

Figure 1. Odds ratios for hypertension by number of oral health disorders including Community Periodontal Index of Treatment Needs (CPITN) stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C. Data are adjusted odds ratio (95% confidence interval). Analyses were controlled for age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, physical activity, daily sugar-sweetened soft drink intake, and nocturnal sleep duration.

bleeding and malocclusion is a strong risk for hypertension remains hypothetical, but activation of inflammation, worse masticatory performance, and breathing disorders may be present and thus increase the risk of hypertension.

In this study, adjusted R^2 values in the model after adding the number of oral health components were higher than without including oral markers or after adding individual oral health markers, suggesting that the concomitance of these oral health disorders seems to jointly contribute to the risk of hypertension. The precise mechanism by which the concomitance of several oral health disorders is an independent risk for hypertension remains hypothetical but is likely multifactorial. In this study, a significant graded relationship between the number of components present and the corresponding body mass index, as well as bite force, was found. Worse masticatory performance, obstructive breathing disorders, periodontal inflammation, and obesity may be present in the case of concomitant oral health disorders and thus enhance the risk of hypertension. On the other hand, in this study, 42.6% of subjects with the lowest quartile of remaining tooth number corresponded to Eichner index C. Although these two oral health markers essentially do not mean the same thing, the remaining tooth number and Eichner index influenced each other. More generally, all of the oral health disorders examined in this study are relatively inter-related. Therefore, our results should be also interpreted as indicating that moderately or severely impaired, but not mildly impaired, oral health is associated with increased risk of hypertension.

Lifestyle changes are widely recognized to lower blood pressure or to reduce the risk of developing hypertension.²⁹ Of these, the lifestyle variables reported in this study have been suggested to be important factors modulating blood pressure.^{29–31} Except for daily sugar-sweetened soft drink intake, we did not find a significantly worse lifestyle in the groups with a higher number of components of oral health

Table 5. Association between number of oral health disorder components—Community Periodontal Index of Treatment Needs stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C—and differences in blood pressure in subjects not taking antihypertensive medication (n = 1,148)

Models	1			2			≥3		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P trend
Systolic blood pressure									
Age- and sex-adjusted	Reference			Reference			Reference		
Multivariable-adjusted ^a	0.77	-1.81 to 3.34	0.56	2.79	-0.82 to 6.40	0.13	5.36	1.07 to 9.66	<0.01
Diastolic blood pressure	Reference			Reference			Reference		
Age- and sex-adjusted	Reference			Reference			Reference		
Multivariable-adjusted ^a	0.24	-2.30 to 2.78	0.85	2.98	-0.55 to 6.51	0.10	5.41	1.16 to 9.66	0.03
Age- and sex-adjusted	Reference			Reference			Reference		
Multivariable-adjusted ^a	0.16	-1.32 to 1.64	0.83	1.46	-0.62 to 3.54	0.17	2.51	0.04 to 4.98	0.04
Multivariable-adjusted model included age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, daily sugar-sweetened soft drink intake, physical activity, and nocturnal sleep duration.	Reference			Reference			Reference		
	-0.16	-1.61 to 1.29	0.83	1.41	-0.60 to 3.42	0.17	2.36	-0.06 to 4.78	0.06

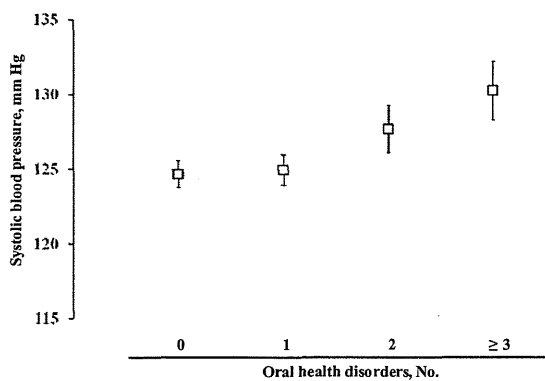


Figure 2. Adjusted mean systolic blood pressure by number of oral health disorders including Community Periodontal Index of Treatment Needs (CPITN) stage 4, presence of gingival bleeding, sex-specific lowest quartile of remaining tooth number, and Eichner index C in subjects not taking antihypertensive medication ($n = 1,148$). Data are adjusted mean \pm SE. The P value for trend was 0.03. Analyses were controlled for age, sex, body mass index, diabetes, dyslipidemia, estimated glomerular filtration rate, smoking status (3 categories), daily alcohol intake, daily fruit intake, physical activity, daily sugar-sweetened soft drink intake, and nocturnal sleep duration.

disorders; rather, significantly lower prevalences of current smoking, daily sugar-sweetened soft drink intake, and longer nocturnal sleep duration were found in hypertensive subjects than in those without, suggesting that some hypertensive subjects in this study had already instituted lifestyle changes. Modification of lifestyle as a result of oral health disorders has been speculated to be another possible cause of development of hypertension;^{9,13} however, our results may support the existence of a direct association of oral health disorders with hypertension.

Our analysis has several limitations. First, the design of this study does not allow us to clarify the underlying mechanism. Indeed, reverse causality whereby hypertension leads to oral health disorders cannot be excluded. Another recent study showed a negative association between periodontal disease and incident hypertension.³² Second, several important inflammatory and metabolic markers, such as C reactive protein and insulin, were not measured in our study. Unmeasured variables, such as salt intake and sleep disorders, may affect the observed results. Nonetheless, the use of 4 oral health markers that refer to different manifestations of oral disease and cover both the presence and the extent of disease indicates that the results are not coincidental, hence limiting any bias resulting from using only 1 oral health disorder variable.

In conclusion, there is an additive relationship between oral health disorders and increased odds of hypertension and raised SBP in the Japanese urban population. Our results also suggest that moderately or severely impaired oral health—that is, several concomitant oral health disorders—is associated with risk of hypertension. Our findings emphasize that poor oral health might have a direct relationship with hypertension, and this might have important implications for public health. The next crucial step is to investigate whether oral health disorders are causally linked to

hypertension in a longitudinal setting. If so, dental therapy might be used in clinical practice to reduce the development of hypertension.

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DISCLOSURE

The authors declared no conflict of interest.

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Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category: The Suita Study

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Brief Reports

Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category The Suita Study

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Background and Purpose—We aimed to clarify the association of chronic kidney disease (CKD) with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure categories in an urban general population.

Methods—We studied 3466 Japanese individuals (35–93 years old) in the Suita Study. Carotid atherosclerosis was expressed as the maximum carotid intima-media thickness and the presence of stenosis (>25%). The estimated glomerular filtration rate was calculated using the equations recommended by the Japanese Society of Nephrology. CKD was defined as estimated glomerular filtration rate <60 mL/min per 1.73 m². Blood pressure categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

Results—The multivariable-adjusted maximum carotid intima-media thickness and odds ratio for stenosis in subjects with estimated glomerular filtration rate <50 mL/min per 1.73 m² were greater than those in subjects with estimated glomerular filtration rate ≥90 mL/min per 1.73 m². When subjects were stratified according to blood pressure categories, the multivariable-adjusted maximum carotid intima-media thickness was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension. Similarly, the impact of CKD on stenosis was evident only in subjects with hypertension (multivariable-adjusted odds ratios for stenosis [95% confidence interval] were 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension compared with non-CKD/optimal blood pressure).

