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Coronary Artery Calcium Progression Among the US and Japanese Men.

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Coronary artery calcification progression among the United States and Japanese men: the Multi-Ethnic Study of Atherosclerosis (MESA) and Shia Epidemiological Study of Subclinical Atherosclerosis (SESSA)

Short title: CAC progression among US and Japanese men

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ABSTRACT

Background

The risk of coronary heart disease remains low in Japan, although distributions of several coronary risk factors have become comparable to those in the United States (US). We prospectively compared coronary atherosclerosis burden, measured with coronary artery calcification (CAC) progression, between men in the 2 countries.

Methods

In 2 population-based samples of 1,712 White, Black, Hispanic, Chinese men in the US and 697 Japanese men in Japan aged 45–74 years without clinical cardiovascular disease, we quantified CAC progression by serial computed tomography with a median of 3.4 and 5.2 years between scans, respectively.

Results

Among White, Black, Hispanic, Chinese, and Japanese men free of baseline CAC, incident CAC was observed in 35.2%, 26.9%, 29.2%, 18.9%, and 29.2%, respectively. After adjustment for times between scans, demographics, behaviors, coronary risk factors, and their changes between scans, White men had significantly higher incident CAC than Japanese men (relative risk, 1.75; 95% confidence interval, 1.33, 2.29). Among those with detectable CAC at baseline, after similar adjustments, all the US race/ethnic groups had significantly greater annual changes in CAC score [mean (95% confidence interval), 39.4 (35.2, 43.6) for White; 26.9 (21.4, 32.4) for Black; 30.6 (24.7, 36.5) for Hispanic; 30.2 (22.6, 37.8) for Chinese men] than Japanese men [15.9 (10.1, 21.8)].

Conclusion

We found higher incident CAC among White men and greater increases in existing CAC among all the US race/ethnic groups than among Japanese men. These differences persisted despite adjustment for differences in coronary risk factors.

Key words: coronary atherosclerosis, coronary artery calcification, risk factor, prospective study, ethnic groups

INTRODUCTION

Compared with the United States (U.S.) and other developed countries, Japan has uniquely had a much lower rates of coronary heart disease (CHD) mortality, and this has largely been attributed to population-wide lower concentrations of serum total cholesterol (1,2). Recently, however, the levels of several coronary risk factors have become comparable between the US and Japan, particularly among men (2). Serum total cholesterol levels in Japanese men have steadily increased and reached levels similar to those observed in US men (2). In addition, Japanese men have similar or higher prevalence of hypertension, diabetes mellitus, and cigarette smoking compared with US men (2). Thus, some epidemiologic studies in Japan have observed a trend of increasing CHD incidence among men due to less favorable coronary risk factor profiles (3,4), whereas overall CHD incidence in the U.S appears to be declining in recent years (5-7). Given these changing trends between the US and Japan, it is of interest to investigate whether there is still a difference in the burden of coronary atherosclerosis between the 2 countries and, if there is, whether the difference between the 2 countries could be explained by the discrepancy in the distributions of traditional coronary risk factors.

Coronary artery calcification (CAC) is a well-established marker for coronary atherosclerosis (8) that, as assessed by the quantitative Agatston score (9), correlates well with histologic coronary plaque burden (10,11), and its presence and progression are strongly

predictive of future coronary events (12,13). Comparing CAC scores is, therefore, likely to offer investigators the opportunity to gain insight into the overall burden of subclinical atherosclerosis. We previously found that CAC prevalence among Japanese men was substantially lower than among US White men, even after adjustment for traditional coronary risk factors (14,15). However, these studies were restricted to cross-sectional design and it remains unclear whether a difference in CAC progression exists between the 2 groups. In addition, no data are available on the comparison of CAC burden between Black, Hispanic, and Chinese men in the US and Japanese men in Japan.

In the present study, using 2 prospective community-based cohorts of US [the Multi-Ethnic Study of Atherosclerosis (MESA)] and Japanese men [the Shia Epidemiological Study of Subclinical Atherosclerosis (SESSA)], we aimed to compare the progression of CAC across multiethnic cohorts in the 2 countries and to determine whether race/ethnic differences persist after adjusting for concurrent traditional coronary risk factors.

