all'. One is for employees and their dependants and the other is for self-employed individuals, such as farmers and fishermen, retirees and their dependants. The 2 systems respectively cover 65.3% and 34.7% of the overall population. All prices are strictly controlled by a fee schedule that is set by the National Government, and calculated on the basis of 'fee-for-service'. The fee schedule is constant, regardless of insurance system. Furthermore, the same fee schedule applies to all clinics and hospitals that are approved to provide medical services under the public medical insurance system.

Study Population

Our study cohort comprised 4,535 Japanese beneficiaries of the National Health Insurance (NHI). Details of the cohort study have been reported elsewhere[9,21,22] Briefly, the 40–69-year-old participants lived in 7 rural towns and a village in Shiga Prefecture, West Japan, and had undergone a baseline survey between 1989 and 1991. In 1990, the study area had 82,155 residents, including 31,564 individuals aged 40–69 years, of whom 11,900 were NHI beneficiaries. Therefore, the participants in the present study represented approximately 38% of all NHI beneficiaries in this age group within this community. Monthly NHI claim files for over 10 years within the Shiga NHI Organizations were linked with the baseline survey data. Deleting the names of the participants from the linked data protected their privacy. We excluded 57 participants as a result of information missing from the baseline survey. Accordingly, 4,478 participants (1,921 men and 2,557 women) were included in the analysis. The Institutional Review Board of Shiga University of Medical Science for ethical issues approved the present study (No.16-15).

Baseline Survey and Follow-up

The baseline survey was performed by standardized methods in accordance with the Manual for Health Check-ups under the Medical Service Law for the Aged, issued by the Japan Public Health Association in 1987[23] Public health nurses measured blood pressure with a standard mercury sphygmomanometer in individuals who had rested for at least 5 min. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or taking anti-hypertensive medication. Diabetes was defined as a history of diabetes or glucosuria detected by a spot urine test with a dipstick containing a color pad. Serum high-density lipoprotein (HDL)-cholesterol and triglycerides as a marker of dyslipidemia were not measured at the baseline examination. Accordingly, dyslipidemia was defined as hypercholesterolemia with a total cholesterol level ≥5.69 mmol/L (220 mg/dl).

All participants were classified into the following categories on the basis of clustering of cardiovascular risk factors (hypertension, diabetes and hypercholesterolemia): none, 1, and 2–3. Because visceral fat accumulation was not measured at the baseline survey and the prevalence of obesity (BMI >30 kg/m^2) was very low (1.3%), we used a BMI of 25 kg/m^2 or greater as an indicator of being overweight in the present study[24] Smoking and alcohol consumption habits were determined from interviews administered by the public health nurses.

Information on medical expenditures for each participant was obtained from the monthly NHI claim files, starting from April in the year following their initial health check-up until March 2001. Medical expenditures are expressed in Japanese yen and US dollars (ie, 100 Japanese yen= $US 0.848, at the exchange rates published on November 7th, 2006). Data regarding medical expenditures for each individual differed depending on the period of subscription to the NHI. The medical expenditures for each participant were therefore divided by the period of subscription, and are expressed as expenditures per month of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.

Data Analysis

We evaluated medical expenditures per person per month in each of 3 categories according to the number of cardiovascular risk factors. Because the distribution of real medical expenditures was positively skewed, the data were logarithmically transformed to normalize the distribution and the results are expressed as geometric means. For participants with expenditures of 0 yen per month, logarithmic transformations were achieved by replacing 0 yen with 1 yen. Fifteen participants had total medical expenditures of 0 yen and 16 had outpatient medical expenditures of 0 yen. To compare total and outpatient medical expenditures per person in each category we performed an analysis of covariance after adjusting for age, sex, BMI, smoking (non-smoker or current smoker) and alcohol consumption (none, occasional or daily consumption) with the Bonferroni correction for multiple post-hoc comparisons. A similar analysis was also performed after stratifying by BMI at 25 kg/m^2. The significance of multiplicative interaction between risk factor clustering and being overweight for medical expenditures was examined by cross-product terms in the model. Because 2,604 participants had inpatient medical expenditures of 0 yen, logarithmic transformations were not performed, and we applied the Kruskal–Wallis test to compare inpatient medical expenditures among the 3 categories.

Furthermore, we compared the medical expenditures per person between overweight and normal weight participants with individual cardiovascular risk factors.

Finally, we calculated excess medical expenditures attributable to the number of metabolic risk factors. The excess medical expenditures were estimated as follows: Σ [(the arithmetic mean of total medical expenditures in each of the 5 groups except for normal weight and no risk factor group, ie, (1) normal weight with 1 risk factor, (2) normal weight with 2 or 3 risk factors, (3) overweight alone, (4) overweight with 1 other risk factor, and (5) overweight with 2 or 3 other risk factors−the arithmetic mean of total medical expenditures in normal weight and no risk factor group)×(the number of individuals in each of the 5 categories.)]. We also examined the ratio of excess medical expenditure to the entire total medical expenditures of the population.

The statistical package SPSS 14.0J for Windows performed these analyses. All probability values were 2-tailed and the significance level was established at $p<0.05$.