Conclusions—In a general population, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension. (*Stroke*. 2013;44:3537–3539.)

Key Words: carotid artery diseases ■ carotid intima-media thickness ■ hypertension ■ renal insufficiency, chronic

Chronic kidney disease (CKD) has been shown to be an independent risk factor for cardiovascular disease in general populations.¹ Recently, we have shown that even slight renal dysfunction, with an estimated glomerular filtration rate (eGFR) of 50 to 59 mL/min per 1.73 m², results in an increased risk of cardiovascular disease in an urban general population.²

One possible explanation for the association of CKD with cardiovascular disease is that CKD-related nontraditional risk factors accelerate atherosclerosis independent of traditional vascular risk factors.³ However, there is controversy as to whether CKD is independently associated with carotid intima-media thickness (IMT).⁴ This may be because the impact of CKD, especially mild kidney disease, on carotid atherosclerosis is somewhat limited. CKD seems to increase the risk

of carotid atherosclerosis when hypertension and impaired glucose metabolism are present.⁵ We hypothesized that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant cardiovascular risk factors. Thus, we aimed to clarify the association of CKD with carotid atherosclerosis and the impact of CKD on carotid atherosclerosis according to blood pressure (BP) categories in an urban general population.

Patients and Methods

We sequentially enrolled 3,446 individuals (1,844 women and 1,602 men, 35–93 years old [62±11 years]) who underwent regular health checkups and carotid ultrasonography between April 2002 and March 2004 from the participants in the Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases. Each index of

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Table 1. Adjusted Max-IMT According to eGFR Category

	eGFR, mL/min per 1.73 m ²				P Value for Trend
	≥90	60–89	50–59	<50	
Men	236	1106	174	86	
Age adjusted	1.44±0.04	1.47±0.02	1.52±0.05	1.64±0.07*	0.078
Multivariable adjusted	1.43±0.04	1.48±0.02	1.51±0.05	1.63±0.07*	0.134
Women	436	1214	137	57	
Age adjusted	1.21±0.02	1.20±0.01	1.22±0.03	1.38±0.05†	0.014
Multivariable adjusted	1.21±0.02	1.20±0.01	1.21±0.03	1.34±0.05*	0.079

Means±SD (mm). eGFR indicates estimated glomerular filtration rate; and max-IMT, maximum carotid intima-media thickness. * $P<0.05$ and † $P<0.01$ vs eGFR≥90.

carotid atherosclerosis was defined as follows. Max-IMT was defined as the maximum IMT in the entire scanned area. Stenosis was defined as the presence of a stenotic area ≥25% on a cross-sectional scan. The eGFR was calculated using equations recommended by the Japanese Society of Nephrology.⁶ The subjects were categorized into 4 groups (eGFR ≥90, 60–89, 50–59, and <50 mL/min per 1.73 m²) as in our previous study.² CKD was defined as an eGFR <60 mL/min per 1.73 m². BP categories (optimal, normal, high-normal BP, and hypertension) were based on the European Society of Hypertension and European Society of Cardiology 2007 criteria.⁷ The association of eGFR category with carotid atherosclerosis and the association of CKD with carotid atherosclerosis according to BP categories were examined using analysis of covariance and logistic regression analysis, after adjusting for cardiovascular risk factors as covariates (see Methods in the online-only Data Supplement).

Results

CKD was identified in 16.2% (eGFR=50–59: 10.9%; eGFR<50: 5.3%) of men and in 10.5% (7.4%, 3.1%) of women (see Table I in the online-only Data Supplement.). The multivariable-adjusted max-IMT and odds ratio for stenosis in subjects with eGFR<50 were significantly greater than those in subjects with eGFR≥90; however, the max-IMT and odds ratio in subjects with eGFR=50 to 59 were not significantly different from those in subjects with eGFR≥90 (Tables 1 and 2). Consequently, the max-IMT and odds ratio for stenosis in the whole CKD sample were not significantly greater than those in the eGFR≥90 group.

When subjects were stratified according to BP categories, the multivariable-adjusted max-IMT in the hypertension category was significantly greater in both sexes. The max-IMT was significantly greater in CKD subjects than in non-CKD subjects only in subjects with hypertension (Figure [A]). The prevalence of stenosis was higher in subjects with high-normal BP and hypertension in all subjects. The impact of CKD on the prevalence of stenosis was more pronounced in subjects with hypertension (multivariable-adjusted odds ratio [95% confidence interval], 2.21 [1.53–3.19] in non-CKD/hypertension and 3.16 [2.05–4.88] in CKD/hypertension; Figure [B]). Similar trends were found in the analysis of stenosis in men.

Discussion

In our study, CKD was independently associated with carotid atherosclerosis in subjects with hypertension, but not in nonhypertensive subjects. This is the first study to show the combined impact of CKD and hypertension on carotid atherosclerosis in an urban general population.

In previous studies in general populations, only one study reported that reduced kidney function was a strong predictor of greater carotid IMT at baseline and progression of carotid atherosclerosis independent of vascular risk factors.⁸ Another study found no independent association of eGFR with carotid IMT.⁹ In our study, eGFR <50 mL/min per 1.73 m²

Table 2. Adjusted Odds Ratios (95% CI) for Stenosis According to eGFR Category

	eGFR, mL/min per 1.73 m ²				Odds Ratio/10 mL per min eGFR Increase
	≥90	60–89	50–59	<50	
Men and women	672	2320	311	143	
Cases of stenosis	47	318	69	48	
Age adjusted	1	1.09 (0.78–1.53)	1.34 (0.87–2.06)	1.91 (1.16–3.14)	0.94 (0.88–1.01)
Multivariable adjusted	1	1.17 (0.83–1.66)	1.37 (0.88–2.13)	1.79 (1.07–2.98)	0.94 (0.88–1.01)
Men	236	1106	174	86	
Cases of stenosis	22	226	51	32	
Age adjusted	1	1.37 (0.84–2.23)	1.71 (0.96–3.04)	1.86 (0.96–3.04)	0.95 (0.87–1.03)
Multivariable adjusted	1	1.56 (0.94–2.57)	1.85 (1.02–3.36)	1.81 (0.91–3.59)	0.95 (0.87–1.04)
Women	436	1214	137	57	
Cases of stenosis	25	92	18	16	
Age adjusted	1	0.85 (0.52–1.37)	0.99 (0.50–1.96)	2.38 (1.12–5.06)	0.93 (0.84–1.04)
Multivariable adjusted	1	0.84 (0.51–1.38)	0.91 (0.45–1.84)	2.04 (0.93–4.47)	0.95 (0.85–1.06)

CI indicates confidence interval; and eGFR, estimated glomerular filtration rate.

