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Original Contribution

Less Subclinical Atherosclerosis in Japanese Men in Japan than in White Men in the United States in the Post–World War II Birth Cohort

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Coronary heart disease incidence and mortality remain very low in Japan despite major dietary changes and increases in risk factors that should have resulted in a substantial increase in coronary heart disease rates (Japanese paradox). Primary genetic effects are unlikely, given the substantial increase in coronary heart disease in Japanese migrating to the United States. For men aged 40–49 years, levels of total cholesterol and blood pressure have been similar in Japan and the United States throughout their lifetimes. The authors tested the hypothesis that levels of subclinical atherosclerosis, coronary artery calcification, and intima-media thickness of the carotid artery in men aged 40–49 years are similar in Japan and the United States. They conducted a population-based study of 493 randomly selected men: 250 in Kusatsu City, Shiga, Japan, and 243 White men in Allegheny County, Pennsylvania, in 2002–2005. Compared with the Whites, the Japanese had a less favorable profile regarding many risk factors. The prevalence ratio for the presence of a coronary calcium score of $\geq$10 for the Japanese compared with the Whites was 0.52 (95% confidence interval: 0.35, 0.76). Mean intima-media thickness was significantly lower in the Japanese (0.616 mm (standard error, 0.005) vs. 0.672 (standard error, 0.005) mm, $p < 0.01$). Both associations remained significant after adjusting for risk factors. The findings warrant further investigations.

atherosclerosis; cohort studies; coronary disease; Japan; men; risk factors

Abbreviations: CCS, coronary calcium score; CHD, coronary heart disease; CI, confidence interval; IMT, intima-media thickness.

Coronary heart disease (CHD) mortality in Japan has been uniquely low among industrialized countries (1). This low rate has largely been attributed to diet: low intake of saturated fat and cholesterol, resulting in low levels of total cholesterol (e.g., 4.13 mmol/liter (160 mg/dl) in Japan vs. 6.19 mmol/liter (240 mg/dl) in the United States in the 1960s) (1). Dietary intake of fat and serum levels of total cholesterol have steadily increased with the westernization of lifestyle in Japan (2, 3). CHD mortality in Japan, however, has been decreasing since the 1970s (4). Furthermore, a recent report showed that CHD incidence is much lower in Japan than in other industrialized countries (5).

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Even for men in the post–World War II birth cohort, who adopted a westernized lifestyle in childhood and young adulthood, CHD mortality is much lower in Japan than in Whites in the United States (6) despite the fact that total cholesterol and blood pressure have been similar between the populations throughout their lifetimes (2, 6–11). Moreover, rates of smoking in this birth cohort have been much higher in the Japanese (2, 11).

Careful evaluation of CHD mortality showed that low CHD mortality among men in the post–World War II birth cohort in Japan is not due to misclassification of cause of death (4, 12). Additionally, a recent autopsy study of young men continued to report a much lower prevalence of coronary atherosclerosis in the Japanese in Japan than in Whites in the United States (13). Traditional risk factors for CHD predict CHD in Japanese men similar to men in the United States, but at much lower rates (1, 14). Low CHD rates in the Japanese are not due to genetics or host susceptibility because CHD incidence and mortality increased substantially in migrants to the United States within one to two generations (15, 16). There are three possible reasons for the low CHD mortality among men in Japan: lower amounts of coronary atherosclerosis, reduced amounts of vulnerable plaques given the same amount of atherosclerosis, and a lower prevalence of risk factors related to thrombosis and clinical events.

In this study, we tested the null hypothesis that among men aged 40–49 years from population-based samples, levels of subclinical atherosclerosis are not different between the Japanese in Japan and Whites in the United States. We evaluated subclinical atherosclerosis by coronary artery calcification and intima-media thickness (IMT) of the carotid artery.

MATERIALS AND METHODS

Subjects

Participants were population-based samples of 493 randomly selected men aged 40–49 years: 250 Japanese from Kusatsu City, Shiga, Japan, and 243 Whites from Allegheny County, Pennsylvania. Exclusion criteria were 1) clinical cardiovascular disease, 2) type 1 diabetes, 3) cancer except skin cancer in the past 2 years, 4) renal failure, and 5) genetic familial hyperlipidemias. In Japan, men aged 40–49 years living in Kusatsu City were randomly selected based on the Basic Residents' Register of the city, which has information on name, age, and sex of residents. All Japanese nationals are required by law to register. Each selected man was mailed an invitation to the study to determine whether he was willing to participate. In the United States, White men aged 40–49 years living in Allegheny County were randomly selected based on the voter registration list, which has information on name, age, sex, and race of registered voters. The voter registration list is very complete. Each selected man was mailed an invitation to the study to determine whether he was willing to participate. Participation rates were about 50 percent at both centers.

