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Coronary Plaque Burden and Adverse Plaque Characteristics Are Increased in Healthy Relatives of Patients With Early Onset Coronary Artery Disease

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ABSTRACT

OBJECTIVES This study characterized and quantified subclinical atherosclerosis by coronary computed tomography angiography (CTA) in first-degree relatives of patients with early onset coronary artery disease (CAD).

BACKGROUND A strong family history of CAD is an important risk factor for adverse cardiovascular events. Whether predisposed individuals suffer an increased burden of coronary atherosclerosis and adverse plaque features is not known.

METHODS We included 88 healthy middle-aged first-degree relatives from 59 families with early onset CAD. Participants were matched by age and sex with 88 control patients with atypical angina or nonanginal chest pain and no family history of CAD, referred for coronary CTA. A blinded analysis of plaque burden and composition was performed using semiautomated plaque quantification software. The relative differences between the median volumes or the odds ratios (OR) were compared between groups, using a mixed model.

RESULTS First-degree relatives had significantly more affected coronary segments than controls (0 segments: 30% vs. 49%, respectively; 1 to 2 segments: 27% vs. 32%, respectively; 3 to 4 segments: 18% vs. 6%, respectively; and ≥5 segments: 25% vs. 14%, respectively; $p = 0.001$). In a multivariate model, the relative differences of total plaque, total calcified plaque (CP), total noncalcified plaque (NCP), and total low-density NCP (LD-NCP) were 5.8 (95% confidence interval [CI]: 2.8 to 11.9), 2.6 (95% CI: 1.5 to 4.5), 5.8 (95% CI: 2.9 to 12.0), and 3.6 (95% CI: 2.1 to 6.1), respectively. The adjusted OR of any positive remodeling plaque or any LD-NCP plaque was 4.2 (95% CI: 1.2 to 14) and 4.2 (95% CI: 1.9 to 9.5), respectively.

CONCLUSIONS Healthy first-degree relatives of patients with early onset CAD have an increased coronary plaque burden compared with symptomatic patients. The plaques display characteristics associated with myocardial ischemia and adverse coronary events. (J Am Coll Cardiol Img 2017;10:1128–35) © 2017 by the American College of Cardiology Foundation.

A family history of coronary artery disease (CAD) is a major risk factor of a poor clinical outcome (1). In epidemiological studies, premature onset CAD has been associated with a 2 to 3 times increased risk of CAD in first-degree relatives. Risk is inversely related to patient age at the first manifestation of CAD. Accordingly, the risk of a poor clinical outcome in first-degree relatives of patients with clinical CAD before 45 years of age may be more than 10-fold increased (2).

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Plaques causing myocardial ischemia or acute coronary syndromes (ACS) display unique compositional features (3). Vulnerable plaques are characterized by the presence of a lipid-rich necrotic core, a low content of calcified material, and extrinsic plaque remodeling (3-5). These features may be directly visualized and quantified noninvasively by coronary computed tomography angiography (CTA) (6). Accordingly, measurements of plaque burden and composition determined by coronary CTA have been proven to predict outcome beyond conventional anatomic coronary CTA readings (7-10).

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It has been demonstrated that the risk of having coronary artery calcium is increased in healthy individuals with a family history of CAD (11). However, data for measurements of subclinical CAD, beyond coronary artery calcium, are sparse. One study of asymptomatic first-degree relatives of patients with early onset CAD found subclinical plaques, assessed by coronary CTA, present in almost one-half of the relatives, with noncalcified plaque accounting for 70% to 90% of the total plaque burden in groups <65 years of age (12). However, no control group was present, and thus, it remains unknown whether a family history of CAD is associated with specific features of coronary atherosclerosis. Therefore, we aimed to assess plaque burden and composition by using coronary CTA in relatives with a family history of early onset CAD and compare them with controls without such predisposition.