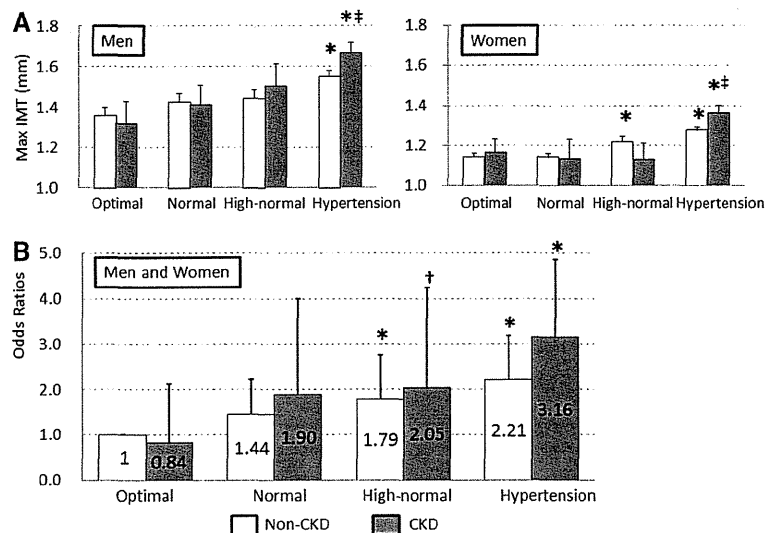


Figure. Multivariable-adjusted maximum carotid intima-media thickness (max-IMT; A) and odds ratios for stenosis (B) according to blood pressure (BP) category in subjects with and without chronic kidney disease (CKD). *P<0.05; †P=0.053 vs non-CKD/optimal BP; ‡P<0.05 vs non-CKD subjects in the same BP category.

was independently associated with carotid atherosclerosis, whereas CKD was not. The inconsistent results of these studies might be attributable in part to different eligibility criteria, background, or methods for evaluating renal function. An alternative explanation is that the association of CKD with carotid atherosclerosis may be somewhat limited.

In a recent Japanese study, CKD was associated with increased IMT only in subjects with hypertension.⁵ Similarly, we showed that CKD was independently associated with carotid atherosclerosis in subjects with hypertension, whereas there was no significant impact of CKD in nonhypertensive subjects. Our results suggest that the impact of CKD on carotid atherosclerosis differs according to the presence of concomitant vascular risk factors. CKD may not directly contribute to early carotid atherosclerosis but may rather accelerate the endowment of atherosclerosis in the setting of progressive endothelial dysfunction in those with hypertension.

We could not demonstrate a causal relationship between CKD, hypertension, and carotid atherosclerosis because of the cross-sectional design of our study. However, carotid atherosclerosis reflects the cumulative effects of cardiovascular risk factors that are present over many years. In the future, we plan to determine whether the coexistence of CKD and hypertension increases the risk of carotid atherosclerosis in a prospective study.

In conclusion, the association of CKD with carotid atherosclerosis was modest, but CKD was independently associated with carotid atherosclerosis in subjects with hypertension in an urban general population. Our results suggest that the presence of hypertension should be considered for risk stratification of CKD for improved stroke prevention.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL**Impact of chronic kidney disease on carotid atherosclerosis
according to blood pressure: The Suita Study****Supplemental Methods****The Suita Study**

Suita City is located adjacent to Osaka City, which belongs to the second largest metropolitan area in Japan. The Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases, is based on a random sampling of 12,200 Japanese urban residents.^{1, 2} The participants have been visiting the National Cerebral and Cardiovascular Center every 2 years since 1989 for regular health checkups. Written informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Evaluation of renal function

Serum creatinine (Cr) was measured by the kinetic Jaffé method. The estimated glomerular filtration rate (eGFR) was calculated from the Cr value and age, using equations recommended by the Japanese Society of Nephrology.³

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{age}^{-0.287} \times \text{Cr}^{-1.094} \text{ (for men)}$$

$$\text{and eGFR (mL/min/1.73m}^2\text{)} = 194 \times \text{age}^{-0.287} \times \text{Cr}^{-1.094} \times 0.739 \text{ (for women).}$$

Carotid Ultrasound Measurements

Carotid atherosclerosis was evaluated by high-resolution ultrasonography with a 7.5-MHz transducer that produced an axial resolution of 0.1 mm. We measured the carotid arteries from the superior border of the collarbone to the inferior margin of the mandible. Details of the methods used for the carotid ultrasonic examination have been previously published.⁴

Measurement of Blood Pressure

Well-trained physicians measured blood pressure (BP) three times with the subject in a seated position using a mercury column sphygmomanometer, an appropriately sized cuff and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken as the average of the second and third measurements, which were separated by more than 1 minute. Subjects were classified into one of four BP categories (optimal, normal, high-normal and hypertension) based on BP values according to the European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 criteria⁵: optimal (SBP <120 mmHg and DBP <80 mmHg), normal (SBP=120~129 mmHg and DBP=80~84 mmHg), high-normal BP (SBP=130~139 mmHg and DBP=85~89 mmHg), and hypertensive (SBP ≥140 mmHg and DBP ≥90 mmHg or the use of antihypertensive drugs). If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the two BP categories.

Covariates

We performed routine blood tests that included serum total cholesterol, HDL cholesterol and glucose levels. Fasting serum glucose categories were defined as follows⁶: diabetes mellitus (DM, fasting serum glucose ≥7.0 mmol/L (126 mg/dL) or the use of medications for DM), impaired fasting glucose (fasting serum glucose levels from 5.6~6.9 mmol/L (100~125 mg/dL), and normoglycemia (fasting serum glucose levels <5.6 mmol/L (<100 mg/dL). Physicians or nurses administered questionnaires covering personal habits and present illness. Smoking and drinking status were divided into current, former and never. Body mass index (BMI) was calculated as weight (kg) divided by height (m)².

Statistical analysis

The association of GFR category with carotid atherosclerosis index was examined using analysis of covariance (ANCOVA) to compare the maximum intima-media thickness among subjects according to GFR category. In addition, logistic regression analysis was to estimate odds ratios (OR) and 95% confidence intervals (CI) for the relationship between stenosis and each GFR category, adjusting for covariates (age, smoking and drinking status, BP category, blood glucose category, total and HDL cholesterol (quartile), and body mass index). To examine the combined impact of CKD and

BP category on carotid atherosclerosis, we analyzed the association between BP category and the carotid atherosclerosis index in subjects with and without CKD, using ANCOVA and logistic regression analysis, adjusting covariates (age, smoking and drinking status, blood glucose category, total and HDL cholesterol and body mass index). A P value <0.05 was considered significant for all comparisons. All analyses were performed with SAS statistical software (version 8.2; SAS Institute, Cary, NC, USA).