Results

The prevalence of being overweight was 21.0% (men, 18.1%; women, 23.3%) of the entire study population. Table 1 summarizes the baseline risk characteristics of the 4,478 participants grouped according to risk factor clustering. Among them, 12.9% (men, 10.7%; women, 14.5%) had 2 or 3 risk factors, and 39.5% (men, 40.8%; women,

Table 1 Baseline Risk Characteristics in 1989–1991 of 4,478 National Health Insurance Beneficiaries in Shiga, Japan, Grouped by Sex and Risk Status

Risk characteristics	Risk status category			p value
	None	1 risk factor	2 or 3 risk factors	
Men				
No. of participants (%)	931 (48.5)	782 (40.7)	208 (10.8)	
Age (years)*	52.4±8.3	55.2±8.0	55.6±8.0	<0.01
Body mass index (kg/m²)*	22.1±2.5	22.9±2.7	24.0±2.9	<0.01
Smoking habit†				
Current smoker (%)	61.0	58.7	59.1	0.61
Drinking habit†				
Non-drinker (%)	21.3	19.4	22.1	
Occasional drinker (%)	22.4	19.3	24.0	0.18
Daily drinker (%)	56.3	61.3	53.8	
Hypertension (%)	0.0	67.4	94.7	<0.01
Hypercholesterolemia (%)	0.0	23.0	76.9	<0.01
Diabetes (%)	0.0	9.6	35.1	<0.01
Women				
No. of participants (%)	1,204 (46.1)	984 (38.5)	369 (14.4)	
Age (years)*	52.0±8.1	56.0±7.5	58.2±6.5	<0.01
Body mass index (kg/m²)*	22.3±2.7	23.4±3.1	24.4±2.9	<0.01
Smoking habit†				
Current smoker (%)	3.6	3.3	2.7	0.71
Drinking habit†				
Non-drinker (%)	79.9	79.6	80.8	
Occasional drinker (%)	16.5	16.2	15.4	0.92
Daily drinker (%)	3.6	4.3	3.8	
Hypertension (%)	0.0	54.2	97.6	<0.01
Hypercholesterolemia (%)	0.0	43.6	93.8	<0.01
Diabetes (%)	0.0	2.2	12.5	<0.01

*One way analysis of variance.
†Chi-square test.
Values located after the mark, ±, indicate standard deviation.

Table 2 Medical Expenditures (Total, Outpatient and Inpatient) per Person Grouped by Number of Cardiovascular Risk Factors, After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	No. of participants	Medical costs per person per month				
		Total		Outpatient		Inpatient
		Arithmetic mean	Adjusted geometric mean	Arithmetic mean	Adjusted geometric mean	Arithmetic mean
None	2,135	16,400 yen (139 dollars)	7,361 yen (62 dollars)	8,545 yen (72 dollars)	5,420 yen (46 dollars)	7,872 yen (67 dollars)
1 risk factor	1,766	23,002 yen (195 dollars)	9,382 yen† (80 dollars)	12,470 yen (105 dollars)	7,034 yen† (60 dollars)	10,538 yen (89 dollars)
2 or 3 risk factors	577	25,090 yen (213 dollars)	10,562 yen† (90 dollars) p<0.01*	15,494 yen (131 dollars)	7,929 yen† (67 dollars) p<0.01*	9,597 yen (81 dollars) p<0.01‡

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
*Analysis of covariance adjusted for age, sex, body mass index, smoking habit and drinking habit.
†Significance, vs none, for multiple post-hoc comparisons with Bonferroni correction, p<0.05.
‡Kruskal Wallis test.

38.6%) had 1 risk factor. In both groups with 1 or more risk factors, the prevalence of hypertension was highest followed by hypercholesterolemia. Smoking and alcohol consumption did not significantly differ between the 3 groups in both men and women. The mean BMI values were higher in participants with more risk factors.

Total person-years were 40,815 and the mean follow-up was 9.0 years. Sex-specific analyses of the medical expenditures among the 3 categories showed similar results for men and women. Therefore, we reported our findings for men and women combined. Table 2 shows that during follow-up, the total medical expenditures per person per month with 2–3 risk factors (25,090 yen or $US 213) and with 1 risk factor (23,002 yen or $US 195) were higher than those in the group with no risk factors (16,400 yen or $US 139). The geometric means of total medical expenditures after adjusting for other confounding factors showed significant differences in personal medical expenditures between the 3 categories.

Table 3 shows the medical expenditures per person in normal weight and overweight groups stratified by a BMI of 25.0 kg/m². The total medical expenditures were highest in overweight individuals with 2–3 risk factors (26,782 yen or $US 227). On the contrary, the total medical expenditures were lowest in the normal weight group with no risk factors (15,377 yen or $US 130). The relationship between

Table 3 Total Medical Expenditures per Person Grouped by Number of Cardiovascular Risk Factors, Stratified by Having Overweight (BMI ≥25.0) or Not After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	*No. of participants*	*Total medical costs per person per month*	
		Arithmetic mean	*Adjusted geometric mean*
None			
BMI<25.0	*1,849*	*15,377 yen (130 dollars)*	*6,985 yen (59 dollars)*
BMI≥25.0	*286*	*23,011 yen (195 dollars)*	*9,168 yen† (78 dollars)*
1 risk factor			
BMI<25.0	*1,336*	*24,245 yen (206 dollars)*	*9,091 yen† (77 dollars)*
BMI≥25.0	*430*	*19,143 yen (162 dollars)*	*10,703 yen† (91 dollars)*
2 or 3 risk factors			
BMI<25.0	*351*	*24,002 yen (203 dollars)*	*10,263 yen† (90 dollars)*
BMI≥25.0	*226*	*26,782 yen (227 dollars)*	*12,048 yen† (102 dollars) p<0.01**

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
**Analysis of covariance adjusted for age, sex, smoking habit and drinking habit.*
†Significance, vs none without overweight, for multiple post-hoc comparisons with Bonferroni correction, p<0.05.
BMI, body mass index.

