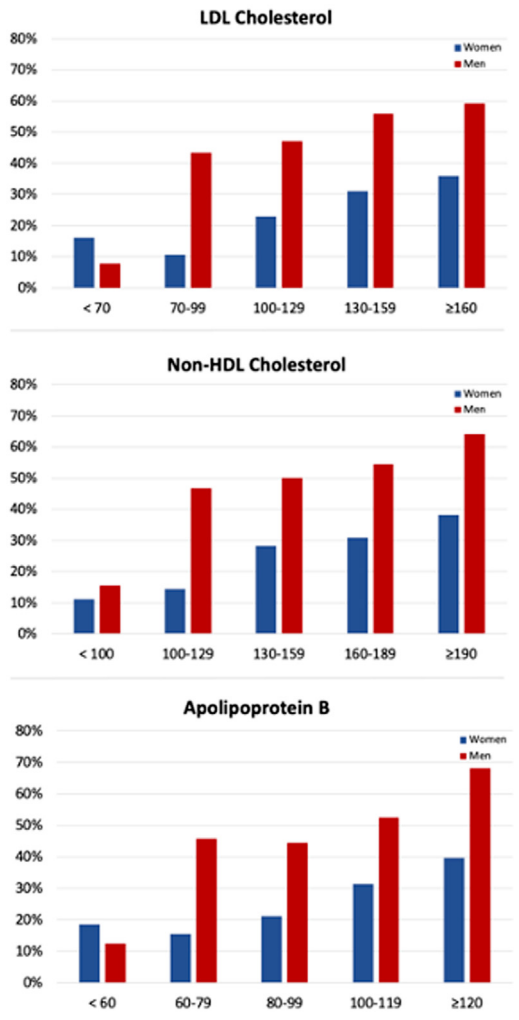
Evidence describing CCTA-detected coronary atherosclerosis among asymptomatic low-risk adults is sparse, and the MiHeart Study is the first large study to specifically evaluate U.S. adults. In the SCAPIS (Swedish CArdioPulmonary bioImage Study),

FIGURE 1 Prevalence of Coronary Atherosclerosis Among Asymptomatic Adults Without Traditional Risk Factors Based on Serum Lipoproteins



Prevalence (%) of coronary atherosclerosis detected by coronary computed tomography angiography is shown with stratification by serum cholesterol in MiHeart Study participants not taking lipid-lowering therapy and without hypertension, diabetes, or active tobacco use. Prevalence of coronary artery calcium (CAC) is also shown. Cholesterol values are in mg/dL. The number of study participants within each category of cholesterol is shown. All *P* values were <0.001 for coronary plaque and CAC across categories of serum lipoprotein levels. LDL = low-density lipoprotein; MiHeart = Miami Heart; non-HDL = non-high-density lipoprotein.

FIGURE 2 Prevalence of Coronary Atherosclerosis Among Asymptomatic Men and Women Without Traditional Risk Factors Based on Serum Lipoproteins



Prevalence (%) of coronary atherosclerosis detected by coronary computed tomography angiography is shown with stratification by serum cholesterol and sex in MiHeart Study participants not taking lipid-lowering therapy and without hypertension, diabetes, or active tobacco use. Cholesterol values are in mg/dL. All *P* values were <0.01 for men and women across categories of serum lipoprotein levels. Abbreviations as in Figure 1.

35% of men and 25% of women 50 to 64 years of age with low ASCVD risk in Sweden had coronary plaque on CCTA.[4] We found higher prevalence in U.S. men (51%) with similar prevalence (24%) in women, though the prior study did not specifically evaluate risk factor-free individuals, prevalence based on atherogenic lipoproteins, or high-risk plaque features. In a prior study of asymptomatic Korean middle-aged adults without risk factors, 21% had coronary atherosclerosis on CCTA and increased age, male sex, and higher LDL-C were significant predictors of plaque,[10] similar to our study. Among Koreans with LDL-C <100 mg/dL, 17% had coronary plaque. However, prevalence based on lower LDL-C levels, non-HDL-C, and apoB, as well as detailed plaque features, were not reported.

