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Coronary Artery Calcium Improves Risk Assessment in Adults With a Family History of Premature Coronary Heart Disease

Results From Multiethnic Study of Atherosclerosis

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Background—The prognostic value of coronary artery calcium (CAC) or carotid intima-media thickness (CIMT) among asymptomatic adults with a family history (FH) of premature coronary heart disease is unclear.

Methods and Results—Multiethnic Study of Atherosclerosis enrolled 6814 adults without known atherosclerotic cardiovascular disease (ASCVD). Hard ASCVD events were ascertained over a median follow-up of 10.2 years. We estimated adjusted-hazard ratios for CAC and CIMT categories using Cox regression, both within and across FH status groups. Improvement in discrimination with CAC or CIMT added to variables from the ASCVD pooled cohort equation was also evaluated using receiver-operating characteristic curve and likelihood ratio analysis. Of 6125 individuals (62±10 years; 47% men) who reported information on FH, 1262 (21%) had an FH of premature coronary heart disease. Among these, 104 hard ASCVD events occurred. Crude incidence rates (per 1000 person-years) for hard ASCVD were 4.4 for CAC, 0 (n=574; 46% of the sample); 8.8 for CAC, 1 to 99 (n=368); 14.9 for CAC, 100 to 399 (n=178); and 20.8 for CAC, ≥400 (n=142). Relative to CAC=0, adjusted hard ASCVD hazard ratios for each CAC category among persons with an FH were 1.64 (95% confidence interval, 0.94–2.87), 2.45 (1.31–4.58), and 2.80 (1.44–5.43), respectively. However, there was no increased adjusted hazard for hard ASCVD in high versus low CIMT categories. In participants with an FH of premature coronary heart disease, CAC improved discrimination of hard ASCVD events (P<0.001). However, CIMT did not discriminate ASCVD (P=0.70).

Conclusions—Nearly half of individuals reporting FH have zero CAC and may receive less net benefit from aspirin or statin therapy. Among persons with an FH, CAC is a robust marker of absolute and relative risk of ASCVD, whereas CIMT is not. **(*Circ Cardiovasc Imaging*. 2015;8:e003186. DOI: 10.1161/CIRCIMAGING.115.003186.)**

Key Words: atherosclerosis ■ carotid intima-media thickness ■ primary prevention ■ vascular calcification

Hereditary factors play an important role in the development of atherosclerotic cardiovascular disease (ASCVD). Indeed, the presence of a family history (FH) of premature coronary heart disease (CHD) was one of the earliest recognized cardiovascular risk factors.[1,2] For example, previous studies suggest that adjusted risk for ASCVD events is ≈2-fold higher in persons who report that both the parents had premature CHD (relative to no parental history).[3] Elevated ASCVD risk has also been demonstrated in those who have an FH of premature CHD in any first degree relative.[4] Indeed, despite the imperfect sensitivity of self-reported FH (68%–86% in some analyses),[5] the presence of FH has been shown to stratify disease risk when screening is applied to the general population.[6]

See Clinical Perspective

However, the incorporation of FH into clinical practice guidelines and risk estimation algorithms has been limited as FH is both nonmodifiable and often not independent of other established risk factors.[7] In addition, the genetics of ASCVD is complex and there is marked heterogeneity in both penetrance

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and severity of the disease phenotype among relatives of probands with a history of premature CHD. Thus, information on FH of premature CHD is not routinely incorporated into traditional risk stratification methods, such as the Framingham risk score and the recently released pooled cohort equation (PCE) for ASCVD.[8] Nevertheless, the 2013 American Heart Association–American College of Cardiology prevention guidelines recommend that providers assess FH status to further define, and potentially reclassify, ASCVD risk assessment for adults in whom the appropriate allocation of preventive therapies remains uncertain after the patient–provider risk discussion.[8]

However, because of complex inheritance patterns and the fact that FH is self-reported and, thus, may be subject to reporting error (eg, there is low sensitivity with a tendency for under-reporting),[7] assessment of subclinical atherosclerosis could add clinically useful prognostic information in persons who report an FH of ASCVD. For example, previous studies have shown that patients with FH of premature CHD often have an increased prevalence of elevated coronary artery calcium (CAC)[9] and carotid intima-media thickness (CIMT).[10,11] Consequently, the yield from subclinical atherosclerosis testing is higher in persons with FH, an important consideration given that these noninvasive measures have consistently been shown to predict future ASCVD and CHD in cohorts of varied age and demographic make-up.[12,13]

Therefore, we sought to determine whether the extent of subclinical atherosclerosis burden (by either CAC or CIMT) could better stratify risk for ASCVD and CHD events beyond traditional risk factors among individuals with a self-reported FH of premature CHD. Such information could help to determine the clinical value of pursuing further imaging before allocating lifelong preventive pharmacotherapy in persons who report an FH of premature CHD. Please note that, unless otherwise stated, the abbreviation FH throughout this text specifically denotes a family history of premature CHD.

Methods

Study Population

The Multiethnic Study of Atherosclerosis (MESA) recruited 6814 participants between 2000 and 2002 across 6 field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN).[14] Participants were between 45 and 84 years of age, identified themselves as white, black, Hispanic, or Chinese American, and were free of clinical ASCVD at baseline. Because detailed FH data were only available from MESA visit 2 (including information on age of CHD onset in relatives of MESA participants, which is required to determine whether FH is premature or not), we only included persons who attended both visit 1 (when CAC and CIMT imaging were obtained) and visit 2. Of the 6201 persons who attended both visits, a total of 71 subjects were excluded for missing CIMT data (all subjects had CAC data), 5 were omitted because of missing outcomes data, 97 were missing low-density lipoprotein-cholesterol information, and 113 were missing other variables of interest in the models. Notably, 150 study participants (2% of the MESA sample overall) died between visits 1 and 2. After exclusions, 6125 participants were available for the main analysis. Institutional Review Boards at each site approved the study, and all participants gave written informed consent.