METHODS

DESIGN AND STUDY POPULATION. The present study was a cross-sectional, single-center study. Patients who had undergone percutaneous coronary intervention or a coronary artery bypass graft procedure before the age of 40 at Aarhus University Hospital, Denmark (13), and did not have familial hypercholesterolemia, were requested to contact first-degree relatives between 30 and 65 years of age for participation in the present study. Exclusion criteria included known CAD, atrial fibrillation, an estimated glomerular filtration rate <30 ml/min, obesity (i.e., a body mass index >30 kg/m^2), known allergy to contrast, and pregnancy. A physician (M.K.C.) obtained information about medical history, current medication, smoking, and angina symptoms. Definitions of cardiovascular risk factors matched the criteria used in the Western Denmark Cardiac Computed Tomography Registry (14). Thus, hypertension and dyslipidemia were present if the relatives received medical treatment, and diabetes was present if diagnosed previously or if hemoglobin A1c (HbA1c) was >48 mmol/mol. Premature CAD was defined as CAD in males <55 years of age and in females <65 years of age. Current smoking was defined as any smoking within the past month, and angina symptoms were classified according to standard practice (15). Height and weight were measured, and the body mass index was calculated. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, HbA1c, and creatinine were measured. Estimated glomerular filtration rate and low-density lipoprotein cholesterol (LDL-C) were calculated. A systematic coronary risk evaluation (SCORE) was performed (16).

Control patients were identified from the Western Denmark Cardiac Computed Tomography Registry. The control group consisted of symptomatic patients without known CAD and without any family history of CAD (defined as absence of premature CAD in any first-degree family member). Eligible controls underwent calcium scoring and coronary CTA at the Department of Cardiology, Aarhus University Hospital, Denmark, between June 1, 2010, and April 15, 2015, on suspicion of CAD. For each relative, 1 control patient with the same age and sex was randomly chosen among eligible controls (**Figure 1**) using Stata/IC 13.1 software (Stata Corp., College Station, Texas). In controls, the updated Diamond-Forrester pre-test probability of significant CAD was calculated (17).

The study was approved by the National Committee on Health Research Ethics (record number: 1304078) and the Danish Data Protection Agency (record number: 1-16-02-480-13).

CT IMAGE ACQUISITION AND MANUAL ASSESSMENT. Coronary CTA was performed using a dual-source CT scanner (Somatom Definition Flash; Siemens, Forchheim, Germany) using an acquisition protocol previously described (18). Briefly, scans were performed with and without contrast. Coronary artery calcium was determined using the Agatston method (19). Sublingual nitroglycerin (0.8 mg) was administered prior to the contrast scan in all patients, and beta-blockers as needed, targeting a heart rate <60 beats/min. The same acquisition protocol was used for relatives and controls. Computed tomography images were manually evaluated by an experienced reader (J.M.J.) blinded to the clinical data. The Agatston score was recorded, and analysis of the coronary CTA was performed on segments ≥2 mm, using an 18-segment model (20,21). The number of evaluable segments was recorded, and segments

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CAD = coronary artery disease