Informed consent was obtained from all participants. The study was approved by the institutional review boards of Shiga University of Medical Science, Otsu, Japan, and the University of Pittsburgh, Pittsburgh, Pennsylvania.

Study protocol

Body weight and height were measured while the participant was wearing light clothing without shoes. Waist girth was measured at the level of the umbilicus while the participant was standing erect. Blood pressure was measured in the right arm of the seated participant after he emptied his bladder and sat quietly for 5 minutes, using an automated sphygmomanometer (BP-8800; Colin Medical Technology, Komaki, Japan) and an appropriate-sized cuff. The average of two measurements was used.

Venipuncture was performed early in the clinic visit after a 12-hour fast. The samples at both centers were shipped on dry ice to the University of Pittsburgh. Serum lipids, including total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides, were determined with the standardized methods according to the Centers for Disease Control and Prevention. Serum glucose was determined by using a hexokinase–glucose-6-phosphate-dehydrogenase-enzymatic assay, serum insulin by using a radioimmunoassay (Linco Research Inc., St. Charles, Missouri), C-reactive protein by using a calorimetric-competitive-enzyme-linked-immunosorbent assay, and fibrinogen by using an automated-clot-rate assay (Diagnostica Stago, Parsippany, New Jersey).

A self-administered questionnaire was used to obtain information on demography, smoking habits, alcohol drinking, and other factors. Pack-years were calculated as years of smoking multiplied by number of cigarettes smoked per day divided by 20. Alcohol drinking was assessed as whether the participant drank beer, wine, liquor, sake (Japanese rice wine), or other alcoholic beverages, with quantity and frequency. Alcohol drinkers were defined as those who drank alcohol $\geq$2 days per week. Ethanol consumption per day was estimated, assuming that concentrations of alcohol were 5 percent for beer, 12 percent for wine, 40 percent for liquor, and 16 percent for sake. Those who exercised were defined as those who regularly exercised $\geq$1 hour per week.

Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or use of antihypertensive medications. Diabetes mellitus was defined as fasting serum glucose level $\geq$7 mmol/liter or use of antidiabetic medications.

Electron-beam computed tomography

The scanning was performed with a GE-Imatron C150 EBT scanner (GE Medical Systems, South San Francisco, California) at both centers. Scanners were calibrated regularly by technicians following a standardized protocol. Heart scanning was performed following a standardized protocol to produce 30–40 contiguous, 3-mm-thick transverse images from the level of the aortic root to the apex of the heart. Images were obtained during maximal breath holding by using electrocardiogram triggering (60 percent of the R-R interval) so that each 100-m-second exposure was obtained during the same phase of the cardiac cycle.

One trained reader at the Cardiovascular Institute, University of Pittsburgh, read the images, using a DICOM (Digital Imaging and Communications in Medicine) workstation and software by AccuImage (AccuImage Diagnostic Corporation, San Francisco, California). The software program implements the widely accepted Agatston scoring method (17). Coronary artery calcification was considered present when three contiguous pixels (area = 1 mm^2) greater than 130 Hounsfield units were detected overlying the vessels of interest. A coronary calcium score (CCS) was calculated for each region of interest by multiplying the area of all significant pixels by a grade number (one, two, three, four) indicative of the peak computed tomography number (Hounsfield unit). The reader was blinded to a participant's characteristics and the study centers. The reproducibility of the electron-beam computed tomography scans had an intraclass correlation of 0.98.

IMT

Before the study began, sonographers at both centers received training for carotid scanning at the ultrasound laboratory in Pittsburgh. We applied continuous-quality-assessment programs developed by the laboratory to assure scanning quality (18). A Toshiba 140A scanner (Tokyo, Japan) equipped with a 7.5-MHz-linear-array imaging probe was used at both centers. The sonographers scanned the right and left common carotid arteries, the carotid bulbs, and the internal carotid arteries. For the common carotid arteries segment, both near and far walls were examined 1 cm proximal to the bulb. For the bulb area and internal carotid arteries, only the far walls were examined. The scans were recorded on videotape and were sent to the laboratory for scoring.