METHODS

Study population

The study population consisted of male participants who were free of clinical cardiovascular diseases from 2 cohort studies: MESA in the US and SESSA in Japan. MESA was designed to examine the prevalence, incidence, and progression of subclinical atherosclerosis and their risk factors in a multiethnic cohort in the U.S (16). In brief, 6814 participants aged 45–84 years who identified themselves as White, Black, Hispanic, or Chinese were recruited from 6 US communities (Forsyth County, North Carolina; northern Manhattan and the Bronx in New York City; Baltimore City and Baltimore County, Maryland; St. Paul, Minnesota; Chicago, Illinois; and Los Angeles County, California) at baseline (2000–2002), and they were followed up to exam 6 (2016–2018). SESSA is also an ongoing prospective study of subclinical atherosclerosis and its determinants in a community-based sample of Japanese residents (17). In brief, Japanese men aged 40–79 years who lived in Kusatsu City, Shiga, Japan were examined at baseline (2006–2008) and followed-up (2010–2014). Candidates were identified on the basis of a random sample from the Kusatsu City Basic Residents' Registration, which includes the name, age, and sex of all city residents (15). In both cohorts, we analyzed only participants who gave informed consent, and the study protocol was approved by each institution's institutional review board.

For the present study, we limited our analyses to those aged 45–74 years at baseline

to ensure comparability, as this age range is found in both cohorts. CAC data were used to estimate CAC progression from the baseline (2000–2002) to follow-up examinations (exam 3, 2004–2005 or exam 4, 2005–2007) in MESA and from the baseline (2006–2008) to follow-up examinations (2010–2014) in SESSA, to ensure comparability that the follow-up period was mostly identical in the both cohorts. In MESA, CAC data in exam 4 were chosen in men who underwent both follow-up examinations (exam 3 and 4) to make the follow-up period more comparable (n = 59). The MESA population included 1,994 men with both baseline (2000–2002) and follow-up (exam 3, 2004–2005 or exam 4, 2005–2007) examinations. The SESSA population also included 853 men with both baseline (2006–2008) and follow-up (2010–2014) surveys. We excluded MESA and SESSA participants who were not 45–74 years of age at baseline (n = 259 and 151, respectively) and with missing key covariates of interest (n = 23 and 5, respectively).

CAC measurement

A detailed description of the method of CAC measurement in MESA has been given elsewhere (18). The protocol used to assess CAC in SESSA was the same as that in the preceding community-based multicenter study (14,19). In brief, for the 2 protocols, imaging software automatically identified a lesion of candidate CAC on the basis of predefined criteria. Then a reader reviewed each candidate lesion to either accept or reject it and scored

the accepted lesions according to the method of Agatston et al. (9). The criteria for automated identification were somewhat different between the 2 protocols. In MESA, 3 criteria needed to be met: computed tomography (CT) attenuation of ≥130 Hounsfield Units (HU), 4 contiguous pixels (1.15 mm^3 for 4-detector-row CT; 1.38 mm^3 for electron-beam CT), and location within an 8-mm radius of the coronary artery trajectory (18). In SESSA, a CAC lesion was considered to be present with 3 contiguous pixels (1 mm^3) with attenuation of ≥130 HU (15,17). In MESA, participants were scanned twice at each exam, and the average of Agatston scores obtained from the 2 images was used in the analysis (20). In SESSA, participants were scanned once for each exam by either electron-beam CT or 16-detector-row CT (17). Based on a study of the duplicate images from 99 SESSA participants read at both imaging centers (i.e., MESA and SESSA), we observed high intraclass correlation coefficients (ICCs) for correlation between MESA and SESSA, regardless of the type of CT [for electron-beam CT, ICC = 0.96 (95% confidence interval: 0.93, 0.98); for multidetector-row CT, ICC = 0.95 (95% confidence interval): 0.91, 0.97], and we found overall agreement across Agatston score levels from 0 to 3,500, with no evidence of systematic difference (21).

