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Noncalcified Coronary Plaque Volumes in Healthy People with a Family History of Early-Onset Coronary Artery Disease

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Abstract

Background—Although age and sex distributions of calcified plaque (CCP) have been well described in the general population, noncalcified plaque (NCP) distributions remain unknown. This is important because NCP is a putative precursor for clinical CAD and could serve as a sentinel for aggressive primary prevention, especially in higher risk populations. We examined the distributions of NCP and CCP in healthy 30-74 year old individuals from families with early-onset coronary artery disease (CAD).

Methods and Results—Participants in the GeneSTAR family study (N=805), mean age 51.1 ± 10.8 years, 56% female, were screened for CAD risk factors and for coronary plaque using dual-source CT angiography. Plaque volumes (mm^3) were quantified using a validated automated method. The prevalence of coronary plaque was 57.8% in males and 35.8% in females ($p<0.0001$). NCP volume increased with age ($p<0.001$) and was higher in males than females ($p<0.001$). Although NCP, as a percent of total plaque, was inversely related to age ($p<0.01$), NCP accounted for most of the total plaque volume at all ages, especially in males and females <55 years (>70% and >80%, respectively). Higher Framingham risk was associated with the number of affected vessels ($p<0.01$) but 44% of males and 20.8% of females considered intermediate risk had left main and/or 3-vessel disease involvement.

Conclusions—The majority of coronary plaque was noncalcified, particularly in younger individuals. These findings support the importance of assessing family history and suggest that early primary prevention interventions may be warranted at younger ages in families with early onset CAD.

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Keywords

atherosclerosis; plaque distribution; CT angiography; family study; asymptomatic

ECG gated noncontrast computed tomography is routinely used to quantify calcified coronary plaque (CCP) to assess coronary artery disease (CAD) risk in higher risk healthy populations. CCP is associated with CAD risk factors, particularly male sex and older age, and is generally less useful in younger people [1, 2]. Coronary plaque calcification is a late manifestation of atherosclerosis [3]. Earlier stages of atherogenesis are represented by noncalcified or mixed composition plaques containing extracellular lipid and fibrous tissue [4, 5] and are particularly prone to plaque rupture, thrombosis, and acute CAD events [6, 7]. Thus, CCP on noncontrast CT imaging is used as a marker for subclinical CAD and as a proxy for the extent of atherosclerosis. However, because this method cannot detect noncalcified plaque (NCP) [8, 9] it does not necessarily reflect the true extent of coronary artery plaque [10]. The extent of subclinical NCP, a putative precursor for CAD events, may have important implications for primary prevention, especially in younger people from higher risk populations.

Familial-clustered CAD accounts for ~60% of all CAD prior to 65 years of age [11-13]. A positive family history of early-onset CAD in a parent or sibling is associated with a markedly increased risk of CAD events [11, 14]. Apparently healthy adults from these families have a high prevalence of inducible ischemia by myocardial perfusion imaging [15] but the extent of total coronary plaque and NCP remains unknown. To date only coronary calcium scores have been studied, with higher levels found in persons from families with early-onset CAD[16, 17]. Because plaque vulnerability is so closely linked to incident CAD events and NCP is more likely to represent vulnerable plaque, we designed this study to examine the true extent of total coronary plaque, inclusive of NCP, using multidetector computed tomographic angiography (CTA) in healthy asymptomatic members of early-onset CAD families.

Methods

Sample and Recruitment

Participants (n=805) were randomly selected and then recruited (92% of those invited participated) from the larger ongoing Genetic Study of Atherosclerosis Risk (GeneSTAR), a prospective study of 4000 individuals designed to characterize genetic and biological factors associated with cardiovascular disease phenotypes in 883 families with early-onset coronary heart disease. Probands <60 years of age with documented acute myocardial infarction, unstable angina with coronary revascularization, or acute angina with angiographic evidence of a flow-limiting stenosis of >50% diameter in at least one coronary artery were identified during hospitalization and excluded. Apparently healthy siblings and the offspring of the probands and siblings were eligible if they were 30 to 75 years of age and had no known personal history of CAD. Siblings and offspring were excluded if they had systemic autoimmune disease, known allergy to iodinated contrast media, or chronic kidney disease.