Our study focused on both noncalcified and calcified coronary plaque, with findings that are generally consistent with studies that have only evaluated CAC. In the PESA (Progression of Early Subclinical Atherosclerosis) study, atherosclerosis by vascular ultrasound or CAC was present in 50% of Spanish adults (mean age 45 years) without risk factors and in 38% of those with optimal risk factor profiles, including those with LDL-C <100 mg/dL. Coronary artery calcium was infrequent (11%) but more prevalent at higher LDL-C levels; presence of noncalcified coronary plaque could not be assessed as in our study.[9] Among U.S. adults in the MESA cohort without traditional risk factors (median age 54 years) and with LDL-C levels <160 mg/dL,[17] 29.1% had CAC >0. In this study, higher LDL-C and non-HDL-C levels were associated with greater prevalence of CAC and higher incidence of subsequent cardiovascular events.[17] More generally, other studies have demonstrated that CAC is relatively common in younger, relatively low-risk populations and associated with development of clinical ASCVD.[18-20] Unlike any similar prior investigations, we showed that coronary plaque on CCTA is common across atherogenic lipoprotein levels typically considered optimal for a primary prevention population (eg LDL-C <100 mg/dL, non-HDL-C <130 mg/dL, and apoB <80 mg/dL), even in the absence of traditional modifiable risk factors. Furthermore, higher levels of all atherogenic lipoprotein measures were associated with greater prevalence of coronary plaque in our cohort after adjustment for other factors.

These findings have several important implications. First, we showed that subclinical coronary atherosclerosis can occur in more than one-third of healthy U.S. adults 40 to 65 years of age without hypertension, diabetes, or tobacco use, even if they have low (<5%) estimated 10-year ASCVD risk and relatively high socioeconomic status. This is particularly true of men, with more than half having coronary plaque by age 50 years despite their low risk. Importantly, coronary plaque was found in >40% of low-risk men even with lipoprotein measures that might be considered optimal without lipid-lowering therapy (LDL-C 70-99, non-HDL-C 100-129, or apoB 60-79 mg/dL). More than one-third of low-risk

