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Thoracic Aortic Calcification and Coronary Heart Disease Events: the Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background—The presence and extent of coronary artery calcium (CAC) is an independent predictor of coronary heart disease (CHD) morbidity and mortality. Few studies have evaluated interactions or independent incremental risk for coronary and thoracic aortic calcification (TAC). The independent predictive value of TAC for CHD events is not well-established.

Methods—This study used risk factor and computed tomography scan data from 6,807 participants in the Multi-Ethnic Study of Atherosclerosis (MESA). Using the same images for each participant, TAC and CAC were each computed using the Agatston method. The study subjects were free of incident CHD at entry into the study.

Results—The mean age of the study population (n=6807) was 62±10 years (47% males). At baseline, the prevalence of TAC and CAC was 28 % (1,904/6,809) and 50% (3393/6809), respectively. Over 4.5±0.9 years, a total of 232 participants (3.41%) had CHD events, of which 132 (1.94%) had a hard event (myocardial infarction, resuscitated cardiac arrest, or CHD death). There was a significant interaction between gender and TAC for CHD events (p<0.05). Specifically, in women, the risk of all CHD event was nearly 3-fold greater among those with any TAC (hazard ratio: 3.04, 95% CI: 1.60–5.76). After further adjustment for increasing CAC score, this risk was attenuated but remained robust (HR: 2.15, 95% CI: 1.10–4.17). Conversely, there was no significant association between TAC and incident CHD in men. In women, the likelihood ratio chi square statistics indicate that the addition of TAC contributed significantly to predicting

incident CHD event above that provided by traditional risk factors alone (chi square= 12.44, $p=0.0004$) as well as risk factors + CAC scores (chi square= 5.33, $p=0.02$). On the other hand, addition of TAC only contributed in the prediction of *hard* CHD events to traditional risk factors (chi-square=4.33, $p=0.04$) in women, without contributing to the model containing both risk factors and CAC scores (chi square=1.55, $p=0.21$).

Conclusion—Our study indicates that TAC is a significant predictor of future coronary events only in women, independent of CAC. On studies obtained for either cardiac or lung applications, determination of TAC may provide modest supplementary prognostic information in women with no extra cost or radiation.

Keywords

atherosclerosis; cardiac CT; coronary calcium; multi-detector CT; prognosis; thoracic atherosclerosis

Introduction

As part of the development of atherosclerotic plaques, calcium is deposited in the arterial wall by a process that is histologically similar to bone formation.ⁱ Coronary calcium occurs exclusively in atherosclerotic arteries and is absent in the normal vessel wall. Thoracic calcification may be atherosclerotic and also contribute to aortic stiffness, which has also been associated with adverse outcomes.ⁱⁱ Computed tomography (CT), with or without ECG gating, can be used to detect and quantify calcified plaques in multiple vascular beds, including the thoracic aorta.

Evidence exists that the presence of either coronary artery calcification (CAC) or thoracic aortic calcification (TAC) detected by both chest radiographs and CT are associated with an increased risk of cardiovascular events.^{ii,iii,iv} Evidence is lacking as to whether the measurement of TAC and quantification into a score adds to the information provided by CAC in the stratification of subjects for cardiovascular events and mortality. In this context, the utility of using TAC as part of a CVD risk formulation is important to determine since TAC scores can be easily obtained during assessment of CAC and without additional CT scanning. Furthermore, while CAC may not be accurately assessed without cardiac gating, TAC can easily be quantified on all chest CT scans obtained for a variety of indications. Indeed, it is estimated that more than 62 million diagnostic CT scans per year are obtained annually in the United States, with 31% (19.2 million) used for visualization of the lungs.^v These studies could potentially be read for the presence of TAC at the time of interpretation, with the resulting information be used by clinicians to further risk stratify patients for cardiovascular disease. Accordingly, the primary aim of our study was to assess the predictive value of TAC for cardiovascular events (CVE) and whether this association is independent of coronary heart disease (CHD) risk factors as well as CAC in a population-based, multi-ethnic study.