Baseline Measurements

At the baseline MESA visit (July 2000 to September 2002), study participants completed self-administered questionnaires, standardized interviews, and in-person examinations of lifestyle characteristics, medical history, anthropometric measurements, and laboratory data. Body mass index was calculated as weight in kilograms divided by height in meters squared. High-density lipoprotein-cholesterol was measured using the cholesterol oxidase method. Low-density lipoprotein-cholesterol was calculated using the Friedewald equation.[15] Diabetes mellitus was defined using the 2003 American Diabetes Association criteria[16] of a fasting glucose ≥126 mg/dL or use of insulin or oral hypoglycemic medications. Hypertension was defined using the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure criteria[17] as either a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, a history of physician-diagnosed hypertension, or taking a medication for hypertension. Study participants also self-reported personal habits, such as alcohol and current tobacco use (defined as having smoked a cigarette in the past 30 days and >100 cigarettes in a lifetime).

CAC and CIMT Assessment

The details of the MESA cardiac CT protocol have been published elsewhere.[18] Briefly, baseline CAC at MESA visit 1 was quantified using the Agatston scoring method.[19] CAC was measured either by electron-beam computed tomography or by multidetector row helical computed tomography, depending on the field center. Interobserver agreement (κ=0.93) and intraobserver agreement (κ=0.90) were high.[20]

The intima-media layer of the carotid arterial wall was measured at visit 1 using high-resolution B-mode ultrasonography of the near and far walls of the left and right common carotid arteries; the mean maximum value, in millimeters, of the common CIMT was used in the analysis.[21] The intraclass correlation coefficients for intrareader and inter-reader reproducibility of common carotid measurements were 0.98 and 0.86, respectively.[21] A standardized protocol with quality control procedures was used and interpretation was performed at a centralized reading station in Tufts Medical Center, Boston, MA.[21]

FH Assessment

Detailed information on FH of premature CHD was ascertained in the majority of participants (n=6201) in an ancillary study at MESA visit 2 (September 2002 to February 2004). Participants were asked if any member of their immediate family (first-degree relative: mother, father, siblings, or children) experienced a fatal or nonfatal myocardial infarction or cardiac procedure (coronary bypass surgery, balloon angioplasty, and intracoronary stenting). Response options were Yes, No, and Do Not Know. For the purposes of this analysis, Do Not Know responses were counted as No responses. If a participant reported Yes for a disease in a first degree relative, the age at diagnosis was also ascertained. We defined FH of premature CHD as having at least 1 first-degree relative with CHD occurring before the age of 55 years in male relatives and before the age of 65 years in female relatives.

Definition and Ascertainment of Events

A detailed description of the event adjudication process has been previously published.[14] For the purpose of this study, we analyzed 2 separate clinical end points, (1) hard CHD: defined to include myocardial infarction, resuscitated cardiac arrest, or CHD death; and (2) hard ASCVD: defined as the events comprising of hard CHD, plus stroke or stroke death.

Statistical Analysis

Baseline characteristics in each of the 2 FH of premature CHD status groups (positive or negative) were compared using ANOVA for continuous variables and χ^2 or Wilcoxon rank sum testing for categorical variables. CAC score was classified into the following categories: 0, 1 to 99, 100 to 399, and ≥400 Agatston Units. Because no established

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clinical cut-points exist for CIMT and to create subgroups with comparable numbers of events to the CAC categories, CIMT was categorized according to the following percentile distributions: ≤50, 51 to 75, 76 to 90, and >90th percentiles.

For each event, we used Cox proportional hazard regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) comparing persons with an FH of premature CHD to those without. The proportionality assumption was confirmed visually using log–log plots. Models were adjusted for age, sex, race, MESA site, cigarette smoking, hypertension status, diabetes mellitus status, body mass index, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and cholesterol-lowering medications. We further adjusted for CAC as a continuous variable, log[CAC+1], in a mediation analysis. We also tested for multiplicative interaction between FH status and each of sex, race, and age categories (<55 or ≥55 years) in the association with incident events.

In addition, we constructed adjusted Cox models, within each FH status group, according to CAC and CIMT categories using CAC=0 and CIMT ≤50th percentile as the reference groups, respectively. These models were adjusted for the same variables listed above. Sensitivity analyses for CIMT were also conducted by quartile. Furthermore, both transformed CAC (log[CAC+1]) and untransformed CIMT (mm) were also modeled in a continuous fashion. We also formally tested for multiplicative interaction between FH and either CAC or CIMT categories in the association with incident events.

For each event, we calculated the area under the receiver-operating characteristic curves using Harrell C-statistic for models with and without CAC or CIMT (both modeled continuously) in those with an FH of premature CHD. The base model for this area under the curve analysis consisted of the variables included in the PCE equation for ASCVD risk (age, sex, race, systolic blood pressure, treatment for hypertension, high-density lipoprotein-cholesterol, total cholesterol, diabetes mellitus, and smoking). Improvement in discrimination was determined using the likelihood ratio test.[22] All statistical analyses were performed with the use of Stata version 13.0 (StataCorp). A 2-sided $P<0.05$ was considered statistically significant.

Results

The final study population consisted of 6125 individuals (mean baseline age, 62±10 years; 48% men). Overall, 21% (n=1262) of MESA participants reported an FH of premature CHD. The FH group had a higher percentage of subjects who were women, white or black ethnicity, overweight, diabetic, hypertensive, or on lipid-lowering therapy (Table 1). Patients with an FH of premature CHD also had a higher proportion of persons with CAC ≥400 or CIMT values >90th percentile.

After a median of 10.2 years follow-up, a total of 382 hard ASCVD and 243 hard CHD events were recorded in the sample overall. Among those with an FH of premature CHD, 104 hard ASCVD and 67 hard CHD events occurred (Table I in the Data Supplement for numbers among each race/ethnicity group). In crude analyses, hard ASCVD and hard CHD event rates were higher among those with an FH of premature CHD compared with those without: 8.7 and 5.5 (per 1000 person-years; $P=0.0007$) versus 6.0 and 3.7 ($P=0.004$), respectively.

Among persons with and without an FH, there was a graded relationship between both higher CAC and CIMT categories and increasing absolute event rates over follow-up. For example, the lowest crude rate for hard CHD (1.2 per 1000 person-years) was seen in those without a reported FH and without CAC (CAC, 0). In contrast, the highest hard CHD event rates occurred in those with an FH of premature CHD and CAC ≥400: 14.5 per 1000 person-years (Figure 1A). Importantly, the incidence rates for both hard ASCVD and hard CHD (per 1000 person-years) were as low as 4.4 and 2.3, respectively, in persons who reported an FH but who had CAC=0. We also found a graded increase in risk for CHD and ASCVD events according to CIMT categories among persons without an FH of premature CHD. However, the relationship between increasing CIMT categories and events was less consistent for those with an FH of premature CHD (Figure 1B).