TABLE 3 Characteristics of MiHeart Participants With Optimal Risk Factors

	Overall (N = 184)	Men (n = 30)	Women (n = 154)	*P* Value (Men vs Women)
Age, y	50 (46-55)	49 (46-51)	50 (47-55)	0.19
Race/ethnicity				0.46
Non-Hispanic White	92 (50.0)	13 (43.3)	79 (51.3)	
Non-Hispanic Black	1 (0.5)	0 (0.0)	1 (0.6)	
Non-Hispanic Asian	4 (2.2)	1 (3.3)	3 (1.9)	
Non-Hispanic other	0 (0.0)	0 (0.0)	0 (0.0)	
Non-Hispanic ≥1 race	0 (0.0)	0 (0.0)	0 (0.0)	
Hispanic/Latino	82 (44.6)	14 (46.7)	68 (44.2)	
Unknown/not disclosed	5 (2.7)	2 (6.7)	3 (1.9)	
Education				0.17
Less than high school	0 (0.0)	0 (0.0)	0 (0.0)	
High school	7 (3.8)	0 (0.0)	7 (4.5)	
Some college, no degree	13 (7.1)	2 (6.7)	11 (7.1)	
Bachelors degree	98 (53.3)	12 (40.0)	86 (55.8)	
Postgraduate studies	66 (35.9)	16 (53.3)	50 (32.5)	
Not disclosed	0 (0.0)	0 (0.0)	0 (0.0)	
Income, $				0.57
<25,000	4 (2.2)	1 (3.3)	3 (1.9)	
25,000 to <50,000	6 (3.3)	0 (0.0)	6 (3.9)	
50,000 to <75,000	9 (4.9)	1 (3.3)	8 (5.2)	
75,000 to <150,000	56 (30.4)	7 (23.3)	49 (31.8)	
≥150,000	84 (45.7)	18 (60.0)	66 (42.9)	
Not disclosed	25 (13.6)	3 (10.0)	22 (14.3)	
Family history of ASCVD				
Any MI	21 (11.4)	4 (13.3)	17 (11.0)	0.72
Premature MI	7 (3.8)	1 (3.3)	6 (3.9)	0.88
Any stroke	21 (11.4)	3 (10.0)	18 (11.7)	0.79
Premature stroke	2 (1.1)	0 (0.0)	2 (1.3)	0.53
Body mass index, kg/m^2	22.7 (21.0-23.6)	23.6 (22.5-24.6)	22.4 (20.9-23.5)	<0.001
Body mass index categories, kg/m^2				>0.99
Underweight (BMI <18.5)	5 (2.7)	0 (0.0)	5 (3.2)	
Normal weight (BMI 18.5-24.9)	179 (97.3)	30 (100.0)	149 (96.8)	
Overweight/Obese (BMI ≥25.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Current/Former smoker	0 (0.0)	0 (0.0)	0 (0.0)	-
Prior hypertension	0 (0.0)	0 (0.0)	0 (0.0)	-
Blood pressure, mm Hg				
Systolic blood pressure	106 (100-111)	111 (104-114)	106 (99-110)	0.002
Diastolic blood pressure	68 (64-72)	70 (67-73)	68 (64-71)	0.03
Prior diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	-
Fasting glucose, mg/dL	88 (84-92)	86 (83-91)	88 (84-92)	0.59
HbA1c, %	5.3 (5.1-5.5)	5.4 (5.2-5.5)	5.3 (5.1-5.5)	0.74
Lipids, mg/dL				
Total cholesterol	202 (181-222)	194 (178-215)	204 (184-228)	0.18
Non-HDL cholesterol	126 (104-147)	136 (115-156)	122 (103-146)	0.07
LDL cholesterol	108 (88-130)	120 (101-136)	106 (88-129)	0.07
HDL cholesterol	76 (64-88)	56 (50-64)	80 (67-91)	<0.001
Triglycerides	66 (55-81)	70 (53-90)	66 (55-80)	0.65
Apolipoprotein B	84 (70-98)	91 (82-102)	82 (70-98)	0.07
Lipoprotein(a) >125 nmol/L, %	24 (13.0)	4 (13.3)	20 (13.0)	0.96

Continued on the next page

women were also found to have plaque either at the highest levels of serum atherogenic lipoproteins or by age 60 years. Heterogeneity in prevalence of CAC has previously been demonstrated regardless of risk,[19] and our results further demonstrate the limitations of using risk calculations to identify existing coronary plaque on CCTA. Given that subclinical coronary plaque is associated with increased risk of clinical

TABLE 3 Continued

	Overall (N = 184)	Men (n = 30)	Women (n = 154)	*P* Value (Men vs Women)
Medication use				
Lipid-lowering medications	0 (0.0)	0 (0.0)	0 (0.0)	-
Statins	0 (0.0)	0 (0.0)	0 (0.0)	-
Aspirin	9 (5.0)	2 (6.7)	7 (4.5)	0.64
10-y estimated ASCVD risk				0.004
<5%	181 (98.4)	27 (90.0)	154 (100.0)	
5% to 7.4%	3 (1.6)	3 (10.0)	0 (0.0)	
≥7.5%	0 (0.0)	0 (0.0)	0 (0.0)	

Values are median (IQR) or n (%). Among participants not on lipid-lowering therapy and without hypertension, diabetes, or active tobacco use, optimal risk factors were further defined as having all of the following: systolic blood pressure <120 mm Hg, diastolic blood pressure <80 mm Hg, fasting glucose <100 mg/dL, HbA1c<5.7%, BMI <25 kg/m^2, HDL-C >40 mg/dL, triglycerides <150 mg/dL, and no former tobacco use. Abbreviations as in Table 1.