The study was approved by the Johns Hopkins Medicine Institutional Review Board and all participants gave informed consent.

Participant Screening

Participants underwent a comprehensive risk factor screening following a 12-hour overnight fast. Medical history, pedigree and family history information, and current medication use were elicited. A physical exam was performed by a study physician. Height was determined using a fixed stadiometer and weight was measured on a balance scale with the subject wearing light clothing and no shoes. Body mass index (BMI) was calculated as kg/m^2. Current cigarette smoking behavior was assessed by self-report and verified by expired carbon monoxide (CO) levels of ≥8 ppm. Blood pressure was measured according to the American Heart Association guidelines three times over the course of the day. Hypertension was defined as an average blood pressure ≥140 mmHg systolic, or ≥90 mmHg diastolic, and/or use of an antihypertensive drug. Blood was obtained and total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured using the United States Centers for Disease Control standardized methods [18]. Low-density lipoprotein (LDL) cholesterol was estimated using the Friedewald formula [19] for persons with triglyceride levels up to 400 mg/dl. Direct measurement of LDL cholesterol using ultracentrifugation was used for persons with triglyceride levels ≥4.52 mmol/l (400 mg/dL) (n=5). Glucose concentration was measured using the glucose oxidase method; [20] type 2 diabetes was defined as a physician diagnosed history, a fasting glucose level ≥6.99 mmol/l (126 mg/dl), and/or use of prescribed hypoglycemic medications. We calculated the 10-year Framingham Risk Score (FRS) to categorize siblings as low risk (<10%), intermediate risk (10-20%), or high risk (≥20%) for total CAD events based on their risk factor levels [21].

Assessment of Subclinical Coronary Plaque

All participants underwent coronary CTA using a newest generation dual-source multi-detector scanner (SOMATOM Definition Flash, Siemens Medical Solutions, Forchheim, Germany). Because of the high temporal resolution and excellent image quality of the scanner, beta-blockade was not necessary for reducing the heart rate [22]. A noncontrast scan was first performed to determine the coronary artery calcium volume as well as the traditional Agatston score. Subsequently coronary CTA was performed to examine the presence, location, composition, and severity of any coronary plaque. Approximately 80 mL of isosmolar contrast agent (320 mg iodine/mL) was injected at 6 mL/s. Prospective ECG-gating was used in patients with low, steady heart rates (<65 bpm) and little heart rate variability. For patients with variable heart rates or heart rates >65 bpm, retrospective gating with dose modulation was used. Tube potential was selected on a per patient basis by the performing technologist assessment of patient size; 100 kV was used for patients that were not overweight or obese, otherwise 120 kV was used. We reconstructed 0.75-mm thick axial slices at 0.4-mm intervals with a B26 kernel; 10 reconstructions were done at 10% increments in the R-R interval. All scans were evaluated with the CT radiologist blinded to the participants' risk factor profiles. The coronary arterial tree was segmented according to the standard American Heart Association classification,[23] and the segments were investigated for plaque and luminal narrowing. Any focal stenoses >50% in severity were

identified with the use of quantitative software (COR Analyzer System, Rcadia Medical Imaging, Haifa, Israel) [24, 25] and verified by the expert reader.

Quantitative Plaque Volumes

The volume of CCP was measured on a workstation (Leonardo Multimodality Workstation, Syngo, Siemens Medical Solutions, Malvern, PA) using noncontrast images. Regions of interest were placed over each of the coronary arteries and a threshold of >130 HU was used for determining per vessel volumes of CCP (mm^3) using standard validated methods [26, 27]. Vessel CCP volumes were summed for a total CCP volume. A total Agatston score was also determined using standard methods [28].

