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Original Contribution

Cross-Sectional Comparison of Coronary Artery Calcium Scores Between Caucasian Men in the United States and Japanese Men in Japan

The Multi-Ethnic Study of Atherosclerosis and the Shiga Epidemiological Study of Subclinical Atherosclerosis

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The incidence of coronary heart disease in the United States has declined, and prevalences of several coronary disease risk factors have become comparable to those in Japan. Therefore, the burden of coronary atherosclerosis may be closer among younger persons in the 2 countries. We aimed to compare prevalences of coronary atherosclerosis, measured with coronary artery calcium scores, between men in the 2 countries by age group (45–54, 55–64, or 65–74 years). We used community-based samples of Caucasian men in the United States (2000–2002; $n = 1,067$) and Japanese men in Japan (2006–2008; $n = 832$) aged 45–74 years, stratifying them into groups with 0, 1, 2, or ≥3 of the following risk factors: current smoking, overweight, diabetes, dyslipidemia, and hypertension. We calculated adjusted odds ratios of US Caucasian men's having Agatston scores of ≥10, ≥100, and ≥400 with reference to Japanese men. Overall, the odds of Caucasian men having each Agatston cutoff point were greater. The ethnic difference, however, became smaller in younger age groups. For example, adjusted odds ratios for Caucasian men's having an Agatston score of ≥100 were 2.05, 2.43, and 3.86 among those aged 45–54, 55–64, and 65–74 years, respectively. Caucasian men in the United States had a higher burden of coronary atherosclerosis than Japanese men, but the ethnic difference was smaller in younger age groups.

atherosclerosis; coronary artery calcium; ethnic group; men

Abbreviations: BMI, body mass index; CAC, coronary artery calcium; CDC, Centers for Disease Control and Prevention; CHD, coronary heart disease; CT, computed tomography; CRMLN, Cholesterol Reference Method Laboratory Network; EDTA, ethylenediaminetetraacetic acid; HU, Hounsfield Units; ICC, intraclass correlation coefficient; MESA, Multi-Ethnic Study of Atherosclerosis; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis.

The Seven Countries Study and other evidence previously suggested that Japan had one of the lowest rates of coronary heart disease (CHD) mortality in the developed world, and this was largely attributed to its low serum total cholesterol level in comparison with other countries, including the United States (1, 2). More recently, however, prevalences of several coronary disease risk factors have reached similar levels in Japan and the United States, particularly among middle-aged men (2). For example, serum total cholesterol levels have steadily increased in Japanese men aged 40–49 years since the 1960s, while those in US men have decreased, reaching levels (200–210 mg/dL) that are comparable between the 2 countries (2). Moreover, epidemiologic studies conducted in different areas of Japan have indicated a trend of increasing CHD incidence (3, 4), while the overall incidence of CHD in the United States is estimated to have declined in recent years (5–7).

Given these changing trends between the United States and Japan, it is of interest to compare the CHD burden between the 2 countries by age group, because there may be graded relationships in CHD burden between the countries across age groups. To obtain a definite answer, one should wait to observe clinical CHD trends in the 2 populations over time, which is time-consuming and labor-intensive. In contrast, comparing subclinical measures of atherosclerosis affords investigators a unique opportunity to obtain insight into the burdens of coronary atherosclerosis. Coronary artery calcium (CAC) level is a well-documented marker for coronary atherosclerosis (8), and the Agatston score (9), a quantitative measure of CAC level, is shown to correlate well with autopsy-confirmed coronary artery plaque levels (10, 11). Therefore, comparison of CAC scores is likely to provide a better assessment of the overall burden of subclinical CHD than a focus on individual risk factors. We have previously shown that middle-aged Japanese men in Japan have a lower burden of CAC than Caucasian men in the United States, even after accounting for traditional risk factors (12). However, the age range of the samples was too narrow (40–49 years) to evaluate the difference by age group. In the present study, we compared community-based samples of men in a broader age range who were recruited from 6 study sites in the United States (the Multi-Ethnic Study of Atherosclerosis (MESA)) and 1 site in Japan (the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA)).

The objectives of the study were: 1) to compare CAC scores between Caucasian men in the United States and Japanese men in Japan, accounting for the different distributions of conventional coronary disease risk factors, and 2) to examine whether the magnitude of the difference in CAC between the 2 populations, if it exists, differed according to age group.

