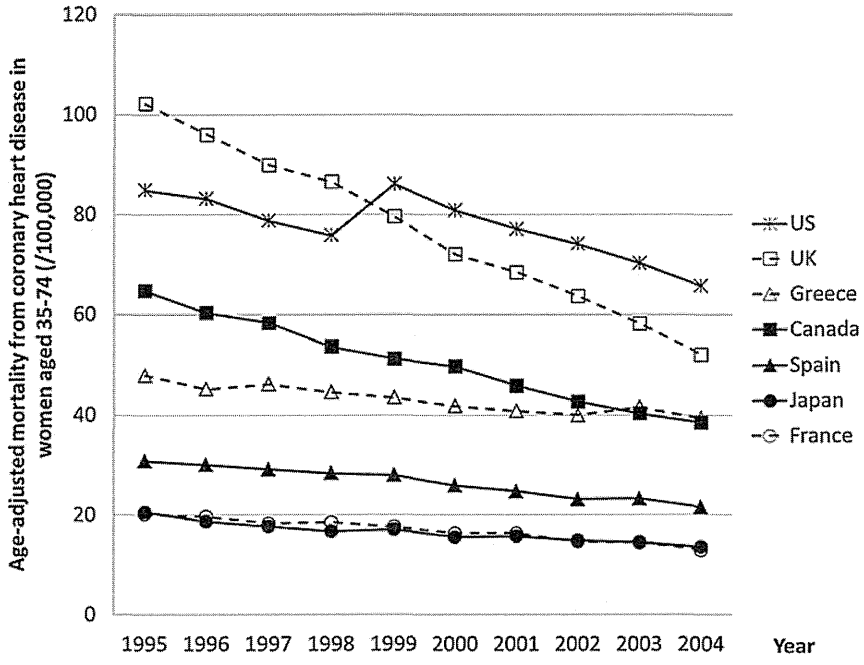

FIG. 1. Recent trend in aged-adjusted mortality from coronary heart disease in women in selected countries. Data were obtained from the World Health Organization Statistical Information System (www.who.int/whosis). For age adjustment, a new World Health Organization standard was used. To define coronary 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, CIRCS 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 smoking[49–51]) (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 wit 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 criteria[53] 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 Ac1 (HbA1c) show that prevalence of type 2 diabetes was similar between women aged 60–69 years (i.e., 14.1% in Japanese[7] 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 Japan[7] 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 (p 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+ (p 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 (p 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) (p=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 (029, 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 (≥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 (097–1.28)
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– 1.13.150) ($p=0.009$)
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.

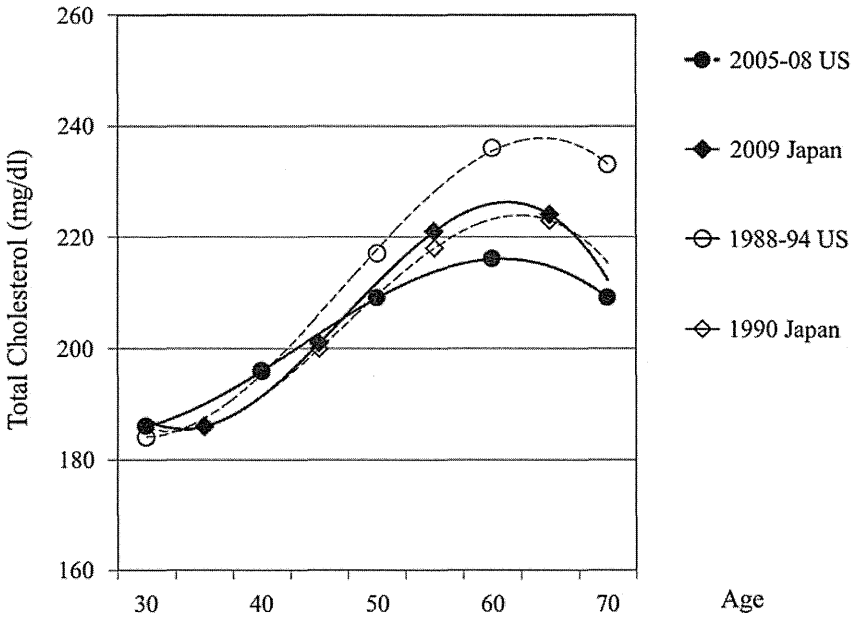

FIG. 2. Trend in serum total cholesterol in women in Japan and the United States.

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]

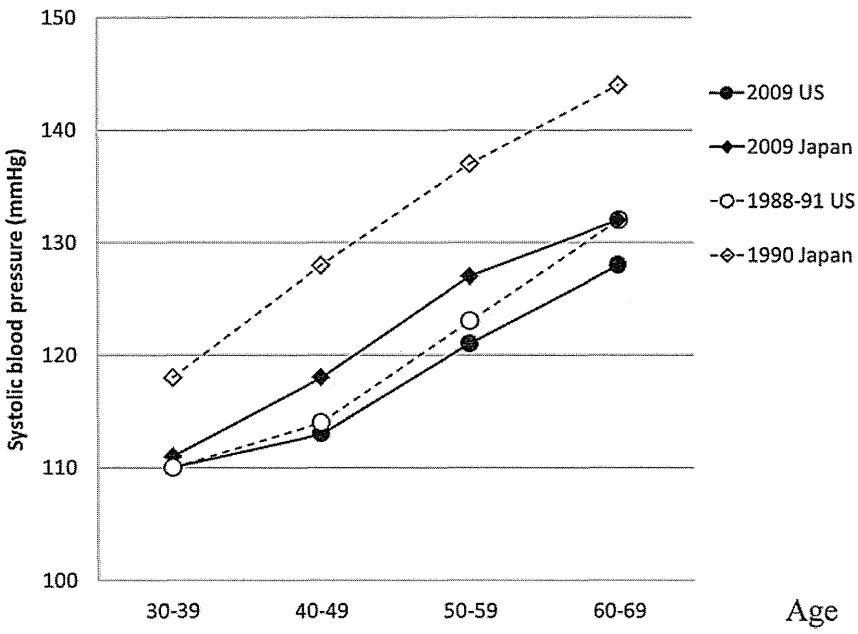

FIG. 3. Trend in systolic blood pressure in women in Japan and the United States.