For each affected coronary segment, noncalcified plaque volumes (mm^3) were quantified using AUTOPLAQ (Cedars-Sinai Medical Center, Los Angeles, CA), as previously described [29]. This automated method of NCP measurement has high interobserver correlation (r=0.97) [30], and has been previously validated against intravascular ultrasound (IVUS)[29]. For the present study, we also found excellent reproducibility for measured NCP volumes (intraobserver r=0.99, mean percent error 3.6%) based on two blinded reads performed 6-12 months apart on a random sample (N=30). To quantify each affected segment, CTA images were examined in multiplanar format and proximal and distal limits of the plaque were manually marked. Control points defining the lumen center-line were placed. Subsequent NCP plaque quantification was then fully automated using adaptive algorithms that are scan specific per individual [29]. Segmental NCP volumes were summed for a total NCP volume per vessel, including the left main (LM), left anterior descending (LAD), left circumflex (LCX), and right coronary arteries (RCA). The vessel specific volumes were summed for a total NCP volume. Total coronary plaque (TCP) was calculated as the sum of CCP + NCP. The percent of total plaque consisting of NCP and CCP was calculated by dividing by TCP for each. For stenoses >50% in severity, plaques were classified as noncalcified (no calcium), calcified (>50% volume calcified plaque), or mixed (≤50% volume calcified plaque), based on the quantified volumetric measurements.

Statistical Analyses

Standard descriptive analyses were used to examine distributions of sociodemographic and CAD risk factor variables. The Kolmogorov-Smirnov statistic was used to test for normality of continuous variables. The median and interquartile range of NCP and CCP volumes, as well as the relative amount of NCP and CCP to total plaque volume, were examined by age and sex in subjects with coronary plaque. Total coronary plaque was transformed as log [TCP + 0.5(minimum)], given the non-normal distribution and presence of zero plaque in many individuals. Standard multivariable regression analyses were performed predicting plaque outcomes using the Generalized Estimating Equations (GEE) to account for nonindependence within families. The Cochran Armitage Trend test was used to examine trends across Framingham Risk categories for the prevalence of plaque, including by vessel location, and stenoses >50%. Given the variability of strength of family history within families, we used pedigree information in separate analyses in a subset of full siblings of affected probands to determine the incremental effect of strength of sibling history on subclinical coronary plaque burden. TCP volumes in participants with a greater number of

siblings affected with clinically manifest CAD (strong family history, defined as ≥50% of siblings in the family) were compared to those with a lesser sibling history (only the proband or <50% of siblings affected in the family). A multivariable GEE regression model controlled for age, sex, race, current smoking, hypertension, diabetes, LDL cholesterol, statin medication use, and within family correlations. Logistic regression predicting any stenoses >50% was performed with the same dependent variables and inclusion of the transformed CCP, NCP, or TCP volumes, and the area under the curve (AUC) calculated.

Results

Population Demographics and Presence of Coronary Plaque

The study population consisted of 805 apparently healthy individuals identified from 388 families with the onset of CAD <60 years of age (one index case per family, 2.1 ± 1.5 participants per index case). Study participants were siblings (n=424) of the index patient or adult offspring of the index patient or the siblings (n=381). The sample was 56.1% female and 39.2% African American. All were healthy and without any chest pain or angina-equivalent symptoms. Overall, 45.5% of the total population had subclinical coronary plaque, including 5.5% with exclusively NCP without any CCP. Population demographics and CAD risk factors by the presence or absence of any coronary plaque are shown in Table 1. Coronary plaque was significantly associated with older age, male sex, white race, hypertension, diabetes, lower HDL cholesterol and higher triglyceride levels. There was no difference in mean LDL cholesterol levels but subjects with plaque were more likely to be taking a statin medication, suggesting that subjects with plaque had an a priori higher LDL cholesterol levels that triggered initiation of statin therapy. Subjects with plaque had a significantly higher 10-year mean Framingham Risk Score than those without plaque but overall most subjects were in the low Framingham risk group.

Prevalence of Coronary Plaque

Figure 1 shows the prevalence of coronary plaque for males and females by age. The prevalence of coronary plaque increased with age in both males and females ($p<0.0001$ for both). The prevalence of coronary plaque was significantly higher in males at all age ranges until after age 65 years when both sexes had a prevalence >80% ($p<0.0001$ and $p=0.08$, respectively). Even in the youngest age group 30 to 45 years, nearly one quarter of males had plaque, increasing to nearly 60% in those 45 to 54 years. Using calcium scoring alone, 39.8% of all participants were identified as having plaque, whereas the addition of NCP information from the CTA identified 45.2% of the population as having plaque. The additive value of CTA varied by age, sex and race. Of the 364 persons with plaque on CTA, 87.9% had plaque on CAC screening, yielding an incremental identification of plaque by CTA of 12.1% overall.