CP = calcified plaque

CTA = computed tomography angiography

HDL-C = high-density lipoprotein cholesterol

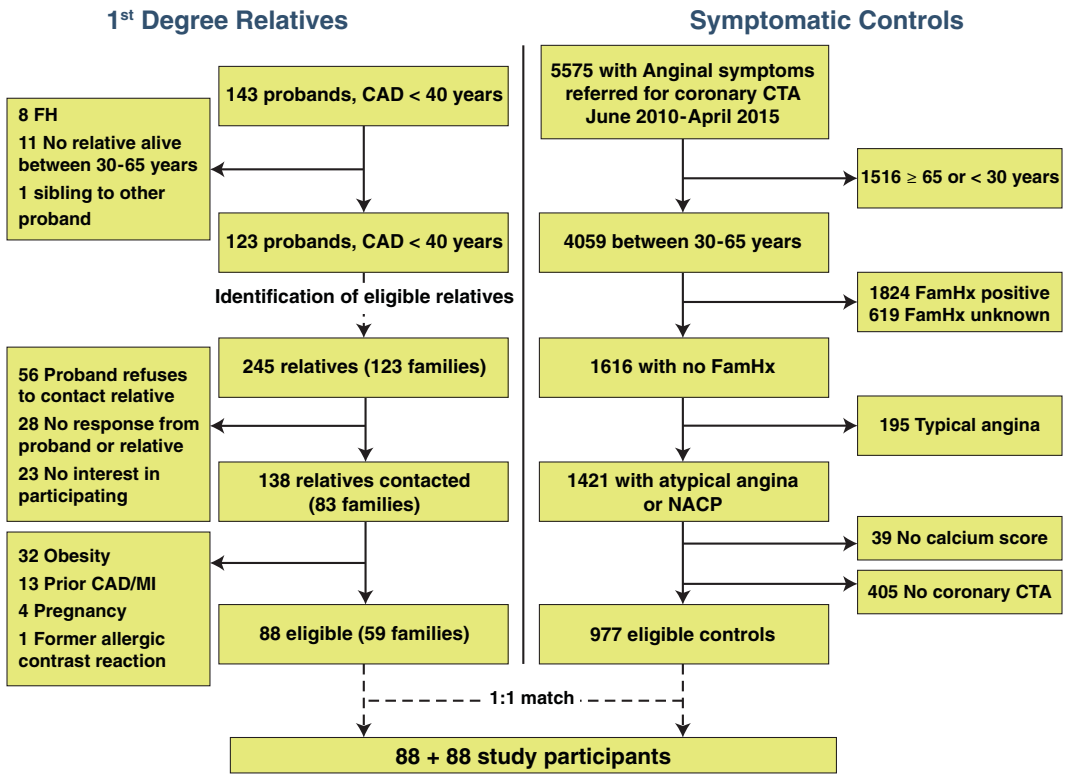
LDL-C = low-density lipoprotein cholesterol

LD-NCP = low-density noncalcified plaque

NCP = noncalcified plaque

SCORE = systematic coronary risk evaluation

FIGURE 1 Flow Diagram of Selection of Study Participants



CAD = coronary artery disease; CTA = computed tomography angiography; FamHx = family history of coronary artery disease; FH = familial hypercholesterolemia; MI = myocardial infarction; NACP = nonanginal chest pain.

with plaque were identified. A visual stenosis severity >50% was considered obstructive. Proximal CAD was defined as any CAD in the left main artery or any of the proximal segments of the left anterior descending, circumflexus, or right coronary artery (segment 1, 5, 6, or 11) (20).

SEMIAUTOMATED PLAQUE QUANTIFICATION. A semiautomated plaque analysis was performed by an experienced reader (M.K.C.) blinded to the clinical data, using Autoplaq software (Autoplaq version 9.7, Cedars-Sinai Medical Center, Los Angeles, California) (22). For each lesion, the proximal and distal center points of the plaque were manually identified in Autoplaq, using multiplanar coronary CTA images, followed by automated segmentation of plaque and vessel borders. Hence, vessel volume and volumes of calcified plaque (CP), non-CP (NCP), and low-density NCP (LD-NCP) (i.e., NCP plaque with attenuation <30 Hounsfield units) (4) were computed. Remodeling index was defined as the maximum vessel area at any point across the center line divided by the vessel area at the proximal plaque-free center point. Positive remodeling was defined as a remodeling index of ≥1.1 (23).

STATISTICAL ANALYSIS. Data are number and proportions, mean ± SD, or median (interquartile range [IQR]), as appropriate. Differences in patient characteristics and CT acquisition data between groups were compared using logistic, ordinal, or linear regression models, with robust variance estimation to account for the possible family clustering effect or using Somers' D with the clustering option specified. Outcome data (CAD metrics) were analyzed, measuring the total burden within each individual. Ordinal outcome variables were analyzed using ordinal logistic regression with robust variance estimation. For binary and continuous outcome variables, mixed-effects models were used, and continuous variables were log-transformed as log (variable + 0.5). The odds ratios (OR) or median ratios (as a measurement of the relative differences between groups) were compared. In adjusted analyses, age, sex, active smoking, hypertension, dyslipidemia, LDL-C, and number of evaluable segments were incorporated simultaneously.