Supplemental Table I. Characteristics of study subjects according to eGFR category

	GFR in men, mL/min/1.73m ² (n = 1602)				GFR in women, mL/min/1.73m ² (n = 1844)			
	≤90	60-89	50-59	<50	≤90	60-89	50-59	<50
Patients, n	236	1106	174	86	436	1214	137	57
Age, y	57±11	67±11	72±8	78±7	59±9	64±11	71±9	74±8
BP category								
Optimal BP, %	31	20	14	8	35	31	21	9
Normal BP, %	18	19	19	11	18	19	10	5
High normal BP, %	13	17	12	11	15	13	14	11
Hypertension, %	38	44	55	70	32	37	55	75
Diabetes mellitus, %	14	11	13	15	7	5	8	9
Total cholesterol, mg/dL	199±33	199±31	200±30	196±35	215±32	217±31	216±32	207±33

HDL cholesterol, mg/dL	59±16	55±14	52±13	51±13	66±16	65±15	61±13	63±16
Body mass index, kg/m ²	23±3	23±3	23±3	23±3	22±3	22±3	23±3	22±4
Current smoking, %	43	29	20	17	8	6	6	4
Current drinking, %	74	68	58	50	32	27	20	16

Values are the means±standard deviation or percent.

GFR, glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein

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Do Differences in Risk Factors Explain the Lower Rates of Coronary Heart Disease in Japanese Versus U.S. Women?

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Abstract

Background: Mortality from coronary heart disease (CHD) in women in Japan is one of the lowest in developed countries. In an attempt to shed some light on possible reasons of lower CHD in women in Japan compared with the United States, we extensively reviewed and analyzed existing national data and recent literature.

Methods: We searched recent epidemiological studies that reported incidence of acute myocardial infarction (AMI) and examined risk factors for CHD in women in Japan. Then, we compared trends in risk factors between women currently aged 50–69 years in Japan and the United States, using national statistics and other available resources.

Results: Recent epidemiological studies have clearly shown that AMI incidence in women in Japan is lower than that reported from other countries, and that lipids, blood pressure (BP), diabetes, smoking, and early menopause are independent risk factors. Comparing trends in risk factors between women in Japan and the United States, current levels of serum total cholesterol are higher in women in Japan and levels have been similar at least since 1990. Levels of BP have been higher in Japan for the past 3 decades. Prevalence of type 2 diabetes has been similar in Japanese and white women currently aged 60–69 for the past 2 decades. In contrast, rates of cigarette smoking, although low in women in both countries, have been lower in women in Japan.

Conclusions: Differences in risk factors and their trends are unlikely to explain the difference in CHD rates in women in Japan and the United States. Determining the currently unknown factors responsible for low CHD mortality in women in Japan may lead to new strategy for CHD prevention.

Introduction

JAPANESE WOMEN IN JAPAN HAVE EXPERIENCED the greatest longevity for the past 25 years.¹ This is partly due to a constant decline in mortality from coronary heart disease (CHD) since the 1960s, although CHD mortality in women in Japan was one of the lowest in developed countries.² Low CHD mortality in Japan in the 1960s was attributed to low dietary intake of saturated fat and cholesterol, resulting in low serum levels of total cholesterol (e.g., 160 mg/dL in Japan and 240 mg/dL in the United States).³ The hypothesis at that time was that with Western acculturation, CHD rates in Japan would increase. In fact, CHD mortality in Asian countries has

increased with concomitant rise in serum total cholesterol except for Japan.^{4,5} Between 1960 and 1990, dietary intake of both total fat and animal protein almost tripled,^{6,7} and the current dietary intake of cholesterol in women in Japan is higher than in the United States (i.e., 199 vs. 128 mg/1,000 kcal).⁸ The current levels of total cholesterol in women aged 50–69 years in Japan are higher than those in the United States.⁹ The absence of increase in CHD is unusual, given that during this period, dietary-related diseases (e.g., colon and breast cancer in women and colon and prostate cancer in men increased substantially).¹⁰ It is important to note that low CHD mortality in women in Japan is not a function of high mortality from other causes (e.g., stroke, cancer).¹

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Low CHD mortality in Japanese in Japan does not appear to be due primarily to genetics or host susceptibility because CHD incidence and mortality increased substantially in Japanese migrants to the United States within one to two generations.¹¹ Additionally, we have recently documented that levels of atherosclerosis assessed as calcification of the coronary artery and aorta and intima-media thickness (IMT) of the carotid artery in Japanese American men are not only higher than those in Japanese men in Japan, but are also higher compared with white Americans.^{12,13} We have previously reported that low CHD mortality in middle-aged men in Japan compared with the United States is very unlikely due to misclassification of cause of death,¹⁴ difference in risk factors,^{15,16} or cohort effect.¹⁶ In an attempt to shed some light on possible reasons of lower CHD in women in Japan compared to the United States, we extensively reviewed and analyzed existing national data and recent literature.

Materials and Methods

Data on CHD mortality were obtained from the World Health Organization (WHO) Statistical Information System (www.who.int/whosis). For age-adjusted mortality from CHD, a new WHO standard was used.¹⁷ To define CHD we used codes I20–25 in the International Statistical Classification of Diseases and Related Health Problem 10th Revision (ICD-10) and codes 410–414 in ICD-9. To depict the international trend in CHD mortality from 1995 to 2004, we chose Canada, France, Greece, Japan, Spain, the United Kingdom, and the United States.

To compare trends in risk factors between women in Japan and the United States, data were obtained from the National Health and Nutrition Examination Surveys (NHANES) in the United States,^{18,19} the National Health and Nutrition Survey and the National Survey of Cardiovascular Diseases in Japan^{6,7,20} as well as published articles (Table 1).^{21–23} Prevalence of diabetes in white women in 2007–2010 in the United States was estimated using the NHANES dataset available at a web site of the Centers for Disease Control and Prevention.¹⁹

For incidence of acute myocardial infarction (AMI) and the association of risk factors with CHD in women in Japan, we identified epidemiological studies published after 2001 that reported the data in women and men separately, because no

previous epidemiological studies in Japan reported the association only in women. We identified these studies using review papers we and others published in 2008,^{24,25} articles citing these review papers, a website listing cardiovascular epidemiology studies conducted in Japan with their publications,²⁶ and PubMed.

Results

Between 1995 and 2004, age-adjusted CHD mortality in women was declining in each country (Fig. 1). During this period, women in France and Japan had the lowest and women in the United Kingdom and the United States had the highest CHD mortality. A five-fold difference existed in age-adjusted CHD mortality (per 100,000) in 2004 between Japan and the United States: 13.5 in Japan versus 65.6 in the United States.