Trained readers at the laboratory digitized the best image for scoring and then measured the average IMT across 1-cm segments of near and far walls of the common carotid arteries and the far wall of the carotid bulb and internal carotid arteries on both sides. Measurements from each location were then averaged to produce an overall measurement of IMT. The readers were blinded to a participant's characteristics and the study centers. Under continuous-quality-assessment programs, correlation coefficients between sonographers and between readers for average IMT were 0.96 and 0.99, respectively (18).

Statistical analyses

To compare risk factors between the populations, a *t* test, the Mann-Whitney *U* test, or a chi-square test was used. To examine associations of CCS with risk factors in each population, subjects were divided into three categories based on CCS: 0, <10 (>0 and <10), and ≥10. To examine associations of IMT with risk factors in each population, subjects were divided into three tertiles by using the same cutpoints for both Japanese and White men. A linear trend was used to test a trend across the three groups.

To compare prevalence of coronary artery calcification between the populations, a multivariate-adjusted prevalence ratio was calculated (19). Two cutpoints were used to define the presence of coronary artery calcification: CCS = 0 and CCS = 10. General-linear-model analyses were performed to calculate multivariate-adjusted IMT. For these analyses, traditional risk factors were entered (model I), followed by C-reactive protein and fibrinogen (model II) and other factors (model III).

All *p* values were two tailed. A *p* value of <0.05 was considered significant. SAS software (release 8.02; SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

RESULTS

A profile of many risk factors for the Japanese was less favorable than or similar to that for the Whites, including blood pressure, total cholesterol, low density lipoprotein cholesterol, triglycerides, glucose, smoking, hypertension, and diabetes (table 1). Exceptions were body mass index, waist girth, high density lipoprotein cholesterol, insulin, fibrinogen, and C-reactive protein. Median pack-years of smoking and ethanol consumption were significantly higher in the Japanese than in the Whites: 18.9 (interquartile range, 3.0–30.0) versus 0 (interquartile range, 0–0), respectively, pack-years ($p < 0.01$) and 14.3 g/day (interquartile range, 2.0–42.5) versus 2.9 g/day (interquartile range, 0.9–16.0), respectively, of ethanol consumption ($p < 0.01$).

Levels of subclinical atherosclerosis were significantly lower in the Japanese than in the Whites. Prevalence of CCS ≥10 and CCS >0 was significantly lower among the Japanese compared with the Whites (figure 1). The distributions of CCS were skewed in both populations. Among those whose CCS was >0, 49 (59.8 percent) of the Japanese and 55 (47.0 percent) of the Whites had a CCS of <10; seven (8.5 percent) of the Japanese and 13 (11.1 percent) of the Whites showed a CCS of ≥100. Mean IMT was significantly lower in the Japanese than in the Whites: 0.616 mm (standard error, 0.005) for the Japanese and 0.672 mm (standard error, 0.005) for the Whites ($p < 0.01$).

The associations of coronary artery calcification with risk factors were similar between the populations (table 2). In both populations, the category of CCS was associated with age, body mass index, blood pressure, low density lipoprotein cholesterol, triglycerides, fibrinogen, hypertension, and diabetes. Rates of hypertension were 21.4 percent for CCS = 0, 40.8 percent for CCS <10, and 30.3 percent for CCS ≥10 in the Japanese (p for trend = 0.05) and 10.3, 16.4, and 24.2 percent, respectively, in the Whites (p for trend = 0.01). Rates of diabetes were 3.6, 6.1, and 9.1 percent, respectively, in the Japanese (p for trend = 0.15) and 1.6, 1.8, and 3.2 percent, respectively, in the Whites (p for trend = 0.48). There was no interaction between risk factors and populations in predicting the category of CCS, except for insulin. In the Whites, levels of insulin were linearly associated with CCS category whereas, in the Japanese, levels of insulin in the category of CCS ≥10 were significantly lower than those in the category of CCS <10.

The associations of IMT with risk factors were similar between the populations (table 3). Category of IMT was significantly associated with age, body mass index, blood pressure, hypertension, and diabetes in both populations.