Age and Sex Distribution of Noncalcified and Calcified Plaque Volumes

Of those subjects with coronary plaque, females were twice as likely to have exclusively NCP compared to males, (16.8% vs 8.3%, $p= 0.01$). The volumes of NCP and CCP by age and sex in subjects with plaque are shown in Table 2. NCP volume was strongly associated with older age and male sex, $p<0.0001$ for both. CCP volume was also associated with older

age and male sex, <0.0001 and p=0.0002, respectively. The total Agatston score is shown for comparison with calculated CCP volumes. Agatston scores were highly correlated with CCP volumes (r=0.98) with similar distributions by age and sex.

Figure 2 shows the composition of total plaque volume by age and sex in subjects with plaque. NCP accounted for more than half of TCP in both sexes at all ages and represented more than 75% of TCP in men, and 80% in women <55 years of age. NCP, as a percent of TCP, was significantly and inversely related to increasing age in both men and women (p<0.01). Adjusting for age, the percent of TCP that was non-calcified tended to be higher in females (p=0.06).

Multivariable regression analysis controlling for age, sex, race, statin medication use, and intrafamilial correlation was performed for the transformed volumes of TCP. Covariates in the model included LDL cholesterol level, body mass index, and the presence of hypertension, diabetes, and current smoking behavior. All modifiable risk factors were independently associated with TCP, including the presence of hypertension (p=0.005), diabetes (p=0.05), and current smoking behavior (p=0.0004), as well as higher LDL cholesterol levels (p=0.02). Higher body-mass-index showed a near significant association (p=0.08).

Using the family design of this study to examine the significance of family history to TCP, we examined TCP volumes in a subset of 338 full siblings of affected probands with a strong sibling history (n=49) compared to those with a lesser sibling history (n=289). In this subset, subjects were 58.9±7.4 years of age (range 36 to 74); 55% female; 36% African American. Subjects with a strong sibling history (n=49) were 3.0 times (95% CI 1.3–6.6) more likely to have any coronary plaque and had markedly greater volumes of all forms of plaque than those with a lesser sibling history (n=289) (Table 3). A strong sibling history remained a significant independent predictor of TCP volume when adjusted for all other variables in multivariate GEE regression analysis.

Distributions of Plaque Characteristics by Framingham Risk

The sex-specific distributions of plaque characteristics by 10-year FRS categories are shown in Table 4. The majority of men and women were low FRS (72% and 88%, respectively), or intermediate-risk (20% and 11%, respectively). Although higher FRS was associated with a higher prevalence of plaque and more vessels involved, there was a high prevalence of plaque even in low or intermediate FRS men, with approximately 50% and 75% affected, respectively. Similarly over 30% of low-risk and 50% of intermediate risk women had plaque. Three vessel and/or left main involvement occurred in nearly 15% of low risk men and over 40% of intermediate risk men. Plaque was most prevalent in the LAD in both sexes. In intermediate risk men and women, LAD plaque was present in 70% and 50%, respectively. Nearly one quarter of intermediate risk males had measurable disease in the LM coronary artery. The overall prevalence of at least one stenosis >50% in severity was approximately 8% and 21% in low and intermediate risk males, respectively, and was composed primarily of mixed plaques containing both NCP and CCP. Given that 39% of subjects with coronary plaque and 15% of subjects without coronary plaque were taking statin medications, we performed the same analyses in 254 males (n=124 with plaque) and

342 females (n=98 with plaque) who were not taking statin medications and found similar sex-specific distributions of FRS categories and the same significant trends for the prevalence of plaque phenotypes across FRS categories. Although this was a cross-sectional study and the incremental value of CTA over coronary calcium alone for clinical outcomes is yet to be determined in this population, noncalcified plaque volume was significantly associated with the presence of at least one stenosis >50% ($p<0.0001$), independent of all traditional risk factors. Total plaque volume improved the AUC from 0.87 to 0.90 compared to the Agatston Score alone ($p=0.04$).