ASCVD,[18,20-25] our results indicate lipid-lowering through improved diet and lifestyle and potentially medical therapy should be strongly considered even in the lowest risk adults, with statin initiation guided by shared decision-making, presence of risk-enhancing factors and potentially CAC testing.[7,26,27]

Second, given that we observed a consistent increase in atherosclerosis prevalence with rising serum levels of atherogenic lipoproteins, our findings emphasize the importance of reducing atherogenic lipoproteins to prevent or delay coronary plaque from developing. Average serum cholesterol values are much lower in populations that have not adopted Western dietary patterns,[28-32] including an indigenous Bolivian population with rare risk factors and the lowest prevalence of CAC on record, even into older age.[33] As noted above, higher LDL-C has previously been associated with greater prevalence of atherosclerosis in asymptomatic Korean and Spanish populations without traditional risk factors.[9,10] Persistently high serum levels of LDL-C over time are also associated with developing CAC in the future.[34,35] Importantly, once calcified coronary plaque develops, ASCVD risk likely cannot be restored to the lowest level of risk even with lipid-lowering therapy.[36,37] Our study is also consistent with data from prospective cohorts demonstrating that achieving lower serum LDL-C earlier in life is

TABLE 4 Predictors of Coronary Atherosclerosis After Multivariable Adjustment

LDL Cholesterol			Non-HDL Cholesterol			Apolipoprotein B		
	Adjusted OR (95% CI)	*P* Value		Adjusted OR (95% CI)	*P* Value	Characteristic	Adjusted OR (95% CI)	*P* Value
Cohort without traditional risk factors								
LDL-C (per 10 mg/dL)	1.13 (1.08-1.18)	<0.001	Non-HDL-C (per 10 mg/dL)	1.12 (1.08-1.16)	<0.001	ApoB (per 10 mg/dL)	1.20 (1.13-1.27)	<0.001
Age (per 5 y)	1.43 (1.28-1.60)	<0.001	Age (per 5 y)	1.44 (1.29-1.61)	<0.001	Age (per 5 y)	1.44 (1.29-1.61)	<0.001
Men	3.81 (2.86-5.10)	<0.001	Men	3.69 (2.77-4.94)	<0.001	Men	3.70 (2.76-4.97)	<0.001
Lp(a) ≥125 nmol/L	1.46 (1.01-2.09)	0.043	Lp(a) ≥125 nmol/L	1.46 (1.01-2.10)	0.041	Lp(a) ≥125 nmol/L	1.50 (1.04-2.16)	0.029
-	-	-	-	-	-	Family history of premature ASCVD	1.73 (0.98-3.03)	0.056
Cohort with optimal risk factors								
LDL-C (per 10 mg/dL)	1.11 (0.97-1.27)	0.13	Non-HDL-C (per 10 mg/dL)	1.11 (0.99-1.26)	0.087	ApoB (per 10 mg/dL)	1.11 (0.90-1.36)	0.32
Age (per 5 y)	1.50 (1.08-2.11)	0.018	Age (per 5 y)	1.50 (1.09-2.11)	0.015	Age (per 5 y)	1.54 (1.11-2.17)	0.011
Men	6.17 (2.48-15.90)	0.002	Men	6.02 (2.44-15.30)	0.001	Men	6.11 (2.46-15.60)	<0.001

Traditional risk factors were defined as hypertension, diabetes, or active tobacco use; participants on lipid-lowering therapy were also excluded. Among participants without traditional risk factors, optimal risk factors were further defined as having all of the following: systolic blood pressure <120 mm Hg, diastolic blood pressure <80 mm Hg, fasting glucose <100 mg/dL, HbA1c<5.7%, BMI <25 kg/m^2, HDL-C >40 mg/dL, triglycerides <150 mg/dL, and no former tobacco use. Multivariable adjusted analyses were performed using stepwise selection of candidate variables (serum lipoprotein value, age, sex, race/ethnicity, family history of premature ASCVD, BMI, HbA1c, systolic blood pressure, diastolic blood pressure, HDL-C, triglycerides, and Lp(a) ≥125 nmol/L). All variables included in each of the final models are shown. Each lipoprotein category (LDL-C, non-HDL-C, and apoB) was analyzed separately.

apoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

CENTRAL ILLUSTRATION **Coronary Atherosclerosis in Asymptomatic U.S. Adults Without Traditional Risk Factors**