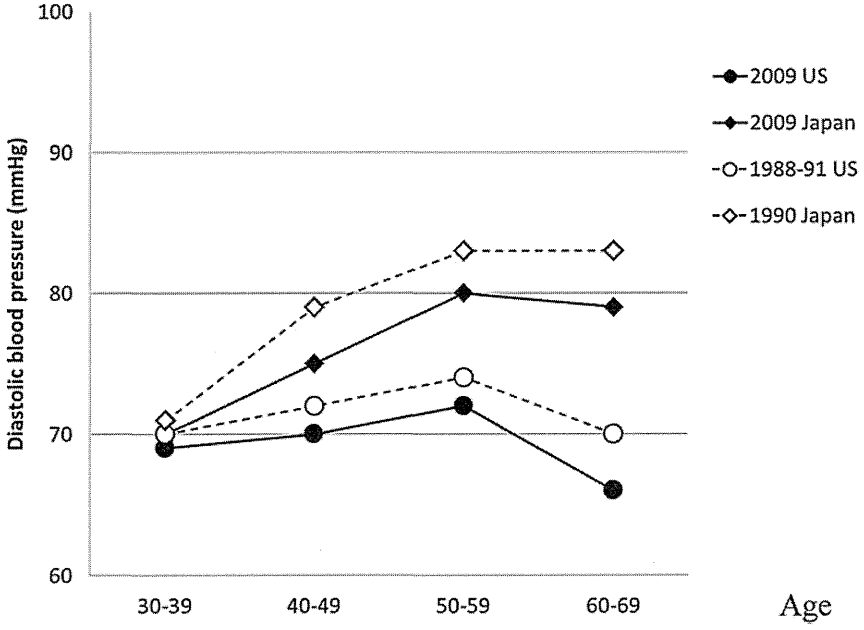

FIG. 4. Trend in diastolic blood pressure in women in Japan and the United States.

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 Japan[58] 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

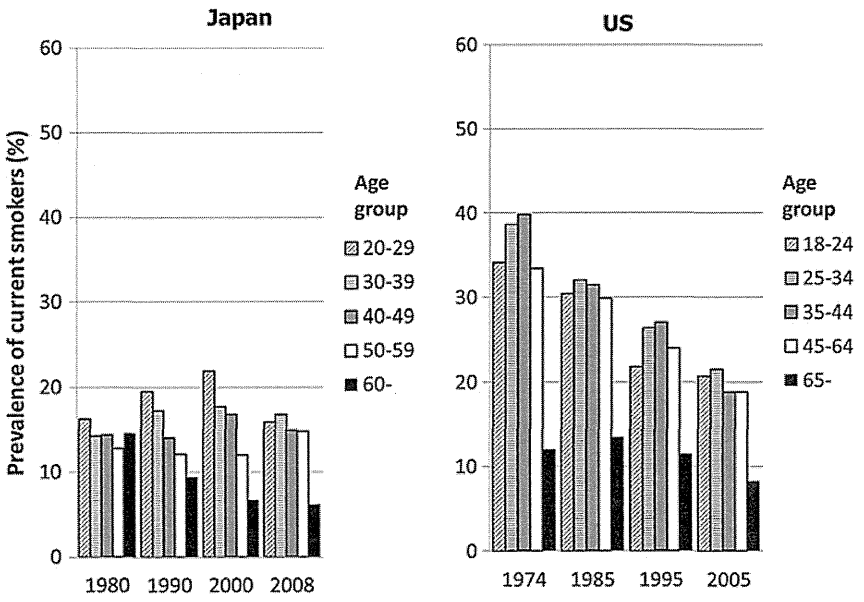

FIG. 5. Trend in rates of cigarette smoking in women in Japan and the United States.

in middle-aged women between Japan and the United States around 1990. Data from the Suita Study, the only population-based study in urban area in Japan where >70% of Japanese live, show that in 1990–1994 mean levels of LDL-C and HDL-C (mg/dL) were 126 and 57 in women aged 40–49 years, respectively and 146 and 57 in women aged 50–59 years, respectively. NHANES III (1988–1994) reported that corresponding numbers were 131 and 56 in women aged 45–54 years, respectively and 144 and 56 in women aged 55–64 years, respectively.[59]

We observed that levels of BP in currently aged 50–69 years have been higher in Japan than in the United States at least for the past two decades. The difference in clinical guidelines for hypertension in the past accounts to some extent for the differences in levels of BP. For example, the 1990 National Survey of Circulatory Disorders in Japan used the criteria of hypertension as systolic BP ≥ 160 mmHg, or diastolic BP ≥ 95 mmHg, or on hypertension medication, based on the WHO criteria,[60] whereas the Fifth Report of the Joint National Committee on Detection, Education, and Treatment of High Blood Pressure in the United States in 1993 defined hypertension as systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg.[61]

Rates of cigarette smoking have been lower in women in Japan than in the United States, which could partly contribute to lower CHD rates in women in Japan. Meanwhile rates of cigarette smoking in men in Japan have been much higher than in the United States for the past 3 decades (e.g., 70 to 50% in Japan[6,20] versus 40 to 30% in the United States).[15] Passive smoking is an independent risk factor for CHD both in Japan[62] and the US,[63] about 30% higher risk for CHD in passive smokers compared to never smokers. Thus, it is unlikely that the difference in rates of cigarette smoking largely accounts for the difference in CHD rates between women in Japan and the United States.

Our results showed that prevalence of diabetes in women currently aged 60–69 years has been similar between Japan and the United States for the past two decades, whereas that in women currently aged 50–59 years in the United States was almost twice as high as in Japan. Because CHD rates in women aged 50–59 years is lower than that in women aged 60–69 years, the difference in prevalence of diabetes in women aged 50–59 years is unlikely to largely contribute to the difference in CHD rates between Japan and the United States. It is speculated that the difference in the prevalence of diabetes in younger generation is due to the difference in recent trend in BMI between Japan and the United States.[64] Between 1980 and 2010, BMI in women in Japan remained similar whereas that in women in the United States much increased.

It is possible that the difference in BMI contributes to the difference in CHD in women between Japan and the United States. Major plausible intermediary factors linking obesity and CHD are BP, total cholesterol, and type 2 diabetes.[65,66] The current study has shown that it is very unlikely that the difference in these factors contributes to the difference in CHD in women between Japan and the United States. Although we have investigated other possible intermediary factors including C-reactive protein,[12] fibrinogen,[12] adiponectin,[67] D-dimer,[68] von Willebrand factor,[68] and lipoprotein-associated phospholipase A_2[69] in our study in men, none of these factors significantly contributed to the difference in atherosclerosis. These observations need to be confirmed in the future study in women.

Early menopause is significantly associated with increased risk of CHD both in Japan[52] and the United States.[70] Meanwhile, associations of age at menarche with CHD are equivocal.[52,71,72] Available data show that the age at natural menopause in women in Japan is earlier whereas the age at menarche is similar between the two countries: 49.3 in Japan versus 51.3 in the United States for menopause and 12.5 in Japan and 12.8 in the United States for menarche.[73] Thus, the difference in age at menopause is unlikely to contribute to the lower rate of CHD in women in Japan. Although a rate of oral contraceptive use in women in Japan is very low as compared with other developed countries[74] because it was introduced in 1999,[75] recent epidemiological studies show that use of oral contraceptives including past use is not associated with increased risk of CHD.[76]

Lower prevalence of hysterectomy in Japan than in the United States[77] is unlikely to be a significant factor responsible for lower CHD rates in Japan. This is because hysterectomy is not the major determinant of CHD over traditional risk factors. We have recently reported from the Women's Health Initiative Observational Study[78] that the hazard ratio of hysterectomy for incident cardiovascular disease was 1.26 (95% CI: 1.16–1.36, $p < 0.001$), which was attenuated after adjusting traditional CHD risk and other factors to 1.10 (95% CI: 1.00–1.21, $p = 0.042$). The results suggest that a more adverse profile of CHD risk factors in women who had undergone hysterectomy compared with those who had not, rather than hysterectomy itself, is associated with CHD. Moreover, given the hazard ratio of 1.10 after adjusting for CHD and other risk factors, population-attributable risk[79] of hysterectomy for CHD is very low.