Model validation was performed by inspection of QQ-plots for residuals and random effects and by drawing residuals against fitted values. Intraobserver variability of plaque characteristics was assessed by using Bland-Altman analysis in a random sample of 20 scans. Two-sided p values ≤0.05 were considered statistically significant. Statistical analyses were performed using Stata/IC 13.1 software.

RESULTS

A flowchart illustrating study inclusion is shown in Figure 1. In total, 88 relatives and 88 controls were included. Patient characteristics and a detailed overview of the number of relatives affected by CAD are presented in Tables 1 and 2, respectively. Age was 47.8 ± 7.9 years and 94 subjects (53%) were men. Relatives were at high-risk of CAD as all had a first-degree family member with early onset CAD, and 28 subjects (32%) had multiple affected first-degree family members (Table 2). Total cholesterol and HDL-C were higher among relatives than among controls, and lipid-lowering treatment tended to be more frequent among controls. Other characteristics were similarly distributed between groups. There were no differences between groups regarding coronary CTA acquisition characteristics (Table 3).

Three relatives reported nonanginal chest pain, and 1 relative reported dyspnea. One of these relatives had no CAD, and the 3 remaining relatives had nonobstructive CAD. When evaluated by SCORE, 42 relatives (48%) were categorized as low-risk (<1% 10-year risk of a fatal cardiovascular event), 42 (48%) were at intermediate-risk (1% to 4% 10-year risk), while 1 (1%) and 3 (3%) were at high-risk (5% to 9% 10-year risk) and very-high risk (≥10% 10-year risk), respectively. In controls, median pre-test probability of obstructive CAD was 25% (IQR: 14% to 38%).

In Table 4, CAD characteristics in relatives and controls are presented. The prevalence of CAD was higher in relatives than in controls, 62 (70%) versus 45 (51%), respectively (p = 0.016). In relatives, Agatston scores were higher, and CAD was more often associated with the presence of obstructive lesions and proximal locations than in controls.

Table 5 shows results of the semiautomated plaque analysis, and the plaque distributions are presented in Figure 2. Intraobserver agreement was excellent (Online Figure 1). The total plaque volume, total plaque length, and volumes of CP, NCP, and LD-NCP were significantly higher in relatives. Relatives were more likely to have 1 or more plaques with positive remodeling (crude OR: 2.4 [95% confidence interval (CI): 1.3 to 4.5], p = 0.004; adjusted OR: 4.2 [95% CI: 1.2 to 14.0], p = 0.021), as well as 1 or more plaques containing LD-NCP (crude OR: 2.5 [95% CI: 1.3 to 5.0], p = 0.008; adjusted OR: 4.2 [95% CI: 1.9 to 9.5], p = 0.001).

TABLE 1 Patient Characteristics

	Relatives (n = 88)	Controls (n = 88)	p Value
Age, yrs	47.8 ± 7.9	47.8 ± 7.9	-
Males	47 (53)	47 (53)	-
Antihypertensive treatment	14 (16)	24 (28)	0.106
Lipid-lowering treatment	13 (15)	23 (26)	0.068
Diabetes	3 (3)	6 (7)	0.322
Current smoking	20 (23)	27 (32)	0.163
BMI, kg/m^2			0.359
<18.5	1 (1)	0 (0)	
18.5–25.0	27 (30.7)	33 (38.4)	
25.0–30.0	60 (68.2)	36 (41.9)	
≥30.0	0 (0)	17 (19.8)	
Symptoms			-
Typical angina	0 (0)	0 (0)	
Atypical angina	0 (0)	56 (64)	
Nonanginal chest pain	3 (3)	26 (30)	
Dyspnea	1 (1)	6 (7)	
Total cholesterol, mmol/l	5.3 (4.6–5.8)	4.8 (4.3–5.6)	**0.046**
HDL-C, mmol/l	1.5 (1.2–1.7)	1.3 (1.1–1.6)	**0.009**
LDL-C, mmol/l	3.1 (2.4–3.7)	2.8 (2.3–3.6)	0.551
Triglycerides, mmol/l	1.4 (1.0–1.9)	1.5 (0.9–2.1)	0.983
e-GFR, ml/min	91 (80–107)	95 (85–107)	0.178