TABLE 1. Characteristics* of male study participants aged 40–49 years in Kusatsu City, Shiga, Japan, and in Allegheny County, Pennsylvania, in 2002–2005†

	Japanese men ($n = 250$)	White men ($n = 243$)	p value
Age (years)	45.2 (2.80)	45.1 (2.9)	>0.75
BMI‡ (kg/m^2)	23.8 (3.1)	27.8 (4.1)	<0.01
Waist girth (cm)	85.3 (8.3)	98.3 (11.1)	<0.01
SBP (mmHg)	125.1 (16.4)	122.9 (11.2)	0.07
DBP (mmHg)	76.5 (11.9)	73.6 (8.5)	<0.01
Total cholesterol (mmol/liter)	5.66 (0.94)	5.48 (0.99)	0.04
LDL‡ cholesterol (mmol/liter)	3.47 (0.92)	3.49 (0.89)	>0.75
HDL‡ cholesterol (mmol/liter)	1.39 (0.33)	1.24 (0.33)	<0.01
Triglycerides (mmol/liter)	1.55 (1.17–2.05)	1.42 (1.04–2.09)	0.07
Fasting glucose (mmol/liter)	5.88 (0.89)	5.56 (0.64)	<0.01
Insulin (pmol/liter)	72.2 (31.3)	105.6 (59.0)	<0.01
Fibrinogen (μmol/liter)	7.37 (1.90)	8.67 (2.07)	<0.01
CRP‡ (mg/liter)	0.32 (0.15–0.67)	0.87 (0.49–1.83)	<0.01
Smoker	49.2	5.3	<0.01
Drinker	66.8	45.3	<0.01
Exercise	26.8	73.3	<0.01
Hypertension	26.4	15.2	<0.01
Hypertension medications	4.0	8.6	0.04
Diabetes	4.8	2.1	0.14
Diabetes medications	1.2	0.4	0.64
Lipid-lowering medications	3.2	11.5	<0.01

* Definitions—smoker: current smoking; drinker: drinking alcohol ≥2 days a week; exercise: exercising ≥1 hour per week; hypertension: systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or use of antihypertension medications; diabetes: fasting glucose level ≥7 mmol/liter or use of diabetes medications.

† Values are expressed as mean (standard deviation) or median (interquartile range) for continuous variables or as percentage for categorical variables.

‡ BMI, body mass index (weight in kilograms ÷ height in meters squared); LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein.

Rates of hypertension were 21.0, 24.0, and 42.9 percent from the low to high tertile groups of Japanese (p for trend < 0.01) and 8.5, 13.0, and 20.0 percent, respectively, for the Whites (p for trend $= 0.04$). Rates of diabetes were 2.9, 3.1, and 12.1 percent from the low to high tertile groups of Japanese (p for trend $= 0.03$) and 0, 1.4, and 3.5 percent, respectively, for the Whites (p for trend $= 0.12$). There was no interaction between risk factors and populations in predicting IMT category.

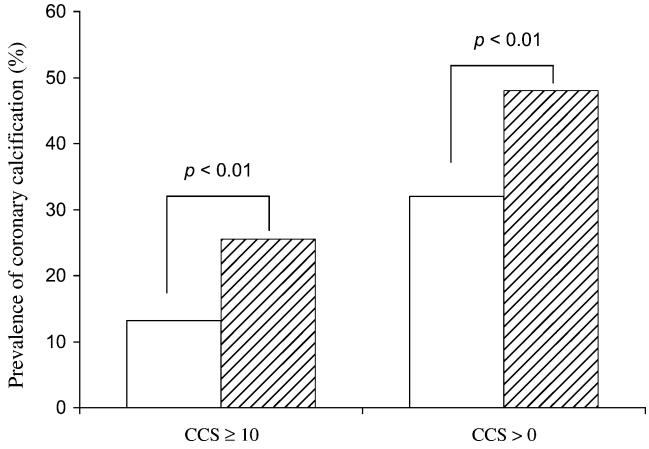

FIGURE 1. Prevalence of coronary artery calcification (%) in Japanese men aged 40–49 years in Kusatsu City, Shiga, Japan (white bars) and in White men aged 40–49 years in Allegheny County, Pennsylvania (striped bars) in 2002–2005. CCS, coronary calcium score.