Evidence from migrant studies of Japanese and multiethnic studies in the United States does not support the hypothesis that the Japanese are genetically protected against CHD. Migrant studies of Japanese to the United States clearly show an increase in CHD and atherosclerotic burden in Japanese Americans as compared to Japanese in Japan. The NIHON-SAN study, a cross-sectional study of cardiovascular disease and its risk factors in middle-aged Japanese men living in Japan, Hawaii, and California in the 1960s, has shown that CHD mortality is significantly higher in Japanese Americans than in Japan.[80] We have reported from a population-based study of Japanese and Japanese and white American men aged 40–49 years that levels of atherosclerosis assessed as coronary artery calcification and carotid IMT in Japanese Americans are higher or similar compared with U.S. whites.[12] Although CHD mortality in Japanese Americans is reported to be lower compared with white Americans,[81–83] a more recent study has shown that CHD mortality is similar between young Japanese and white American women. Using U.S. Census data and California mortality data in 1990 and 2000, Palaniappan et al. reported age-, sex-, and ethnic-specific CHD mortality for six ethnic groups in California.[84] Although standardized mortality ratios (SMR) of CHD in women aged 45–64 years and 65–84 years are much lower in Japanese Americans than in white Americans, SMR of CHD in women aged 24–44 years is very similar between the two groups.

Given that the lower rates of CHD and atherosclerosis in Japan than in the United States are unlikely to be primarily due to differences in traditional risk or genetic factors, the most likely hypothesis is that there are common source exposures in the diet among Japanese in Japan, which accounts

for their low CHD rates and atherosclerosis. The international collaborative study of macro- and micro-nutrients and blood pressure, which provides the most comprehensive dietary data in the United States and Japan[85] and other dietary studies[86] show that Japanese have markedly high intake of marine n-3 fatty acids (1,000 mg/day in Japan vs. 100 mg/day in the U.S.)[87] and isoflavones (25 ~ 50 mg/day in Japan vs. < 2 mg/day in the U.S.).[86]

A large prospective cohort study in Japan supports the hypothesis that dietary intake of marine n-3 fatty acids and isoflavones are protective against CHD in Japan. The Japan Public Health Center-Based Study, a population-based cohort of individuals aged 40–59 years in Japan, following more than 40,000 individuals for about 10 years, reported that dietary intake of marine n-3 fatty acids had a significant inverse association with myocardial infarction after adjusting for history of hypertension and diabetes, medication for hyperlipidemia and other potential confounders.[88] This study also reported that that dietary intake of soy isoflavones had a significant inverse association with incidence of myocardial infarction in women even after adjusting for the above-mentioned factors.[89] Additionally, we have recently reported that high serum percentage of marine n-3 fatty acids significantly contributed to the difference in levels of atherosclerosis assessed as coronary artery calcification and carotid IMT between Japanese and whites.[12] It is unlikely that marine n-3 fatty acids or soy isoflavones exert their potential protective effects against CHD through total cholesterol, HDL-C, BP, or glucose homeostasis because recent systematic reviews show that effects of marine n-3 fatty acids or soy isoflavones on these factors are clinically insignificant.[90–92] A large-scale randomized clinical trial (RCT) of marine n-3 fatty acids recently conducted in Japan demonstrated their clear benefit on CHD events,[93] although several recent RCTs failed to show their benefits.[94–96] The discrepancy is at least due to the difference in dosage of marine n-3 fatty acids in RCT and background dietary intake of marine n-3 fatty acids as described above. No RCT of isoflavones on CHD has been reported, although many RCTs of isoflavones on CHD risk factors have been reported.[90,97 98]

Limitations of this study warrant discussion. Mortality statistics are subject to misclassification without validation study. However, the fact that validated AMI incidence is much lower in Japan than in all the registries in other countries strongly indicate that low CHD mortality in Japan is not due to misclassification. Although we compared the trend in risk factors between Japan and the United States using primarily national survey data, these data may not be directly compared, because measurements are not strictly standardized between the countries. Factors other than those described in this paper that may be independently associated with CHD risk in each population, such as physical inactivity, psychosocial factors, and medical practice[55,99,100] could contribute to the difference in CHD rates in women between Japan and the Unites States.

In conclusion, we have shown that CHD mortality in women in Japan is much lower than in women in the United States. Differences in risk factors and their trends are unlikely to explain the difference in CHD rates in women in Japan and the United States. The results from migrant studies of the Japanese to the United States and international studies do not support the notion that Japanese are genetically protected against atherosclerosis and CHD. Investigating factors responsible for low CHD rates in women in Japan is important and may lead to new strategy for CHD prevention.

Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Akira Sekikawa, MD, PhD
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh
130 North Bellefield Avenue, Suite 546
Pittsburgh, PA 15213

E-mail: akira@pitt.edu

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Original Article

Effect of Age on the Association Between Waist-to-Height Ratio and Incidence of Cardiovascular Disease: The Suita Study

Yukako Tatsumi[1,2], Makoto Watanabe[1], Yoshihiro Kokubo[1], Kunihiro Nishimura[1], Aya Higashiyama[3], Tomonori Okamura[4], Akira Okayama[5], and Yoshihiro Miyamoto[1]

[1]Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan
[2]Department of Mathematical Health Science, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan
[3]Department of Environmental and Preventive Medicine, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan
[4]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan
[5]The First Institute for Health Promotion and Health Care, Japan Anti-tuberculosis Association, Tokyo, Japan

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ABSTRACT

Background: Waist-to-height ratio (WHtR) has been shown to be a useful screening tool for metabolic syndrome and cardiovascular disease (CVD). We investigated the association of WHtR with CVD incidence by age group.

Methods: We conducted a 13.0-year cohort study of Japanese adults (2600 men and 2888 women) with no history of CVD. WHtR was calculated as waist circumference (cm) (WC) divided by height (cm). We stratified participants by sex and age group (30–49, 50–69, ≥70 years). Using the Cox proportional hazards model, we calculated hazard ratios (HRs) and 95% CIs for CVD in relation to WHtR quartile for participants aged 50 to 69 years and 70 years or older.