Table 4 Total Medical Expenditures per Person Grouped by Type of Cardiovascular Risk Factors, Stratified by Having Overweight (BMI ≥25.0) or Not After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	*No. of participants*	*Total medical costs per person per month*	
		*Adjusted geometric mean (Model 1)**	*Adjusted geometric mean (Model 2)***
Hypertension			
BMI<25.0	*1,098*	*9,045 yen (77 dollars)*	*11,407 yen (97 dollars)*
BMI≥25.0	*519*	*11,026 yen† (94 dollars)*	*12,991 yen (110 dollars)*
Hypercholesterolemia			
BMI<25.0	*803*	*9,252 yen (78 dollars)*	*9,210 yen (78 dollars)*
BMI≥25.0	*312*	*10,420 yen† (88 dollars)*	*10,551 yen (89 dollars)*
Diabetes			
BMI<25.0	*153*	*15,308 yen (130 dollars)*	*15,139 yen (128 dollars)*
BMI≥25.0	*63*	*18,974 yen (161 dollars)*	*19,497 yen (165 dollars)*

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
**Model 1, analysis of covariance adjusted for age, sex, smoking habit and drinking habit.*
***Model 2, analysis of covariance adjusted for age, sex, smoking habit, drinking habit and other risk factors except for categorized risk factor; for example, in hypertension, hypercholesterolemia and diabetes were adjusted.*
†Significance, between normal weight and overweight, p<0.05.
Abbreviation see in Table 3.

the number of risk factors and adjusted geometric means of medical expenditures in both the normal weight and overweight groups was positively graded. The increase in the rate of medical expenditures according to the number of risk factors was not parallel; however, the interaction term between the number of cardiovascular risk factors and overweight criteria did not reach statistical significance (p=0.351). Individual medical expenditures per month were higher in overweight individuals, than in the normal weight group when the number of other cardiovascular risk factors was consistent.

Table 4 shows the medical expenditures between overweight and normal weight participants with hypertension, hypercholesterolemia and diabetes. The medical expenditures per person in all 3 groups were higher in the overweight group than in the normal weight group. The difference in medical expenditures between overweight and normal weight were largest in diabetics.

The calculated excess medical expenditures attributable to normal weight individuals with 1 risk factor, those who were of normal weight with 2–3 risk factors, only overweight, overweight with 1 other risk factor and overweight with 2–3 other risk factors were 11,847,648 yen, 3,027,375 yen, 2,183,324 yen, 1,619,380 yen and 2,577,530 yen, respectively. Fig 1 shows the share of each excessive medical cost of the total medical expenditures of the entire population. The excess medical expenditures of the 2 normal weight categories combined (16.5%) were higher than

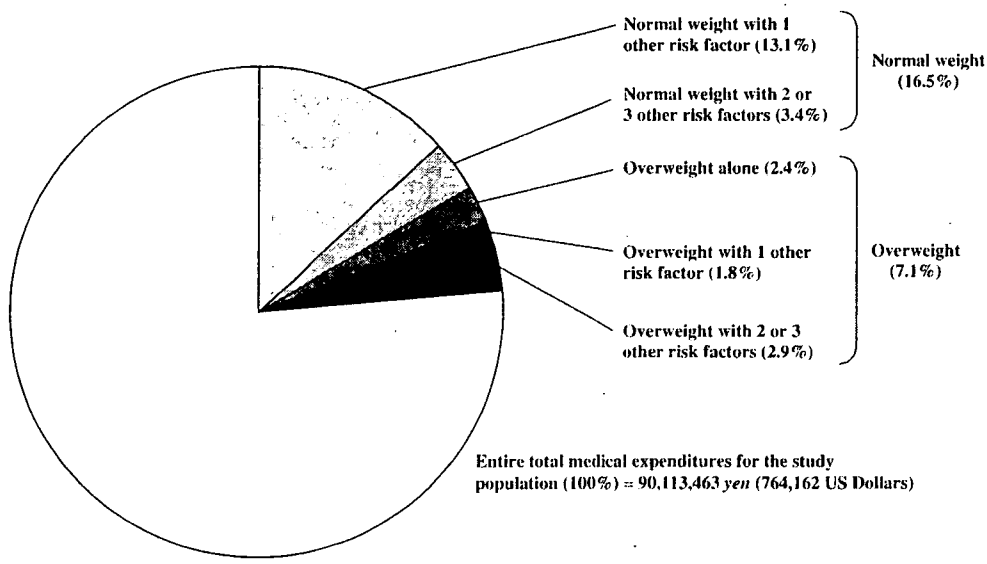

Fig 1. Ratio (%) of excess medical expenditures related to number of cardiovascular risk factors stratified by body mass index (25 kg/m^2) in whole population after 10-year follow-up, from 1990 to 2001, in National Health Insurance in Shiga, Japan (men and women combined). White area represents predicted medical expenditures if all participants were of normal weight without risk factors.

those of 3 overweight categories combined (7.1%).