Discussion

In this first study of the age and sex distributions of noncalcified coronary plaque in healthy men and women from families with early-onset CAD, we found a strikingly high prevalence of coronary plaque, even in participants under 45 years of age. Importantly, noncalcified plaque was more prevalent than calcified plaque, particularly in those <55 years of age, in whom 75-80% of plaque was noncalcified. It is noteworthy that coronary calcium may markedly underestimate the total plaque burden in this population. In addition, we found a high prevalence of triple vessel and/or left main artery plaque. This is particularly striking considering that the majority of participants had a low or intermediate FRS. Finally, we were able to demonstrate that strength of sibling history was an independent predictor of the presence and extent of total coronary plaque. These findings suggest that conditioning aggressive primary prevention on traditional coronary calcium scoring algorithms or on the Framingham Risk Score, which does not include family history, may obviate appropriate risk reduction interventions in high risk individuals, such as young men and women with a family history of early-onset CAD.

Although a positive family history of CAD has been independently associated with higher coronary calcium scores[16, 17], there is a paucity of data regarding the prevalence of NCP in asymptomatic populations with a few studies reporting on older, higher-risk individuals referred to CTA for clinical suspicion of CAD[31, 32] or in Asian populations[33]. We did not have a control population for a direct comparison of NCP, but the degree of age, sex, and race specific coronary calcification using the Agatston Score was notably higher than that observed in the Multi-Ethnic Study of Atherosclerosis (MESA)[34]. Importantly, given the excess risk of incident CAD already demonstrated in the GeneSTAR family population[35] and their concomitant higher rates of silent myocardial ischemia on stress myocardial perfusion imaging[15], it is most likely that the prevalence and amount of noncalcified and total coronary plaque are also greater than would be seen in the general population. Moreover, strength of sibling history of early-onset CAD was independently associated with TCP volumes, highlighting the fact that family history is an important determinant of our findings. The classification by sibling history into lesser vs. greater family risk was in part based on previous studies showing that ≥2 affected first-degree relatives conveys the highest risk[36, 37]. Further studies using continuous comprehensive family history scores are needed to support heritability of NCP.

Multiple studies have shown that the presence of CCP in asymptomatic individuals from the general population is associated with incident CAD events [38-40]. However, calcium scores

reflect the stage of plaque progression and maturity [3], and do not necessarily reflect the true atherosclerotic burden [10] or the degree and location of coronary stenoses [41], especially in younger individuals. Vulnerable coronary plaques have been thought to be predominantly noncalcified and nonstenotic [6, 7] and the presence of such noncalcified plaques on CTA are correlated with acute coronary syndromes [42]. The observed high prevalence of NCP in our study in subjects at young ages could reflect a more aggressive process of early-onset vascular aging; this may at least in part explain the higher CAD event rates observed at younger ages in populations with a strong family history of early-onset CAD [35, 43].

CTA tends to overestimate calcified plaque and underestimate noncalcified plaque when compared to IVUS [44]. Most studies report the burden of coronary calcium using the Agatston scoring system which is calculated by multiplying the lesion area by a weighted attenuation coefficient, derived to better reflect overall plaque burden and disease severity [28]. We used the calcium volume score representing actual CCP volumes (mm^3) for comparison with NCP (mm^3). This method has improved reproducibility with significantly less interscan variablility than the Agatston scoring method, especially with lower levels of CCP [45, 46]. However, calculated CCP volumes tend to overestimate true CCP volumes at higher plaque densities and thus our results likely underestimate the relative extent of NCP to total plaque[46].

Our findings highlight the importance of family history in the development of aggressive coronary artery disease at young ages. However, current primary prevention guidelines still do not provide specific recommendations for individuals with a family history of early-onset coronary disease. Although most subjects in the current study were low or intermediate risk using the FRS, traditional modifiable risk factors were significantly associated with higher total coronary plaque volumes independent of age and sex, suggesting a role for earlier aggressive risk factor modification in apparently healthy persons from high-risk families. However, longitudinal studies are needed to further elucidate the significance of NCP volumes and characteristics, in vulnerable asymptomatic populations. Thus we would not recommend expensive screening for NCP using CTA at this time. However, CTA is a promising modality to improve upon CCP screening, especially now that low-radiation dose CTA allows for screening of both NCP and CCP at near equivalent radiation doses as CAC screening alone.[47]