Results: Men aged 50 to 69 years in the highest quartile had significantly increased risks of CVD and coronary heart disease as compared with the lowest quartile; the HRs (95% CI) were 1.82 (1.13–2.92) and 2.42 (1.15–5.12), respectively. Women aged 50 to 69 years in the highest quartile had a significantly increased risk of stroke (HR, 2.43; 95% CI, 1.01–5.85). No significant results were observed in men or women aged 70 years or older. The likelihood ratio test showed that the predictive value of WHtR was greater than that of WC among men aged 50 to 69 years.

Conclusions: The association between WHtR and CVD risk differed among age groups. WHtR was useful in identifying middle-aged Japanese at higher risk of CVD and was a better predictor than WC of CVD, especially in men.

Key words: waist-to-height ratio; age difference; cardiovascular disease

INTRODUCTION

Obesity and central obesity are closely tied to metabolic risks.[1,2] Waist circumference (WC) is an index of central obesity[3] and is an important component in the diagnostic criteria for metabolic syndrome.[4] Several meta-analyses have reported an association of WC with cardiovascular disease (CVD) and mortality.[5,6] Recently, waist-to-height ratio (WHtR) was shown to be a useful global clinical screening tool for cardiometabolic risk and CVD.[7,8]

WHtR is easy to measure, and the cut-off point for WHtR is subject to less ethnic variation.[7,8] However, WHtR could differ among age groups because whole-body fat distribution and WC change considerably with age[9,10] and because height differs among generations.[11] It is thus important to consider age in assessing the association between WHtR and CVD risk, but few previous studies have done so.[12,13] Therefore, in this long-term prospective cohort study of a Japanese urban population, we investigated the effect of WHtR on CVD risk among participants classified by age group.

METHODS

Study population

The Suita Study is a prospective population-based cohort study of an urban area of Japan and was established in 1989. The details of this study have been described elsewhere.[14–16] Briefly, 6407 men and women aged 30 to 83 years underwent

Address for correspondence. Yukako Tatsumi, Department of Preventive Cardiology, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan (e-mail: y-tatumi@sahs.med.osaka-u.ac.jp).

a baseline survey at the National Cerebral and Cardiovascular Center between September 1989 and March 1994. Among them, a total of 919 were excluded due to past history of CVD ($n = 208$), loss to follow-up ($n = 535$), and missing data ($n = 176$). The remaining 5488 participants (2600 men and 2888 women) were included in the analysis. This cohort study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Baseline examination

Blood samples were centrifuged immediately after collection, and a routine blood examination was performed, including measurement of serum levels of total cholesterol and glucose. About 96% of participants had fasted for at least 8 hours before the blood test. Well-trained physicians used a standard mercury sphygmomanometer to measure blood pressure in triplicate on the right arm after 5 minutes of rest. Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of antihypertensive agents. Diabetes was defined as a fasting plasma glucose level of at least 7.0 mmol/L (126 mg/dL), a non-fasting plasma glucose level of at least 11.1 mmol/L (200 mg/dL), or use of antidiabetic agents. Hypercholesterolemia was defined as a total cholesterol level of at least 5.7 mmol/L (220 mg/dL) or use of antihyperlipidemic agents. Participants were wearing light clothing during height and weight measurement. WC was measured at the umbilical level, with the participant in a standing position. WHtR was defined as WC (cm) divided by height (cm). Body mass index (BMI) was defined as weight (kg) divided by the height (m) squared. Public-health nurses obtained information on participants' smoking, drinking, and medical histories.

Endpoint determination

The endpoint determination has been previously reported.[14–16] The endpoints of the present study were (1) date of first coronary heart disease (CHD) or stroke event; (2) date of death; (3) date of departure from Suita city; or (4) December 31, 2007. The first step in the survey of CHD and stroke was checking the health status of all participants by means of clinical visits every 2 years and a yearly questionnaire (by mail or telephone). For the second step, in-hospital medical records of participants suspected of having CHD or stroke were reviewed by registered hospital physicians, who were blinded to the baseline information. In addition, to complete the survey, we also conducted a systematic search of death certificates to identify cases of fatal CHD and stroke. In Japan, all death certificates are forwarded to the Ministry of Health, Welfare, and Labour and coded for the National Vital Statistics. The criteria for myocardial infarction were based on the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease projects.[17] In addition to myocardial infarction, we also evaluated coronary angioplasty, coronary artery bypass grafting, and sudden cardiac death, all of which were included in the definition of CHD. Stroke was defined according to criteria from the US National Survey of Stroke and was confirmed by computed tomography.[18] Classification of stroke was based on examination of computed tomography scans, magnetic resonance images, and autopsy findings.

Statistical analysis

To assess the association between age and WHtR, we analyzed mean WC, height, and WHtR according to age in men and women. Pearson product-moment correlation coefficients between height and waist were calculated by sex and age group (30–49, 50–69, ≥70 years). Participants were categorized based on quartiles of WHtR by sex and age group. To compare baseline characteristics among WHtR quartiles, analysis of variance was used for continuous variables and the χ^2 test was used for dichotomous and categorical variables.

The Cox proportional hazards model was used to investigate the association between WHtR and CVD risk only among participants aged 50 to 69 years and 70 years or older, because there were too few CVD cases (men: 17, women: 11) for statistical analysis among those aged 30 to 49 years. Interaction terms were added to the models to assess the interaction between age and WHtR quartile for the risk of CVD. Hazard ratios (HRs) and 95% CIs were computed, and the lowest quartile of WHtR was defined as the reference group. To adjust for confounding factors, we included age, smoking status (current, quit, or never), and drinking status (current, quit, or never) in the model. Cardiometabolic risk factors such as hypertension, diabetes, and hypercholesterolemia were not included in the model because central obesity is upstream in the "metabolic domino".[19] However, in sensitivity analysis, we adjusted for hypertension, diabetes, and hypercholesterolemia to confirm that WHtR was an independent risk factor. The same analysis was performed for WC. In addition, to further assess cut-off points for WHtR, the highest quartile was dichotomized by median WHtR (ie, upper Q4 and lower Q4), and HRs and 95% CIs were estimated. The likelihood ratio test was used to compare the predictive values of WHtR with WC, as follows. First, we calculated the −2 logarithm likelihood for the model including the confounding factors, age, smoking, and drinking status ($-2\,ln[L_c]$). Second, we calculated the −2 logarithm likelihood for the model including the confounding factors plus WHtR ($-2\,ln[L_{c+WHtR}]$). The difference, ie, ($-2\,ln[L_c] - (-2\,ln[L_{c+WHtR}])$), had an approximate χ^2 distribution with 1 degree-of-freedom. The same analysis was performed for WC.

All P values were 2-tailed, and a P value less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS (Version 20.0J; Japan IBM, Tokyo, Japan).