Discussion

We performed a follow-up study of a Japanese community between 1990 and 2001 and found a positive graded relationship between clustering of cardiovascular risk factors and personal medical expenditures irrespective of being overweight. The mean personal medical cost was higher in overweight, than in normal weight individuals when the number of other risk factors was consistent. Furthermore, the total medical expenditures were the highest in overweight individuals with 2–3 risk factors. Nevertheless, the excess medical expenditures in these participants in entire population were only a few percent and the excess expenditures observed in normal weight categories were rather higher than those in overweight categories.

Findings from the Framingham study have already shown that the risk of atherosclerotic disease increases with combinations of risk factors, such as hypertension, glucose intolerance and hypercholesterolemia[25] Japanese epidemiological studies have also found similar results in community[6] and occupational[26] settings. However, few studies to our knowledge have investigated the association between cardiovascular risk clustering or metabolic syndrome and medical expenditures[13,14] Most other studies have focused on the effect of hypertension combined with diabetes on medical economics[22,27,28]

The continuous increase in medical expenditures is an important concern in most developed countries[29] Furthermore, the effect of cardiovascular diseases on medical economics is a major concern. For example, the medical expenditures for cardiovascular disease including hypertension was 20.4% of the total national medical expenditures in the Japanese population aged 45–69 years, which was larger than any other disease groups during 2001[30] The effective way to control medical expenditures incurred by cardiovascular diseases is to detect those at high risk and provide intensive health and lifestyle guidance or opportunities for early clinical visits for primary care. The present findings showed that overweight people with cardiovascular risk clustering should be detected as priority targets for a high-risk strategy[31] and that overweight people with cardiovascular risk factors such as hypertension, hypercholesterolemia and diabetes can also be potential targets for high-risk strategies that could significantly affect individual medical expenditures. If an individual has accumulated visceral fat or impaired glucose tolerance, which is now classified as a metabolic syndrome, then their medical expenditures should be reduced by implementing appropriate dietary measures and by increasing physical activity.

By contrast, irrespective of high individual medical expenditures, the proportion of excess medical expenditures in the normal weight categories with 1 or more other risk factors was higher than those of all overweight categories combined. The low proportion of excess medical expenditures incurred by overweight individuals is a result of relatively small number of overweight participants identified in the present study. The 1989 to 1991 baseline survey defined only 21% of participants as being overweight (25 kg/m^2 or more). Accordingly, from the viewpoint of an entire population and a population strategy[31] regardless of being overweight, the presence of other cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia significantly effects medical expenditures. Normal weight people with other risk factors, especially in non-Western populations with a low prevalence of obesity, should be carefully considered.

The present study has several limitations. First, the public medical insurance system in Japan differs from that in other countries. Therefore, absolute values of medical expenditures for the participants in the present study might not be directly relevant to other populations. Second, we clustered risk factors from a single measurement at the baseline survey, which generated a regression dilution bias. Third, we did not have values for fasting blood glucose,

triglycerides or HDL-cholesterol, which are important components of metabolic syndrome![5] We used BMI as an indicator of being overweight. One report indicates that waist circumference predicts visceral fat accumulation (which plays a major role on atherosclerosis) better than BMI![32] Accordingly, we might have underestimated or misclassified obesity or being overweight by the BMI method. Finally, details of medical diagnoses, medical treatment status (eg, prescriptions), clinical condition and cause of mortality were not available. Thus, further studies are required to clarify the effects of these variables.

In conclusion, cardiovascular risk clustering and being overweight can be a useful predictor of medical expenditures. On the contrary, the sum of excess medical expenditures because of risk factor clustering in normal weight individuals is larger than that in overweight individuals because of the relatively small ratio of overweight individuals in Japan. However, the obesity epidemic is not restricted to Western countries. Furthermore, mean BMI is rapidly increasing in Asian countries such as Japan. Accordingly, being overweight might increase population medical expenditures in the future.

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Appendix 1

The Health Promotion Research Committee of the Shiga NHI Organizations

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Relationship Between Metabolic Risk Factor Clustering and Cardiovascular Mortality Stratified by High Blood Glucose and Obesity

NIPPON DATA90, 1990–2000

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OBJECTIVE — Metabolic syndrome is diagnosed according to several criteria. Of these, some require glucose intolerance and others require obesity for the diagnosis. We investigated the relationship between metabolic risk factor clustering and cardiovascular disease (CVD) mortality stratified by high blood glucose or obesity.

RESEARCH DESIGN AND METHODS — We followed 7,219 Japanese men and women without a history of CVD for 9.6 years. We defined high blood pressure, high blood glucose, high triglycerides, low HDL cholesterol, and obesity as metabolic factors. The multivariate adjusted hazard ratio (HR) for CVD mortality according to the number of clustering metabolic factors was calculated using the Cox proportional hazards model.

RESULTS — During follow-up, 173 participants died of CVD. The numbers of metabolic risk factors and CVD mortality were positively correlated (P_{trend} = 0.07). The HR was obviously higher among participants with than among those without high blood glucose and clustering of ≥2 other metabolic risk factors (HR 3.67 [95% CI 1.49–9.03]). However, the risk increase was only modest in participants without high blood glucose even if they had ≥2 other metabolic risk factors (1.99 [0.93–4.28]). Conversely, metabolic risk factor clustering was related to CVD mortality irrespective of obesity.