Adjusted HR Comparing FH Status Groups

Relative to persons without an FH, those who reported an FH of premature CHD had an adjusted HR for hard ASCVD of 1.35 (95% CI, 1.07–1.71) and an HR for hard CHD of 1.41 (95% CI, 1.05–1.88), overall. Associations between FH and hard ASCVD events were calculated for each race/ethnicity category: HR, 1.08 (95% CI, 0.74–1.56) in whites; 2.09 (95% CI, 1.37–3.19) in blacks; 1.34 (95% CI, 0.85–2.13) in Hispanics; and 0.95 (95% CI, 0.21–4.22) in Chinese. However, there was no interaction between FH and race/ethnicity ($P=0.25$) in the association with these events. In addition, there was no interaction between FH and age (categorized as <55 or ≥55; $P=0.05$) or sex ($P=0.55$).

In the mediation analysis, the association for FH diminished slightly, but remained significant, after further adjusting for CAC in the baseline models (HR, 1.30 [95% CI, 1.03–1.64] for hard ASCVD). For hard CHD, this relationship also remained significant after further adjustment for CAC (HR, 1.33; [95% CI, 1.00–1.78]).

Adjusted HR Within and Across FH Status Groups; Stratified by CAC or CIMT

In the fully adjusted models, increasing HRs for hard ASCVD were seen among higher CAC categories, regardless of the presence or absence of an FH of premature CHD (Table 2). For example, those with an FH had an HR of 2.80 (95% CI, 1.44–5.43) in the CAC ≥400 group (relative to CAC, 0), in contrast to 3.22 (95% CI, 2.15–4.84) in those without an FH. There was no statistical interaction between FH and CAC in the association with ASCVD events ($P=0.28$).

In contrast to CAC, HR for hard ASCVD demonstrated only marginal increases among higher CIMT categories and these associations did not meet statistical significance, either in the presence or absence of an FH of premature CHD. For persons with CIMT >90th percentile, those without an FH had an HR of 1.11 (95% CI, 0.75–1.63), relative to the lowest CIMT category) compared with 0.76 (95% CI, 0.39–1.50) in those with an FH. There was also no interaction between CIMT (either by percentile category or by quartile) with ASCVD events based on FH status ($P=0.21$; Table 2; Table II in the Data Supplement).

Results for hard CHD were qualitatively similar to those for hard ASCVD in fully adjusted models (Table 3). Notably, the HR for hard CHD for each elevated CAC category was relatively higher in those without an FH of premature CHD, compared to those with an FH. For example, the HR for hard CHD was 3.85 (95% CI, 1.65-9.02) in those with CAC ≥400 and an FH (compared with CAC=0) versus 4.87 (95% CI, 2.88-8.24) for the same comparison in those without an FH. However, in addition to the higher crude absolute risk in the group with CAC=0 across FH status groups (higher event incidence rates for those with FH and CAC=0 relative to those

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Table 1. Baseline Characteristics of a Multiethnic, Asymptomatic Cohort According to Family History of Premature Coronary Heart Disease Status

Characteristics	Negative FH (n=4863)	Positive FH (n=1262)	*P* Value*
Age, mean±SD	62±10	62±10	0.73
Sex, n (%)			
Men	2411 (50)	505 (40)	<0.001
Women	2452 (50)	757 (60)	
Race/Ethnicity, n (%)			
White	1884 (39)	547 (43)	<0.001
Chinese American	685 (14)	39 (3)	
Black	1239 (26)	398 (32)	
Hispanic	1055 (22)	278 (22)	
BMI (kg/m^2), mean±SD	28±5	29±6	<0.001
LDL-C (mg/dL), mean±SD	117±31	118±31	0.30
HDL-C (mg/dL), mean±SD	51±15	52±15	0.21
HTN, n (%)	2065 (43)	627 (50)	<0.001
Diabetes mellitus, n (%)	478 (10)	174 (14)	<0.001
Lipid-lowering medication use, n (%)	747 (15)	245 (19)	<0.001
Cigarette smoking, n (%)			
Never	2500 (52)	596 (47)	0.004
Former	1773 (37)	475 (38)	
Current	577 (12)	188 (15)	
Median CAC, Agatston Units (IQR)	0 (78)	5 (104)	<0.001
Mean CIMT (mm±SD)	0.86±0.19	0.88±0.19	0.005
CAC category, n (%)			
CAC, 0	2545 (52)	574 (46)	<0.001†
CAC, 1–99	1222 (25)	368 (29)	
CAC,100–399	652 (13)	178 (14)	
CAC, >400	444 (9)	142 (11)	
CIMT category, n (%)			
≤50th percentile	2495 (51)	593 (47)	0.007†
51st–75th percentile	1189 (24)	332 (26)	
76th–90th percentile	709 (15)	197 (16)	
>90th percentile	470 (10)	140 (11)	

BMI indicates body mass index; CAC, coronary artery calcification; CIMT, carotid intima-media thickness; FH, family history; HDL-C, high-density lipoprotein-cholesterol; HTN, hypertension (defined by JNC VI Criteria); IQR, interquartile range; and LDL-C, low-density lipoprotein-cholesterol.

**P* Value for continuous variables was calculated using student *t* test and for categorical variables using χ^2 test.

†*P* Value was calculated using Wilcoxon rank sum test.

without FH and CAC=0; Figure 1A), there was also higher adjusted relative risk in the CAC=0 and positive FH of premature CHD group (relative to the CAC=0 and negative FH group), with an HR for hard CHD of 1.54 (95% CI, 0.79–3.01) for the comparison. In contrast, CIMT (by percentile group or quartile) was not associated with hard CHD (Table 3; Table III in the Data Supplement). Similar to hard CVD, there was also no interaction between CAC or CIMT and FH status (*P*=0.49 and *P*=0.51, respectively). All HRs for both events were consistent with the categorical results above when CAC and CIMT were modeled continuously (Tables 2 and 3).

Addition of CAC Versus CIMT for Discrimination of Incident ASCVD and CHD Events

The addition of CAC to the base model comprising the variables from the PCE for ASCVD risk estimation led to an increase in the Harrell C-statistic for hard CHD from 0.74 to 0.77 (*P*=0.0005), whereas the addition CIMT was not significant (*P*=0.97). Similar results for hard ASCVD were obtained when either CAC or CIMT were added to the base model (base area under the curve, 0.75; base plus CAC, 0.77; *P*=0.0004 and base plus CIMT, 0.75; *P*=0.70; Figure 2). Results were similar for those without FH (Data Supplement).