Other measurements

In MESA, blood pressure was measured 3 times after the participant had emptied his bladder completely and had rested in a seated position for 5 minutes using a Dinamap Pro 1000

automated oscillometric sphygmomanometer (Critikon Company, Tampa, Florida) and an appropriately sized cuff. The average of the last 2 measurements was used in the analysis. In SESSA, blood pressure was measured twice consecutively on the right arm of the seated participant after the participant had emptied his bladder and had sat quietly for 5 minutes, using an automated oscillometric sphygmomanometer (BP-8800; Omron Healthcare Co. Ltd., Kyoto, Japan) with an appropriately sized cuff, and the average of the 2 measurements was used. In MESA, a central laboratory (University of Vermont, Burlington, Vermont) measured levels of total and high-density lipoprotein (HDL) cholesterol [using ethylenediaminetetraacetic acid (EDTA) plasma], and plasma glucose in blood samples obtained after a 12-hour fast. Measurements of the lipids were standardized according to the protocol of the US Centers for Disease Control and Prevention (CDC)/Cholesterol Reference Method Laboratory Network (CRMLN). In SESSA, blood samples were obtained early in the clinic visit after a 12-hour fast. The samples were sent for routine laboratory tests, including testing for lipids and glucose levels. Serum total cholesterol was determined using enzymatic assays, and HDL cholesterol was measured using a direct method (Determiner-C-TC and Determiner-L HDL-c, respectively; Kyowa Medix, Tokyo, Japan). Serum lipid levels were determined at a single laboratory (Shiga Laboratory; MEDIC, Shiga, Japan) that had been certified for standardized lipid measurements according to the CDC/CRMLN. Plasma glucose levels were determined from sodium fluoride–treated plasma using a

hexokinase/glucose-6-phosphate dehydrogenase enzymatic assay. Low-density lipoprotein (LDL) cholesterol levels were calculated using the Friedewald equation in both MESA and SESSA. For comparison, we converted all of the lipid values in MESA (obtained by EDTA plasma) to their serum equivalents by multiplying them by 1.03 in order to match the values in SESSA, following a recommendation by the National Cholesterol Education Program (22). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. In both MESA and SESSA, a self-administered questionnaire was used to obtain information on demographics, medical history, medication use, smoking habits, and other pertinent factors. Trained staff members confirmed the reported information with each participant. Diabetes mellitus was defined as fasting glucose concentration ≥126 mg/dL, or insulin or oral hypoglycemic medication use, and hypertension was defined as systolic/diastolic blood pressure ≥140/90 mmHg or antihypertensive medication use (15,16).

Statistical analysis

Distribution of demographics, behavioral and coronary risk factors, and medication uses among White, Black, Hispanic, and Chinese men in the US were compared with Japanese men in Japan using a *t* test or Wilcoxon rank-sum test for continuous variables and a χ^2 test or Fisher's exact test for proportions.

Progression of CAC was defined in 2 ways, as previously described by Kronmal et

al. (23): 1) incident CAC was defined as detectable CAC (CAC score >0) at the follow-up examination in men free of detectable CAC (CAC score = 0) at baseline examination; and 2) annual change in CAC score in men who had detectable CAC (CAC score >0) at baseline examination. The following multivariable models were fitted: Model 1 was adjusted for age and education (high school or more vs. less than high school) at baseline; Model 2 was adjusted for Model 1 covariates plus cigarette smoking status (never/former/current), pack-years of smoking, BMI, systolic blood pressure, antihypertensive medications use (yes/no), total cholesterol, HDL cholesterol, statin use (yes/no), and diabetes mellitus (yes/no) at baseline; and Model 3 was adjusted for Model 2 covariates plus changes in the behavioral and coronary risk factors and medication use between CT scans. CT scanner changes at some sites of MESA and in SESSA between baseline and follow-up influenced the magnitude of CAC progression, and a term for scanner pair was included in all models (15,23). For incident CAC analysis, time between CT scans was also included in all models. Our primary analysis for the annual change in CAC score among those with detectable CAC at baseline did not control for baseline CAC score. Incorporating CAC score in the model would lead to overcorrection/overmodeling because risk factors that produce baseline CAC also contribute to CAC progression (23,24). In other words, baseline CAC is not a confounder but part of the causal pathway for the relation between risk factors and CAC progression. In a secondary analysis, we explored whether race/ethnic differences persisted after further adjustment for

baseline CAC score (23).