METHODS

Study populations

The study population consisted of male participants from 2 cohort studies: MESA in the United States and SESSA in Japan.

MESA was designed to study the prevalence, risk factors, and progression of subclinical cardiovascular disease in a multiethnic cohort in the United States. A detailed description of the study design and methods has been published previously (13). In brief, 6,814 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) between 2000 and 2002. All participants were free of clinical cardiovascular disease. Only Caucasian men from MESA were analyzed in the present study.

SESSA is a study of subclinical atherosclerosis and its determinants in a community-based sample of Japanese residents (14). Japanese men aged 40–79 years who lived in Kusatsu City, Shiga, Japan, were examined between May 2006 and March 2008. Candidates were identified on the basis of a random sample from the Kusatsu City Basic Residents' Register, which includes the name, age, and sex of all city residents. All of the participants were without clinical cardiovascular disease or other severe diseases (15).

For the present study, we limited our analyses to persons aged 45–74 years at baseline to ensure comparability, as this age range is found in both cohorts.

CAC measurements

A detailed description of the method of CAC measurement in MESA has been given elsewhere (16). The protocol used to assess CAC in SESSA was the same as that in the preceding community-based multicenter study (12). 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 (1.86 mm^2 for 4-detector-row CT; 1.83 mm^2 for electron-beam CT), and location within an 8-mm radius of the coronary artery trajectory (16), whereas in SESSA, a CAC lesion was considered to be present with 3 contiguous pixels (1 mm^2) with attenuation of ≥130 HU. In MESA, all of the participants were scanned twice, and the average of each Agatston score obtained from the 2 images was used in the analysis (17). In SESSA, participants were scanned once by either electron-beam CT or 16-detector-row CT (18). 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 the levels of Agatston score from 0 to 3,500, with no evidence of systematic difference (18).

Other measurements

In MESA, blood pressure was measured 3 times after the participant had rested in a seated position for 5 minutes using a Dinamap Pro 1000 automated oscillometric sphygmomanometer (Critikon Company, Tampa, Florida) and an appropriate-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 for urinalysis and had sat quietly for 5 minutes, using an automated oscillometric sphygmomanometer (BP-8800; Omron Colin, Tokyo, Japan) with an appropriate-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 cholesterol, triglycerides (using ethylenediamine-tetraacetic acid (EDTA) plasma), plasma glucose, and high-sensitivity C-reactive protein 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 and triglyceride levels were determined using enzymatic assays, and high-density lipoprotein cholesterol was measured using a direct method (Determiner-C-TC, Determiner-C-TGL, 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 cholesterol level was 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 (19). 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 demographic characteristics, medical history, medication use, smoking habits, and other pertinent factors. Trained staff members confirmed the reported information with each participant.

We used the following 5 components as conventional coronary disease risk factors: current smoking, overweight status (defined as BMI ≥25), diabetes mellitus (defined as fasting glucose concentration ≥126 mg/dL or medication use), dyslipidemia (defined as low-density lipoprotein cholesterol concentration ≥160 mg/dL, high-density lipoprotein cholesterol concentration <40 mg/dL, or medication use), and hypertension (defined as systolic/diastolic blood pressure ≥140/90 mm Hg or medication use). In both cohorts, we analyzed only those participants who gave informed consent, and the study protocol was approved by each institution's institutional review board.

Statistical analysis

First, we conducted the following analyses separately according to 10-year age group (45–54, 55–64, and 65–74 years). Each group of participants was further divided into 4 categories according to the presence of the 5 conventional risk factors (number of risk factors = 0, 1, 2, or ≥3). We then calculated the crude prevalences of CAC scores less than 10, 10–<100, 100–<400, and 400 or greater. These cutoff values were selected owing to their clinical significance and consistency with previous studies (20–22). Second, we performed logistic regression to obtain odds ratios for Caucasian men's risk of having CAC scores greater than or equal to 10, 100, and 400, with reference to Japanese men, in each age group. Third, we tested for interaction of age group with the association between race and each CAC score cutoff by inserting a product term (age group × ethnicity (Caucasian/Japanese)) into each model. For adjustment, the following covariates were used in the "base component" model: age (years), education (high school or more vs. less than high school), and CT type (electron-beam CT or multidetector-row CT). Model 1 further adjusted for lifetime pack-years of smoking, systolic blood pressure (mm Hg), low-density lipoprotein cholesterol concentration (mg/dL), plasma glucose concentration (mg/dL), and treatment (yes/no) for hypertension, dyslipidemia, and diabetes mellitus. Model 2 further adjusted for BMI. Model 3 further adjusted for alcohol consumption status (current, former, or never), since alcohol drinking is a possible confounder given its reported association with CAC (23).