Discussion

In this community-based multiethnic cohort, FH of premature CHD was an independent risk factor for both hard ASCVD and hard CHD events, even with adjustment for baseline subclinical atherosclerosis burden. Nonetheless, we demonstrate that CAC testing is more effective than CIMT at stratifying absolute and relative risk for both ASCVD and CHD in those with an FH of premature CHD. In addition, almost half of those individuals reporting a positive FH had zero CAC and were at low absolute risk for events over a median of 10 years of follow-up. Furthermore, the addition of CAC added significant prognostic information for discrimination for CHD events in persons with an FH of premature CHD, whereas the addition of CIMT did not.

Adjusted ASCVD Risk Comparing Persons With and Without an FH of Premature CHD

In this modern multiethnic cohort, FH of premature CHD is an independent risk factor for events >10 years. Although there was a trend for higher relative risk among blacks with an FH of premature CHD (with weaker findings for other ethnicities—Table I in the Data Supplement), we did not find interaction, suggesting that the associations between FH status and outcomes were statistically similar by race.

In addition, and motivated by recent reports,[23] we also examined whether CAC mediated the effect of FH on subsequent ASCVD. Confirming previous research, we found no significant reduction in the impact of FH on ASCVD risk when CAC was added to our models, suggesting that, although CAC is able to stratify risk in both the presence and the absence of FH, the effect of a positive FH on events does not seem to be mediated through CAC. In line with this finding, other investigators have reported that noncalcified coronary plaque (not captured by CAC) is more prevalent among those with an FH, particularly in persons <55 years of age.[24] Furthermore, our findings are additive to a recent report that demonstrated an increased relative risk (despite a low absolute risk) for cardiovascular events among intermediate risk subjects with any FH and zero CAC (we note that this report did not examine persons with premature FH specifically).[25]

ASCVD Risk Within the Premature FH Group; Stratified by Subclinical Atherosclerosis

Our results may also inform risk prognostication and treatment decisions in persons reporting an FH of premature

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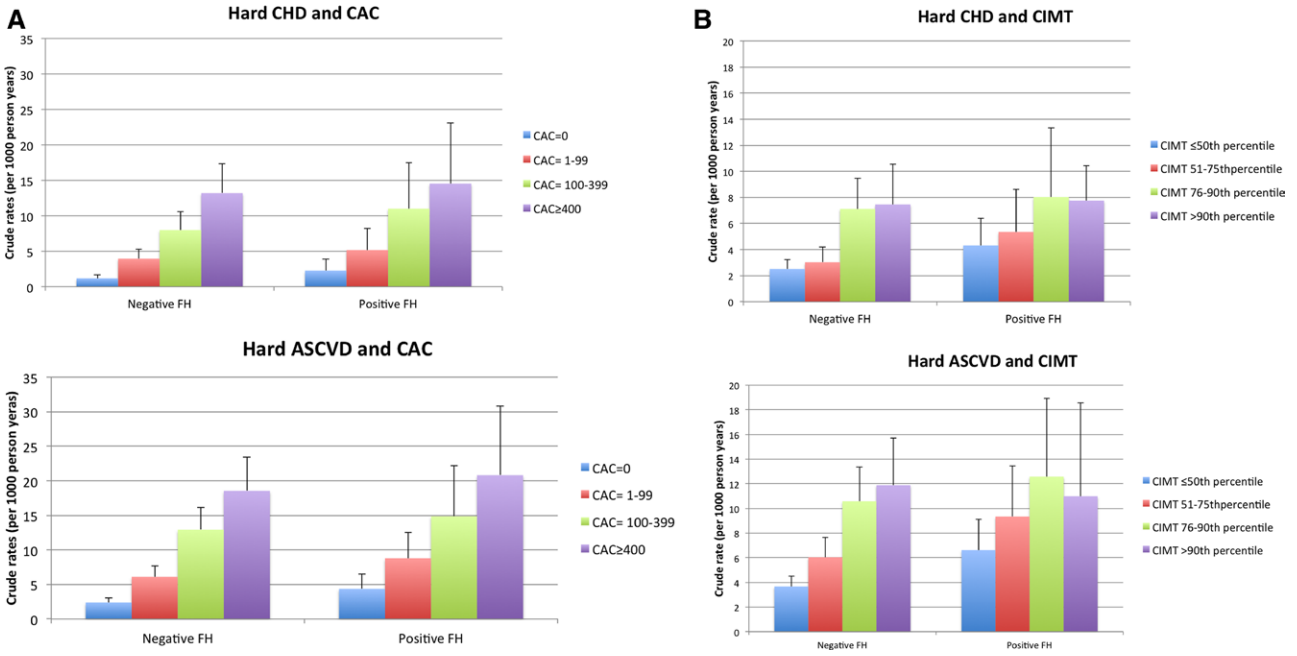

Figure 1. A, Hard atherosclerotic cardiovascular disease (ASCVD) and coronary heart disease (CHD) event rates (per 1000 person-years) with increasing coronary artery calcium (CAC) score categories, according to family history of premature coronary heart disease (FH) of premature CHD status. **B**, Hard ASCVD and CHD event rates (per 1000 person-years) with increasing carotid intima-media thickness (CIMT) categories, according to FH of premature CHD status.

CHD. Specifically, the addition of CAC to a model comprised variables from the PCE improved discrimination of incident CHD. In addition, we found a wide range of absolute event rates based on CAC values. In fact, nearly one half of individuals (46%) with an FH of premature CHD in this study were at low 10-year cardiovascular risk because of the absence of CAC. This finding may be explained, at least in part, by the fact that not all individuals with an FH will share the same familial risk factors, genes or lifestyle, as their affected family members. Similarly, there are often errors in the self-reporting of FH, which could lead to misclassification.