CONCLUSIONS — Our findings suggest that glucose tolerance plays an important role in CVD mortality. Because the prevalence of nonobese participants with several metabolic risk factors was quite high and their CVD risk was high, excluding them from the diagnosis of metabolic syndrome because of the absence of obesity might overlook their risk.

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Abbreviations: CVD, cardiovascular disease; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The World Health Organization (WHO) states that individual risk factors for cardiovascular disease (CVD) convey greater CVD risk. Furthermore, even though each one of these risk factors alone is not serious, the risk becomes more "powerful" when they are combined (1). Metabolic syndrome is the concept of clustering risk factors comprising insulin resistance, abdominal fat distribution, dyslipidemia, and hypertension (2–5).

Several institutions have established their own diagnostic criteria for metabolic syndrome. The National Cholesterol Education Program (NCEP) considers that each metabolic factor has the same importance (6), whereas the WHO requires impaired glucose tolerance among its criteria to diagnose metabolic syndrome (7). Finally, the International Diabetes Federation (IDF) and the Japanese guidelines require central obesity defined by waist circumference to diagnose metabolic syndrome (8,9). Thus, whether a relationship between metabolic risk factor clustering and CVD mortality differs according to obesity or impaired glucose tolerance, which are both required for a diagnosis of metabolic syndrome, should be determined. Thus, in the present study, we investigated the association between metabolic factor clustering and CVD mortality stratified according to obesity or impaired glucose tolerance in a population-based cohort study in the Japanese general population.

RESEARCH DESIGN AND METHODS

— Cohort studies of the National Survey on Circulatory Disorders, Japan, are referred to as NIPPON DATA (National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged). NIPPON DATA includes two cohort studies. Baseline data were surveyed in 1980 and in 1990 (NIPPON DATA80 and NIPPON DATA90), and

Table 1—*Means and prevalence of baseline characteristics of 2,999 men and 4,220 women aged ≥30 years (NIPPON DATA90, 1990)*

Baseline risk characteristics	Number of metabolic factors					
	0	1	2	3	4	5
n	1,604	2,657	1,643	942	336	37
Women (%)	67.3	54.3	59.4	55.4	56.9	56.0
Age (years)	44.1 ± 11.0	52.7 ± 13.6	56.0 ± 13.4	56.1 ± 12.5	58.0 ± 13.2	58.6 ± 11.2
BMI (kg/m^2)	20.9 ± 2.0	21.9 ± 2.4	24.1 ± 3.2	25.5 ± 3.1	26.7 ± 2.4	27.8 ± 2.0
Systolic blood pressure (mmHg)	114.9 ± 8.8	137.2 ± 19.7	141.8 ± 19.0	145.8 ± 17.4	149.2 ± 16.4	154.3 ± 18.4
Diastolic blood pressure (mmHg)	71.7 ± 7.5	82.1 ± 11.4	84.3 ± 11.4	86.7 ± 10.8	88.1 ± 11.5	89.7 ± 12.0
Total cholesterol (mg/dl)	194.2 ± 32.0	198.6 ± 36.2	206.0 ± 37.9	217.3 ± 40.8	224.6 ± 42.7	237.8 ± 43.7
Triglycerides (mg/dl)	78 (57–106)	95 (70–127)	127 (91–176)	192 (131–252)	255 (205–346)	269 (214–363)
HDL cholesterol (mg/dl)	63.5 ± 12.8	58.2 ± 14.6	49.5 ± 13.2	42.4 ± 10.9	37.5 ± 7.8	36.2 ± 6.8
Blood glucose (mg/dl)	92.6 ± 13.5	98.4 ± 22.5	105.5 ± 33.0	114.4 ± 45.9	126.5 ± 51.3	196.7 ± 69.7
High blood pressure (%)	0.0	72.1	82.8	93.7	99.4	100
High triglycerides (%)	0.0	2.8	20.0	55.1	89.3	100
Low HDL cholesterol (%)	0.0	16.1	46.0	73.5	93.2	100
High blood glucose (%)	0.0	2.1	11.7	19.2	33.3	100
Drinking						
Never drinker (%)	73.8	64.0	70.9	66.8	73.8	73.0
Ex-drinker (%)	2.3	2.7	3.4	3.8	3.3	10.8
Current drinker (%)	23.9	33.3	25.7	29.4	22.9	16.2
Smoking						
Never smoker (%)	65.8	58.2	61.6	58.1	54.2	56.8
Ex-smoker (%)	8.6	11.2	11.8	12.3	13.7	10.8
Current smoker (%)	25.6	30.6	26.6	29.6	32.1	32.4
Physical activity						
Yes (%)	18.9	20.3	20.6	21.2	19.3	24.3
No for physical problems (%)	3.4	5.3	6.8	7.1	9.0	10.8
No for other reasons (%)	77.7	74.4	72.6	71.8	71.7	64.9

Data are %, mean ± SD, or median (interquartile range). Metabolic factors were defined as follows: obesity as BMI ≥25 kg/m^2, high blood pressure as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or medication, high blood glucose as nonfasting blood glucose ≥140 mg/dl and/or medication, high triglycerides as nonfasting triglycerides ≥200 mg/dl and/or medication, low HDL cholesterol as HDL cholesterol ≤40 md/dl for men or ≤50 mg/dl for women.

the details of these cohorts have been reported (10–15). Here, we analyzed data from NIPPON DATA90 because the baseline survey of NIPPON DATA80 does not include some important metabolic factors such as HDL cholesterol.