In describing demographic characteristics, we used a t test or Wilcoxon rank-sum test for continuous variables and a χ^2 test or Fisher's exact test for proportions, as appropriate. Each statistical test was set to be significant at $P < 0.05$ (2-sided P value). SAS software (version 9.2; SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

RESULTS

Characteristics of the participants are given in Table 1. Of the 1,067 Caucasian men (mean age = 60.0 (standard deviation, 8.5) years) and 832 Japanese men (mean age = 63.3 (standard deviation, 7.4) years) studied, 9.8% and 14.2% had no risk factors, whereas 27.3% and 21.4% had ≥3 risk factors, respectively (data not tabulated). This trend of Caucasian men having greater numbers of risk factors than Japanese men was seen across all age groups. Caucasian men had significantly greater BMIs and tended to have a higher prevalence of dyslipidemia, but they smoked fewer cigarettes in all age groups and tended to have less hypertension and diabetes mellitus, particularly among those aged ≥55 years. Medications for hypertension and dyslipidemia were used more commonly among Caucasians than among Japanese. Overall, Caucasian men were in higher CAC categories more often than Japanese men.

Figure 1 shows crude prevalences of CAC scores greater than or equal to 10, 100, and 400 according to number of risk factors. In both ethnic groups, the overall burden of CAC increased as the number of risk factors increased, across all age groups. Regardless of the number of risk factors, however, the crude prevalence of high CAC scores (≥100 and ≥400) was generally greater in Caucasian men than in Japanese men. This was particularly evident among those aged 55–64 years and 65–74 years. For example, the percentage of Caucasian men aged 55–64 years with a CAC score greater than or equal to 100 ranged from 12.1% (0 risk factors) to 44.7% (≥3 risk factors), whereas the corresponding percentages of Japanese men ranged from 9.3% to 24.3% (Figure 1B).

In logistic regression analyses, the ethnic difference increased with age (Figure 2), and the odds of Caucasian men's having CAC scores greater than or equal to 10 tended to be higher than those of Japanese men in all age groups (Table 2). For example, the odds ratios for Caucasian men's

Table 1. Characteristics of Caucasian Men in the United States (2000–2002) and Japanese Men in Japan (2006–2008), by Age Group, in the Multi-Ethnic Study of Atherosclerosis and the Shiga Epidemiological Study of Subclinical Atherosclerosis, Respectively

	Age Range (years) and Ethnicity														
	45–54					55–64					65–74				
	Caucasian (*n* = 333)		Japanese (*n* = 119)		*P* Value[a]	Caucasian (*n* = 341)		Japanese (*n* = 350)		*P* Value[a]	Caucasian (*n* = 393)		Japanese (*n* = 363)		*P* Value[a]
	Mean	%	Mean	%		Mean	%	Mean	%		Mean	%	Mean	%	
Age, years	49.8		50.3		0.156	59.4		60.7		<0.001	69.2		70.1		<0.001
High school education or more		99.1		95.0	0.005		94.7		86.6	<0.001		93.6	77.4		<0.001
Body mass index[b]	28.1		23.9		<0.001	28.3		23.6		<0.001	28.1		23.4		<0.001
Systolic blood pressure, mm Hg[c]	117		128		<0.001	122		136		<0.001	129		140		<0.001
LDL cholesterol concentration, mg/dL[d]	126		127		0.714	123		126		0.340	117		127		<0.001
HDL cholesterol concentration, mg/dL[d]	45		59		<0.001	46		59		<0.001	47		59		<0.001
Glucose concentration, mg/dL[d]	90		102		<0.001	95		101		0.002	97		105		<0.001
Overweight status[e]		75.1		31.1	<0.001		76.0		30.9	<0.001		77.4	26.7		<0.001
Hypertension[f]		22.5		26.9	0.336		33.7		53.1	<0.001		48.9	66.1		<0.001
Use of medication for hypertension[g]		18.3		10.9	0.061		30.2		26.9	0.330		43.3	35.5		0.030
Dyslipidemia[h]		52.0		26.1	<0.001		57.2		30.3	<0.001		52.9	37.5		<0.001
Use of medication for dyslipidemia[g]		12.0		11.8	0.943		23.5		8.3	<0.001		22.6	18.3		0.056
Diabetes mellitus[i]		5.1		6.7	0.508		7.3		12.6	0.022		7.9	20.4		<0.001
Use of medication for diabetes[g]		3.6		3.4	1.000		4.7		9.1	0.021		4.8	14.0		<0.001
Current smoking		16.8		47.1	<0.001		13.5		37.1	<0.001		7.4	27.5		<0.001
Pack-years of smoking[j]	0		4		<0.001	0		8		<0.001	0		4		<0.001
Current alcohol drinking		77.2		83.2	0.168		75.4		80.0	0.143		74.6		74.7	0.975
No. of coronary disease risk factors[k]															
0		11.7		22.7	0.006		9.7		15.4	0.007		8.4		10.2	0.017
1		32.1		37.0			27.0		33.7			25.2		34.4	
2		33.0		26.1			35.8		29.7			35.9		31.4	
≥3		23.1		14.3			27.6		21.1			30.5		24.0	
CAC score (i.e., Agatston score)															
<10		68.5		79.0	0.170		39.6		56.0	<0.001		21.4		40.5	<0.001
10–<100		18.3		13.4			28.2		26.0			19.3		29.2	
100–<400		10.8		5.9			18.8		11.1			28.5		19.0	
≥400		2.4		1.7			13.5		6.9			30.8		11.3	