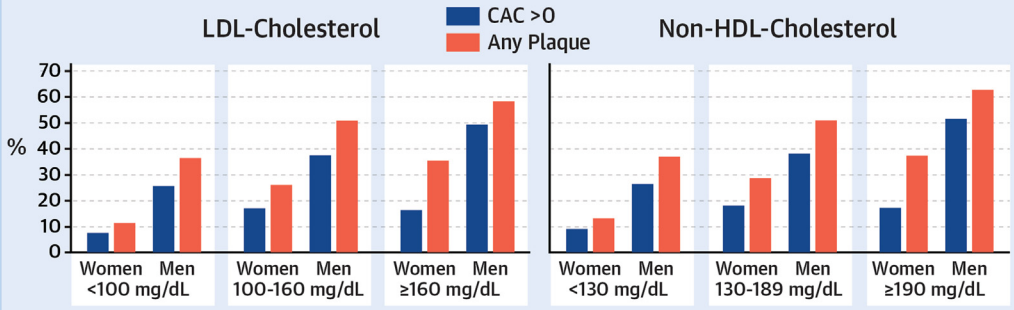
MiHeart Study Participants With Coronary Computed Tomography Angiography

1,033 Asymptomatic U.S. Adults Without Traditional Risk Factors

Mean Age 51 (IQR:46-56) Years

86% with 10-Year ASCVD Risk <5%

Prevalence of Coronary Atherosclerosis Based on Serum Cholesterol



Predictors of Coronary Atherosclerosis After Multivariable Adjustment

LDL-Cholesterol	
Characteristic	Adjusted OR (95% CI)
LDL-C (per 10 mg/dL increase)	1.13 (1.08-1.18)
Age (per 5-year increase)	1.43 (1.28-1.60)
Men	3.81 (2.86-5.10)
Lp(a) ≥125 nmol/L	1.46 (1.01-2.09)
Non-HDL-Cholesterol	
Characteristic	Adjusted OR (95% CI)
Non-HDL-C (per 10 mg/dL increase)	1.12 (1.08-1.16)
Age (per 5-year increase)	1.44 (1.29-1.61)
Men	3.69 (2.77-4.94)
Lp(a) ≥125 nmol/L	1.46 (1.01-2.10)
Apolipoprotein B	
Characteristic	Adjusted OR (95% CI)
ApoB (per 10 mg/dL increase)	1.20 (1.13-1.27)
Age (per 5-year increase)	1.44 (1.29-1.61)
Men	3.70 (2.76-4.97)
Lp(a) ≥125 nmol/L	1.50 (1.04-2.16)
Family history of premature ASCVD	1.73 (0.98-3.03)

Faridi KF, et al. JACC Adv. 2024;3(7):101049.

Prevalence (%) of any coronary atherosclerosis detected by coronary computed tomography angiography is shown with stratification by sex and serum cholesterol levels in MiHeart Study participants not taking lipid-lowering therapy and without hypertension, diabetes, or active tobacco use. Prevalence of coronary artery calcium (CAC) is also shown. Multivariable adjusted analyses were performed using stepwise selection of variables. All variables included in final models are shown. LDL-C, non-HDL-C, and apoB were analyzed separately.
apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcification; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; other abbreviations as in Figure 1.

important for preventing clinical ASCVD over the lifespan, regardless of other risk factors.[38-42]

Given this evidence, lifestyle habits that effectively lower atherogenic lipoproteins including high dietary fiber consumption from whole plant foods, low saturated fat intake (eg, <7% of total daily calories) and maintenance of healthy body weight as recommended by current guidelines remain central for prevention of atherosclerosis from early life through middle age.[43-47] As fewer than 1 in 10 Americans currently meet guidelines for limiting saturated fat or consuming the recommended amount of dietary fiber,[48] improved diet quality should be continually emphasized.

Since apoB-containing lipoproteins cause atherosclerosis and lifetime risk of ASCVD is high for the majority of the population, use of lipid-lowering therapies in low-risk adults based on shared decision-making and possible use of CAC testing are strategies which warrant further investigation but nonetheless can also be considered in current clinical practice.[49,50] Notably, significant stenosis (1.9%) and high-risk plaque features (3.4%) were infrequent in this low-risk cohort, and only 1.1% of adults with optimal risk factors had high-risk plaque features. Given differences in coronary plaque prevalence based on other risk factors (59.1% in the excluded cohort with at least 1 traditional risk factor including 9.8% with high-risk plaque, compared to 35.9% in the risk factor-free cohort and 21.2% in the subgroup with an optimal risk factor profile), primordial prevention of hypertension, diabetes, and tobacco use as well as prediabetes, metabolic syndrome, and obesity remains paramount for prevention of atherosclerosis.