The difference in the prevalence of CCS ≥10 and mean IMT between the populations remained significant after adjusting for traditional risk factors (model I in table 4) and further adjusting for C-reactive protein and fibrinogen (model II), which were more favorable in the Japanese. Further adjusting for other factors did not attenuate the associations either (model III). The difference in the prevalence of CCS >0, however, did not remain after adjusting for risk factors.

A U-shaped association of ethanol consumption with coronary artery calcification was observed in both populations, but such an association with IMT was not found in either population. The odds ratio for CCS ≥10 in light (<15 g of ethanol per day) or moderate (15–<30 g of ethanol per day) alcohol drinkers compared with nondrinkers of alcohol was not significant in either population. In the Japanese, the odds ratios were 0.53 (95 percent confidence interval (CI): 0.17, 1.70; $p = 0.29$) for light drinkers, 0.36 (95 percent CI: 0.07, 1.89; $p = 0.23$) for moderate drinkers, and 1.24 (95 percent CI: 0.47, 3.32; $p = 0.67$) for heavy drinkers (≥30 g of ethanol per day). In the Whites, the respective odds ratios were 0.81 (95 percent CI: 0.38, 1.74; $p = 0.59$), 1.01 (95 percent CI: 0.39, 2.63; $p > 0.75$), and 1.11 (95 percent CI: 0.34, 3.62; $p > 0.75$). The results were similar when the presence of coronary artery calcification was defined as CCS >0.

DISCUSSION

This population-based study shows that among men aged 40–49 years, levels of subclinical atherosclerosis are lower in the Japanese than in Whites. The evidence that levels of subclinical atherosclerosis evaluated by two different measures are lower in the Japanese supports the conclusion that, for men in this age range, the Japanese have less atherosclerosis than Whites do. Our observation that in men aged

TABLE 2. Associations of coronary artery calcification with risk factors in Japanese men aged 40–49 years in Kusatsu City, Shiga, Japan, and in White men aged 40–49 years in Allegheny County, Pennsylvania, in 2002–2005**

	CCS†† category							
	Japanese men				White men			
	0 ($n = 168$ (67%))	<10 ($n = 49$ (20%))	≥10 ($n = 33$ (13%))	*p* value	0 ($n = 126$ (52%))	<10 ($n = 55$ (23%))	≥10 ($n = 62$ (26%))	*p* value
Age (years)	44.8 (2.9)	45.6 (2.7)	46.5 (2.3)	—†,#	44.7 (2.9)	44.8 (3.0)	46.2 (2.6)	—†,§,#
BMI†† (kg/m^2)	23.1 (2.8)	25.1 (2.9)	24.9 (3.7)	—†,#	26.4 (3.1)	28.9 (4.6)	29.4 (4.7)	—†,#
SBP†† (mmHg)	123.5 (15.1)	129.2 (18.0)	127.4 (19.1)		121.3 (11.0)	122.5 (11.5)	126.4 (11.0)	—†,#
DBP†† (mmHg)	74.9 (11.3)	80.4 (12.3)	78.7 (13.3)	—†	75.5 (71.7)	73.9 (8.2)	77.4 (7.8)	—#
LDL†† cholesterol (mmol/liter)	3.39 (0.94)	3.51 (0.83)	3.85 (0.86)	—†,#	3.37 (0.96)	3.69 (0.83)	3.57 (0.74)	—*
HDL†† cholesterol (mmol/liter)	1.40 (0.33)	1.33 (0.29)	1.39 (0.39)		1.29 (0.35)	1.21 (0.27)	1.17 (0.33)	—¶
Triglycerides (mmol/liter)	1.46 (1.06–1.94)	1.63 (1.38–2.39)	1.64 (1.23–2.23)	—†,#	1.28 (0.96–1.70)	1.66 (1.10–1.23)	1.55 (1.06–2.16)	—*,¶
Fasting glucose (mmol/liter)	5.77 (0.59)	6.14 (1.48)	6.05 (0.88)		5.51 (0.48)	5.49 (0.56)	5.72 (0.91)	—*,¶
Insulin (pmol/liter)	67.4 (28.5)	88.9 (33.3)	71.5 (34.7)	—‡	90.3 (38.2)	120.1 (63.9)	124.3 (77.8)	—†,#
Fibrinogen (μmol/liter)	7.17 (1.85)	7.64 (1.81)	7.99 (2.15)	—¶	8.41 (1.71)	8.72 (1.85)	9.12 (2.75)	—¶
CRP†† (mg/liter)	0.33 (0.15–0.66)	0.27 (0.15–1.00)	0.27 (0.15–0.74)		0.82 (0.40–1.59)	0.95 (0.59–2.02)	0.99 (0.56–1.81)	
Smoker	47.0	57.1	30.3	—‡	5.6	1.8	8.1	
IMT†† (mm)	0.603 (0.060)	0.632 (0.080)	0.656 (0.067)	—†,#	0.651 (0.091)	0.678 (0.083)	0.709 (0.119)	—†,#