Abbreviations: CAC, coronary artery calcium; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; SESSA, Shiga Epidemiological Study of Subclinical Atherosclerosis.

[a] *P* values were based on the *t* test or Wilcoxon rank-sum test for continuous variables and on the χ^2 test or Fisher's exact test for proportions, as appropriate.

[b] Weight (kg)/height (m)^2.

[c] Blood pressure values were the average of the last 2 of 3 measurements in MESA, whereas blood pressure values in SESSA were the average of the first 2 measurements.

[d] For lipids, LDL cholesterol was calculated using the Friedewald equation in both MESA and SESSA. In MESA, values for total cholesterol, HDL cholesterol, and triglycerides were obtained using plasma ethylenediaminetetraacetic acid samples and then converted to serum equivalents by multiplying by 1.03. The corresponding values in SESSA were determined using serum samples.

[e] Overweight was defined as body mass index ≥25.

[f] Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mm Hg or medication use.

[g] Percentage is expressed as a proportion of all participants in the specified group.

[h] Dyslipidemia was defined as LDL cholesterol concentration ≥160 mg/dL, HDL cholesterol concentration <40 mg/dL, or medication use.

[i] Diabetes mellitus was defined as fasting glucose concentration ≥126 mg/dL or medication use.

[j] The median value is shown because of a skewed data distribution.

[k] The following risk factors were assessed: current smoking, overweight status, hypertension, dyslipidemia, and diabetes mellitus.