STUDY LIMITATIONS. This study has several limitations. All data were collected at a single time point, and therefore measured serum levels of atherogenic lipoproteins do not necessarily represent lifelong exposure to prior levels of LDL-C, non-HDL-C, or apoB. Data on dietary patterns and physical activity were also not available. Though associations between lipoproteins and coronary atherosclerosis in the optimal risk factor subgroup appeared to be similar to the larger cohort, this cohort was smaller, contained very few men, and may have been underpowered to detect significant associations. Similarly, associations with high-risk plaque features could not be definitively determined due to their low prevalence. The MiHeart Study cohort is also not necessarily representative of the general U.S. population, as many participants were employees of a large health system and most had a college degree with a relatively high income. More than 90% of participants also identified as either non-Hispanic White or Hispanic/Latino, and findings could differ in other racial and ethnic groups. Lastly, clinical outcomes were not prospectively assessed in this study. Longitudinal studies assessing the relationship between atherogenic lipoproteins, subclinical coronary plaque on CCTA, and ASCVD events in low-risk adults can help further inform clinical evaluation and management.

CONCLUSIONS

Among healthy asymptomatic middle-aged adults without traditional ASCVD risk factors in the U.S., coronary atherosclerosis on CCTA is common even at lower serum levels of LDL-C, non-HDL-C, and apoB. Coronary atherosclerosis is more prevalent at higher levels of serum lipoproteins for both men and women, and high-risk plaque features are present but relatively infrequent in low-risk adults. These findings emphasize the importance of lipid-lowering strategies to prevent the development and progression of atherosclerosis in adults regardless of risk factors.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Miami Heart Study was funded by Baptist Health South Florida. Dr Faridi has received research funding from the NIH/NHLBI (K23HL161424), outside the scope of the current work. Dr Budoff has received grant support from General Electric. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Kamil F. Faridi, Section of Cardiovascular Medicine, Department of Medicine Yale School of Medicine 300 George Street, Suite 759, New Haven, Connecticut 06511, USA. E-mail: kamil.faridi@yale.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Coronary atherosclerosis detected by coronary CTA is present in more than one-third of asymptomatic, healthy middle-aged U.S. adults not on lipid-lowering therapy and without hypertension, diabetes, or active tobacco use. In this low-risk population, coronary atherosclerosis is common even at serum cholesterol levels frequently considered optimal, and increasingly prevalent at higher serum levels of LDL-C, non-HDL-C, and apoB, though high-risk plaque features are relatively infrequent.

COMPETENCY IN PATIENT CARE: Given the high prevalence of coronary atherosclerosis among low-risk middle-aged adults, lowering of atherogenic lipoproteins with improved diet and lifestyle as well as potential use of medical therapy should be strongly considered even if traditional risk factors are absent and predicted risk of ASCVD is low.

TRANSLATIONAL OUTLOOK: Findings from this study emphasize the importance of reducing serum atherogenic lipoproteins from early life through middle age to prevent or delay development of atherosclerosis. Further studies are needed to clarify optimal timing of risk assessment based on nontraditional risk factors, use of supplemental imaging such as coronary artery calcium scoring, and implementation of lipid-lowering therapy in low-risk adults.

REFERENCES

1. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76:2982-3021.

2. Strong JP, Malcom GT, McMahan CA, et al. Prevalence and extent of atherosclerosis in adolescents and young adults: implications for prevention from the pathobiological determinants of atherosclerosis in youth study. *JAMA*. 1999;281:727-735.

3. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *N Engl J Med*. 1998;338:1650-1656.

4. Bergstrom G, Persson M, Adiels M, et al. Prevalence of subclinical coronary artery atherosclerosis in the general population. *Circulation*. 2021;144:916-929.

5. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459-2472.

6. National Cholesterol Education Program Expert Panel. Third report of the National cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and Treatment of high blood cholesterol in adults (adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.

7. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of Cardiology/American heart association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73:e285-e350.

8. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1-full report. *J Clin Lipidol*. 2015;9:129-169.

9. Fernandez-Friera L, Fuster V, Lopez-Melgar B, et al. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. *J Am Coll Cardiol*. 2017;70:2979-2991.

10. Won KB, Park GM, Yang YJ, et al. Independent role of low-density lipoprotein cholesterol in subclinical coronary atherosclerosis in the absence of traditional cardiovascular risk factors. *Eur Heart J Cardiovasc Imaging*. 2019;20:866-872.

11. Sachdeva A, Cannon CP, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get with the Guidelines. *Am Heart J*. 2009;157:111-117.e2.

12. Expert Dyslipidemia Panel of the International Atherosclerosis Society. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia--full report. *J Clin Lipidol*. 2014;8:29-60.

13. Nasir K, Cainzos-Achirica M, Valero-Elizondo J, et al. Coronary atherosclerosis in an asymptomatic U.S. Population: Miami Heart study at Baptist Health South Florida. *JACC Cardiovasc Imaging*. 2022;15:1604-1618.

14. Nasir K, Ziffer JA, Cainzos-Achirica M, et al. The Miami Heart Study (MiHeart) at Baptist Health South Florida, A prospective study of subclinical cardiovascular disease and emerging cardiovascular risk factors in asymptomatic young and middle-aged adults: the Miami Heart Study: Rationale and Design. *Am J Prev Cardiol*. 2021;7:100202.

15. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American college of Cardiology/American heart association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;74:e177-e232.

16. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of coronary artery disease, Council on cardiovascular Surgery, American heart association. *Circulation*. 1975;51:5-40.

17. Zhou Z, Ong KL, Whelton SP, et al. Impact of blood lipids on 10-year cardiovascular risk in individuals without dyslipidemia and with low risk factor burden. *Mayo Clin Proc*. 2022;97:1883-1893.

18. Silverman MG, Blaha MJ, Krumholz HM, et al. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. 2014;35:2232-2241.

19. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates According to American college of Cardiology/American heart association cholesterol management guidelines: MESA (Multi-Ethnic study of atherosclerosis). *J Am Coll Cardiol*. 2015;66:1657-1668.

20. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD)

events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J*. 2018;39:2401–2408.

21. Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 Years with incident coronary heart disease and death. *JAMA Cardiol*. 2017;2:391–399.

22. Williams MC, Kwiecinski J, Doris M, et al. Low-attenuation Noncalcified plaque on coronary computed tomography angiography Predicts myocardial infarction: results from the Multicenter SCOT-HEART trial (Scottish computed tomography of the HEART). *Circulation*. 2020;141:1452–1462.

23. Andreini D, Magnoni M, Conte E, et al. Coronary plaque features on CTA can identify patients at increased risk of cardiovascular events. *JACC Cardiovasc Imaging*. 2020;13:1704–1717.

24. Reynolds HR, Shaw LJ, Min JK, et al. Outcomes in the ISCHEMIA trial based on coronary artery disease and ischemia severity. *Circulation*. 2021;144:1024–1038.

25. Andreini D, Pontone G, Mushtaq S, et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. *JACC Cardiovasc Imaging*. 2012;5:690–701.

26. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary calcium Score and cardiovascular risk. *J Am Coll Cardiol*. 2018;72:434–447.

27. Golub IS, Termeie OG, Kristo S, et al. Major global coronary artery calcium guidelines. *JACC Cardiovasc Imaging*. 2023;16:98–117.

28. Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am J Med*. 1988;84:739–749.

29. McMurry MP, Cerqueira MT, Connor SL, et al. Changes in lipid and lipoprotein levels and body weight in Tarahumara Indians after consumption of an affluent diet. *N Engl J Med*. 1991;325:1704–1708.

30. O'Keefe JH Jr, Cordain L, Harris WH, et al. Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. *J Am Coll Cardiol*. 2004;43:2142–2146.