* $p < 0.05$ between CCS = 0 and CCS <10.
† $p < 0.01$ between CCS = 0 and CCS <10.
‡ $p < 0.05$ between CCS <10 and CCS ≥10.
§ $p < 0.01$ between CCS <10 and CCS ≥10.
¶ $p < 0.05$ for trend.
# $p < 0.01$ for trend.
** Values are expressed as mean (standard deviation) or median (interquartile range) for continuous variables or as percentage for categorical variables.
†† CCS, coronary calcium score; BMI, body mass index (weight in kilograms ÷ height in meters squared); SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein; IMT, intima-media thickness.

40–49 years, the Japanese had a lower prevalence of coronary artery calcification is consistent with findings from the largest autopsy-based comparative study of atherosclerosis between the Japanese and Americans (13). To our knowledge, this population-based study is the first to compare subclinical atherosclerosis between Japanese and White men in the post–World War II birth cohort.

Our observation that similar risk factors were associated with coronary artery calcification in both populations indicates that similar risk factors are related to developing atherosclerosis in both populations. The observed associations of coronary artery calcification with risk factors in the Whites are consistent with previous studies of Whites in the United States (20, 21). Our observations are consistent with findings from autopsy studies showing that levels of coronary artery atherosclerosis in young adults are associated with lipids, blood pressure, and cigarette smoking in both Japan (22) and the United States (23, 24).

We observed an interaction between insulin and populations in predicting CCS category. Although the reason is not fully understood regarding the finding that, in the Japanese, levels of insulin in the category of CCS ≥10 were significantly lower than those in the category of CCS <10, one possibility is lower insulin secretion in the Japanese than in Whites. A study reported that among subjects with impaired glucose tolerance, the insulin response in Whites increases compared with that in those with normal glucose tolerance, whereas it decreased in the Japanese (25). For both the Japanese and the Whites, rates for those with impaired glucose tolerance are likely to be much higher in the category of CCS ≥10 than in the category of CCS <10.

We observed no interaction between risk factors and populations in predicting IMT category. Although we found significant linear associations of IMT with low density lipoprotein cholesterol for only the Whites and with glucose for only the Japanese, the lack of the significant association of IMT with low density lipoprotein cholesterol in the Japanese and with glucose in the Whites may be due to the small sample size.

Higher ethanol consumption in the Japanese did not explain the lower levels of subclinical atherosclerosis in the Japanese compared with the Whites. Some (26, 27), but not all (28, 29), epidemiologic studies reported significant U-shaped associations of ethanol consumption with coronary

TABLE 3. Associations of intima-media thickness of the carotid artery with risk factors in Japanese men aged 40–49 years in Kusatsu City, Shiga, Japan, and in White men aged 40–49 years in Allegheny County, Pennsylvania, in 2002–2005**