Current guidelines recommend that providers consider the assessment of additional novel risk factors (which are not contained in the PCE equation for ASCVD risk estimation) to guide statin allocation and help inform the patient–provider risk discussion, particularly when the decision to proceed with preventive pharmacotherapy, such as with statins, remains uncertain.[8] Of relevance to this analysis, the assessment of either FH of premature CHD or CAC was endorsed by the guideline committee to help reclassify risk in uncertain situations (level IIb of evidence). However, as mentioned above, a potential limitation to using FH of premature CHD alone is that penetrance can vary enormously and FH is by nature self-reported and, thus, subject to misclassification because of reporting error.[26]

In this context, our results suggest that, for those reporting an FH of premature CHD and in whom preventive treatment decisions are uncertain, CAC may be a useful adjunctive test before commencing lifelong statin therapy.[8] Furthermore, aspirin use for primary ASCVD prevention is endorsed for those considered higher risk (10-year risk >10%; class IIa evidence),[27] although it is frequently prescribed to low risk individuals on the basis of FH status (a practice that is not guideline driven). However, the use of aspirin in low-risk populations may be outweighed by an increased risk of bleeding[28] and our results also suggest that CAC may also be a useful adjunctive test before commencing aspirin in persons with an FH of premature CHD.

Study Limitations

The results of our study should be interpreted in the context of several limitations. First, this is an observational study and our conclusions are hypothesis generating. Accurate FH assessment can be limited by reporting errors.[29] Because of high specificity and comparatively lower sensitivity, some subjects with a positive FH are falsely classified in the group of subjects without FH, which may result in underestimation of the risk associated with an FH of premature CHD. Second, details on FH of premature CHD were only assessed at MESA examination 2 and could introduce selection bias because of the fact that some MESA participants died from an ASCVD or CHD related event after visit 1, when CAC and CIMT imaging were obtained, but before visit 2, and were excluded from the analysis. However, to perform our analyses using visit 1 FH data would have required that we use FH of any CHD (regardless of age of onset) as the exposure variable. Given the prevalence of CHD in the United States, the presence of FH of any CHD is common (43% of the MESA sample), is nonspecific, and is far less likely to reflect the underlying exposure of interest in our analysis (shared genetic risk factors for CHD among family members). In this context, we used an asynchronous analytic approach (visit 1 imaging data

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Table 2. Multivariable-Adjusted* Hazards Ratios (95% CI) for the Association of CAC and CIMT With Hard ASCVD Events, Stratified by Family History of Premature CHD

	Hazard Ratios (95% CI)		Hard ASCVD Events	
	Negative FH (n=4863)	Positive FH (n=1262)	Negative FH (n=278)	Positive FH (n=104)
CAC, 0	1 (ref)	1 (ref)	60	25
CAC, 1–99	1.75 (1.22–2.50)	1.64 (0.94–2.87)	72	30
CAC, 100–399	2.78 (1.91–4.06)	2.45 (1.31–4.58)	76	24
CAC, >400	3.23 (2.15–4.86)	2.80 (1.44–5.43)	70	25
P Value for interaction		0.28†		
CIMT ≤50th percentile	1 (ref)	1 (ref)	90	38
CIMT, 51st–75th percentile	0.93 (0.67–1.29)	1.18 (0.71–1.95)	69	29
CIMT, 76–90th percentile	1.27 (0.90–1.80)	1.30 (0.74–2.28)	69	23
CIMT, >90th percentile	1.11 (0.75–1.63)	0.76 (0.39–1.50)	50	14
P Value for interaction		0.21†		
ln (CAC+1)	1.20 (1.13–1.26)	1.17 (1.07–1.29)	…	…
P Value for interaction		0.28†		
Continuous CIMT	1.54 (0.82–2.89)	0.89 (0.32–2.49)	…	…
P Value for interaction		0.21†		

Continuous CAC units are log-transformed Agatston Units, continuous CIMT units are per millimeter change in thickness. ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CI, confidence interval; CIMT, carotid intima-media thickness; and FH, family history of premature CHD.

*Adjusted for age, sex, race, Multiethnic Study of Atherosclerosis site, cigarette smoking, hypertension, diabetes, body mass index, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and cholesterol-lowering medications.

†Interaction terms are for differences in event hazard for each exposure, comparing those with and without an FH.

and visit 2 FH data). We think this is justified for several reasons: (1) few people died between visits 1 and 2 (150 of 6814 participants); (2) of those who did die, the proportion with a positive FH of any CHD was statistically similar to the proportion of those with an FH of any CHD among the persons included in our analysis; (3) the time between

Table 3. Multivariable-Adjusted* Hazards Ratios (95% CI) for the Association of CAC and CIMT With Hard CHD Events Stratified by Family History of Premature CHD

	Hazard Ratios (95% CI)		Hard CHD Events	
	Negative FH (n=4863)	Positive FH (n=1262)	Negative FH (n=176)	Positive FH (n=67)
CAC, 0	1 (ref)	1 (ref)	30	13
CAC, 1–99	2.35 (1.46–3.78)	1.93 (0.91–4.10)	47	18
CAC, 100–399	3.54 (2.14–5.85)	3.52 (1.58–7.84)	48	18
CAC, >400	4.87 (2.88–8.24)	3.85 (1.65–9.02)	51	18
P Value for interaction		0.49†		
CIMT, ≤50th percentile	1 (ref)	1 (ref)	62	25
CIMT, 51st–75th percentile	0.70 (0.46–1.08)	1.02 (0.54–1.94)	35	17
CIMT, 76th–90th percentile	1.20 (0.79–1.84)	1.29 (0.64–2.60)	47	15
CIMT, >90th percentile	0.94 (0.58–1.52)	0.87 (0.38–1.96)	32	10
P Value for interaction		0.51†		
ln (CAC+1)	1.25 (1.17–1.35)	1.22 (1.09–1.37)	…	…
P Value for interaction		0.39†		
Continuous CIMT	1.30 (0.59–2.90)	1.20 (0.35–4.13)	…	…
P Value for interaction		0.60†		

Continuous CAC units are log-transformed Agatston Units, continuous CIMT units are per millimeter change in thickness. CAC indicates coronary artery calcium; CHD, coronary heart disease; CIMT, carotid intima-media thickness; and FH, family history of premature CHD.

*Adjusted for age, sex, race, Multiethnic Study of Atherosclerosis site, cigarette smoking, hypertension, diabetes mellitus, body mass index, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and cholesterol-lowering medications.

†Interaction terms are for differences in event hazard for each exposure, comparing those with and without an FH.