Conclusion

Apparently healthy men and women from families with early onset CAD have a high prevalence of subclinical CAD, composed primarily of noncalcified plaque. These findings highlight the importance of screening for family history and the implementation of primary preventive interventions at younger ages in both men and women with a family history of early-onset CAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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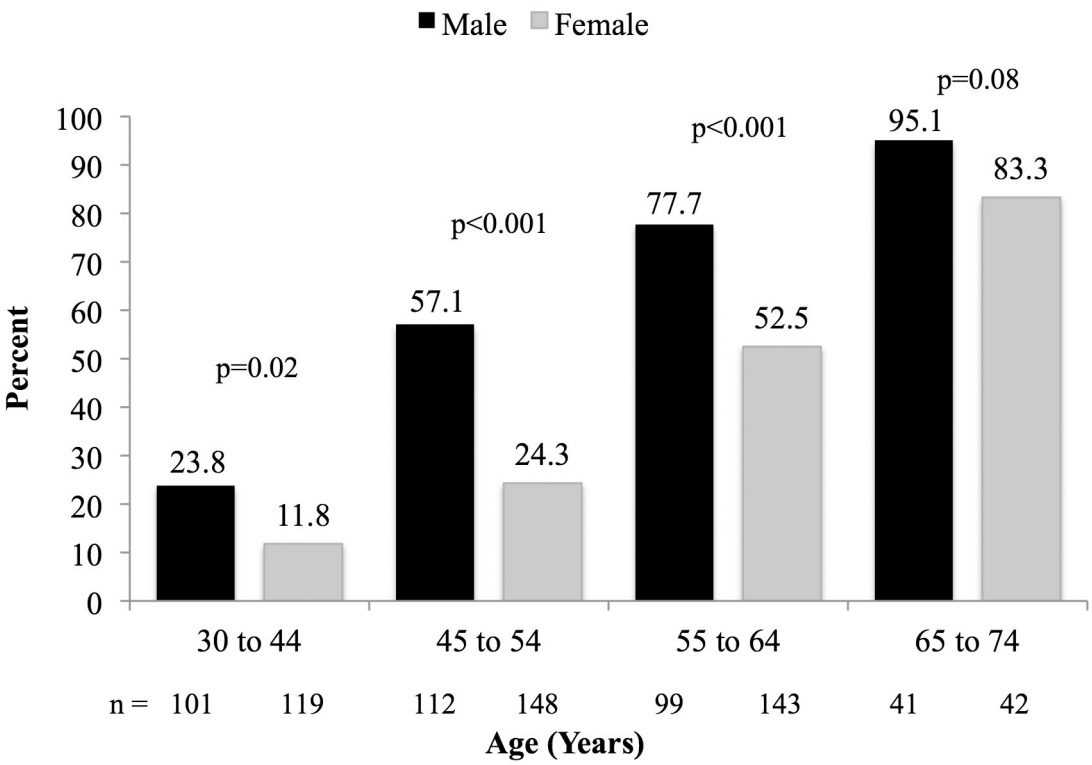

Figure 1. Prevalence of totoal plaque by age* and sex† (N=805)

* p <0.0001 for age trend in both males and females

† p <0.0001 for overall sex differences by age group (ANOVA)