	IMT†† category (mm)							
	Japanese men				White men			
	Low: <0.598 (n = 105 (42%))	Middle: 0.598–0.665 (n = 96 (38%))	High: >0.665 (n = 49 (20%))	p value	Low: <0.598 (n = 59 (24%))	Middle: 0.598–0.665 (n = 69 (28%))	High: >0.665 (n = 115 (47%))	p value
Age (years)	44.4 (2.8)	45.3 (2.8)	46.6 (2.4)	—†,§,#	44.1 (2.9)	45.0 (2.7)	45.6 (2.9)	—†,#
BMI†† (kg/m^2)	22.7 (2.7)	24.2 (2.9)	25.0 (3.6)	—†,#	26.1 (3.0)	28.2 (4.2)	28.3 (4.4)	—†,#
SBP†† (mmHg)	122.9 (15.7)	124.3 (15.6)	131.6 (18.0)	—†,‡,#	119.9 (9.7)	122.3 (11.4)	124.7 (11.6)	—†,#
DBP†† (mmHg)	75.2 (11.8)	75.8 (11.0)	80.7 (13.3)	—†,‡,#	71.4 (7.0)	73.4 (8.8)	74.9 (8.9)	—*,¶
LDL†† cholesterol (mmol/liter)	3.41 (0.93)	3.49 (0.92)	3.58 (0.90)		3.34 (0.95)	3.33 (0.84)	3.66 (0.86)	—*,§,¶
HDL†† cholesterol (mmol/liter)	1.45 (0.31)	1.33 (0.33)	1.35 (0.38)		1.29 (0.36)	1.20 (0.28)	1.23 (0.34)	
Triglycerides (mmol/liter)	1.51 (1.15–1.98)	1.60 (1.21–2.03)	1.50 (1.13–2.19)		1.21 (0.95–1.86)	1.45 (1.06–2.00)	1.46 (1.04–2.11)	
Fasting glucose (mmol/liter)	5.70 (0.48)	5.96 (1.15)	6.09 (0.90)	—*,¶	5.47 (0.43)	5.55 (0.56)	5.60 (0.75)	
Insulin (pmol/liter)	69.5 (27.1)	75.0 (35.4)	72.2 (30.6)		100.7 (60.4)	110.4 (59.7)	105.6 (56.9)	
Fibrinogen (μmol/liter)	7.16 (1.66)	7.45 (2.17)	7.37 (1.90)		8.47 (1.69)	8.65 (1.96)	8.78 (2.31)	
CRP†† (mg/liter)	0.27 (0.15–0.51)	0.43 (0.15–0.90)	0.29 (0.15–0.72)		0.80 (0.40–1.91)	0.87 (0.44–1.88)	0.92 (0.54–1.56)	
Smoker	53.3	42.7	53.1		6.8	4.3	5.2	
CCS†† >0	22.9	27.4	48.2	—§,#	30.9	58.0	55.6	—†,#
CCS ≥10	6.0	8.3	25.3	—§,#	16.0	27.2	33.3	—#

* $p < 0.05$ between low and middle.
† $p < 0.01$ between low and middle.
‡ $p < 0.05$ between middle and high.
§ $p < 0.01$ between middle and high.
¶ $p < 0.05$ for trend.
# $p < 0.01$ for trend.
** Values are expressed as mean (standard deviation) or median (interquartile range) for continuous variables or as percentage for categorical variables.
†† IMT, intima-media thickness; BMI, body mass index (weight in kilograms ÷ height in meters squared); SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C-reactive protein; CCS, coronary calcium score.

artery calcification and IMT. We found a U-shaped association of ethanol consumption with coronary artery calcification in both populations, but the association was not significant in either population. We did not observe a U-shaped association of ethanol consumption with IMT in either population. Adjusting for ethanol consumption did

TABLE 4. Multivariate-adjusted prevalence ratios for the presence of CCS* ≥10 and CCS >0 as well as multivariate-adjusted mean IMT* of the carotid arteries in Japanese men aged 40–49 years in Kusatsu City, Shiga, Japan, compared with White men aged 40–49 years in Allegheny County, Pennsylvania, in 2002–2005

	CCS for Japanese men compared with White men						IMT (mean (standard error)) (mm)		
	≥10			>0			Japanese men	White men	p value
	Prevalence ratio	95% CI*	p value	Prevalence ratio	95% CI	p value			
Crude	0.52	0.35, 0.76	<0.01	0.68	0.55, 0.85	<0.01	0.616 (0.005)	0.672 (0.005)	<0.01
Model I†	0.51	0.31, 0.83	<0.01	0.94	0.71, 1.25	0.67	0.622 (0.006)	0.666 (0.006)	<0.01
Model II‡	0.52	0.32, 0.85	<0.01	0.95	0.71, 1.27	0.74	0.621 (0.006)	0.667 (0.007)	<0.01
Model III§	0.53	0.31, 0.92	0.02	0.98	0.71, 1.36	0.91	0.623 (0.006)	0.665 (0.007)	<0.01

* CCS, coronary calcium score; IMT, intima-media thickness; CI, confidence interval.
† Adjusted for age, body mass index, systolic blood pressure, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, glucose, insulin, and pack-years of smoking.
‡ Further adjusted for C-reactive protein and fibrinogen.
§ Further adjusted for alcohol drinking, exercise, and medications for hypertension, diabetes, and hyperlipidemia.

not attenuate the differences in prevalence of coronary artery calcification or IMT (data not shown).