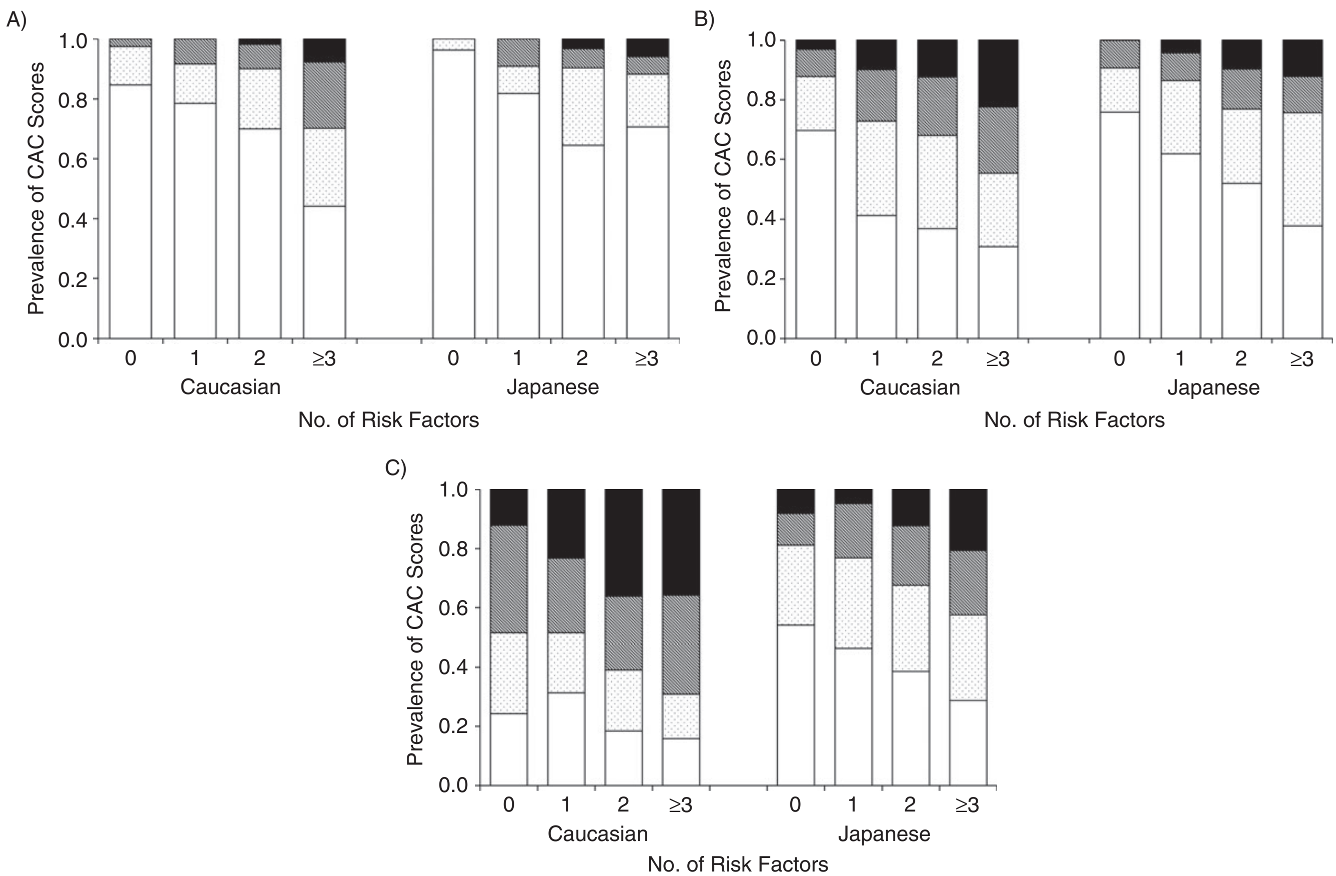

Figure 1. Crude prevalences of coronary artery calcium (CAC) scores of 0–9, 10–99, 100–399, and ≥400 according to number of coronary disease risk factors among Caucasian men in the United States (2000–2002) and Japanese men in Japan (2006–2008) aged 45–74 years in the Multi-Ethnic Study of Atherosclerosis and the Shiga Epidemiological Study of Subclinical Atherosclerosis, respectively. Results are shown for the age groups 45–54 years (A), 55–64 years (B), and 65–74 years (C), respectively. In each bar, CAC scores of 0–9, 10–99, 100–399, and ≥400 are displayed as open white squares, dots, gray squares, and solid black squares, respectively. The following coronary disease risk factors were assessed: current smoking, overweight (defined as body mass index (weight (kg)/height (m)^2) ≥25), hypertension (defined as systolic/diastolic blood pressure ≥140/90 mm Hg or medication use), dyslipidemia (defined as low-density lipoprotein cholesterol concentration ≥160 mg/dL, high-density lipoprotein cholesterol concentration <40 mg/dL, or medication use), and diabetes mellitus (defined as fasting glucose concentration ≥126 mg/dL or medication use).

having CAC scores greater than or equal to 10 in reference to Japanese men were 2.84, 2.95, and 3.75 for those aged 45–54, 55–64, and 65–74 years, respectively, after adjustment for age, education, CT type, smoking, systolic blood pressure, low-density lipoprotein cholesterol, glucose, treated hypertension, treated dyslipidemia, and treated diabetes mellitus (model 1; P for interaction by age group = 0.030). For higher CAC scores (≥100 and ≥400), the overall pattern in model 1 remained essentially the same except that the ethnic difference in odds was no longer statistically significant in the youngest age group (Table 2). Adjustment for BMI resulted in attenuation of point estimates for all of the CAC cutoffs, particularly for CAC scores greater than or equal to 400 in the youngest age group. However, adjustment for BMI (model 2) and alcohol drinking (model 3) did not change the increasing pattern in the odds ratios for older Caucasian men to have CAC scores greater than or equal to 100 or 400 compared with Japanese men in the same age group.