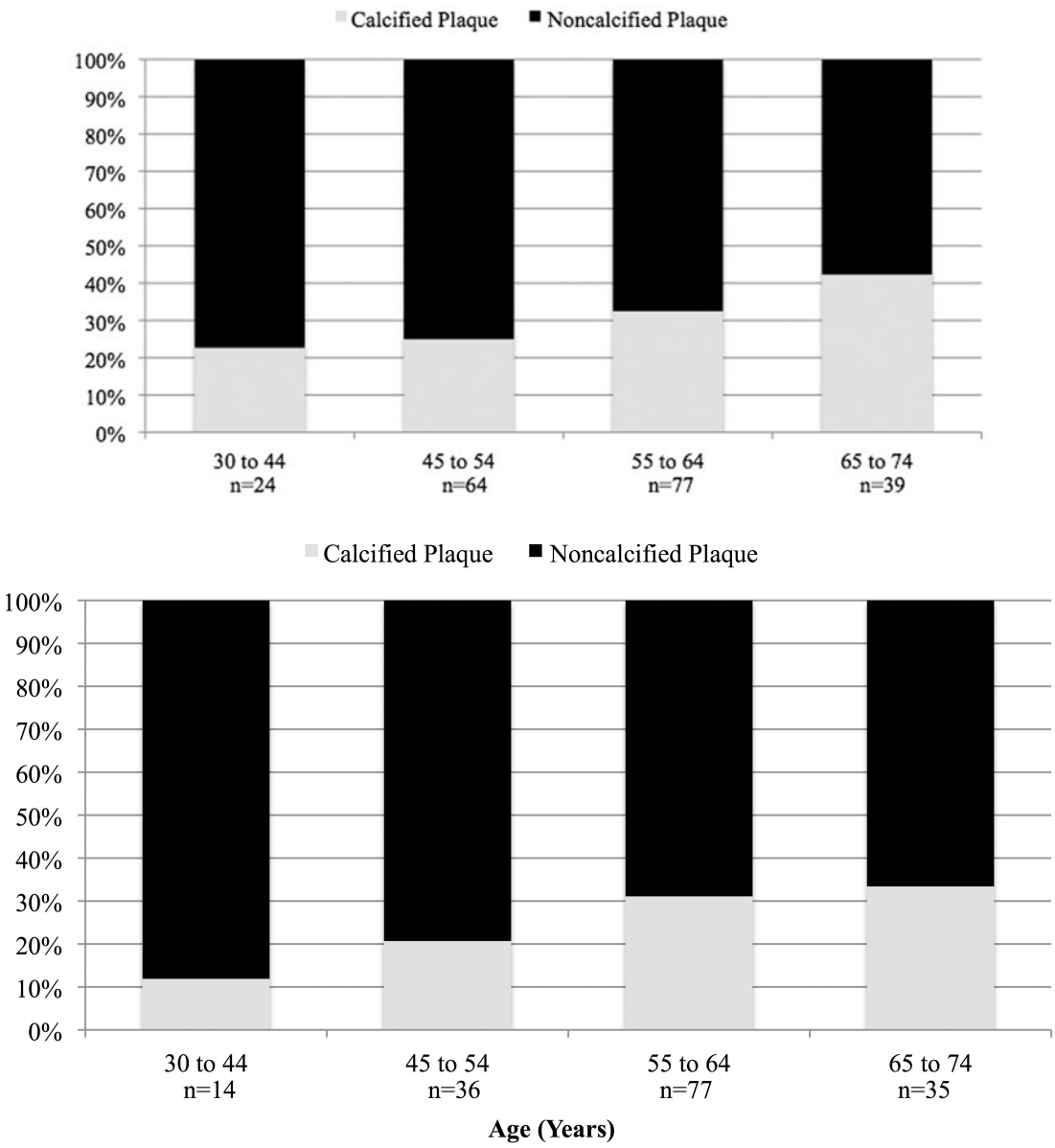

Figure 2. Percent Coronary Plaque Volumes by Composition, Age, and Sex in Subjects with Plaque

A. Male (N=204)

*p<0.0001 for percent calcified plaque with increasing age group

B. Female (N=162)

*p=0.007 for percent calcified plaque with increasing age group

Table 1

Population demographics and coronary artery disease risk factors by the absence or presence of coronary plaque (N=805)*