AMI incidence in women in Japan, evaluated using the protocol of the WHO MONICA Project (Monitoring of Trends and Determinants in Cardiovascular Disease)²⁷ was much lower compared to other countries. The Takashima AMI Registry covering about 55,000 individuals reported that age-adjusted incidence of AMI in women aged 25–74 years was 18.0/100,000²⁸ and that the incidence was the lowest as compared to the incidence in registries from the WHO MONICA Project.²⁷ Age-adjusted incidence of AMI in women aged 35–64 in Takashima was 9.1/100,000, which was less than a tenth of that in the United Kingdom (256/100,000), the United States (139/100,000), and Finland (86–165/100,000) and even less than a half of that in France (37–77/100,000), and China (37/100,000).²⁸ AMI incidence in women in other registries in Japan was reported and similarly low.^{24,29}

Additionally, there is little evidence that AMI incidence in women in Japan has increased recently. The MIYAGI-AMI registry study, which covers more than 2 million individuals, the largest AMI registry in Japan, reported AMI incidence in women between 1979 and 2009.³⁰ Age-adjusted incidence of AMI in women remained similar or appeared to be slightly decreasing between 1987 and 2008, although it increased between 1979 and 1986. The Circulatory Risk in Communities Study (CIRCS) which covers more than 30,000 individuals reported that age-adjusted incidence of sudden cardiac death in women in Japan significantly decreased from 1981 to 2005.³¹ Age-adjusted incidence of sudden cardiac death (per 100,000) was 50.6, 39.5, 27.1, 16.7, and 18.2 during 1981–1985, 1986–1990, 1991–1995, 1996–2000, and 2001–2005 respectively. Although the Takashima AMI registry reported a significant increase in AMI incidence in women from 1990–1992 to 1993–1995, there was no increase since 1993–1995 to 1999–2001.³² Several other studies reported trends in AMI incidence in women in Japan but the number of cases was too small to examine the trend.^{33–36}

Up until 2009, epidemiological studies did not show significant independent associations of lipids with CHD in women in Japan (Table 2).^{37–42} Japan Atherosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC), a project pooling the data from cohort studies in Japan examined the association of total cholesterol and non-high-density lipoprotein cholesterol (non-HDL-C) with AMI incidence in 13,477 women and 8,953 men aged 40–89 years at baseline with an average follow-up of 7.6 years.³⁸ The study reported that among women incidence rate ratio for one standard

TABLE 1. SOURCES OF INFORMATION USED IN COMPARING STATISTICS BETWEEN JAPAN AND THE UNITED STATES

	<i>Japan</i>	<i>United States</i>
Mortality	WHO Statistics	WHO Statistics
Trend in total cholesterol	NHNS/NSCD	NHANES
Trend in blood pressure	NHNS/NSCD	NHANES
Trend in smoking	NHNS/NSCD	NHANES
Diabetes	Published literature	NHANES
Incidence of AMI	Published literature	Published literature

AMI, acute myocardial infarction; NHANES, National Health and Nutrition Examination Survey; NHNS, National Health and Nutrition Survey; NSCD: National Survey of Cardiovascular Diseases; WHO, World Health Organization.

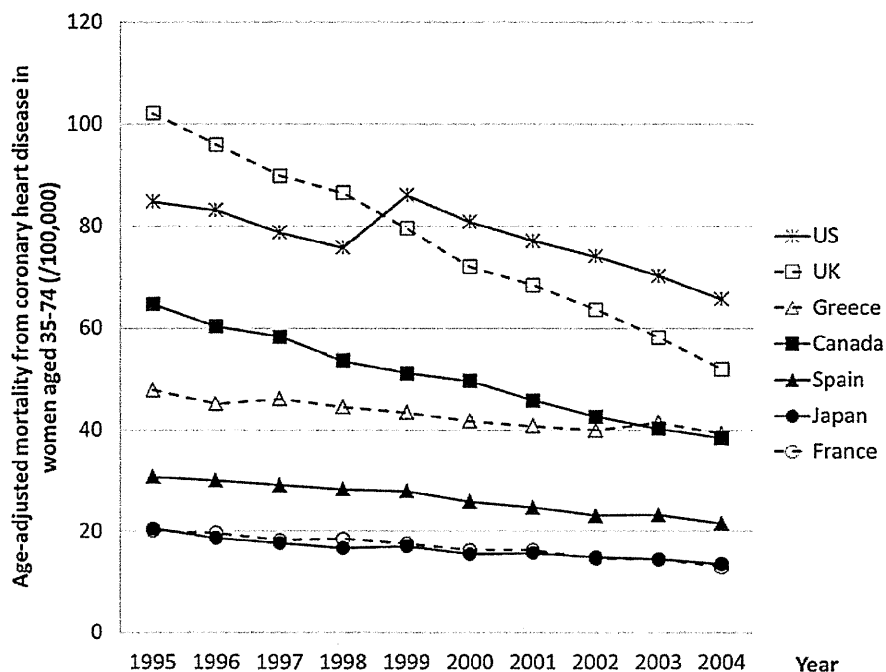


FIG. 1. Recent trend in aged-adjusted mortality from coronary heart disease in women in selected countries. Data were obtained from the World Health Organization Statistical Information System (www.who.int/whosis). For age adjustment, a new World Health Organization standard was used. To define coronary heart disease (CHD) we used codes I20-25 in the International Statistical Classification of Diseases and Related Health Problem 10th Revision (ICD-10) and codes 410-414 in ICD-9.

deviation (SD) increase of cholesterol was 1.54 (95% confidence interval [CI]: 1.14-2.09) after adjusting for body-mass index (BMI), blood pressure (BP), diabetes, high-density lipoprotein cholesterol (HDL-C), and current smoking. Similarly, among women incidence rate ratio for one SD increase of non-HDL-C was 1.65 (95% CI: 1.22-2.24) after adjusting for the same variables. Following JALS-ECC, CIRCIS examined the association of low-density lipoprotein cholesterol (LDL-C) with CHD and AMI incidence in 4,897 women and 3,079 men aged 40-69 years at baseline and reported that among women hazard ratio for AMI incidence for one SD increase of LDL-C was 1.42 (95% CI, 1.05-1.91) after adjusting for categories of BP, glucose, HDL-C, and triglycerides, medications for BP and lipids, BMI, smoking status and other variables.³⁷ Likewise, among women hazard ratio for CHD for one SD increase of LDL-C was 1.25 (95% CI, 1.00-1.55) after adjusting for the same variables. Similarly, recent epidemiological studies in women in Japan reported a significant independent association of each of other traditional risk factors (i.e., BP,^{40,43-47} diabetes,^{29,40,48} cigarette smoking⁴⁹⁻⁵¹) (Table 3) and early menopause.⁵²

Figure 2 shows levels of serum total cholesterol in women in Japan and the United States in the most recent data and data around 1990.^{6,18-20} Comparing the most recent data in women currently aged 50-69 years, levels of serum total cholesterol were higher in women in Japan than in the United States. Moreover, in this birth cohort of women, levels of serum total cholesterol in Japan and the United States were very similar around 1990. Thus, among women currently aged 50-69 years, serum levels of total cholesterol in Japan had been similar or higher as compared with the United States at least for the past two decades.

Figure 3 shows levels of systolic BP in women in Japan and white women in the United States in the most recent data and data around 1990.^{6,18-21} Comparing the most recent data in women currently aged 50-69 years, levels of systolic BP were high in women in Japan. Furthermore, in this birth cohort,

levels of systolic BP were much higher in Japan than in the United States around 1990. Thus, among women currently aged 50-69 years, levels of systolic BP in Japan had been higher than in the United States at least for the past two decades. Similarly, we observed that among women currently aged 50-69 years, levels of diastolic BP in women in Japan had been higher than the United States at least for the past two decades (Fig. 4).