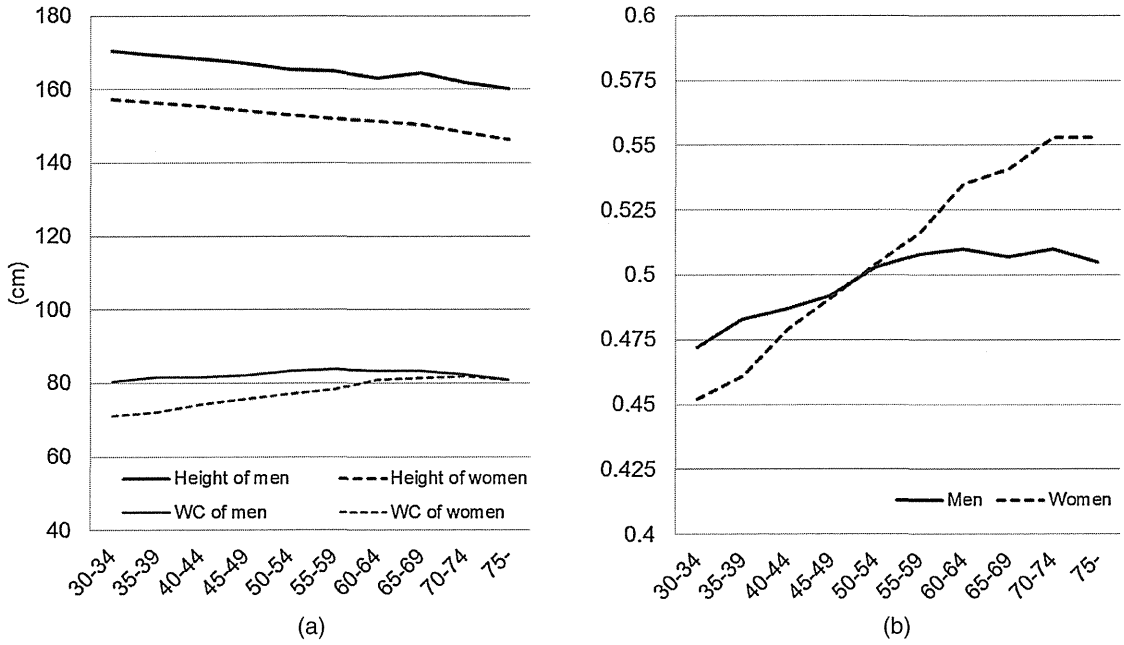

Figure. (a) Average WC (waist circumference), height, and (b) waist-to-height ratio according to age (The Suita Study, Japan)

RESULTS

During the follow-up period (mean, 13.0 years), 428 CVD events (184 CHD and 244 strokes) were observed. The Figure shows average WC, height, and WHtR by sex and age. WC in men increased up to age 50 years, remained almost unchanged from age 50 to 69 years, and decreased at age 70 years or older. WC in women younger than 75 years increased with advancing age and decreased in women aged 75 years or older, as compared with women aged 70 to 74 years. Height decreased with advancing age in both sexes. WHtR in men increased until approximately age 60 years. WHtR in women younger than 75 years increased with advancing age. The Pearson product-moment correlation coefficients (95% CI) between height and WC were 0.16 (0.09–0.22), 0.24 (0.19–0.30), and 0.13 (0.04–0.22) among men aged 30 to 49, 50 to 69, and 70 years or older, respectively, and 0.07 (0.01–0.13), 0.07 (0.02–0.13), 0.09 (−0.003–0.19) among women in the respective age groups.

Tables 1 and 2 summarize the baseline characteristics according to WHtR quartile (results among men and women aged 30–49 years are shown in eTable 1.) The prevalence of hypertension significantly differed by WHtR quartile, except among men aged 70 years or older. The prevalence of hypercholesterolemia and diabetes significantly differed by WHtR quartile among men and women aged 50 to 69 years.

Table 3 shows multivariable-adjusted HRs and 95% CIs for CVD and its subtypes according to WHtR quartile. A significant interaction was observed between age and WHtR for CVD among men (P for interaction = 0.02). Men aged 50 to 69 years in the highest quartile had significantly higher risks of CVD and CHD as compared with men in the lowest quartile; the HRs (95% CI) were 1.82 (1.13–2.92) and 2.42 (1.15–5.12), respectively. There were significant linear increases in the HRs for CVD, CHD, and ischemic stroke in men aged 50 to 69 years. After further adjustment for hypertension, diabetes, and hypercholesterolemia, the HRs (95% CI) were 1.46 (0.90–2.36) and 1.89 (0.89–4.03), respectively (eTable 3). Women aged 50 to 69 years in the highest quartile had a significantly higher risk of stroke than did those in the lowest quartile; the HR (95% CI) was 2.43 (1.01–5.85). There were significant linear increases in the HRs of CVD and stroke in women aged 50 to 69 years. After further adjustment for hypertension, diabetes, and hypercholesterolemia, the HR (95% CIs) was 2.06 (0.84–5.04) (eTable 3).

When men aged 50 to 69 years in the highest quartile were dichotomized by median WHtR (0.56), the HR (95% CI) for CVD was 1.37 (0.76–2.46) for those in the lower WHtR group and 2.34 (1.38–3.97) for those in the upper WHtR group (eTable 2). When women aged 70 years or older in the highest quartile were dichotomized by median WHtR (0.65), the HR for CVD was 1.42 (0.63–3.18) for those in the lower WHtR group and 2.33 (1.10–4.94) for those in the upper WHtR group. After adjustment for hypertension, diabetes, and hypercholesterolemia, the HRs in the upper WHtR decreased but remained significant, ie, 1.78 (1.04–3.05) among men aged 50 to 69 years and 2.16 (1.02–4.61) among women aged 70 years or older.

Table 4 shows the HRs and 95% CIs for CVD in relation to WC quartile. Among men aged 50 to 69 years in the highest quartile, the HR for CVD was 1.63 (1.03–2.59), although the HRs of CVD did not show a significant linear increase in this group. Among women aged 50 to 69 years, a significant linear

Table 1. Baseline characteristics of men, according to age group and quartile of waist-to-height ratio: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P*-value
Age 50–69 years					
No. of subjects	308	304	304	308	
Waist-to-height ratio	0.374–0.475	0.476–0.508	0.509–0.536	0.537–0.761	
Waist, cm	74.0 ± 4.3	81.2 ± 2.9	85.7 ± 3.1	92.8 ± 5.5	<0.01
Height, cm	165.0 ± 5.3	164.9 ± 5.6	164.4 ± 5.4	163.7 ± 5.3	0.01
Age, years	59.0 ± 5.3	59.1 ± 5.2	59.1 ± 5.5	59.4 ± 5.3	0.77
Body mass index, kg/m^2	20.1 ± 1.7	22.1 ± 1.5	23.7 ± 1.5	25.9 ± 2.3	<0.01
Hypertension, %	31	35	45	51	<0.01
Diabetes, %	6	7	9	11	0.045
Hypercholesterolemia, %	23	28	40	35	<0.01
Smoking status (current/quit/never), %	58/25/17	50/31/19	46/35/19	44/38/19	0.01
Drinking status (current/quit/never), %	79/2/19	74/4/22	79/4/17	76/4/21	0.58
Age ≥70 years					
No. of subjects	120	120	124	119	
Waist-to-height ratio	0.352–0.472	0.473–0.508	0.509–0.543	0.544–0.688	
Waist, cm	70.6 ± 5.0	79.8 ± 3.4	84.9 ± 3.3	92.2 ± 5.6	<0.01
Height, cm	162.5 ± 6.0	162.2 ± 5.7	161.3 ± 5.3	159.3 ± 6.0	<0.01
Age, years	74.0 ± 3.0	73.5 ± 2.7	74.1 ± 2.7	73.7 ± 2.9	0.40
Body mass index, kg/m^2	18.5 ± 1.7	21.3 ± 1.7	22.7 ± 1.4	25.6 ± 2.0	<0.01
Hypertension, %	42	44	51	57	0.07
Diabetes, %	4	7	7	8	0.70
Hypercholesterolemia, %	23	29	26	31	0.46
Smoking status (current/quit/never), %	37/48/16	42/41/18	38/47/15	30/50/19	0.66
Drinking status (current/quit/never), %	58/8/33	62/11/28	62/6/32	65/8/28	0.73