DISCUSSION

In this comparison between the United States and Japan, we have demonstrated that the burden of coronary atherosclerosis, assessed by CAC score, is greater among Caucasian men in the United States than among Japanese men in Japan aged 45–74 years, even after accounting for conventional risk factors. Importantly, the magnitude of the difference in CAC between Caucasian and Japanese men appeared to be smaller in younger age groups.

We previously reported that Caucasian men aged 40–49 years had a significantly higher CAC burden than Japanese men in the same age range, even after accounting for known risk factors (24). The present study extended such a comparison to an older age group, up to 74 years of age. To our knowledge, this is the first study that has compared the burdens of coronary atherosclerosis between the United States and Japan by age group.

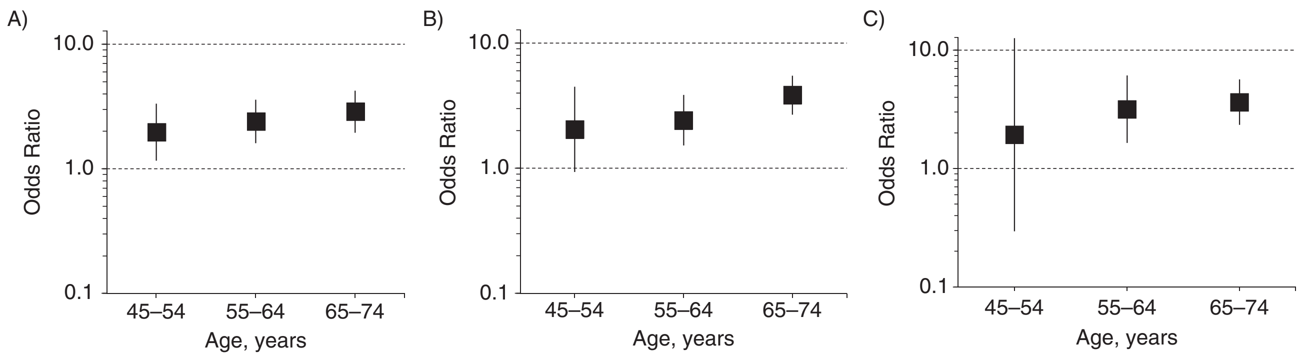

Figure 2. Odds ratios for Caucasian men's (2000–2002) having coronary artery calcium (CAC) scores greater than or equal to 10, 100, and 400 with reference to Japanese men (2006–2008), by age group (45–54, 55–64, or 65–74 years), in the Multi-Ethnic Study of Atherosclerosis and the Shiga Epidemiological Study of Subclinical Atherosclerosis, respectively. Each box and vertical line represent a point estimate and 95% confidence interval for the odds ratios for Caucasian men's having CAC scores of ≥10 (A), ≥100 (B), and ≥400 (C) in reference to Japanese men. The odds ratios were adjusted for a "base component" as follows: age (years), education (high school or more vs. less than high school), and type of computed tomography (CT) (electron-beam CT or multidetector-row CT). A *P* value for interaction less than 0.05 indicates a significant difference in odds ratios across age groups. Odds ratios in each age group (45–54, 55–64, and 65–74 years) for the 3 CAC score cutoffs were as follows: 1.97, 2.41, and 2.88 (*P* for interaction by age group ($P_{interaction}$) = 0.047) for CAC score ≥10; 2.05, 2.43, and 3.86 ($P_{interaction}$ = 0.020) for CAC score ≥100; and 1.93, 3.17, and 3.64 ($P_{interaction}$ = 0.016) for CAC score ≥400.