METHODS

Recruitment and Baseline Examination

The MESA cohort^{vi} is a longitudinal, population-based study of 6,814 men and women, free of clinical cardiovascular disease, aged 45–84 at baseline recruited from six Field Centers: Baltimore, MD ; Chicago, IL; Forsyth County, NC ; Los Angeles, CA ; New York, NY ; and St. Paul, MN. Specific ethnicity groups enrolled included white, black, Hispanic and Chinese. Over 50% of the participants enrolled were female. The baseline visit took place between July 2000 and September 2002. The study was approved by Institutional Review Boards at each site and all participants gave written informed consent. The design of the study has been described in detail previously,^{vi} but we describe the collection of pertinent variables here.

Baseline medical history, anthropometric measurements, and laboratory data for the present study were taken from the first examination of the MESA cohort (July 2000 to August 2002). These self-administered questionnaires were available in English, Spanish, and Chinese. Information about age; gender, ethnicity, and medical history were obtained by questionnaires. Resting blood pressure was measured three times in the seated position, and the average of the 2nd and 3rd readings was recorded. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of baseline blood pressure lowering medication. Body mass index was calculated from the equation weight (kg)/ height (m²). Total and HDL-C were measured from blood samples obtained after a 12-hour fast. LDL-C was estimated by the Friedewald equation. Current smoking was defined as having smoked a cigarette in the last 30 days. Diabetes mellitus was defined as a fasting glucose ≥ 126 mg/dL or use of hypoglycemic medications.

Measurement of CAC

Computed Tomographic Scanning—Scanning centers assessed coronary calcium by chest computed tomography using either a cardiac-gated electron-beam computed tomography scanner (Chicago, Los Angeles, and New York Field Centers) or a multi-detector computed tomography system (Baltimore, Forsyth County and St. Paul Field Centers). Three sites used an Imatron C-150XL CT scanner (GE-Imatron, San Francisco, CA), and three sites used a multidetector CT scanner (four slice). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA in Torrance, CA). We used the average Agatston score for the two scans in all analyses.^{vii} Carr et al have reported the details of the MESA computed tomography scanning and interpretation methods.^{viii}

Image slices were obtained with the participant supine, with no couch angulation. A minimum of 35 contiguous images with a 2.5- or 3-mm slice thickness was obtained, starting above the left main coronary artery and extending to the bottom of both ventricles. Each scan was obtained in a single breath hold. Section thickness of 2.5–3 mm, field of view of 35 cm, and a matrix of 512 $\times$ 512 were used to reconstruct raw image data. The nominal section thickness was 3.0 mm for electron beam CT and 2.5 mm for four-detector row CT.

Spatial resolution can be described by the smallest volume element, or voxel, for the protocol for each system: 1.15 mm³ for four-detector row CT (0.68 × 0.68 × 2.50 mm) and 1.38 mm³ for electron beam CT (0.68 × 0.68 × 3.00 mm).

An ancillary study, supported by the National Institutes of Health, was performed to retrospectively measure aortic and valvular calcification on the scans obtained for the MESA study.^{ix} This study was approved by the Institutional Review Board of our institution. In this study, ascending and descending thoracic aortic calcification (ATAC and DTAC, respectively) were measured from the aortic annulus to the lower edge of the pulmonary artery (ATAC) and from the lower edge of the pulmonary artery to the cardiac apex (DTAC) and were quantified by using the same lesion definition for coronary calcification (see above). The aortic arch is not visualized on these scans and, thus, is not included in the assessment.

Events Surveillance

To date, the cohort has been followed for incident cardiovascular events for a median of 49 months.^{x, xi} At intervals of 9–12 months, a telephone interviewer contacted each participant to inquire about interim hospital admissions, cardiovascular outpatient diagnoses, and deaths. In order to verify self-reported diagnoses, we requested copies of all death certificates and medical records for hospitalizations and outpatient cardiovascular diagnoses and conducted next-of-kin interviews for out of hospital cardiovascular deaths. We obtained records on 98% of reported hospitalized cardiovascular events. Information was available on 95% of reported outpatient diagnostic encounters.