Continuous data with a normal distribution were analyzed with analysis of variance: mean ± SD.
Dichotomous and categorical data were analyzed with the χ^2 test.
Q, quartile; hypertension was defined as systolic blood pressure/diastolic blood pressure ≥ 140/90 mm Hg or current use of antihypertensive medications; diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/L, a non-fasting plasma glucose level ≥ 11.1 mmol/L, or current use of antidiabetic medications; hypercholesterolemia was defined as a total serum cholesterol level ≥ 5.7 mmol/L or current use of antihyperlipidemic medications.

increase was observed in the HRs for CVD (P for trend = 0.04). However, after further adjustment for hypertension, diabetes, and hypercholesterolemia, these associations were no longer significant among men or women.

The χ^2 values for the likelihood ratio test were 6.49 ($P = 0.01$) for WHtR and 3.63 ($P = 0.06$) for WC among men aged 50 to 69 years, and 4.45 ($P = 0.03$) for WHtR and 4.54 ($P = 0.03$) for WC among women aged 50 to 69 years.

DISCUSSION

Our main findings were that WHtR was significantly positively associated with CVD and CHD risk among men aged 50 to 69 years and with stroke risk among women aged 50 to 69 years. Among men, there was a significant interaction between age and WHtR for CVD incidence. Among women aged 50 to 69 years, there was a borderline association between a WHtR in the highest quartile and increased CVD risk. In addition, among women aged 70 years or older, a WHtR in the upper level of the highest quartile was associated with significantly elevated CVD risk. These findings suggest that the association between WHtR and CVD incidence differs according to age and sex.

Two previous studies, in the United States and China, reported that the association between WHtR and CVD risk was stronger among younger adults as compared with elderly adults.[12,13] We too observed a significantly stronger association between WHtR and CVD risk among relatively young adults (age 50–69 years) as compared with elderly adults (age ≥70 years), which supports the results of previous studies. Consequently, these findings suggest that age stratification is important in estimating the association between WHtR and CVD risk.

In this population, physical frame, eg, WC and height, differed by age group. It has been reported that WC and the ratio of abdominal fat to whole-body fat differ by age.[9,10] In addition, the National Health and Nutrition Examination Survey in Japan noted that height clearly differed by generation.[11] This generational difference in physical frame, as well as aging, could lead to age differences in the association between WHtR and CVD risk.

A recent meta-analysis reported an optimal cut-off point of 0.50 for WHtR in both sexes.[7] However, the present findings suggest that, regardless of age or sex, a cut-off of 0.50 is somewhat low for identifying individuals at higher risk for CVD. The association with CVD risk was of at least

Table 2. Baseline characteristics of women, according to age group and quartile of waist-to-height ratio: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P*-value
Age 50–69 years					
No. of subjects	337	340	335	339	
Waist-to-height ratio	0.348–0.472	0.473–0.520	0.521–0.568	0.569–0.838	
Waist, cm	67.3 ± 4.1	75.4 ± 3.3	82.7 ± 3.4	92.1 ± 6.6	<0.01
Height, cm	153.0 ± 4.7	151.8 ± 4.9	152.1 ± 5.1	150.3 ± 5.2	<0.01
Age, years	57.6 ± 5.3	58.5 ± 5.3	59.5 ± 5.2	60.5 ± 5.4	<0.01
Body mass index, kg/m^2	19.8 ± 2.0	21.7 ± 2.0	23.1 ± 2.3	25.9 ± 3.3	<0.01
Hypertension, %	21	32	36	52	<0.01
Diabetes, %	2	3	5	9	<0.01
Hypercholesterolemia, %	49	57	57	62	0.01
Smoking status (current/quit/never), %	11/2/86	11/3/86	9/3/88	12/5/84	0.43
Drinking status (current/quit/never), %	26/2/73	29/2/69	28/2/71	31/1/68	0.75
Postmenopausal, %	90	94	95	94	0.06
Age ≥70 years					
No. of subjects	103	103	103	103	
Waist-to-height ratio	0.379–0.496	0.497–0.554	0.556–0.602	0.603–0.812	
Waist, cm	68.1 ± 4.4	77.3 ± 4.1	85.6 ± 3.6	95.2 ± 6.4	<0.01
Height, cm	148.4 ± 5.5	147.7 ± 6.1	148.1 ± 5.1	145.8 ± 5.1	<0.01
Age, years	73.8 ± 2.9	73.4 ± 2.7	73.8 ± 2.7	74.0 ± 2.6	0.56
Body mass index, kg/m^2	19.1 ± 2.1	21.3 ± 2.3	23.1 ± 2.1	26.2 ± 2.9	<0.01
Hypertension, %	53	44	50	64	0.03
Diabetes, %	2	5	6	4	0.54
Hypercholesterolemia, %	42	51	53	52	0.32
Smoking status (current/quit/never), %	12/6/83	9/4/87	6/5/89	7/5/88	0.78
Drinking status (current/quit/never), %	22/5/73	18/2/81	19/1/80	19/4/77	0.62
Postmenopausal, %	100	100	100	100	1.00

Continuous data with a normal distribution were analyzed with analysis of variance: mean ± SD.
Dichotomous and categorical data were analyzed with the χ^2 test.
Q, quartile; hypertension was defined as systolic blood pressure/diastolic blood pressure ≥ 140/90 mm Hg or current use of antihypertensive medications; diabetes was defined as a fasting plasma glucose level ≥ 7.0 mmol/L, a non-fasting plasma glucose level ≥ 11.1 mmol/L, or current use of antidiabetic medications; hypercholesterolemia was defined as a total serum cholesterol level ≥ 5.7 mmol/L or current use of antihyperlipidemic medications.

borderline significance for a WHtR in the fourth quartile, except among men aged 70 years or older. Additional analyses showed that the risks markedly increased, particularly in the upper level of the fourth WHtR quartile, among men aged 50 to 69 years and women aged 70 years and older. These results suggest the presence of a threshold rather than a dose-response relation for WHtR, although the present sample was too small to confirm this hypothesis. Additionally, we think that cut-offs should be set in relation to age and sex. On the basis of our results, we propose the following cut-offs (which do not include men aged 70 years or older): 0.560 for men aged 50 to 69 years, 0.569 for women aged 50 to 69 years, and 0.647 for women aged 70 years or older.