A total of 8,384 residents (3,504 men and 4,880 women, aged ≥30 years) from 300 randomly selected districts participated in the survey and were followed until 15 November 2000. The participation rate in this survey was 76.5%. Of the 8,384 participants, 1,165 were excluded because of a history of coronary heart disease or stroke (n = 371), information missing at the baseline survey (n = 636), and failure to access because of incomplete residential access information at the first survey (n = 158). The remaining 7,219 participants (2,999 men and 4,220 women) were included in the analysis.

Table 2—*Multiple adjusted HRs and 95% CIs according to the individual components of metabolic risk factor in 2,999 men and 4,220 women aged ≥30 years (NIPPON DATA90, 1990–2000)*

Component of metabolic factor	*n*	HR (95% CI)
Obesity	1,706	0.87 (0.60–1.27)
High blood glucose	579	1.45 (0.99–2.14)
High blood pressure	4,530	2.07 (1.21–3.52)
High triglycerides	1,259	1.42 (0.95–2.11)
Low HDL cholesterol	2,224	0.79 (0.56–1.12)

HRs were estimated by a Cox proportional hazards model adjusted for sex, age, total cholesterol, smoking habits, drinking habits, physical activity, and other components of metabolic factors. Metabolic factors were defined as in the footnote to Table 1. n is the number of participants who had the conditions.

Follow-up survey

The underlying causes of death in the National Vital Statistics were coded according to the ICD-9 until the end of 1994 and according to the ICD-10 from the start of 1995 until the end of 2000. Details of these classifications are described elsewhere (10–15). The Institutional Review Board of Shiga University of Medical Science (No. 12–18, 2000) approved this study.

Baseline examination

Nonfasting blood samples were obtained at the baseline survey. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected in siliconized tubes containing sodium fluoride and shipped to one laboratory (SRL, Tokyo, Japan) for blood measurements. Plasma glucose was measured enzymatically. Serum triglycerides

Table 3—*Multiple adjusted HRs and 95% CIs according to number of metabolic factors in 2,999 men and 4,220 women ≥30 years (NIPPON DATA90, 1990–2000)*

Number of metabolic factors	n	Person-years	Cardiovascular deaths	HR (95% CI)
0	1,604	15,740	8	1.00 (—)
1	2,657	25,398	67	1.93 (0.92–4.05)
2	1,643	15,526	52	1.94 (0.91–4.13)
3	942	8,999	29	2.12 (0.96–4.70)
4	336	3,167	15	2.44 (1.02–5.84)
5	37	361	2	3.27 (0.69–15.50)
				P_{trend} 0.074

HRs were estimated by a Cox proportional hazards model adjusted for sex, age, total cholesterol, smoking habits, drinking habits, and physical activity. Metabolic factors were defined as in the footnote to Table 1.

and total cholesterol were also measured enzymatically, and HDL cholesterol was measured after heparin-calcium precipitation (16).

BMI was calculated as weight in kilograms divided by the square of height in meters. Baseline blood pressure was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants. Public health nurses obtained information on smoking, alcohol consumption, physical activity, and medical history. We divided participants into four categories of smokers (never-smoked, ex-smoker, and current smoker <20 or ≥20 cigarettes/day) and six categories of drinking (never-drinker; ex-drinker; and current drinker of 1, 2, 3, and 4 gou of sake/day; 1 gou [180 ml] is equivalent to 23 g of alcohol) (11). We divided participants into three categories of physical activity (yes or no for physical problems, and no for any other reason).

We defined metabolic factors as follows: obesity, BMI ≥25 kg/m^2; high blood pressure, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, administration of antihypertensive agents, or any combination of these; and high blood glucose, serum glucose ≥140 mg/dl, medication for diabetes, or both. Because our samples were nonfasting, the postload blood glucose level for diagnosis of impaired glucose tolerance was ≥140 mg/dl (17). We defined high triglycerides as nonfasting serum triglyceride ≥200 mg/dl and also as taking medication for dyslipidemia. Low HDL cholesterol was defined as serum HDL cholesterol ≤40 mg/dl for men and ≤50 mg/dl for women.

Statistical analysis

Continuous variables were compared using ANOVA, and the χ^2 test was used to compare the dichotomized variables to examine differences in baseline characteristics of participants according to the numbers of clustering metabolic factors.

The multivariate adjusted hazard ratio (HR) of all CVD mortality for each group was calculated using the Cox proportional hazards model adjusted for age, sex, total cholesterol, smoking, drinking, and physical activity category. When we calculated HR for an individual component of a metabolic factor, we further adjusted for other components of the metabolic factor. We used nonobese participants without any metabolic factor or participants with neither a metabolic factor nor high blood glucose as references in analyses stratified by obesity or high blood glucose (required component by the IDF and WHO, respectively). Because leaner participants also have a higher CVD mortality risk in Japan, we further analyzed a data subset excluding leaner participants (BMI <18.5 kg/m^2) (18,19).

All CIs were estimated at the 95% level. $P < 0.05$ was considered significant. The Statistical Package for the Social Sciences (version 11.0J; SPSS Japan, Tokyo, Japan) was used to perform all analyses.