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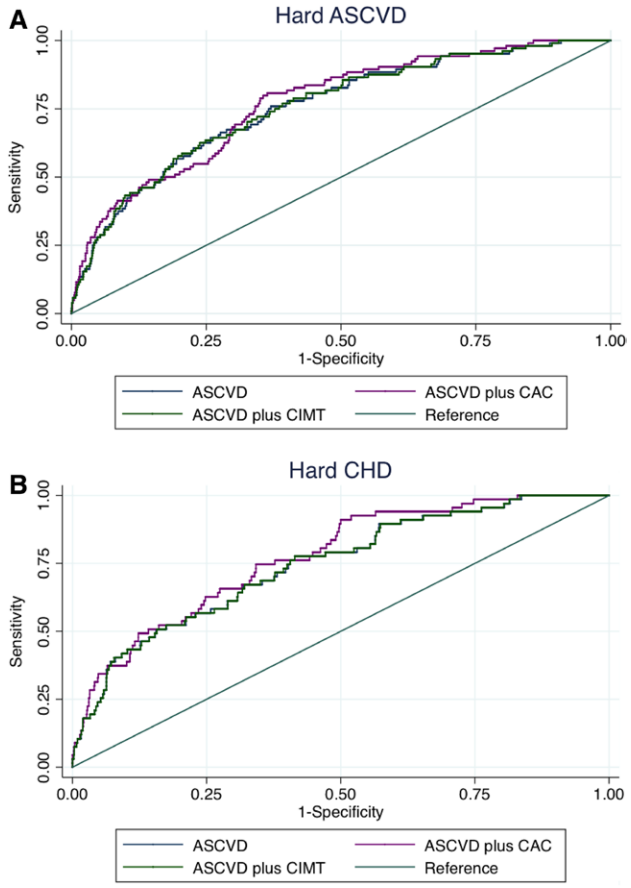

Figure 2. A, Receiver-operating characteristic curves showing area under the curve for incident hard atherosclerotic cardiovascular disease (ASCVD) among those with a family history of premature coronary heart disease (CHD). **B**, Receiver-operating characteristic curves showing area under the curve for incident hard CHD among those with a family history of premature CHD. Carotid intima-media thickness (CIMT) and coronary artery calcium (CAC) were modeled continuously.

visits was short (median time, 1.6 years) making it unlikely that FH data (which are generally fixed) differed between visits for the vast majority of participants; and (4) we also performed sensitivity analyses using the crude visit 1 FH data and the results were all qualitatively similar (Tables IV and V in the Data Supplement).

Conclusions

CAC as a prognostic test seems to perform equally well in persons with and without an FH. Current prevention guidelines endorse (class II, level B recommendation) the assessment of an FH of premature CHD to guide ASCVD prevention treatment strategies.[6] However, in MESA, we found that the risk of ASCVD and CAC distribution was heterogeneous in those reporting a positive FH, with almost half demonstrating zero CAC. We also demonstrate that CAC effectively stratifies absolute and relative risk in persons with an FH, whereas CIMT does not. Thus, before starting lifelong statin or aspirin therapy, it may be reasonable to consider additional CAC testing to enhance ASCVD risk stratification in those who report an FH of premature CHD.

Acknowledgments

We thank the other investigators, the staff, and the participants of the MESA Study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa.nhlbi.org.

Disclosures

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CLINICAL PERSPECTIVE

In the Multiethnic Study of Atherosclerosis, we demonstrate that coronary artery calcium is a potent marker of absolute and relative cardiovascular risk in persons reporting a family history (FH) of premature coronary heart disease, whereas carotid intima-media thickness by ultrasound is not. In our study, nearly half of those with an FH have zero coronary artery calcium and are consequently at low risk for cardiovascular events within 10 years. Furthermore, among those with an FH, we also found that coronary artery calcium adds significant prognostic information to the traditional risk factors included in the new pooled cohort equation model. These findings are of importance, specifically in the context of recent American Heart Association–American College of Cardiology Cholesterol Treatment guidelines; where self-reported FH of premature cardiovascular disease (known to be subject to reporting error) is endorsed as a risk marker to guide allocation of lifelong statin therapy. In summary, these data suggest that coronary artery calcium may be useful as an adjunctive test before changing clinical management based on a self-reported FH of premature coronary heart disease.

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Coronary Artery Calcium Improves Risk Assessment in Adults with a Family History of Premature Coronary Heart Disease: results from MESA

Supplementary Document

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Patel. Subclinical CAD and Family History of CHD.

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Supplementary Figure Ia: Receiver operating characteristic curves showing area under the curve for incident hard ASCVD among those without a family history of premature CHD.
Supplementary Figure Ib: Receiver operating characteristic curves showing area under the curve for incident hard CHD among those without a family history of premature CHD.

Supplementary Table I: Crude event rates (per 1000 person-years) according to race/ethnic group stratified by a family history of premature CHD status.

	Hard ASCVD			Hard CHD		
	Negative FH	**Positive FH**	**p-value**	**Negative FH**	**Positive FH**	**p-value**
White	6.99	7.12	0.91	4.20	5.18	0.34
Chinese	3.44	5.62	0.49	2.38	2.81	0.79
Black	4.86	9.80	0.002	3.14	5.35	0.06
Hispanic	7.02	10.85	0.06	4.47	6.87	0.13

FH – family history of premature coronary heart disease

CHD – coronary heart disease

ASCVD – atherosclerotic cardiovascular disease

Supplementary Table II: Cox proportional hazards regression examining relation of hard ASCVD events with CAC category and CIMT quartile, stratified by FH of premature CHD.

	Cox Proportional Hazard Ratios		Number of Hard ASCVD Events	
	Negative FH (n= 4,863)	**Positive FH** (n= 1,262)	**Negative FH** (n=278)	**Positive FH** (n=104)
CAC 0	1 (ref)	1 (ref)	60	25
CAC 1-99	1.74 (1.21-2.50)	1.64 (0.94-2.87)	72	30
CAC 100-399	2.77 (1.90-4.05)	2.45 (1.31-4.58)	76	24
CAC ≥400	3.22 (2.15-4.84)	2.80 (1.44-5.43)	70	25
p-value for interaction	0.28			
ln (CAC+1)	1.19 (1.13-1.26)	1.17 (1.07-1.29)		
p-value for interaction	0.28			
CIMT 1st Quartile	1 (ref)	1 (ref)	30	15
CIMT 2nd Quartile	1.35 (0.86-2.10)	0.80 (0.41-1.59)	59	22
CIMT 3rd Quartile	1.12 (0.72-1.77)	1.08 (0.56-2.06)	69	29
CIMT 4th Quartile	1.45 (0.93-2.26)	0.93 (0.48-1.82)	120	38
p-value for interaction	0.29			
Continuous CIMT	1.53 (0.82-2.87)	0.89 (0.32-2.49)		
p-value for interaction	0.21			

Adjusted for age, gender, race, MESA site, cigarette smoking, hypertension, diabetes, BMI, LDL-C, HDL-C, cholesterol lowering medications. Continuous CAC units are log-transformed Agatston Units, continuous CIMT units are per millimeter change in thickness.