The risk of CVD among men aged 50 to 69 years, and women aged 70 years, in the upper level of the highest quartile was significantly elevated even after adjustment for hypertension, hyperlipidemia, and diabetes. We believe that there are 2 possible explanations for this finding. First, an extremely high WHtR might actually be an independent risk factor ie, separate from classical cardiometabolic risks. It has been reported that abdominal obesity is related to increased levels of plasminogen activator inhibitor-1, which can lead to blood coagulation.[20] Such background mechanisms might be important. Second, our findings could be due to insufficient adjustment for confounders in the Cox regression model. Irrespective of the reason, men aged 50 to 69 years, and women aged 70 years or older, with extremely high WHtRs have a considerably higher risk for CVD and should be closely monitored.

We previously investigated the association between WC and CVD risk without age stratification[21] and found a significant association between WC and the risks of CVD and stroke among women but no significant association among men. However, the present age-stratified analysis of WC suggests that our previous results were substantially influenced by age. Therefore, we compared WHtR and WC in relation to CVD in analysis stratified by age group and found that the HRs associated with the highest quartile of WHtR were higher than those associated with WC among middle-aged men and that the predictive value of WHtR was greater than that of WC. Several previous studies reported similar results[12,22–24]; therefore our findings are consistent with those

Table 3. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WHtR: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P* for trend
Men					
Age 50–69 years					
Person-years	4070	3069	3879	3842	
CVD, no. of cases	28	31	32	47	
HRs	1	1.14 (0.68–1.90)	1.23 (0.74–2.05)	1.82 (1.13–2.92)	0.01
CHD, no. of cases	10	16	16	23	
HRs	1	1.57 (0.71–3.47)	1.72 (0.77–3.80)	2.42 (1.15–5.12)	0.02
Stroke, no. of cases	18	15	16	24	
HRs	1	0.91 (0.46–1.81)	0.95 (0.48–1.87)	1.56 (0.84–2.89)	0.16
Ischemic stroke, no. of cases	10	9	15	18	
HRs	1	0.99 (0.40–2.43)	1.59 (0.71–3.56)	2.06 (0.94–4.49)	0.04
Age ≥70 years					
Person-years	1055	1128	1193	1155	
CVD, no. of cases	21	29	27	30	
HRs	1	1.36 (0.77–2.39)	1.09 (0.62–1.93)	1.36 (0.78–2.38)	0.45
CHD, no. of cases	13	11	10	15	
HRs	1	0.87 (0.39–1.97)	0.63 (0.28–1.45)	1.09 (0.52–2.30)	0.99
Stroke, no. of cases	8	18	17	15	
HRs	1	2.09 (0.90–4.81)	1.79 (0.77–4.15)	1.84 (0.78–4.35)	0.29
Ischemic stroke, no. of cases	4	12	10	11	
HRs	1	2.84 (0.91–8.83)	2.22 (0.69–7.07)	2.71 (0.86–8.53)	0.18
Women					
Age 50–69 years					
Person-years	4811	4863	4477	4470	
CVD, no. of cases	16	18	21	33	
HRs	1	1.09 (0.56–2.14)	1.32 (0.69–2.54)	1.80 (0.98–3.32)	0.04
CHD, no. of cases	9	4	4	13	
HRs	1	0.47 (0.14–1.51)	0.47 (0.14–1.54)	1.35 (0.56–3.22)	0.43
Stroke, no. of cases	7	14	17	20	
HRs	1	1.85 (0.75–4.60)	2.35 (0.97–5.70)	2.43 (1.01–5.85)	0.04
Ischemic stroke, no. of cases	3	7	9	10	
HRs	1	2.09 (0.54–8.10)	2.78 (0.75–10.33)	2.35 (0.63–8.77)	0.22
Age ≥70 years					
Person-years	1095	1259	1164	1094	
CVD, no. of cases	15	15	13	24	
HRs	1	1.00 (0.48–2.08)	0.91 (0.43–1.93)	1.83 (0.95–3.53)	0.08
CHD, no. of cases	6	7	5	9	
HRs	1	1.23 (0.40–3.77)	0.98 (0.29–3.32)	1.78 (0.62–5.14)	0.34
Stroke, no. of cases	9	8	8	15	
HRs	1	0.85 (0.32–2.23)	0.88 (0.34–2.29)	1.92 (0.83–4.45)	0.11
Ischemic stroke, no. of cases	5	4	4	9	
HRs	1	0.83 (0.22–3.16)	0.77 (0.21–2.91)	1.99 (0.66–6.04)	0.21

Multivariable adjustment was performed for age, smoking, and drinking status. Parentheses indicate 95% CIs for HRs.
Abbreviations: WHtR, waist-to-height ratio; Q, quartile; CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio.

of previous studies. In contrast, WHtR and WC had similar predictive values for CVD among women in the present study. Many previous studies found that WHtR was similar to WC in predicting CVD risk among women.[12,22,24–26] The effect of dividing WC by height might be limited because the correlation of WC with height is weaker among women than among men. Consequently, we believe that WHtR is a better predictor than WC, particularly among middle-aged men.

The superiority of WHtR might be explained by the fact that WHtR, as measured by computed tomography, was more closely correlated than WC with intra-abdominal fat,[27] and a previous study reported that intra-abdominal fat was positively associated with number of cardiometabolic risk factors.[28] In addition, shorter adults tend to have more cardiometabolic risk factors than do taller individuals with a similar WC.[29] This suggests that WHtR, ie, dividing WC by height, is more strongly related than WC to cardiometabolic risk factors. Thus, we believe that WHtR better reflects the accumulation of cardiometabolic risks and leads to superior prediction of CVD.

BMI, along with indices of central obesity, has been an important obesity index in predicting CVD incidence,[30] although a meta-analysis reported that the predictive power of WHtR for CVD was higher than that of BMI.[7] Another report found a significant association between BMI and CVD after adjustment for WHtR[12] and suggested that WHtR and BMI are independently associated with CVD risk. Therefore, it might be better to use both BMI and WHtR to assess obesity.