RESULTS — Table 1 shows the baseline characteristics of the study participants according to the numbers of metabolic factors. Total person-years were 69,170, and the mean follow-up period was 9.6 years. During follow-up, 625 participants died of all causes and 173 died of CVD. Table 2 shows the multiple adjusted HRs and 95% CIs according to individual components of metabolic risk factors.

Table 3 shows the number of deaths, multiple adjusted HRs, and 95% CIs according to various numbers of metabolic factors. The HRs for CVD mortality were higher in the group with more metabolic factors, but the trend was not statistically significant (P_{trend} = 0.074). The relationship between numbers of risk factors and CVD mortality did not differ according to sex ($P_{interaction}$ = 0.70). We therefore combined men and women in the following analyses. The tendency for HR to be higher in those with more metabolic factors was similar for heart disease (three risk factors: HR 2.08 [95%CI 0.67–6.48]; four risk factors: 3.97[1.24–12.72]; five risk factors: not applicable) and stroke (three risk factors: 2.07 [0.67–6.37]; four risk factors: 1.23 [0.30–5.05]; five risk factors: 6.26 [CI, 1.13–34.60]) mortality. The HR tendency for all-cause mortality was similar, but the number of clustering metabolic factors was not significantly related to all-cause mortality (three risk factors: 1.16 [0.81–1.65]; four risk factors: 1.18 [0.77–1.80]; five risk factors: 1.44 [0.57–3.63]).

Table 4 shows multiple adjusted HRs (95% CI) due to the number of metabolic factors except high blood glucose stratified by high blood glucose. The HRs trended to increase in both groups (with and without high blood glucose). The HR for CVD in participants with ≥3 metabolic factors but high blood glucose was modest and not statistically significant. Conversely, HRs were obviously higher for participants with high blood glucose and ≥2 other metabolic factors than those for participants with neither metabolic factors nor high blood glucose. The risk increases were statistically significant.

Table 4 also shows multiple adjusted HRs (95% CI) for CVD mortality according to the number of metabolic factors other than obesity stratified by obesity. The relationship between HRs and the numbers of metabolic factors was positive in both obese and nonobese groups. This relationship was unchanged when participants with lower BMI (≥18.5 kg/m^2) were excluded.

CONCLUSIONS — We found that metabolic factor clustering was positively associated with CVD mortality in the general Japanese population. The risk increase in participants with both high blood glucose and ≥2 metabolic factors was significantly higher than in those with neither high blood glucose nor metabolic risk factors. The risk in nonobese participants with more metabolic factors was also increased.

Although investigating the relation-

Table 4—*Blood glucose category–specific multiple-adjusted HRs and 95% CIs according to number of metabolic factors other than high blood glucose and BMI category–specific multiple-adjusted HRs and 95% CIs according to the number of metabolic factors other than obesity in 2,999 men and 4,220 women aged ≥30 years (NIPPON DATA90, 1990–1999)*

	Number of metabolic factors	*n*	Person-years	Cardiovascular deaths	HR (95% CI)	HR (95% CI)
High blood glucose						
Without	0	1,604	15,740	8	1.00 (—)	
	1	2,600	24,867	65	1.91 (0.91–4.02)	
	2	1,451	13,796	45	1.99 (0.93–4.28)	
	≥3	985	9,522	22	1.61 (0.71–3.67)	
With	0 and 1	249	2,241	9	1.78 (0.68–4.67)	
	2	181	1,638	12	3.67 (1.49–9.03)	
	≥3	149	1,267	12	3.25 (1.31–8.06)	
BMI						
<25 kg/m²	0	1,604	15,740	8	1.00 (—)	1.00 (—)
	1	2,474	23,576	67	1.98 (0.94–4.17)	2.14 (0.85–5.43)
	2	993	9,282	37	1.95 (0.90–4.25)	2.24 (0.86–5.82)
	≥3	442	4,108	24	2.83 (1.25–6.39)	3.35 (1.25–8.95)
≥25 kg/m²	0 and 1	833	8,045	15	1.75 (0.73–4.16)	2.12 (0.76–5.89)
	2	551	5,339	10	1.47 (0.57–3.75)	1.78 (0.59–5.19)
	≥3	322	3,080	12	2.37 (0.96–5.89)	2.84 (0.99–8.17)

HRs were estimated by a Cox proportional hazards model adjusted for sex, age, total cholesterol, smoking habits, drinking habits, and physical activity. High blood glucose was defined as nonfasting blood glucose ≥140 mg/dl and/or medication. Metabolic factors were defined as follows: obesity as BMI ≥25 kg/m², high blood pressure as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or medication, high triglycerides as nonfasting triglycerides ≥200 mg/dl and/or medication, low HDL cholesterol as HDL cholesterol ≤40 mg/dl for men or ≤50 mg/dl for women. In the group with high blood glucose, 0 and 1 metabolic factors were combined because we found only two cardiovascular deaths in the group whose number of metabolic factors was 0. *HRs (95% CI) were analyzed for participants with BMI >18.5 kg/m². Metabolic factors were defined as follows: high blood pressure as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or medication, high blood glucose as nonfasting blood glucose ≥140 mg/dl and/or medication, high triglycerides as nonfasting triglycerides ≥200 mg/dl and/or medication, low HDL cholesterol as HDL cholesterol ≤40 mg/dl for men or ≤50 mg/dl for women. In the group with BMI ≥25 kg/m², 0 and 1 metabolic factors were combined because we found no cardiovascular death in the group whose number of metabolic factors was 0.