Trained personnel abstracted medical records suggesting possible cardiovascular events. Two physicians independently classified and assigned incidence dates. If, after review and adjudication, disagreements persisted, a full mortality and morbidity review committee made the final classification. For purposes of this study, we used either hard CHD event (definite or probable MI, resuscitated cardiac arrest, or CHD death) or all incident CHD events as the endpoint, including definite or probable MI, resuscitated cardiac arrest, fatal CHD, definite angina, and probable angina if accompanied by revascularization. Reviewers classified MI as definite, probable, or absent, based primarily on combinations of symptoms, ECG, and cardiac biomarker levels. In most cases, definite or probable MI required either abnormal cardiac biomarkers (2 times upper limits of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, and ST-T evolution or new LBBB, and biomarker levels 1–2 times upper limits of normal. Reviewers classified resuscitated cardiac arrest when a patient successfully recovered from a full cardiac arrest through cardiopulmonary resuscitation (including cardioversion). Angina was classified, except in the setting of MI, as definite, probable, or absent. Definite or probable angina required symptoms of typical chest pain or atypical symptoms. Probable angina required, in addition to symptoms, a physician diagnosis of angina and medical treatment for it. Definite angina required one or more additional criteria, including CABG surgery or other revascularization procedure; 70% or greater obstruction on coronary angiography; or evidence of ischemia by stress tests or by resting ECG. We

considered coronary revascularization or a physician diagnosis of angina or CHD, in the absence of symptoms, to not be angina.

Fatal CHD required a documented MI within the previous 28 days, chest pain within the 72 hours before death, or a history of CHD, and required the absence of a known non-atherosclerotic or non-cardiac cause of death. Follow-up information was not available in 5 individuals and they were excluded from the final analyses. .

For purposes of this study, all incident CHD and hard CHD events were considered as the primary endpoints. All CHD events included definite or probable MI, resuscitated cardiac arrest, fatal CHD, definite angina, and probable angina if accompanied by revascularization. Hard CHD events were classified as nonfatal myocardial infarction or coronary heart disease related death.

Statistical Methods

We used chi-square tests for discrete variables and one-way analysis-of-variance tests for continuous variables to test for differences in demographic and risk factors between participants with and without coronary events. We constructed Kaplan–Meier cumulative-survival curves for major coronary events (myocardial infarction, resuscitated cardiac arrest, or death from coronary heart disease) and for any coronary event. The data were analyzed according to presence or absence of TAC in the overall cohort as well as stratification by gender

We used Cox proportional-hazards regression to estimate hazard ratios for major coronary events and for any coronary event according to the presence of TAC. Thoracic aorta calcification was examined both as a stratified variable (absence/presence) and as a continuous variable. The potential interaction between gender and TAC was assessed in predicting all and hard CHD events. In the analysis treating thoracic calcium score as a continuous variable, we used the logarithm of the thoracic calcium score plus 1 ($\log[\text{TAC} + 1]$). Four models in hierarchal fashion were conducted as follows:.

Model 1: Unadjusted

Model 2: adjusted for age, race and gender (except in gender stratified models)

Model 3: adjusted for age, race, gender, (except in models stratified by gender), body mass index, hypertension, diabetes mellitus, cigarette smoking, family history of heart attack, LDL cholesterol levels, cholesterol lowering medications

Model 4: Model 3+ CAC categories (0, 1–100, 101–400 & >400)

In addition, to determine whether the addition of TAC contributed significantly to the models containing traditional risk factors alone as well as traditional risk factors + CAC scores in predicting future all and hard CHD events the likelihood ratio chi-square statistic was used. All statistical analyses were performed with STATA version 10.0 (Stata Corp., Austin, Texas, <http://www.stata.com>). The level of significance was set at $p < 0.05$ (two-tailed).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written. The manuscript was approved by both the publications and steering committee of MESA.

RESULTS

Study Cohort

The final study population consisted of 6,807 MESA participants (mean age 62 ± 10 years; 53% females) with a mean follow-up period of 4.5 ± 0.9 years. Overall, TAC was seen in 1,904 (28%) of the study population, with females showing a slightly higher prevalence than men (29% vs. 27%, $p=0.037$). In our study, 3009 (44%) had no detectable CAC and TAC, 406 (6%) had TAC>0 in presence of no CAC, 1894 (28%) had CAC>0 but TAC=0 and 1498 (22%) had presence of both CAC and TAC. A higher prevalence of TAC was observed in women among those with CAC >0 (52% vs. 38%, $p<0.0001$) as well with CAC=0 (14% vs. 9%, $p<0.0001$), respectively. Table 1 shows the baseline characteristics of the study cohort according to presence and absence of TAC among men and women. As shown here, individuals who had TAC>0 were older and had a less favorable cardiovascular risk profile and more likely to have CAC.