Figure 5 shows trends in prevalence of current smokers in women in Japan and in the United States.^{6,18-20} Prevalence of current smokers had been consistently lower in women in Japan than in the United States for the past three decades. For example, prevalence of current smokers in women in Japan aged 50-59 years in 2008 was 14.8%. In this birth cohort, the prevalence was 6.8% in 2000, 17.2% in 1990, and 16.2% in 1980. The prevalence of current smokers in women aged 45-64 years in the United States in 2005 was 18.8%. In this birth cohort, the prevalence was 32% in 1985. Thus, among women currently aged 50-69 years, prevalence of current smokers in Japan had been lower than in the United States for the past three decades.

Prevalence of type 2 diabetes and impaired glucose tolerance (IGT) diagnosed by the 1985 WHO criteria⁵³ was similar in women in Japan and white women in the United States in 1990. Prevalence of type 2 diabetes and IGT in women in Japan was 3-4% and 12-13% in their 40's, respectively and 7%-9% and 12-19% in their 50's, respectively.²³ NHANES III (1988-1994) reported that prevalence of type 2 diabetes and IGT in white women was 5% and 11% in their 40's, respectively and 10% and 15% in their 50s, respectively.⁵⁴ Recent data on prevalence of type 2 diabetes based on hemoglobin A1c (HbA1c) show that prevalence of type 2 diabetes was similar between women aged 60-69 years (i.e., 14.1% in Japanese⁷ and 15.7% in whites), although prevalence was lower in women in Japan than in white women aged 50-59 (i.e., 5.6% in women in Japan⁷ and 11.9% in white women). Thus, in women currently aged 60-69 years, prevalence of glucose intolerance had been similar for the past 2 decades, whereas in

TABLE 2. SUMMARY OF RECENT EPIDEMIOLOGICAL STUDIES EXAMINING THE ASSOCIATION OF LIPIDS WITH CORONARY HEART DISEASE AND MYOCARDIAL INFARCTION IN WOMEN IN JAPAN

Study name (reference)	Year published	Age at baseline and study design	Years of follow-up	Population size	Outcome	Number of events	Evaluated lipid	Multivariate-adjusted* hazard ratio or incidence rate ratio (95% confidence interval)
CIRCS (37)	2011	40–69 years Prospective cohort study	Baseline 1975 to 1987 End 2003	4,897	CHD and MI incidence	55 for CHD and 28 for MI	LDL-C	For CHD: HRs were 1.00, 1.21, 3.41, 3.80, and 3.05 for LDL-C categories of <80, 80–99, 100–119, 120–139, and 140+ mg/dL. HR for 30 mg/dL increase of LDL-C was 1.25 (1.00–1.55) For MI: HRs were 1.00, 1.26, 3.69, 8.93, and 5.43 for the same LDL-C categories above. HR for 30 mg/dL increase of LDL-C was 1.42 (1.05–1.91)
JALS-ECC (38)	2010	40–89 years Prospective cohort study by pooling 10 cohort studies	7.6	13,477	MI incidence	37	TC non-HDL-C	HRs were 1.00, 5.99, 3.10, and 8.55 for TC categories of <175, 175–198, 199–223, and 224+ mg/dL (<i>p</i> for trend 0.007). IRR for 1 SD increase of TC was 1.54 (1.14–2.09) HRs were 1.0, 6.18, 6.06, and 9.78 for non-HDL-C categories of <117, 118–141, 142–166, and 167+ (<i>p</i> for trend 0.010). IRR for 1 SD increase of non-HDL-C was 1.65 (1.22–2.24)
Suita (39)	2009	30–79 years Prospective cohort study	11.9	2,525	MI incidence	24	LDL-C	HRs were 1.00, 0.76, and 1.77 for first and second quintiles combined, third and fourth quintiles combined, and fifth quintile (<i>p</i> for trend 0.10)
JMS (40)	2009	19–93 years Prospective cohort study	11.0	7,494	MI incidence	28	TC	HR for 1 mg/dL increase of TC was 1.009 (0.996–1.021) (<i>p</i> =0.168)
JACC (41)	2007	40–79 years Nested case-control study	10	150 cases/ 150 controls	CHD death	69	TC	Odds ratios were 0.57 (0.06–5.47) for TC 240–259 and 2.30 (0.22–23.7) for TC ≥260 as compared with TC <160 mg/dL
NIPPON DATA80 (42)	2003	30–89 years Prospective cohort study	13.2	5,181	CHD death	50	TC	HRs were 0.89 (0.29, 2.73), 1.00, 1.16 (0.55, 2.43), and 1.99 (0.79, 5.03) for TC < 160, 160–199, 200–239, and 240+

*Multivariate adjustments:

CIRCS: age, blood pressure category, antihypertensive medication use, glucose category, body mass index, smoking status, alcohol intake category, lipid lowering medication use, categories of HDL-C, and triglycerides, fasting status, years at entry, and study areas;

JALS-ECC: age, body mass index, HDL-C, blood pressure, diabetes, and current smoking;

The Suita Study: age, body mass index, diabetes, HDL-C, cigarette smoking category, and alcohol intake category;

The JMS cohort study: age, systolic blood pressure, diabetes, and current smoking;

The JACC study: systolic blood pressure, HDL-C, ethanol intake, smoking status, and diabetes;

NIPPON DATA: age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking category, and alcohol intake category.

CHD, coronary heart disease; CIRCS, The Circulatory Risk in Communities Study; HR, hazard ratio; IRR, incidence rate ratio; JACC, Japan collaborative cohort study for evaluation of cancer risk; JALS-ECC, the Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine; JMS cohort, Jichi Medical School cohort; LDL-C, low-density-lipoprotein cholesterol; MI, myocardial infarction; NIPPON DATA, the National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged; non-HDL-C, non-high-density-lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol.