	Plaque Absent (N=439)	Plaque Present (N=366)	p-value
Age, years	46.4 ± 9.7	56.8 ± 9.0	<0.0001
Female sex, %	64.2	35.8	<0.0001
African American, %	41.5	34.4	0.04
Hypertension, %	30.6	57.9	<0.0001
Diabetes, %	8.0	15.9	0.0005
Current smoking, %	18.3	20.5	0.43
LDL cholesterol, mmol/l (mg/dl)	2.92 ± 0.92 (113.7 ± 35.4)	2.92 ± 0.98 (112.8 ± 38.0)	0.73
HDL cholesterol, mmol/l (mg/dl)	1.51 ± 0.45 (58.2 ± 17.5)	1.42 ± 0.43 (55.0 ± 16.6)	0.009
Triglycerides, mmol/l (mg/dl)	1.12 ± 0.62 (105.9 ± 54.7)	1.41 ± 0.91 (125.1 ± 80.4)	0.0001
BMI, kg/m^2	30.0 ± 6.5	30.6 ± 5.5	0.19
Statin medications, %	14.8	39.3	<0.0001
Calculated 10-year Framingham Risk	4.6 ± 3.8	9.6 ± 7.2	<0.0001

* Continuous variables presented as mean ± 1 standard deviation

Table 2

Sex-specific noncalcified and calcified coronary plaque volumes by age group in subjects with any coronary plaque* (N=366)

		Ages 30-44 (N=38)	Ages 45-54 (N=100)	Ages 55-64 (N=154)	Ages 65-74 (N=74)	Age p-value
Noncalcified plaque volume, mm^3	Male	94 [31-161]	115 [51-241]	212 [106-444]	415 [236-653]	<0.0001
	Female	60 [30-227]	93 [54-164]	106 [38-205]	170 [89-282]	0.02
	p-value	0.51	0.35	<0.0001	<0.0001	---
Calcified plaque volume, mm^3	Male	8 [1-38]	19 [4-88]	77 [10-296]	386 [101-776]	<0.0001
	Female	3 [1-22]	14 [1-44]	34 [7-108]	48 [10-303]	0.003
	p-value	0.51	0.12	0.005	0.004	---
Agatston Score	Male	6 [1-46]	16 [3-81]	86 [10-354]	454 [100-931]	<0.0001
	Female	4 [1-24]	9 [0-45]	37 [7-104]	58 [7-351]	0.002
	p-value	0.87	0.13	0.004	0.005	---

*Volumes as median [IQR]

Table 3
Distribution of coronary plaque by strength of sibling history (N=338)

	Strong Sib History (n=49) Median [IQR]	Lesser Sib History (n=289) Median [IQR]	Unadjusted p-value	Adjusted p-value*
Any plaque, %	83.7	63.3	0.007	0.04
Total plaque (mm^3)	278.2 [653.6]	85.3 [314.9]	<0.001	0.05

*A multivariate GEE regression model controlled for age, sex, race, current smoking, hypertension, diabetes, LDL cholesterol, statin medication use, and within family correlations.

Table 4

Sex-specific plaque prevalence and characteristics by Framingham risk group (n=805)

	Male				Female			
Framingham Risk	**Low N=254**	**Intermediate N=72**	**High N=27**	**p-value for trend**	**Low N=396**	**Intermediate N=48**	**High N=8**	**p-value for trend**
Any plaque	49.2	73.6	96.3	<0.0001	31.6	58.3	87.5	<0.0001
#Affected vessels								
0	50.8	26.4	3.7	<0.0001	68.4	41.7	12.5	<0.0001
1	20.5	13.9	11.1		13.9	20.8	25.0	
2	14.6	18.0	25.9		8.4	22.9	25.0	
3	10.6	27.8	37.1		7.3	4.2	37.5	
4	3.5	13.9	22.2		2.0	10.4	0.0	
Location*								
LM	7.1	23.6	33.3	<0.0001	5.6	16.7	25.0	0.0005
LAD	43.7	70.8	92.6	<0.0001	27.5	50.0	75.0	<0.0001
LCX	18.9	45.8	59.3	<0.0001	11.9	29.2	25.0	0.002
RCA	26.0	48.6	77.8	<0.0001	15.7	25.0	62.5	0.0007
At least one stenoses >50%†								
Any plaque	7.5	20.8	40.7	<0.0001	4.6	14.6	0.0	0.07
NCP	1.6	5.6	7.4	0.02	0.5	4.2	0.0	0.07
CCP	2.4	2.8	18.5	0.0008	3.0	6.3	0.0	0.56
Mixed	4.3	15.3	29.6	<0.0001	1.5	6.3	0.0	0.14

*LM: Left main; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery

†NCP: Noncalcified plaque; CCP: Calcified Plaque