Values are mean ± SD, n (%), or median (interquartile range). Cholesterol values are treated or untreated combined. Information about blood pressure treatment, current smoking, BMI, total cholesterol, HDL-C, LDL-C, and triglycerides was missing in 1, 3, 2, 4, 7, 8, and 11 control subjects, whereas LDL-C was missing in 1 relative. Values in **bold** indicate p < 0.05.

BMI = body mass index; e-GFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCAD = premature coronary artery disease (men <55 years of age; women <65 years of age).

DISCUSSION

We compared coronary atherosclerotic burden and composition in first-degree relatives with a family history of early onset CAD with those in symptomatic controls referred for coronary CTA on a suspicion of CAD. Major findings included a higher total plaque

TABLE 2 Family History of CAD in Relatives

	First-Degree Relatives With CAD Onset <55/65 Years-of-Age in Males/Females
1 relative	60 (68)
2 relatives	17 (19)
3 relatives	9 (10)
4 relatives	2 (2)

Values are n (%).

CAD = coronary artery disease.

TABLE 3 CT Acquisition Characteristics

	Relatives (n = 88)	Controls (n = 88)	p Value
CT radiation dose, μGy/cm	226.5 (179.0–271.5)	196.5 (145.0–302.5)	0.139
Heart rate, beats/min	58 ± 7	59 ± 8	0.112
Beta-blockers	73 (83)	68 (77)	0.395
Number of diagnostic segments	13 (12–14)	13 (12–14)	0.689

Values are median (interquartile range), mean ± SD, or n (%). Information on beta-blocker treatment was missing in 1 control subject.

CT = computed tomography.

burden with higher volumes of CP, NCP, and LD-NCP in relatives compared with controls.

The extent of CAD in relatives was remarkable. The prevalence of proximal CAD, obstructive CAD, and involvement of ≥5 segments with CAD were 1.5 to 2 times higher in relatives than in controls (57% vs. 38%, 15% vs. 10%, and 25% vs. 14%, respectively). The prevalence of obstructive CAD in relatives in this study is in accord with that in an investigation of middle-aged asymptomatic individuals with a sibling or parental history of CAD <60 years of age, which demonstrated prevalence of obstructive CAD, as assessed by coronary CTA, ranging from 5% among women in the Framingham low-risk category to 21% in men categorized as intermediate risk (12). The present study adds to these findings by showing that the burden of various metrices of CAD is increased in relatives of patients with overt CAD compared with controls without such predisposition. Of note, the control group in the present study consisted of patients with atypical angina or nonanginal chest pain rather than asymptomatic individuals in whom a lower prevalence of CAD would be expected. In a large-scale observational study of self-referred, middle-aged, asymptomatic individuals in South Korea (24), the prevalence of any CAD and obstructive CAD were 22% and 5%, respectively. Although caution should be used when making direct comparisons due to different ethnicities, those proportions are markedly lower than the 70% and 15%, respectively, observed in relatives in the present study. Compared with other populations at increased cardiovascular risk, our findings are comparable to those of 64% and 17%, respectively, reported in asymptomatic diabetic patients more than 10 years older than the cohort in the present study (25), those of 48% to 85% and 19% to 26% found in middle-aged patients with familial hypercholesterolemia (26,27), and those of 48% to 62% and 18% to 26% in cohorts of stroke patients 15 to 19 years older without prior CAD (28,29). Thus, the present findings indicate that the risk of CAD associated with a genetic predisposition is comparable to the risk conveyed by known risk factors such as diabetes, familial hypercholesterolemia, and stroke.