Japanese men have been known to have a lower burden of CHD compared with men in Western countries, including the United States (2). This has been attributed mainly to a low total cholesterol level in the Japanese population. However, one of the noteworthy recent trends in CHD risk factors between the United States and Japan has been in serum cholesterol levels. While serum cholesterol levels in Japan have increased significantly (2), those in the United States have decreased over the last few decades (25). Evidence for Japanese trends in clinical CHD may be more limited. The Hisayama

Table 2. Adjusted Odds[a] of US Caucasian Men's (2000–2002) Having Coronary Artery Calcium Scores of ≥10, ≥100, and ≥400 in Reference to Japanese Men (2006–2008), Multi-Ethnic Study of Atherosclerosis and Shiga Epidemiological Study of Subclinical Atherosclerosis

CAC Score (i.e., Agatston Score) and Model	Age Range, years									*P* for Interaction by Age Group
	45–54			55–64			65–74			
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value	
CAC score ≥10										
Model 1[b]	2.84	1.52, 5.32	0.001	2.95	1.85, 4.69	<0.001	3.75	2.44, 5.77	<0.001	0.030
Model 2[c]	2.40	1.18, 4.87	0.016	2.52	1.52, 4.20	<0.001	2.96	1.80, 4.87	<0.001	0.034
Model 3[d]	2.30	1.12, 4.70	0.023	2.45	1.46, 4.13	<0.001	3.11	1.88, 5.15	<0.001	0.034
CAC score ≥100										
Model 1	2.80	1.15, 6.84	0.024	2.68	1.57, 4.57	<0.001	5.35	3.53, 8.12	<0.001	0.015
Model 2	2.25	0.83, 6.09	0.111	2.11	1.17, 3.79	0.013	4.18	2.60, 6.70	<0.001	0.016
Model 3	2.27	0.82, 6.26	0.115	1.87	1.02, 3.41	0.043	4.45	2.76, 7.19	<0.001	0.016
CAC score ≥400										
Model 1	3.73	0.30, 45.84	0.304	4.91	2.25, 10.72	<0.001	5.10	3.07, 8.46	<0.001	0.018
Model 2	1.16	0.07, 19.77	0.920	3.73	1.58, 8.79	0.003	4.63	2.63, 8.16	<0.001	0.017
Model 3	1.50	0.07, 30.82	0.795	3.58	1.48, 8.67	0.005	5.15	2.90, 9.16	<0.001	0.019

Abbreviations: CI, confidence interval; CAC, coronary artery calcium; CT, computed tomography; OR, odds ratio.
[a] All models included adjustment for the following "base component": age (years), education (high school or more vs. less than high school), and type of CT (electron-beam CT or multidetector-row CT).
[b] Model 1 = "base component" + pack-years of cigarette smoking + systolic blood pressure (mm Hg) + low-density lipoprotein cholesterol (mg/dL) + plasma glucose (mg/dL) + treated hypertension + treated dyslipidemia + treated diabetes mellitus.
[c] Model 2 = model 1 + body mass index (weight (kg)/height (m)^2).
[d] Model 3 = model 2 + alcohol drinking (current, former, or never).

Study, one of the best-known cohort studies in Japan, showed no clear trend in incident acute myocardial infarction (26). However, 2 recent longitudinal studies in Japan, one from rural areas and the other from urban areas, found an increasing trend in CHD incidence, particularly among men (3, 4). One potential explanation for such an increase is worsening risk factor profiles, including a rise in total cholesterol levels (27) and an increase in BMI (28), which may have led to glucose intolerance and diabetes (2). In contrast, recent community-based studies in the United States have found a decreasing trend in incident CHD (6, 7). This decline was attributed not only to improved clinical management of acute coronary syndrome but also to improvements in levels of CHD risk factors, including lower total cholesterol and systolic blood pressure (5, 7). Given these possibly opposite trends in Japan and the United States, it is a plausible speculation that overall burdens of coronary atherosclerosis in the 2 countries have become closer, at least in men, with each new generation. Our findings on subclinical coronary atherosclerosis, measured as CAC score, seem to be consistent with this speculation, such that the younger age groups in our study had smaller differences in CAC than the older groups.

The observed difference in CAC between the United States and Japan may arise from multiple factors. One such factor may be a difference in duration of exposure to coronary disease risk factors. For example, according to the baseline data of the Seven Countries Study (in which participants were examined between 1958 and 1964), Japanese men aged 40–59 years had much lower cholesterol levels (165 mg/dL) than US men (240 mg/dL) in the same age range (1). Thus, even if current cholesterol levels between the 2 populations are similar, the cumulative association of cholesterol with atherosclerosis may be smaller among Japanese men than among US men, especially for older individuals (29). We explored other candidate factors, including dietary intake of marine-derived n-3 fatty acids, in our previous study of men aged 40–49 years (12). Nevertheless, further study is warranted to further elucidate the reasons for the graded difference in CAC across age groups.