We used relative risk regression (25) to obtain asymptotically unbiased estimates of relative risk for incident CAC among those free of baseline CAC. That is, the probability of incident CAC was modeled as a function of covariates using a generalized linear model with log link and binomial error distribution. We used relative risk regression rather than logistic regression because incidence of CAC was >10% in the both cohorts, so the odds ratio would tend to overestimate the true relative risk. To estimate the annual change in CAC score among those with baseline CAC, we used robust linear regression, down-weighting the influence of participants with very large progression to increase model robustness (23). Analyses are performed using SAS software (version 9.4; SAS Institute, Inc., Cary, North Carolina). Two-tailed *P* values of <0.05 are considered statistically significant.

RESULTS

The final MESA and SESSA cohorts for the current analysis included 1,712 US men (688 White, 449 Black, 375 Hispanic, and 200 Chinese) and 697 Japanese men, respectively. Baseline characteristics of study participants are shown in **Table 1**. Compared with Japanese men, all the US race/ethnic groups were younger, had lower levels of systolic and diastolic blood pressure and total, LDL, and HDL cholesterol, and smoked fewer cigarettes. Additionally, White men had lower prevalence of diabetes than Japanese men. Meanwhile, compared with Japanese men, White, Black, and Hispanic men had greater BMI, White men took more statin medication, and Black men took more antihypertensive medication. Time between CT scans was shorter in MESA than in SESSA. Black, Hispanic, and Chinese men had less CAC prevalence (CAC score >0) compared with Japanese men, whereas among those with detectable CAC (CAC score >0), White, Black, and Hispanic men had greater CAC score than Japanese men.

Table 2 shows incident CAC (CAC score >0) among men without detectable CAC at baseline by race/ethnicity. We observed incident CAC in 35.2% of White, 26.9% of Black, 29.2% of Hispanic, 18.9% of Chinese US men and 29.2% of Japanese men. After adjustment for time between CT scans, demographics, behavioral and coronary risk factors, and medication use at baseline (Model 2), White men had significantly higher incident CAC than Japanese men (relative risk, 1.68; 95% confidence interval, 1.25, 2.25). After further

adjustment for changes in behavioral and coronary risk factors and medication use between CT scans (Model 3), the higher risk for incident CAC in White versus Japanese men persisted (relative risk, 1.75; 95% confidence interval, 1.33, 2.29). Although the point estimates suggested associations in similar directions to the analysis for White men, the differences in incident CAC among Black, Hispanic, and Chinese compared to Japanese men were not statistically significant in the fully-adjusted model.

Table 3 shows annual changes in CAC score among men with detectable CAC (CAC score >0) at baseline by race/ethnicity. Compared with Japanese men, all the US race/ethnic groups had significantly greater annual changes in CAC score after adjustment for demographics, behavioral and coronary risk factors, and medication use at baseline (Model 2). The differences remained significant after further adjustment for changes in behavioral and coronary risk factors and medication use between CT scans (Model 3) [mean progression (95% confidence interval), 39.4 (35.2, 43.6) for White; 26.9 (21.4, 32.4) for Black; 30.6 (24.7, 36.5) for Hispanic; 30.2 (22.6, 37.8) for Chinese men versus 15.9 (10.1, 21.8) for Japanese men]. In the secondary analysis, for comparison between Black, Hispanic, and Chinese and Japanese men, the differences in annual changes in CAC score were attenuated and no longer significant after adjusting for baseline CAC score in addition to the fully adjusted-model (Model 3) (**Supplementary Table 1**).

DISCUSSION

In this community-based longitudinal comparison between White, Black, Hispanic, and Chinese men in the US and Japanese men in Japan aged 45–74 years, we found a higher rate of incident CAC among US White men and greater increases in existing CAC among all the US race/ethnic groups compared with Japanese men, even after adjusting for demographics, behavioral and traditional coronary risk factors, and medication use such as statins at baseline as well as their changes between CT scans. We previously reported that US White men had a higher CAC prevalence than Japanese men even after adjustment for known coronary risk factors (14,15). The present results are generally consistent with and extend the cross-sectional observations by means of a longitudinal comparison between multiethnic (White, Black, Hispanic, and Chinese) and Japanese groups.