TABLE 4 Visual Assessment of CAD

	Relatives (n = 88)	Controls (n = 88)	p Value
Number of affected coronary segments			**0.001**
0 segments	26 (30)	43 (49)	
1–2 segments	24 (27)	28 (32)	
3–4 segments	16 (18)	5 (6)	
≥5 segments	22 (25)	12 (14)	
Severe CAD			**0.017**
No CAD	26 (30)	43 (49)	
Nonobstructive CAD	49 (56)	36 (41)	
Obstructive CAD	13 (15)	9 (10)	
Proximal CAD			**0.011**
No proximal CAD	38 (43)	55 (63)	
Nonobstructive proximal CAD	42 (48)	29 (33)	
Obstructive proximal CAD	8 (9)	4 (5)	
Agatston Score	4.1 (1.9–8.0)	1.0 (0.5–1.8)	**0.004**

Values are n (%) or median (95% confidence interval). Agatston scores were derived from log (Agatston score + 0.5)-transformed values to account for the skewed distributions and zero. Values in **bold** indicate $p < 0.05$.

Nonobstructive CAD = stenosis severity ≤50% based on expert reader visual assessment. Obstructive CAD = stenosis severity >50% based on expert reader visual assessment. Proximal CAD = CAD involving the left main artery or any of the proximal segments of the left anterior descending, circumflexus, or right coronary arteries (segments 1, 5, 6, and 11). Abbreviation as in Table 2.

We observed an approximate 5-times increase in total plaque volume in relatives compared with controls. It has been demonstrated that total plaque volume and total NCP predict future ACS more accurately than conventional coronary CTA readings alone (8). Histologically, high-risk plaques have been identified as fibroatheromas with a thin cap and various degrees of a lipid-rich necrotic core (3). In studies using intravascular ultrasonography, LD-NCP has been shown to reflect lipid cores (4). In the absence of a lipid core, the risk of adverse cardiovascular events is low (3,7,30,31). The adjusted odds ratio of having an LD-NCP-containing plaque and a plaque featuring positive plaque remodeling was 4-fold higher in relatives than in controls. Presence of LD-NCP and positive plaque remodeling have been associated with adverse cardiac events in patients undergoing coronary CTA for suspected or known CAD (7,9) and, thus, may potentially explain the increased risk of ACS in people with a family history of CAD. However, outcome studies are needed in order to corroborate this hypothesis.

Obstructive CAD, positive plaque remodeling, and LD-NCP have all been shown to be independent