ASCVD – atherosclerotic cardiovascular disease
FH – family history of premature coronary heart disease
CHD – coronary heart disease
CAC – coronary artery calcium
CIMT – carotid intima-media thickness
BMI – body mass index
LDL-C – low density lipoprotein-cholesterol
HDL-C - high density lipoprotein-cholesterol

Supplementary Table III: Cox proportional hazards regression examining relation of hard CHD events with CAC category and CIMT quartiles, stratified by FH of premature CHD

	Cox Proportional Hazard Ratios		Number of Hard CHD Events	
	Negative FH (n= 4,863)	**Positive FH** (n= 1,262)	**Negative FH** (n=176)	**Positive FH** (n=67)
CAC 0	1 (ref)	1 (ref)	30	13
CAC 1-99	2.35 (1.46-3.78)	1.93 (0.91-4.10)	47	18
CAC 100-399	3.54 (2.14-5.85)	3.52 (1.58-7.84)	48	18
CAC ≥400	4.87 (2.88-8.24)	3.85 (1.65-9.02)	51	18
p-value for interaction	0.49			
ln (CAC+1)	1.25 (1.17-1.35)	1.22 (1.09-1.37)		
p-value for interaction	0.39			
CIMT 1st Quartile	1 (ref)	1 (ref)	21	8
CIMT 2nd Quartile	1.35 (0.79-2.31)	1.23 (0.51-2.93)	41	17
CIMT 3rd Quartile	0.82 (0.46-1.45)	1.11 (0.46-2.70)	34	16
CIMT 4th Quartile	1.32 (0.77-2.26)	1.28 (0.53-3.11)	80	26
p-value for interaction	0.67			
Continuous CIMT	1.31 (0.59-2.91)	1.20 (0.35-4.13)		
p-value for interaction	0.60			

Adjusted for age, gender, race, MESA site, cigarette smoking, hypertension, diabetes, BMI, LDL-C, HDL-C, cholesterol lowering medications. Continuous CAC units are log-transformed Agatston Units, continuous CIMT units are per millimeter change in thickness.

CHD – coronary heart disease
CAC – coronary artery calcium
CIMT – carotid intima-media thickness
FH – family history of premature coronary heart disease
BMI – body mass index
LDL-C – low density lipoprotein-cholesterol
HDL-C - high density lipoprotein-cholesterol

Supplementary Table IV: Cox proportional hazards regression examining relation of hard ASCVD events with CAC and CIMT, stratified by any family history of CHD (assessed at visit 1).

	No FH of CHD (n= 2,586)	**Any FH of CHD** (n =2,761)
CAC 0	1 (ref group)	1 (ref group)
CAC 1-99	1.65 (1.10-2.46)	1.83 (1.20-2.79)
CAC 100-399	2.33 (1.49-3.63)	2.92 (1.86-4.57)
CAC ≥400	2.85 (1.75-4.6)	3.59 (2.23-5.76)
p-value for interaction	0.93	
CIMT 1st Q	1 (ref group)	1 (ref group)
CIMT 2nd Q	1.10 (0.64- 1.90)	1.13 (0.70-1.81)
CIMT 3rd Q	1.28 (0.76-2.16)	1.05 (0.65-1.70)
CIMT 4th Q	1.42 (0.84-2.39)	1.09 (0.67-1.76)
p-value for interaction	0.10	

Adjusted for age, gender, race, MESA site, cigarette-smoking, hypertension, diabetes, BMI, LDL-C, HDL-C, cholesterol lowering medications.

ASCVD – atherosclerotic cardiovascular disease
CAC – coronary artery calcium
CIMT – carotid intima-media thickness
CHD – coronary heart disease
FH – any family history of coronary heart disease
BMI – body mass index
LDL-C – low density lipoprotein-cholesterol
HDL-C - high density lipoprotein-cholesterol

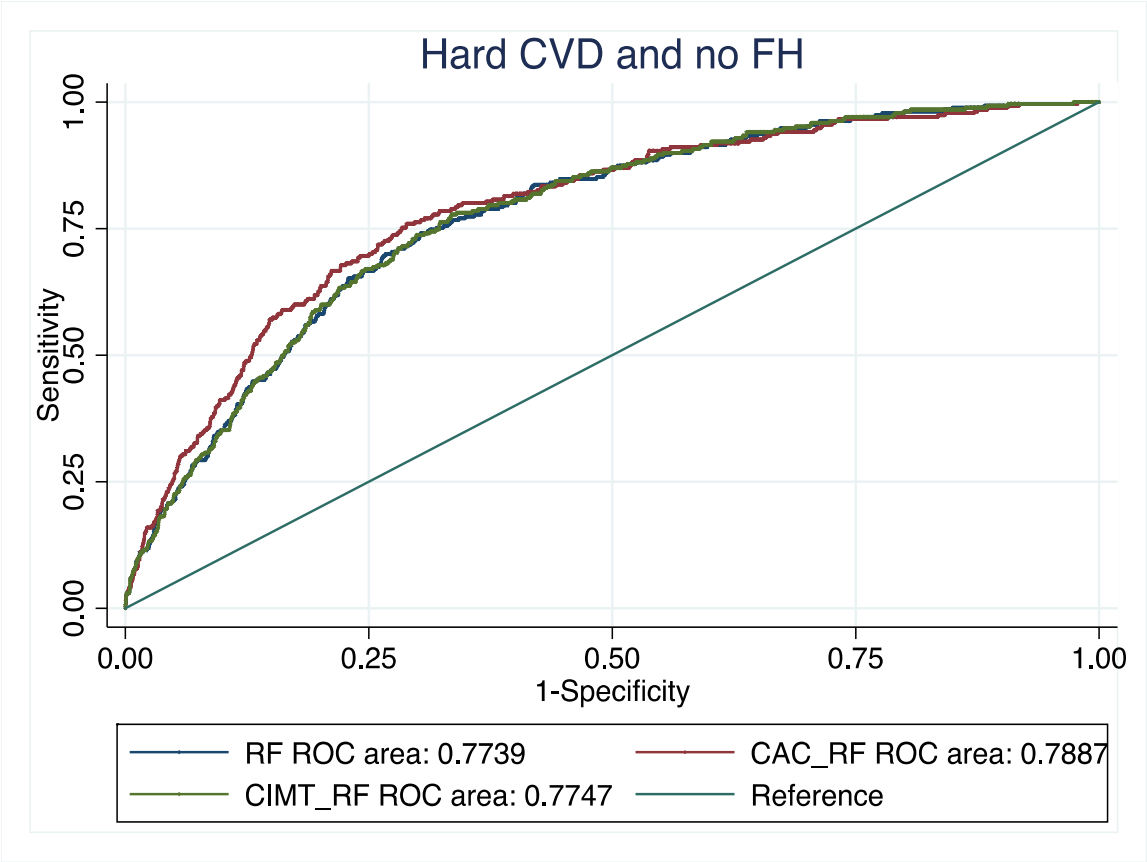
Supplementary Table V: Cox proportional hazards regression examining relation of hard CHD events with CAC and CIMT, stratified by any family history of CHD (assessed at visit 1).