TABLE 3. SUMMARY OF RECENT EPIDEMIOLOGICAL STUDIES EXAMINING THE ASSOCIATION OF BLOOD PRESSURE, DIABETES, AND CIGARETTE SMOKING WITH CORONARY HEART DISEASE AND MYOCARDIAL INFARCTION IN WOMEN IN JAPAN

Study name or first author (reference)	Year published	Age at baseline and study design	Years of follow-up	Population size	Outcome	Number of events	Multivariate-adjusted*,†,‡ hazard ratio or relative risk (95% confidence interval)
Blood Pressure							
JMS (40)	2009	19–93years Prospective cohort study	11.0	7,494	MI incidence	28	HR for 1 mm Hg increase of blood pressure was 1.023 (1.004–1.021) ($p=0.015$)
JPHC (43)	2009	40–69 years Prospective cohort study	11.0	21,688	CHD	59	HRs were 0.64 (0.18–2.27), 2.33 (0.90–6.04), 2.57 (1.03–6.44), 4.14 (1.48–11.58), and 3.37 (0.67–16.94) in women in normal, high normal, mild, moderate, and severe blood pressure as compared with women in optimal blood pressure (p for trend <0.001)
JALS (44)	2009	40–89 years Prospective cohort study by pooling 16 cohort studies	8.4	27,150	MI incidence	72	HR for 1 SD increase of systolic blood pressure was 1.25 (0.99–1.58)
Suita (45)	2008	30–79 years Prospective cohort study	11.7	2,924	MI incidence and sudden cardiac death	65	HR in women with hypertension (\geq stage 1) as compared with optimal blood pressure was 2.97 (1.11–7.91)
Iso H. ²⁵ (46)	2007	40–69 years Prospective cohort study of 5 communities	18	7,656	CHD	42	HR in women with hypertension as compared with women without hypertension was 1.3 (0.6–2.8)
NIPPON DATA 80 (47)	2003	30–89 years Prospective cohort study	14	5,393	Death from heart disease	120	Relative risk with one level increase of WHO category (optimal, normal, high normal, mild, moderate, and severe hypertension) was 1.12 (0.97–1.28)
Diabetes							
Suita (29)	2010	30–79 years Prospective cohort study	11.7	2,835	Coronary artery disease	55	HRs for impaired fasting glucose and diabetes as compared with normoglycemia were 1.36 (0.84–2.19) and 2.66 (1.22–5.80) (p for trend 0.018)
JMS (40)	2009	19–93years Prospective cohort study	11.0	7,494	MI incidence	28	HR for diabetes was 4.372 (1.454–13.150) ($p=0.009$)
Hisayama (48)	2009	40–79 years Prospective cohort study	14	1,384	CHD	37	HR for diabetes as compared with normal glucose tolerance was 3.46 (1.59–7.54) ($p=0.002$)
Cigarette Smoking							
JPHC, TPCS, JACC (49)	2010	40–79 years Prospective cohort study	9.6	140,379	CHD	487	HR for never smokers as compared with current smokers was 0.27 (0.102–0.72)
Suita (50)	2009	30–79 years Prospective cohort study	11.9	2,089	MI incidence	13	HR for current smokers was 8.35 (2.64–26.48)
JPHC (51)	2006	40–69 years Prospective cohort study	11.0	21,513	CHD	66	HR for current smokers was 2.94 (1.42–6.10)

*Variables adjusted in multivariate adjustment in blood pressure analysis:

JPHC: age;

The JMS cohort study: age, diabetes, total cholesterol, and current smoking;

JALS: age, body mass index, total cholesterol, and current smoking;

Suita: age, body mass index, diabetes, hyperlipidemia, smoking, and drinking status;

Iso H.: age, community, total cholesterol, smoking, alcohol intake category, time since last meal, and menopausal status;

NIPPON DATA: age, body-mass index, total cholesterol, diabetes, cigarette smoking category, and drinking category.

†Variables adjusted in multivariate adjustment in diabetes analysis:

Suita: age, body-mass index, hypertension, hyperlipidemia, smoking, and drinking status;

JMS: age, systolic blood pressure, total cholesterol, and current smoking;

Hisayama: age, systolic blood pressure, electrocardiogram abnormalities, body-mass index, total cholesterol, and HDL-C smoking, alcohol intake, and regular exercise.

‡Variables adjusted in multivariate adjustment in cigarette smoking analysis:

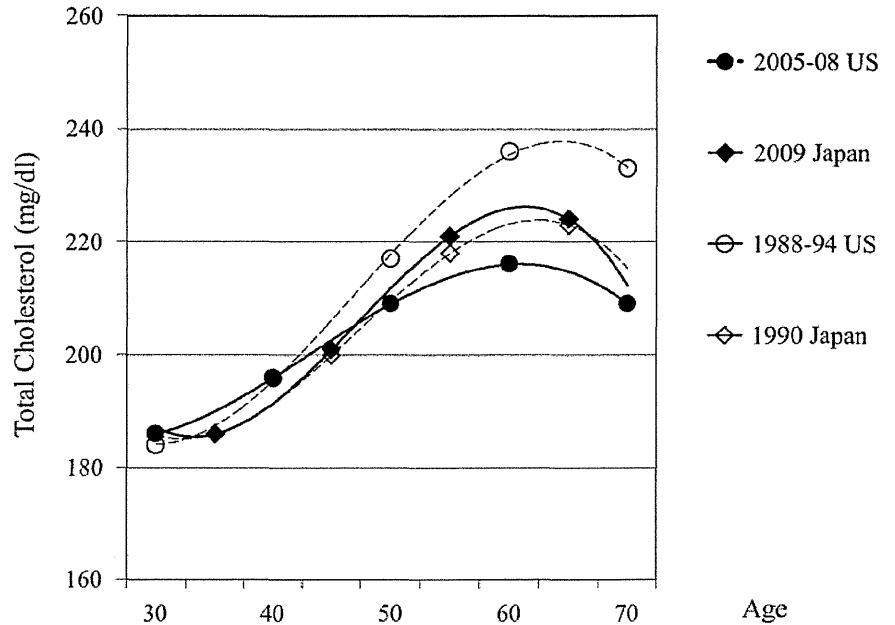
JPHC, TPCS, JACC: age, cohort, and number of years smoked;

Suita: age, body-mass index, blood pressure, non-HDL-C, glomerular filtration rate, and alcohol drinking;

JPHC: age, alcohol, frequency of fruit, vegetable, fish, history of hypertension, diabetes, and hyperlipidemia as well as public health center.

JPHC, Japan Public Health Center-based Prospective Study; TPCS, Three Prefecture Cohort Study.

FIG. 2. Trend in serum total cholesterol in women in Japan and the United States.



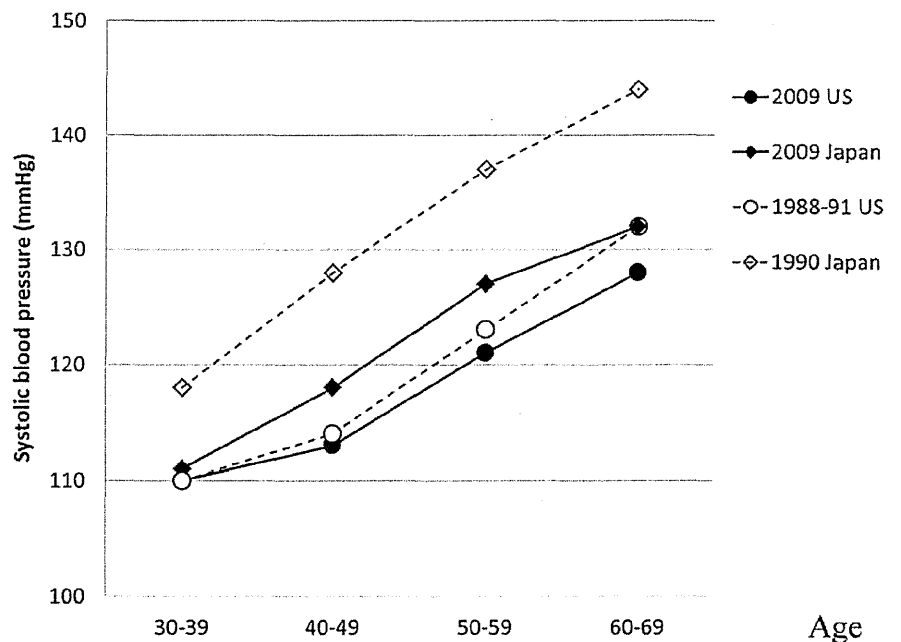
women currently aged 50–59 years, prevalence of type 2 diabetes was much lower in women in Japan than white women in the United States.