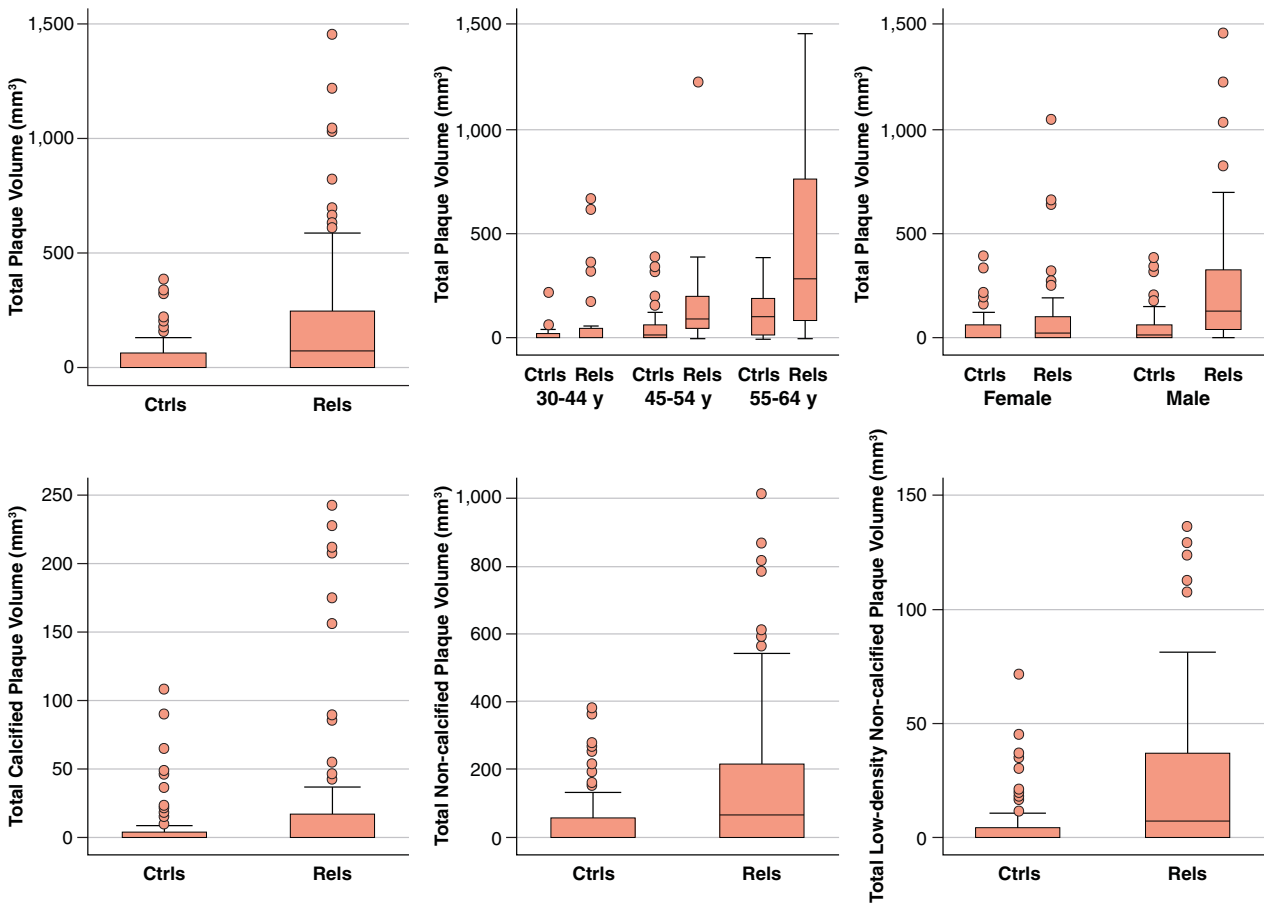
TABLE 5 Assessment of Total Plaque Burden

	Crude				Adjusted			
	Relatives Median (95% CI)	Controls Median (95% CI)	Median Ratio (95% CI)	p Value	Relatives Median (95% CI)	Controls Median (95% CI)	Median Ratio (95% CI)	p Value
Total plaque volume, mm^3	27.0 (14.2–51.0)	5.3 (2.9–9.5)	4.7 (2.1–10.8)	<0.001	29.2 (17.8–47.6)	4.7 (2.6–8.2)	5.8 (2.8–11.9)	**<0.001**
Total plaque length, mm	8.6 (5.2–14.0)	2.4 (1.5–3.8)	3.2 (1.7–5.8)	<0.001	9.1 (6.3–13.2)	2.2 (1.3–3.4)	3.6 (2.1–6.1)	**<0.001**
Total CP, mm^3	2.6 (1.4–4.7)	0.9 (0.5–1.4)	2.3 (1.2–4.2)	0.009	2.8 (1.6–4.6)	0.8 (0.4–1.2)	2.6 (1.5–4.5)	**<0.001**
Total NCP, mm^3	24.3 (13.1–44.9)	4.8 (2.6–8.4)	4.7 (2.1–10.6)	<0.001	26.3 (16.2–42.5)	4.1 (2.2–7.2)	5.8 (2.9–12.0)	**<0.001**
Total LD-NCP, mm^3	5.2 (3.1–8.6)	1.2 (0.7–1.8)	3.4 (2.0–6.0)	<0.001	5.5 (3.6–8.2)	1.0 (0.6–1.5)	4.0 (2.5–6.6)	**<0.001**

Adjusted for age, gender, active smoking, hypertension, dyslipidemia, LDL-C, and number of evaluable segments. Estimates are derived from log (variable + 0.5)-transformed values to account for the skewed distributions and zeros. Values in **bold** indicate $p < 0.05$.