31. Bradbury KE, Crowe FL, Appleby PN, et al. Serum concentrations of cholesterol, apolipoprotein A-I and apolipoprotein B in a total of 1694 meat-eaters, fish-eaters, vegetarians and vegans. *Eur J Clin Nutr*. 2014;68:178–183.

32. Pontzer H, Wood BM, Raichlen DA. Hunter-gatherers as models in public health. *Obes Rev*. 2018;19(Suppl 1):24–35.

33. Kaplan H, Thompson RC, Trumble BC, et al. Coronary atherosclerosis in indigenous South American Tsimane: a cross-sectional cohort study. *Lancet*. 2017;389:1730–1739.

34. Tsao CW, Preis SR, Peloso GM, et al. Relations of long-term and contemporary lipid levels and lipid genetic risk scores with coronary artery calcium in the framingham heart study. *J Am Coll Cardiol*. 2012;60:2364–2371.

35. Paramsothy P, Katz R, Owens DS, et al. Age-modification of lipoprotein, lipid, and lipoprotein ratio-associated risk for coronary artery calcium (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol*. 2010;105:352–358.

36. Liu K, Wilkins JT, Colangelo LA, et al. Does lowering low-density lipoprotein cholesterol with statin Restore low risk in middle-aged adults? Analysis of the Observational MESA study. *J Am Heart Assoc*. 2021;10:e019695.

37. Blaha M, Budoff MJ, Shaw LJ, et al. Absence of coronary artery calcification and all-cause mortality. *JACC Cardiovasc Imaging*. 2009;2:692–700.

38. Navar-Boggan AM, Peterson ED, D'Agostino RB Sr, et al. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. *Circulation*. 2015;131:451–458.

39. Zhang Y, Vittinghoff E, Pletcher MJ, et al. Associations of blood pressure and cholesterol levels during young adulthood with Later cardiovascular events. *J Am Coll Cardiol*. 2019;74:330–341.

40. Domanski MJ, Tian X, Wu CO, et al. Time Course of LDL cholesterol exposure and cardiovascular disease event risk. *J Am Coll Cardiol*. 2020;76:1507–1516.

41. Zhang Y, Pletcher MJ, Vittinghoff E, et al. Association between Cumulative low-density lipoprotein cholesterol exposure during young adulthood and middle age and risk of cardiovascular events. *JAMA Cardiol*. 2021;6:1406–1413.

42. Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Low LDL cholesterol by PCSK9 Variation Reduces cardiovascular mortality. *J Am Coll Cardiol*. 2019;73:3102–3114.

43. Clarke R, Frost C, Collins R, et al. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *BMJ*. 1997;314:112–117.

44. Jenkins DJ, Kendall CW, Popovich DG, et al. Effect of a very-high-fiber vegetable, fruit, and nut diet on serum lipids and colonic function. *Metabolism*. 2001;50:494–503.

45. Jenkins DJ, Kendall CW, Marchie A, et al. Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *JAMA*. 2003;290:502–510.

46. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a Presidential Advisory from the American heart association. *Circulation*. 2017;136:e1–e23.

47. Lichtenstein AH, Appel LJ, Vadiveloo M, et al. 2021 Dietary guidance to Improve cardiovascular health: a Scientific statement from the American heart association. *Circulation*. 2021;144:e472–e487.

48. USDA Agricultural Reearch Service. What We Eat in America. 2022. Accessed November 11, 2023. https://www.ars.usda.gov/northeast-area/beltsville-md-bhnrc/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/wweianhanes-overview

49. Pencina MJ, Pencina KM, Lloyd-Jones D, et al. The Expected 30-year Benefits of early versus delayed primary prevention of cardiovascular disease by lipid lowering. *Circulation*. 2020;142:827–837.

50. Dzaye O, Razavi AC, Dardari ZA, et al. Modeling the recommended age for initiating coronary artery calcium testing among at-risk young adults. *J Am Coll Cardiol*. 2021;78:1573–1583.

KEY WORDS atherosclerosis, coronary CTA, low-risk adults, prevalence, prevention

APPENDIX For supplemental tables and figures, please see the online version of this paper.