	No FH of CHD (n= 3,620)	**Any FH of CHD** (n = 2,686)
CAC 0	1 (ref group)	1 (ref group)
CAC 1-99	2.16 (1.24-3.78)	2.30 (1.30-4.06)
CAC 100-399	3.19 (1.74-5.86)	4.10 (2.28-7.37)
CAC ≥400	4.63 (2.43-8.81)	5.31 (2.86-9.85)
p-value for interaction	0.86	
CIMT 1st Q	1 (ref group)	1 (ref group)
CIMT 2nd Q	1.26 (0.63-2.52)	1.32 (0.73-2.38)
CIMT 3rd Q	0.98 (0.49-1.98)	1.08 (0.59-1.99
CIMT 4th Q	1.48 (0.75-2.93)	1.15 (0.62-2.11)
p-value for interaction	0.19	

Adjusted for age, gender, race, MESA site, cigarette-smoking, hypertension, diabetes, BMI, LDL-C, HDL-C, cholesterol lowering medications.

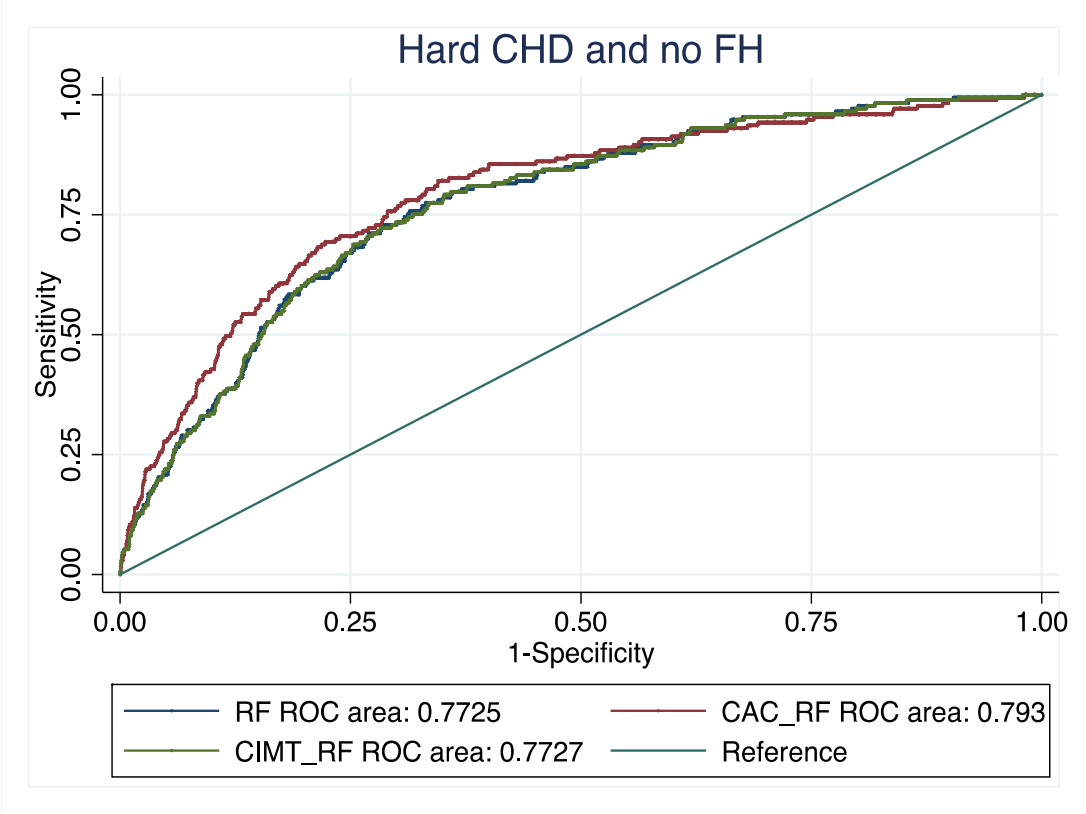
CHD – coronary heart disease
CAC – coronary artery calcium
CIMT – carotid intima-media thickness
FH – any family history of coronary heart disease
BMI – body mass index
LDL-C – low density lipoprotein-cholesterol
HDL-C - high density lipoprotein-cholesterol

Supplementary Figure Ia: Receiver operating characteristic curves showing area under the curve for incident hard ASCVD among those without a family history of premature CHD*.



ASCVD – atherosclerotic cardiovascular disease
FH – family history of premature coronary heart disease
CAC – coronary artery calcium
CIMT – carotid intima-media thickness
*CIMT and CAC were modelled continuously

Supplementary Figure Ib: Receiver operating characteristic curves showing area under the curve for incident hard CHD among those without a family history of premature CHD*.



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CIMT – carotid intima-media thickness
*CIMT and CAC were modelled continuously

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Coronary Artery Calcium Improves Risk Assessment in Adults With a Family History of Premature Coronary Heart Disease: Results From Multiethnic Study of Atherosclerosis

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