Risk of CHD with TAC among Men and Women

A total of 232 participants (3.41%) had CHD events. One hundred and thirty two (1.94%) had a hard CHD event (MI, resuscitated cardiac arrest, or CHD death). Of all CHD events 14 (6%) had probable angina. The respective incidence for all and hard CHD events were 1.89% ($n=68$) and 1.08% ($n=39$) in women, and 5.11% ($n=164$) and 2.90% ($n=93$) in men.

A significant interaction of TAC and gender was found and thus all analyses are presented separately for men and women. In women with TAC>0 vs. TAC=0 the incidence of all CHD events were 4.50% vs. 0.82% ($p<0.0001$) and hard CHD events were 2.58% vs. 0.47% ($p<0.0001$). On the other hand among men with TAC>0 vs. TAC the incidence of all CHD events were 8.50% vs. 3.87% ($p<0.0001$) and hard CHD events were 4.89% vs. 2.17% ($p<0.0001$). Figures 1 and 2 shows the unadjusted Kaplan–Meier cumulative-survival curves for any CHD and hard event according to presence of TAC among men and women, and were statistically significant ($P<0.001$).

Table 2 shows the risk of incident CHD associated with presence of TAC by gender. The interaction between gender and the presence of TAC for incident CHD was significant ($p=0.004$). In unadjusted analyses, the hazard ratio for any CHD event was 5.70 (95% CI: 3.41–9.55) in women and 2.34 (95% CI: 1.72–3.19) in men. After adjustment for demographics and CHD risk factors (model 3), the risk of any CHD was nearly 3-fold greater among those with presence of TAC in women, with no significant association seen in men ($p=0.007$ for interaction). With further adjustment for increasing burden of coronary artery calcified plaque (model 4), the hazard ratio for any CHD event was 2.15 (95% CI: 1.10–4.17) in women & 0.92 (95% CI: 0.64–1.32) in men with presence of TAC ($p=0.027$ for interaction). Similar interactions between gender and risk of hard CHD events were observed (table 2). When TAC was assessed as a continuous variable (a 1-unit increase in

log [TAC+1]) was only associated with CHD events in women (HR 1.13, 95% CI: 1.03–1.24, $p=0.013$), whereas it was not predictive in men (HR 1.03, 95% CI: 0.97–1.10, $p=0.29$). In addition similar results were noted when the analyses were repeated across increasing levels of TAC. In women as compared with no TAC, increasing levels of TAC was significantly associated with CHD events (1st tertile: 3.87, 95% CI: 1.89–7.92; 2nd tertile: 2.51, 95% CI: 1.15–5.52; 3rd tertile: 2.59, 95% CI: 1.19–5.66). The respective hazard ratios in men were 0.98 (0.56–1.65), 1.55 (0.97–2.49) and 1.30 (0.78–2.16).

In women, the likelihood ratio chi square statistics indicate that the addition of TAC contributed significantly to predicting *any* incident CHD event above that provided by traditional risk factors alone (chi square= 12.44, $p=0.0004$) as well as risk factors + CAC scores (chi square= 5.33, $p=0.02$) models. On the other hand, addition of TAC only contributed in the prediction of *hard* CHD events to traditional risk factors (chi-square=4.33, $p=0.04$) in women, without contributing to the model containing both risk factors and CAC scores (chi square=1.55, $p=0.21$). No such additive value was demonstrated for TAC in men (data not shown).

In sub analysis, as shown in figure 3 the unadjusted Kaplan–Meier cumulative-survival curves demonstrate that presence of TAC appeared to be significantly associated with events with events only in presence of CAC. In multivariable analysis, among those without detectable CAC adjusting for risk factors (model 3), TAC was not predictive of CHD events in both women (HR: 0.86, 95% CI: 0.16–4.63) and men (HR: 0.53, 95% CI: 0.06–5.01). On the other hand among individuals with CAC>0 adjusting for demographics and risk factors (model 3), presence of TAC was predictive of CHD events in women (HR: 3.15, 95% CI: 1.50–6.67), however no significant interaction was observed among men (HR: 1.11, 95% CI: 0.77–1.61). On further taking into account CAC scores among those with CAC>0, the relationship of TAC with CHD events although attenuated, remained statistically significant in women (HR: 2.83, 95% CI: 1.32–6.05). No such significant association was observed in men (HR; 0.95, 95% CI: 0.66–1.38).