Table 4. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WC: The Suita Study, Japan

	Q1 (low)	Q2	Q3	Q4 (high)	*P* for trend
Men					
Age 50–69 years					
Person-years	4078	4004	3872	3806	
CVD, no. of cases	32	33	29	44	
HRs	1	1.07 (0.66–1.75)	0.97 (0.58–1.61)	1.63 (1.03–2.59)	0.06
CHD, no. of cases	13	17	12	23	
HRs	1	1.28 (0.62–2.63)	0.96 (0.44–2.12)	2.02 (1.02–4.02)	0.07
Stroke, no. of cases	19	16	17	21	
HRs	1	0.97 (0.50–1.88)	0.96 (0.49–1.86)	1.43 (0.76–2.67)	0.31
Ischemic stroke, no. of cases	13	9	13	17	
HRs	1	0.80 (0.34–1.87)	1.07 (0.49–2.31)	1.64 (0.79–3.41)	0.15
Age ≥70 years					
Person-years	999	1208	1200	1124	
CVD, no. of cases	25	28	27	27	
HRs	1	0.94 (0.55–1.62)	0.91 (0.53–1.58)	1.06 (0.61–1.84)	0.87
CHD, no. of cases	14	11	12	12	
HRs	1	0.67 (0.30–1.47)	0.65 (0.30–1.43)	0.82 (0.38–1.78)	0.60
Stroke, no. of cases	11	17	15	15	
HRs	1	1.29 (0.60–2.77)	1.21 (0.55–2.66)	1.36 (0.62–2.99)	0.52
Ischemic stroke, no. of cases	5	10	10	12	
HRs	1	1.70 (0.58–4.98)	1.82 (0.62–5.37)	2.26 (0.79–6.47)	0.14
Women					
Age 50–69 years					
Person-years	4669	4685	5046	4221	
CVD, no. of cases	15	18	25	30	
HRs	1	1.19 (0.60–2.36)	1.43 (0.75–2.71)	1.87 (1.00–3.51)	0.04
CHD, no. of cases	7	5	5	13	
HRs	1	0.74 (0.24–2.34)	0.65 (0.21–2.08)	1.86 (0.73–4.72)	0.18
Stroke, no. of cases	8	13	20	17	
HRs	1	1.56 (0.65–3.77)	2.06 (0.90–4.70)	1.93 (0.82–4.54)	0.11
Ischemic stroke, no. of cases	4	6	9	10	
HRs	1	1.44 (0.41–5.10)	1.70 (0.52–5.54)	2.00 (0.62–6.52)	0.23
Age ≥70 years					
Person-years	1175	1234	1046	1157	
CVD, no. of cases	16	16	15	20	
HRs	1	1.05 (0.52–2.11)	1.11 (0.54–2.25)	1.45 (0.74–2.83)	0.28
CHD, no. of cases	8	6	7	6	
HRs	1	0.85 (0.29–2.49)	1.21 (0.43–3.43)	0.88 (0.30–2.59)	0.98
Stroke, no. of cases	8	10	8	14	
HRs	1	1.24 (0.49–3.14)	1.10 (0.41–2.93)	2.00 (0.83–4.87)	0.15
Ischemic stroke, no. of cases	5	4	4	9	
HRs	1	0.85 (0.23–3.21)	0.93 (0.25–3.47)	1.86 (0.61–5.61)	0.24

Multivariable adjustment was performed for age, smoking, and drinking status. Parentheses indicate 95% CIs for HRs.
Abbreviations: WC, waist circumference; Q, quartile; CVD, cardiovascular disease; CHD, coronary heart disease; HR, hazard ratio.

Our study has several limitations. First, the number of cases of CVD among participants aged 30 to 49 years was insufficient for statistical analysis. Further study is required to confirm an association between WHtR and CVD risk among younger adults. Second, the effect of visceral fat could not be estimated because we did not use computed tomography to measure abdominal fat distribution. Third, changes in WHtR during the follow-up period were not considered in the present study. Finally, because WC was measured once, the estimated risks might have been underestimated because of regression dilution bias.[31]

In conclusion, the present findings suggest that WHtR is useful in identifying middle-aged Japanese at higher risk of CVD and is more predictable than WC in determining CVD risk, especially among men. In addition, the data indicate that WHtR cut-off points should be set according to sex and age. This study enrolled a limited Japanese population, and further studies with larger and more ethnically diverse samples are required to confirm our findings.

ONLINE ONLY MATERIALS

eTable 1. Baseline characteristics and CVD incidence among men and women aged 30–49 years according to quartile of waist-to-height ratio: the Suita Study, Japan.

eTable 2. Multivariable-adjusted hazard ratios for cardiovascular disease in the upper and lower fourth quartile of WHtR according to sex and age group: the Suita Study, Japan.

eTable 3. Multivariable-adjusted hazard ratios for cardiovascular disease according to sex, age group, and quartile of WHtR: the Suita Study, Japan.
Abstract in Japanese.

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Progress in Cardiovascular Diseases

Worksite Wellness for the Primary and Secondary Prevention of Cardiovascular Disease in Japan: The Current Delivery System and Future Directions

Tomonori Okamura[a,*], *Daisuke Sugiyama*[a], *Taichiro Tanaka*[b], *Seitaro Dohi*[c]

[a]*Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan*
[b]*Division of Environmental and Occupational Health, Department of Social Medicine, Faculty of Medicine, Toho University, Tokyo, Japan*
[c]*Mitsui Chemicals, INC., Tokyo, Japan*

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ABSTRACT

In the Japanese workplace, employers are required to provide annual health checkups for workers in accordance with the "Industrial Safety and Health Law," which also mandates that an occupational physician be assigned to companies employing at least 50 workers. The annual medical examination includes testing for the early detection of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and the metabolic syndrome. This approach has successfully contributed to the extremely low incidence of coronary artery disease among Japanese workers. However, problems such as poor health and the low rate of participation in health checkups among small-scale companies still persist. Furthermore, although most wellness delivery systems in Japan employ strategies targeting high-risk individuals, instituting a strategy addressing the broader population irrespective of screening may be effective in reducing disease risk in the overall population. As a future direction, we should therefore develop practical methods for implementing a population strategy.

Current system for cardiovascular disease prevention in the Japanese worksite

Today, the majority of the Japanese population undergo annual health checkups. More specifically, approximately 70% of men and 60% of women over the age of 20 receive some type of health examination at least once a year.[1] Mass health screening is offered to all individuals in Japan at the worksite, school, community, and so on. In the workplace, employers are required to provide annual medical examinations for workers, and workers are likewise mutually obligated to participate in health evaluations. These requirements are prescribed by Article 66 of the "Industrial Safety and Health Law,"[2] which was established in 1972.

The primary aim of the annual health examination is to identify general health problems among the workers. Article 44 of the "Ordinance on Industrial Safety and Health"[3] lists the health conditions to be assessed in the medical evaluation; these vary according to the changing epidemiology of diseases. For example, mortality due to tuberculosis is decreasing since the end of the Second World War, whereas the prevalence of non-communicable diseases (NCDs) such as

Statement of Conflict of Interest: see page 6.

* Address reprint requests to Tomonori Okamura, M.D., Ph.D., Department of Preventive Medicine and Public Health, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160–8582, Japan.
E-mail address: okamura@z6.keio.jp (T. Okamura).

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