ship between metabolic factor clustering and CVD mortality is important, prospective studies on the topic are still scarce. On the basis of the NCEP and WHO definitions of metabolic syndrome, several investigators have reported that participants with metabolic syndrome or metabolic factor clustering have a high HR of CVD mortality (20–25). Ford (26) summarized prospective cohort studies and reported that the HRs of CVD mortality were 1.65 [5% CI 1.38–1.99] according to the NCEP definition and 1.93 [1.39–2.67] according to the WHO definition, respectively. This result is consistent with our findings that participants with more metabolic factors have a higher risk of CVD mortality. Our results were also comparable with those of a prospective study in Japan showing that the relative risk of cardiac diseases was 2.23 [1.14–4.34] in participants with ≥3 metabolic factors compared with that in participants with <3 metabolic factors (27).

The IDF definition requires obesity for diagnosis of metabolic syndrome. These guidelines explain that central (abdominal) obesity is a prerequisite for this diagnosis because it is easy to assess and independently associated with each of the other metabolic syndrome components (8). The IDF guidelines do not essentially require insulin resistance because it is difficult to measure in day-to-day clinical practice (7,8). However, although increased waist circumference is an important component of metabolic syndrome, some individuals with multiple risk factors and an increased risk of CVD mortality have normal waist circumference (28,29). For example, Katzmarzyk et al. (28) reported that waist circumference is a valuable component of metabolic syndrome, but they also raised the concern that the IDF requirement of an increased waist circumference warranted caution because a large proportion of individuals with normal waist circumference also have multiple risk factors and an increased risk of mortality.

We found here that nonobese participants with three or more metabolic factors had significantly higher HRs for CVD death and that their risk was similar to that of obese participants with the corresponding number of metabolic factors. Thus, a proportion of high-risk participants might be overlooked if obesity is a diagnostic requirement for metabolic syndrome. Waist circumference supposedly indicates visceral fat more accurately than BMI in terms of predicting diabetes (30). However, we did not have any information about waist circumference and used BMI as it closely correlates with waist circumference. Furthermore, BMI has been used to diagnose obesity in many epidemiological studies of metabolic syndrome (22,23), indicating that BMI was acceptable for our purposes. However, because of the use of BMI, we might have underestimated the impact of obesity on CVD mortality. A similar study using waist circumference should clarify the relation.

The WHO guidelines indicate that the presence of diabetes, impaired glucose tolerance, or insulin resistance is necessary for a diagnosis of metabolic syndrome because this condition is considered a special classification for those with the potential for diabetes (manifested as impaired glucose tolerance, impaired fasting glucose, or insulin resistance determined using the hyperinsulinemic-euglycemic clamp) (1,7). Here, we also stratified participants according to blood glucose level and found that the HR was higher among those with than among those without high blood glucose. These findings suggest that glucose toler-

ance plays an important role in CVD mortality. Some reports have shown higher HRs with use of the WHO rather than the NCEP definition of metabolic syndrome. This result means that the participants with impaired glucose tolerance have higher HRs, a finding that the present results support (26). However, several participants with clustering of metabolic factors other than impaired glucose tolerance also had an increased risk of CVD mortality.

Some limitations other than using BMI should be noted about the present study. First, we used nonfasting blood samples and thus we might have misclassified participants with high blood glucose or hypertriglyceridemia. Second, we did not adjust for socioeconomic status because relevant information was not available. However, all Japanese are covered by the national health insurance program and socioeconomic status does not affect access to treatment. Therefore, the impact of socioeconomic status on our findings should be minimal.

In summary, the CVD risk was obviously higher among individuals with than among those without high blood glucose and multiple metabolic risk factors, suggesting that high blood glucose plays an important role in CVD mortality. Conversely, the prevalence of nonobese participants with several metabolic factors was quite high and their CVD risk was high. Thus, metabolic factors should be carefully considered and appropriately managed even among individuals with a BMI <25.

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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 ≥ 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.

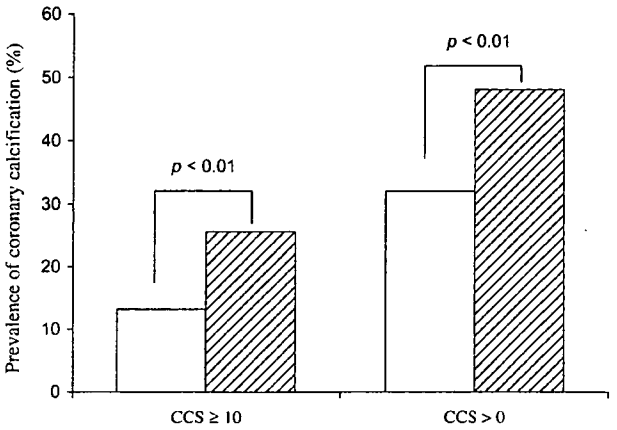

FIGURE 1. Prevalence of coronary artery calcification (%) in Japanese men aged 40–49 years in Kusatsu City, Shiga, Japan (white bars) and in White men aged 40–49 years in Allegheny County, Pennsylvania (striped bars) in 2002–2005. CCS, coronary calcium score.

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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