Discussion

Coronary artery calcified CAC plaque, as measured by cardiac CT, is a measure of subclinical coronary artery disease, is strongly associated with the presence of CHD and CV events and adds to established CVD predictors^{xii,xiii,xiv,xv}. Similarly, TAC has been associated with both atherosclerosis risk factors and inflammatory markers^{xvi,xvii} and an increased CHD and stroke risk^{xviii,xix,xx,xxi}. Furthermore, the individuals with calcification in the descending thoracic aorta have 3.8 times the relative risk for obstructive coronary artery disease (CAD) independent of age.^{xxii} Generally the prevalence of DTAC is relatively low in people under age 60 but increases significantly with age^{xxiii}. Furthermore, the inter-relationship of TAC and CAC is being further explored.^{xxiv} In MESA, DTAC was found to be a strong predictor of CAC independent of CV risk factors^{xvi}. DTAC was more strongly associated with CAC in women and non-white ethnic groups.

Several studies have evaluated the presence of TAC on x-rays or echocardiography, but could not quantify TAC, nor assess whether it provides incremental predictive value to

CAC. These studies linked the presence of aortic calcification on chest x-rayⁱⁱⁱ or aortic atheroma using transesophageal echocardiography^{xxv,xxvi,xxvii,xxviii,xxix} to CV outcomes. In addition, a recent study of helical CT demonstrated that in stable angina pectoris patients, aortic calcification is significantly associated with death and cardiovascular events.^{xxx} However, unlike this study, the authors did not control for coronary calcification, and had insufficient events to discern any gender differences.

In a recent study, Santos et al presented data on 8401 individuals followed for 5 years and reported that TAC was independently associated with all cause mortality (HR 1.61, 95% CI: 1.10–2.27, p=0.015) and the strength of association although slightly stronger in women, was also predictive of events in men^{xxxi} However it must be noted that risk factors were self-reported and the probability of “residual confounding” cannot be ruled out. In addition, the cause of mortality could not be ascertained.

In our prospective study of multiethnic population, among whom all risk factors were calculated we were able to demonstrate that TAC was associated with an increased risk of all and hard CHD events only among women. The results were robust even after taking into account underlying CAC burden. In sub-analysis, although presence of TAC was associated with CHD outcomes in those with CAC>0 among women, however it is important to note that no TAC and CAC interaction was noted. This can be attributed to low prevalence of TAC among women with absence of CAC (13%). In addition, it is important to note that the number of events that occurred among participants with CAC zero scores was extremely low, and we could not ascertain an independent predictive power of TAC in that cohort. Longer evaluation will be needed to ascertain if the isolated presence of TAC is independently predictive of events. In spite of these factors, we believe our study is an important contribution to current literature assessing independent prognostic value of thoracic aortic calcification, in a model including coronary calcified plaque, taking into account gender, ethnicity and race.

A major finding of our study was the presence of a significant gender interaction the predictive value of TAC. In women, TAC was associated with a 3 fold greater risk of incident CHD events, a relationship that remained robust even after taking into risk factors and CAC scores. On the other hand as far as hard CHD are concerned the relationship no longer persisted once CAC scores were taken into account. A low number of hard CHD events may have contributed to this lack of statistical association; it is possible that the relationship becomes more apparent in longer term follow-up. However, among men, determination of TAC did not provide any prognostic information for future CHD risk once traditional risk factors were taken into account.

The reason for this increased event rate among women but not men is not well understood. One explanation related to the gender differences may be that the relation between atherosclerosis and TAC may not be as uniform as CAC. TAC involves two pathophysiological processes: intimal, which is atherosclerotic, and medial,ⁱⁱⁱ which contributes to increased aortic stiffness, while CAC is either solely or mostly entirely atherosclerotic (intimal).^{xxxii} Microvascular disease appears to portend worsening CAD prognosis for women more so than men.^{xxxiii} Pathobiologic data further support gender

differences in the etiology for acute coronary thrombosis with, plaque erosion occurring more often in women as compared to men.^{xxxiv} Since CT cannot differentiate accurately between intimal and medial calcifications, the contributions of medial calcification may be more significant in women, as smaller arteries may make these sheer forces more hazardous. Furthermore, diabetes and hypertriglyceridemia notably increase CHD mortality in women more so than men^{xxxv}, and medial calcification and thoracic calcification are both associated with diabetes. These potential gender difference is important, as women tend to have lower CAC prevalence and severity, yet increased prevalence of TAC.^{xxxvi, xxxvii, xxxviii}