The lower levels of subclinical atherosclerosis in the Japanese are unlikely to be related to some lifestyle or genetic factors specific to Asian populations, because decreasing trends in CHD mortality despite a rise in population levels of total cholesterol in Japan is unique among Asian countries. A recent review of lipids and CHD in Asia showed that CHD mortality in Asian countries increased with a concomitant rise in population levels of total cholesterol, except in Japan (30). For men in the post–World War II birth cohort, that is, men aged 35–44 years, CHD mortality increased during the 1980s through the 1990s in Korea, Taiwan (31), and Beijing, China (32), whereas it decreased in Japan (4, 31).

Our observations that levels of subclinical atherosclerosis remained significantly lower in the Japanese after adjusting for risk factors suggest that some factors other than those we investigated are related to the differences in the levels of subclinical atherosclerosis between the populations. The differences may be associated with the difference in lifetime levels of obesity through adipocytokines or other factors (33), the levels of inflammation through some factors other than C-reactive protein (34), and the lipoprotein distributions (35). Genetic factors are unlikely to be primarily responsible for the lower subclinical atherosclerosis in the Japanese in Japan given the substantial increase in CHD and IMT in Japanese who migrated to the United States (15, 16, 36) and similar prevalence of coronary artery calcification between Japanese-American and White men (37, 38).

Our finding that the prevalence of CCS >0 did not remain significant after adjusting for risk factors may suggest that the prevalence of coronary artery calcification defined as CCS >0 will become similar between the populations in the future if the Japanese retain a less favorable profile regarding many risk factors. We cannot, however, deny the possibility that a low CCS, for example, CCS <10, is an imaging artifact. In fact, among those with scores of CCS >0 and CCS <10, 77.5 percent (38/49) of the Japanese and 69 percent (38/55) of the Whites had a very low CCS (i.e., CCS <5). Meanwhile, we reread 42 randomly selected scans of those categorized as CCS <10, and the results were the same. In addition, for both the Japanese and the Whites, a risk factor profile for those classified as CCS <10 was generally worse than the profile for those designated CCS $= 0$. Likewise, in both the Japanese and the Whites, mean IMT was higher for CCS <10 than for CCS $= 0$ (table 2). Follow-up study of those with a low CCS is therefore important.

Our study has several limitations. The Whites we studied may be healthier than the general White population based on the rate of cigarette smoking. If anything, however, this possibility would make the finding that the Japanese have less subclinical atherosclerosis than Whites more significant. Our observation that, compared with the Whites, the Japanese had a significantly higher prevalence of hypertension may not support our assumption that levels of blood pressure have been similar between the populations throughout their lifetimes. This possibility would make the finding that the Japanese have less subclinical atherosclerosis than Whites more significant. Our study included men, and only those aged 40–49 years. We specifically focused on this particular sex and age group because, unlike older age groups, in this birth cohort, total cholesterol and blood pressure have been similar between Japanese and White men throughout their lifetimes.

Besides, it is possible that ethnic differences in the prevalence of coronary artery calcification could be due to the differences in pathophysiology of coronary artery calcification (38, 39), and CCS might not reflect a real difference in atherosclerotic burden. Lower prevalence of both atherosclerosis and coronary artery calcification in the Japanese than in Whites, however, is consistent with the data from the autopsy study (13) as well as patterns of CHD incidence and mortality (5, 12). In addition, we found lower IMT in the Japanese than in the Whites in this study. Although there was no interaction between risk factors and populations in predicting the category of either CCS or IMT, except for insulin in predicting the category of CCS, this finding may be due to the small sample size.

In conclusion, we found that in men aged 40–49 years, levels of subclinical atherosclerosis evaluated as coronary artery calcification and IMT were significantly lower in the Japanese than in Whites despite similar lifetime total cholesterol and blood pressure levels and significantly higher rates of cigarette smoking by the Japanese. These associations remained significant after adjusting for traditional risk and other factors. The data may suggest that there are some protective factors against atherosclerosis in the Japanese and warrant further investigations.

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