Japanese men have been reported to have a lower CHD burden than US men (2). Recently, however, the distributions of coronary risk factors have reached similar levels in Japan and the US(2). Indeed, we found that Japanese men had higher levels of blood pressure and total and LDL cholesterol and were also 1.5–3 times more likely to smoke cigarettes than the US men. Evidence for recent trends of CHD in Japan is varied. Some prospective studies showed an increased trend in CHD incidence, particularly among men with elevated levels of serum total cholesterol, BMI, and diabetes mellitus (3,4). Conversely, the Hisamaya Study, one of the best-known cohort studies in Japan, found no clear trend in incident acute

myocardial infarction (26). Recently, some population-based studies in the US have observed a decreasing trend in incident CHD (6,7) coincident with improvements in total cholesterol and blood pressure levels (5,7). Given the possible opposite trends in risk factor levels and clinical CHD between Japan and the US, we hypothesized that the overall burden of coronary atherosclerosis may be becoming more similar between the 2 countries as well, especially among men. However, our findings on subclinical atherosclerosis revealed that Japanese men still have less incident CAC or increase in existing CAC than US men.

The observed difference in CAC progression between the US and Japanese men may result from multiple factors. One possible factor may be a difference in duration of exposure to coronary risk factors between the US and Japanese men. Individuals with longer term exposure to coronary risk factors may have higher accumulation of calcified coronary plaque as well as noncalcified plaque before baseline, and it is assumed that such individuals also continue to have more rapid CAC progression thereafter due to a plaque composition shifted from noncalcified to calcified plaque. In fact, even if current total cholesterol levels between the 2 populations are comparable, the cumulative association of total cholesterol with atherosclerosis is smaller among Japanese men than among US men (1,2). This hypothesis is supported by our interesting finding that the difference in advancing existing CAC between the 2 countries was attenuated by further adjustment for baseline CAC score, which is considered related to the long-term cumulative exposure to risk factors (23,27).

It is possible that the differences in CAC do not purely reflect differences in atherosclerosis (28). Statins has been suggested to stabilize plaque by decreasing lipid-rich and necrotic plaque components and increasing plaque calcification (29). In the present study, statin use was more prevalent among White men, although White men still had greater CAC progression than Japanese men after accounting for statin use. Bone or mineral metabolism (30,31) or genetic factors (32,33) are also reported to explain some of the variation in vascular calcification. Moreover, there may be potential race/ethnic differences in the distribution of calcified and non-calcified atherosclerotic plaques. CAC is a quantitative marker of the extent of coronary atherosclerotic plaque, an observation derived from pathologic studies performed mostly in US White men that found strong correlations between histological plaque and calcium area (10,11). Unfortunately, in these pathologic studies, inter-ethnic variation in the calcium-atherosclerotic relationship have not been well described. However, a recent autopsy study found calcified plaque was consistently greater in Whites than in Blacks in all decades (34). Further studies are warranted to elucidate the difference in histological distributions of calcified and non-calcified atherosclerotic plaques between the US and Japanese populations.

The present study is the first prospective comparative evaluation of subclinical atherosclerosis, measured as CAC progression, across population-based multiethnic (White, Black, Hispanic, and Chinese) US and Japanese men with valid comparability for CAC

scores (21). Limitations of the present study warrant consideration. First, the non-standardized measurement in both cohorts might have introduced some bias to the comparison. For example, the values of blood pressure were calculated by average of the second and third measurements in MESA, whereas, those were derived from the average of the first 2 measurements in SESSA. The higher blood pressure observed in Japanese men may be partly due to methodological differences. We made several attempts to overcome this limitation, including comparability evaluation for CAC score (21) as mentioned above, use of CDC/CRMLN-standardized laboratories for lipid measurements, and converting lipid values obtained by EDTA plasma to serum equivalents. However, other potential biases may have been in effect. Second, the different baseline period (2000–2002 and 2006–2008, respectively) and follow-up duration (median, 3.4 and 5.2 years, respectively) in MESA and SESSA may have affected our results. We considered the differences in follow-up duration in the analysis, although their effect would not be completely controlled. As noted above, given the possible opposite trends in incident CHD rates between the 2 countries, we could have confirmed greater difference in CAC progression between the 2 cohorts if we measured CAC in SESSA at the same baseline period and follow-up duration as in MESA. Third, our study may have been underpowered especially to detect the differences in incident CAC among the US men compared to Japanese men; this is because, although the differences were not statistically significant, the point estimates of their relative risks indicated associations in the

same directions between the US men from each group. Finally, we studied only men and the Japanese sample was obtained from a single area, both of which may limit the generalizability of our results.