Literature is scarce on comparison of CAC levels according to age strata in different community-based samples. Erbel et al. (30) compared CAC scores between participants in the Heinz Nixdorf Recall Study in Germany and Caucasian participants in MESA. While participants in the 2 studies had similar mean CAC scores (approximately 240), the authors did not compare CAC scores across age groups. Park et al. (31) reported on CAC levels in 5,239 asymptomatic South Koreans by age stratum (<40, 40–49, 50–59, 60–69, and ≥70 years) and found a crude CAC prevalence apparently similar to that of SESSA. However, use of different age cutoffs and lack of adjustment for risk factors in that study makes exact comparison impossible.

The CT images in SESSA were based on a single scan, and those in MESA were based on duplicate scans. Given this difference, higher cutoff scores for CAC, such as ≥100 or ≥400, could be more meaningful for making a fair comparison, since higher cutoffs tend to have less interscan variability (32). However, it is reassuring that the odds of Caucasians having CAC scores above the 3 cutoffs (≥10, ≥100, and ≥400) relative to Japanese men were similar and consistent in each age group. The lack of statistical significance in odds ratios for CAC scores greater than or equal to 400 observed in the youngest age group was most likely due to the low number of persons with such high CAC scores in that group.

Since greater thoracic diameter causes more image noise, resulting in a spuriously higher CAC score (33), differences in body size may produce overestimation of the true difference in CAC between the ethnic groups. However, we believe that the influence of body size is unlikely to have changed our conclusion, because adjustment for BMI (models 2 and 3) did not alter the overall pattern of difference between US and Japanese men across age groups. One might argue that BMI cutoff values used in defining "comparable" overweight status should differ between Japanese and Caucasians, such that BMI ≥23 is appropriate for the former group (34) while BMI ≥25 should be used for the latter. However, the use of such differential criteria for overweight between the United States and Japan did not alter the results materially (data not shown), and we used continuous variables such as BMI in the logistic regression analyses in place of binary variables such as "overweight" and obtained similar results. Thus, the use of different cutpoints to define a risk factor is unlikely to change our conclusion.

Caution is needed when interpreting our results. First, the measurement methods used in each sample were not standardized a priori. Such nonstandardized measurements may have introduced bias into the comparisons. For example, blood pressure values in MESA were the average of the second and third measurements, whereas those in SESSA were the average of the first 2 measurements. The higher blood pressure observed in Japanese men, therefore, may be due in part to methodological differences. This potential bias, however, may have led to underestimation of the CAC difference between the 2 groups, as the MESA protocol (average of the second and third measurements) tends to give lower values than the SESSA one (average of the first and second measurements). We made several attempts to overcome this limitation, including evaluation of comparability (18), use of nonzero or high cutoff points (32) for CAC scores, 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. The different time periods for CAC measurement between MESA (2000–2002) and SESSA (2006–2008) may have affected our results. Given the possibly opposite trends in incident CHD between the 2 countries, as discussed above, we could have observed greater overall differences in CAC between the cohorts had we measured CAC in SESSA earlier. Second, while the prognostic implication of higher CAC is established among Caucasians in the United States, it is yet to be determined among Japanese men, as only 1 patient-based prospective study has found a predictive property for CAC among Japanese men, to our knowledge (35). It is possible that similar CAC scores between the 2 populations will result in significantly different absolute risks for clinical CHD (36). Third, we studied only men and the Japanese sample was obtained from a single area, both of which limit the generalizability of our results. Fourth, in assessing differences in CAC between the United States and Japan, we considered only current levels of conventional risk factors, without accounting for newer factors such as inflammatory markers. Strengths of this study include the choice of CAC as a reliable and reproducible measure of atherosclerosis, giving us a unique opportunity to assess the burden of subclinical CHD.

In conclusion, we found that Caucasian men in the United States aged 45–74 years had a higher burden of coronary atherosclerosis, as assessed by CAC score, than did Japanese men in Japan of the same age. Moreover, this ethnic difference in CAC appeared to be larger in older age groups, a finding that remained significant even after adjustment for current levels of traditional coronary disease risk factors. Further efforts are needed to elucidate factors responsible for this ethnic difference and to discover whether the increased difference with age is replicated in other studies.

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