CI = confidence interval; CP = calcified plaque; LD-NCP = low-density noncalcified plaque; NCP = noncalcified plaque.

FIGURE 2 Distributions of Plaque and Plaque Subcomponents



Boxes indicate quartiles, and **whiskers** display adjacent values. Values outside range of adjacent values are plotted as outliers. **(Top left)** Total plaque volume in relatives and controls. **(Top middle)** Total plaque volume in relatives and controls stratified by age. **(Top right)** Total plaque volume in relatives and controls stratified by sex. **(Bottom left)** calcified plaque in relatives and controls. One outlier (Relative; total calcified plaque volume: 590.2 mm^3) was removed from the graph for illustrative purposes. **(Bottom middle)** noncalcified plaque in relatives and controls. **(Bottom right)** low-density noncalcified plaque in relatives and controls. Ctrls = controls; Rels = relatives.

predictors of myocardial ischemia (10,21), and therefore, it may seem surprising that the prevalence of these measurements were increased in relatives compared with those in symptomatic controls. The findings, however, are in accord with those of a previous study in asymptomatic middle-aged siblings of patients with CAD onset <60 years of age, demonstrating an 18% prevalence of silent myocardial ischemia determined by nuclear perfusion imaging. Of note, in the latter study, the presence of silent ischemia was associated with an adverse long-term prognosis (32).

Our findings of severe CAD with high-risk features in relatives of patients with early onset CAD potentially is related to the increased risk of subsequent clinical outcomes, however, they do not explain the underlying pathophysiological mechanisms. Those are likely heterogeneous requiring various contributions of an inherited lifestyle and adverse genetic variants of various effect sizes for disease to develop (33). At the general population level, a substantial proportion of this susceptibility may act through pathways of conventional risk factors, and hence, the family history may add little incremental value to current risk assessment models (34). However, this is most likely not the explanation of the higher CAD burden in relatives in this study, as the prevalence of conventional risk factors were equal to or tended to be lower than those of controls. Although hypertension and dyslipidemia were defined as receiving treatment, and therefore could potentially be underdiagnosed in relatives volunteering for participation, it should be acknowledged that most relatives in our study were in the low-to-intermediate SCORE risk category. Thus, they did not qualify for preventive medical treatment (16).

STUDY LIMITATIONS. The single-center and cross-sectional study design has inherent limitations, which potentially may impair the generalizability of the findings. Thus, our analyses should be interpreted as exploratory, and causal relationships cannot be documented. Because of lack of follow-up, we cannot determine whether the high-risk features observed in relatives affect clinical outcomes. In the present study, lipid-lowering treatment tended to be more commonly used in controls and thus lipid levels differed between groups. These differences may potentially have influenced our findings. Interobserver variability of the Autoplaq software was not evaluated in the present study, but that has previously been reported by other studies (21,35). Although the present study may prove the presence of a significant burden of CAD in relatives with a family history of CAD, the size of the differences between the groups is reflected by the choice of symptomatic controls. Estimating the true effect size of a family history of CAD will require further studies using asymptomatic control individuals.

CONCLUSIONS

Healthy relatives of patients with early onset CAD have a high coronary plaque burden and display more unfavorable plaque features compared with symptomatic patients. Larger clinical outcome studies are needed to delineate the increased risk of CAD in relatives to patients with CAD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The burden of coronary atherosclerosis in healthy first-degree relatives of patients with early onset CAD is increased. The observed plaque characteristics have previously been associated with an increased risk of ACS. The findings may explain the increased risk of coronary events in patients with a strong family history of CAD.

TRANSLATIONAL OUTLOOK: The information on plaque burden and composition in patients with a strong family history of CAD may provide a better understanding of the inheritance of the disease. Larger outcome studies are needed to evaluate the genetic basis and clinical implications of these findings.

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KEY WORDS atherosclerosis, composition, coronary artery disease, genetic predisposition to disease, multidetector computed tomography, plaque

APPENDIX For supplemental figures and material, please see the online version of this article.