Discussion

This review of recent cardiovascular epidemiological studies in Japan has shown that traditional risk factors are independently associated with CHD in women in Japan. Additionally, traditional risk factors among women currently aged 50–69 between Japan and the United States: total cholesterol, BP, rates of cigarette smoking and prevalence of diabetes, have generally been similar for the past few decades.

CHD mortality in women in Japan is one of the lowest among developed countries. The fact that much lower incidence of AMI in women in Japan from multiple registries than in all registries of the WHO MONICA project strongly indicates that low CHD mortality in women in Japan is not due to misclassification of cause of death, but rather, is real. Although CHD mortality in women in Japan is very similar to that in France, AMI incidence in women in Japan is less than a half of that in France. This is, to some extent, due to misclassification of cause of death in women in France. In fact, the WHO MONICA project shows that official CHD death in women in registries in France underestimated actual CHD death by 100%.⁵⁵

FIG. 3. Trend in systolic blood pressure in women in Japan and the United States.



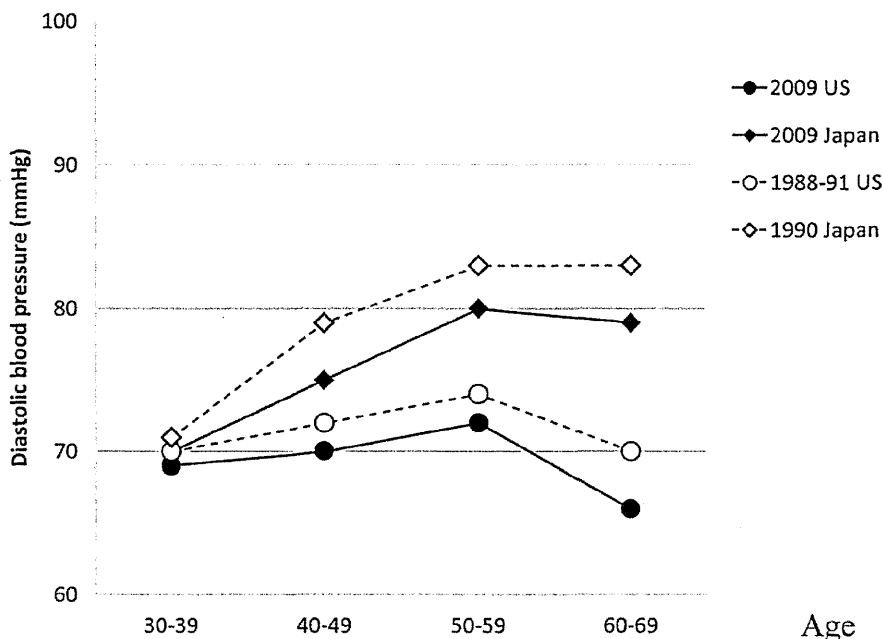


FIG. 4. Trend in diastolic blood pressure in women in Japan and the United States.

Epidemiological studies have shown that each of traditional risk factors, i.e., BP,^{40,43-47} lipids,^{37,38} diabetes,^{27,35,40} cigarette smoking,⁴⁹⁻⁵¹ and age at menopause,⁵² is independently associated with CHD in women in Japan. It is noted, however, that all these epidemiological studies were reported after 2003. This is partly because CHD incidence in women in Japan is too low to detect an independent association of each risk factor without a very large sample size. On the other hand, these independent associations are expected based on observations from autopsy studies. The first nationwide autopsy study in Japan among 2,856 subjects aged 0-39 years conducted around 1980 shows that age, BP, and total cholesterol are risk factors for atherosclerosis of the coronary artery and the aorta for both women and men.⁵⁶ This study employed the same method to evaluate atherosclerosis with

the Pathobiological Determinants of Atherosclerosis in Youth study, which also shows that age, hypertension, LDL-C, and smoking are risk factors for atherosclerosis and that the extent of atherosclerosis is lower in women than in men.⁵⁷

We observed that current levels of total cholesterol in women aged 50-69 years are higher in women in Japan than in the United States. Although it is possible that the difference in rates of statin users contributes to the difference in the levels of total cholesterol, available data show that current rates of statin users in middle-aged women are similar: 14% in Japan⁵⁸ versus 16% in the United States.¹⁸ It is also possible that levels of HDL-C or LDL-C have been different between women in Japan and the United States, even though the levels of total cholesterol have been very similar. Although we do not have trend data of LDL-C or HDL-C, these levels were comparable

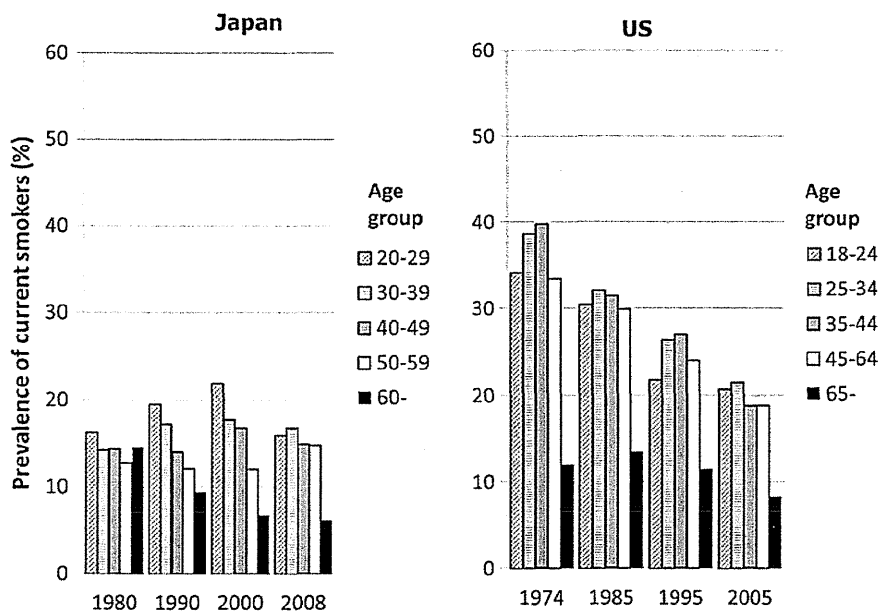


FIG. 5. Trend in rates of cigarette smoking in women in Japan and the United States.