In summary, we found higher incident CAC particularly among US White men, and greater increases in existing CAC among all race/ethnic groups in the US, than among Japanese men in Japan. These differences between the 2 countries were not explained by the discrepancy in the distributions of traditional coronary risk factors. Explanations responsible for these differences should be sought, which may inform clinical interpretation and our understanding of the pathophysiology of coronary atherosclerosis.

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Conflicts of Interest/Disclosures

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Table 1. Baseline characteristics in the US and Japanese men by race/ethnicity

	MESA				SESSA
	White N=688	Black N=449	Hispanic N=375	Chinese N=200	Japanese (Reference) N=697
Age, years	59.9 (8.3)‡	59.5 (8.4)‡	58.4 (8.5)‡	60.2 (8.2)‡	63.2 (7.2)
High school graduate or higher, N (%)	661 (96.1)‡	401 (89.3)*	231 (61.6)‡	173 (86.5)	592 (84.9)
BMI, kg/m^2	28.3 (4.1)‡	28.7 (4.5)‡	28.8 (4.3)‡	24.0 (3.0)	23.6 (2.9)
Blood pressure, mmHg					
Systolic	123.1 (17.5)‡	129.0 (19.1)‡	124.3 (18.6)‡	121.7 (18.1)‡	136.2 (18.4)
Diastolic	74.6 (8.9)‡	77.7 (9.1)‡	75.7 (9.1)‡	75.0 (9.2)‡	80.7 (11.0)
Hypertension, N (%)	285 (41.4)‡	256 (57.0)	148 (39.5)‡	68 (34.0)‡	390 (56.0)
Antihypertensive medication, N (%)	219 (31.8)	203 (45.2)‡	110 (29.3)	47 (23.5)*	216 (31.0)
Cholesterol, mg/dL					
Total	194.4 (36.3)‡	189.3 (36.2)‡	197.7 (37.0)‡	194.5 (33.0)‡	211.1 (33.0)
LDL	120.8 (30.0)†	119.6 (34.3)‡	121.4 (32.8)*	120.7 (29.0)*	125.8 (31.9)
HDL	45.8 (11.8)‡	47.4 (12.6)‡	43.8 (10.2)‡	46.2 (10.5)‡	59.0 (17.0)
Statin medication, N (%)	132 (19.2)‡	58 (12.9)	39 (10.4)	19 (9.5)	77 (11.0)

Fasting glucose, mg/dL	94.6 (24.9)‡	100.0 (29.9)	102.7 (34.5)	101.0 (31.3)	102.8 (20.2)
Diabetes mellitus, N (%)	50 (7.3)‡	79 (17.6)	61 (16.3)	24 (12.0)	112 (16.1)
Antidiabetic medication, N	35 (5.1)‡	60 (13.4)	58 (15.5)*	16 (8.0)	77 (11.0)
(%)					
Smoking, N (%)					
Former	343 (49.9)	186 (41.4)	168 (44.8)	70 (35.0)	357 (51.2)
Current	69 (10.0)‡	95 (21.2)‡	63 (16.8)‡	22 (11.0)‡	218 (31.3)
Pack-years of smoking[δ],	21.0 (7.6, 42.0)‡	17.5 (7.5, 34.0)‡	10.5 (3.0, 25.0)‡	13.4 (2.8, 25.0)‡	32.0 (16.7, 48.0)
median (25, 75%tiles)					
Time between CT scans, years,	3.4 (3.1, 4.7)‡	3.2 (3.0, 4.4)‡	3.5 (3.1, 4.7)‡	3.4 (3.1, 4.5)‡	5.2 (4.3, 5.9)
median (25, 75%tiles)					
Baseline CAC score >0, N (%)	455 (66.1)	211 (47.0)‡	183 (48.8)‡	109 (54.5)‡	464 (66.6)
Baseline CAC Agatston score[¶],	126.4 (25.5, 393.9)‡	75.0 (19.9, 267.5)†	82.7 (21.5, 287.2)‡	60.5 (22.0, 186.0)	40.6 (7.2, 194.2)
median (25, 75%tiles)					