It is also important to note that once CAC was taken into account, we did not find a significant association with TAC among women. This can attributed to the fact that very few hard CHD events were note in this specific subgroup (n=39) and more events as well follow-up will be needed to benefit above and beyond such hard events once CAC is adjusted. Secondly,

In conclusion, our multi-ethnic study population-based prospective study demonstrates that TAC provides additional prognostic information for CHD risk in women above and beyond obtained from assessment of coronary calcification. In addition, TAC can easily be measured on non-gated studies of the chest, and could potentially provide physicians important information of future risk of CHD outcomes in women as this information is clearly identifiable on all CT imaging of chest without extra cost or radiation exposure.^{xxxix}

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Figure 1.
Kaplan Meyer Survival Curves for All CHD Events with TAC

Figure 2.
Kaplan Meyer Survival Curves for Hard CHD Events with TAC

Figure 3.
Kaplan Meyer Survival Curves for All CHD Events with Presence and Absence of TAC and CAC

Table 1
Baseline Characteristics of Study Population Whether the Participant had a Subsequent Coronary Event

Variable	Total (n=6807)			Men (n=3209)			Women (n=3598)		
	No CHD Event (n=6575)	CHD Event (n=232)	P Value	No CHD Event (n=3045)	CHD Event (n=164)	P Value	No CHD Event (n=3530)	CHD Event (n=68)	P Value
Age (years)	62±10	68±9	<0.0001	62±10	67±9	<0.0001	62±10	70±9	<0.0001
Gender (males)	46%	71%	<0.0001	-	-	-	-	-	-
Race									
Whites	38%	45%		39%	44%		38%	49%	
Chinese	12%	7%	0.06	12%	8%	0.39	12%	4%	0.15
African Americans	28%	26%		26%	25%		29%	26%	
Hispanics	22%	22%		22%	23%		21%	21%	
Current smoker	13%	15%	0.004	15%	16%	0.57	12%	13%	0.11
Hypertension	44%	66%	<0.0001	42%	63%	<0.0001	46%	72%	<0.0001
Diabetes Mellitus	14%	29%	<0.0001	15%	29%	<0.0001	13%	29%	<0.0001
Family history of heart attack	40%	50%	0.003	36%	48%	0.003	43%	54%	0.06
BMI kg/m ²	28±5	29±5	0.53	28±4	28±5	0.36	29±5	29±5	0.35
LDL-C (mg/dl)	117±31	120±34	0.12	117±31	122±34	0.04	118±32	117±33	0.92
HDL-C (mg/dl)	51±15	46±14	<0.0001	45±12	43±13	0.01	56±15	55±15	0.22
Lipid lowering meds	10%	11%	<0.0001	16%	21%	0.06	15%	35%	<0.0001

Table 2

Hazard Ratios (95% CI) for Hard CHD Events with TAC (TAC>0 vs. TAC=0)

Events/At Risk	All CHD Events				Hard CHD Events			
	Women (n= 68/3598)	Men (n=164/3209)	P Value for Interaction (Women vs. Men)		Women (n= 39/3598)	Men (n=93/3209)	P Value for Interaction (Women vs. Men)	
Model 1	5.70 (3.41–9.55)	2.34 (1.72–3.19)	0.004		5.71 (2.89–11.28)	2.38 (1.58–3.58)	0.033	
Model 2	3.69 (1.98–6.88)	1.52 (1.06–2.16)	0.006		2.75 (1.22–6.20)	1.58 (0.98–2.54)	0.043	
Model 3	3.04 (1.60–5.76)	1.26 (0.87–1.81)	0.007		2.42 (1.03–5.64)	1.34 (0.82–2.17)	0.036	
Model 4	2.15 (1.10–4.17)	0.92 (0.64–1.32)	0.027		1.74 (0.72–4.24)	1.05 (0.64–1.70)	0.094	

Model 1: Unadjusted

Model 2: adjusted for age, race

Model 3: adjusted for age, race, body mass index, hypertension, diabetes mellitus, cigarette smoking, family history of heart attack, LDL cholesterol levels, cholesterol lowering medications

Model 4: Model 3+ CAC categories (0, 1–100, 101–400 & >400)