Data are presented as mean (SD) unless otherwise specified. For the present analysis, MESA included 1,712 men with both baseline (Exam 1, 2000–2002) and follow-up surveys (Exam 3 or 4, 2004–2007), and SESSA include 697 men with both baseline (2006–2008) and follow-up surveys (2010–2014). The distributions were compared using *t* test or Wilcoxon rank-sum test for continuous variables and a χ^2 test or Fisher's

exact test for proportions. Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mmHg or medication use. Diabetes was defined as fasting glucose ≥126 mg/dl or medication use. ‡p<0.001, †p<0.01, *p<0.05. [δ]Among current and former smokers. [¶]Among those with detectable CAC at baseline. BMI, body mass index; CAC, coronary artery calcification; CT, computed tomography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; SESSA, Shia Epidemiological Study of Subclinical Atherosclerosis; U.S., United States

Table 2. Relative risk regression for incident CAC among men without detectable CAC (CAC score = 0) at baseline by race/ethnicity

	Relative risk (95% confidence interval)				
	MESA				SESSA
	White	Black	Hispanic	Chinese	Japanese (Reference)
	N=233	N=238	N=192	N=91	N=233
No. of incidence (%)	82 (35.2)	64 (26.9)	56 (29.2)	17 (18.9)	68 (29.2)
Model 1	1.53 (1.18, 1.98)‡	1.14 (0.86, 1.52)	1.26 (0.92, 1.73)	0.92 (0.59, 1.44)	1.0
Model 2	1.68 (1.25, 2.25)‡	1.16 (0.84, 1.61)	1.23 (0.87, 1.74)	0.97 (0.61, 1.55)	1.0
Model 3	1.75 (1.33, 2.29)‡	1.20 (0.90, 1.60)	1.26 (0.91, 1.73)	1.08 (0.70, 1.68)	1.0

Incident CAC was defined as detectable CAC (CAC score >0) at the follow-up examination in men free of detectable CAC (CAC score = 0) at baseline examination. Model 1, adjusted for age and education at baseline, CT scanner pair, and time between CT scans; Model 2, adjusted for Model 1 + cigarette smoking status, pack-years of smoking, BMI, systolic blood pressure, antihypertensive medications use, total cholesterol, HDL cholesterol, statin use, and diabetes mellitus at baseline; Model 3, adjusted for Model 2 + changes in cigarette smoking status, pack-years of smoking, BMI, systolic blood pressure, antihypertensive medications use, total cholesterol, HDL cholesterol, statin use, and diabetes mellitus between CT scans. ‡p<0.001, †p<0.01, *p<0.05. Abbreviations are shown in Table 1.

Table 3. Robust regression for annual changes in CAC score among men with detectable CAC (CAC score >0) at baseline by race/ethnicity

	Robust mean progression (95% confidence interval) (Agatston units / year)				
	MESA				SESSA
	White	Black	Hispanic	Chinese	Japanese (Reference)
	N=455	N =211	N=183	N=109	N=464
Crude	39.1	33.4	32.1	26.3	25.6
Model 1	38.7 (34.8, 42.6)‡	32.1 (26.9, 37.3)‡	30.6 (25.0, 36.2)†	25.0 (17.6, 32.3)	19.5 (14.3, 24.6)
Model 2	40.8 (36.6, 45.0)‡	27.7 (22.2, 33.2)†	31.3 (25.4, 37.2)‡	30.6 (22.9, 38.2)†	14.8 (9.0, 20.5)
Model 3	39.4 (35.2, 43.6)‡	26.9 (21.4, 32.4)†	30.6 (24.7, 36.5)‡	30.2 (22.6, 37.8)†	15.9 (10.1, 21.8)

Annual change in CAC was calculated as CAC score in follow-up minus CAC score at baseline divided by time between CT scans in years. Model 1, adjusted for age and education at baseline, and CT scanner pair; Model 2, adjusted for Model 1 + cigarette smoking status, pack-years of smoking, BMI, systolic blood pressure, antihypertensive medications use, total cholesterol, HDL cholesterol, statin use, and diabetes mellitus at baseline; Model 3, adjusted for Model 2 + changes in cigarette smoking status, pack-years of smoking, BMI, systolic blood pressure, antihypertensive medications use, total cholesterol, HDL cholesterol, statin use, and diabetes mellitus between CT scans. ‡$p<0.001$, †$p<0.01$, *$p<0.05$. Abbreviations are shown in Table 1.