atherosclerosis in men differs from that in women. Decreasing postmenopausal female hormones such as estrogen plays a role in production of PGE2 [29].

We have several study limitations. First, due to cross-sectional study design, causal and effect reversal may not occur. However, carotid atherosclerosis appears as results of the accumulation effect of exposure factors for cardiovascular risk factors, such as salivary inflammatory cytokines. Second, the sample size in this study was not enough. However, this is the first investigation to significant association between not only salivary inflammatory cytokines and periodontal disease but also those and carotid atherosclerosis. Third, we did not exclude subjects with chronic infectious and connective tissue disease. However, this study was performed in apparently healthy general population.

In conclusion, higher levels of salivary inflammatory cytokines were positively associated with periodontal disease. Among them, higher salivary IL-6 and TNF-α were positively associated with intensity of carotid atherosclerosis, and furthermore, PGE2 was in women.

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Conflicts of interests

The authors declare that they have no conflict of interests.

Disclosures

Nothing to disclosures.

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References

[1] Gokulakrishnan K, Deepa R, Mohan V. Association of high sensitivity C-reactive protein (hsCRP) and tumor necrosis factor-alpha (TNF-alpha) with carotid intimal medial thickness in subjects with different grades of glucose intolerance- the Chennai Urban Rural Epidemiology Study (CURE-31). Clin Biochem 2008;41:480–5.

[2] Sardo MA, Mandraffino G, Campo S, Saitta C, Bitto A, Alibrandi A, et al. Biglycan expression in hypertensive subjects with normal or increased carotid intima-media wall thickness. Clin Chim Acta. 2009;406:89–93.

[3] Pizzi C, Manzoli L, Mancini S, Bedetti G, Fontana F, Costa GM. Autonomic nervous system, inflammation and preclinical carotid atherosclerosis in depressed subjects with coronary risk factors. Atherosclerosis 2010;212:292–8.

[4] Okazaki S, Furukado S, Abe Y, Tanaka M, Miwa K, Yamagami H, et al. Cerebrovasc Dis 2010;30:180–7.

[5] Scuteri A, Orru M, Morrell C, Piras MG, Taub D, Schlessinger D, et al. Independent and additive effects of cytokine patterns and the metabolic syndrome on arterial aging in the SardiNIA Study. Atherosclerosis 2011;215:459–64.

[6] Freitas WM, Quaglia LA, Santos SN, Soares AA, Japiassú AV, Boaventura V, et al. Association of systemic inflammatory activity with coronary and carotid atherosclerosis in the very elderly. Atherosclerosis 2011;216:212–6.

[7] Liu Z, Lu F, Pan H, Zhao Y, Wang S, Sun S, et al. Correlation of peripheral Th17 cells and Th17-associated cytokines to the severity of carotid artery plaque and its clinical implication. Atherosclerosis 2012;221:232–41.

[8] Guarneri M, Geraci C, Incalcaterra F, Arsena R, Mule G, Vaccaro F, et al. Subclinical atherosclerosis and fetuin-A plasma levels in essential hypertensive patients. Hypertens Res 2013;36:129–33.

[9] Belogui Q, Páramo JA, Orbe J, Benito A, Colina I, Monasterio A, et al. Monocyte cyclooxygenase-2 overactivity: a new marker of subclinical atherosclerosis in asymptomatic subjects with cardiovascular risk factors? Eur Heart J 2005;26: 153–8.

[10] Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. Am Heart J 2007;154:830–7.

[11] Lopez-Jornet P, Berna-Mestre JD, Berna-Serna JD, Camacho-Alonso F, Fernandez-Milian S, Reus-Pintado M. Measurement of atherosclerosis markers in patients with periodontitis: a case-control study. J Periodontol 2012;83: 690–8.

[12] Genco R, Offenbacher S, Beck J. Periodontal disease and cardiovascular disease: epidemiology and possible mechanisms. J Am Dent Assoc 2002;133: 145–225.

[13] Kapellas K, Maple-Brown LJ, Jamieson LM, Do LG, O'Dea K, Brown A, et al. Effect of periodontal therapy on arterial structure and function among aboriginal Australians: a randomized, controlled trial. Hypertension 2014. http://dx.doi.org/10.1161/HYPERTENSIONAHA.114.03359.

[14] Sexton WM, Lin Y, Kryscio RJ, Dawson 3rd DR, Ebersole JL, Miller CS. Salivary biomarkers of periodontal disease in response to treatment. J Clin Periodontol 2011;38:434–41.

[15] Yoon AJ, Cheng B, Philipone E, Turner R, Lamster IB. Inflammatory biomarkers in saliva: assessing the strength of association of diabetes mellitus and periodontal status with the oral inflammatory burden. J Clin Periodontol 2012;39: 434–40.

[16] Lee A, Ghaname CB, Braun TM, Suqai JV, Teles RP, Loesche WJ, et al. Bacterial and salivary biomarkers predict the gingival inflammatory profile. J Periodontol 2013;83:79–89.

[17] Yue Y, Liu Q, Xu C, Loo WT, Wang M, Wen G, et al. Comparative evaluation of cytokines in gingival crevicular fluid and saliva of patients with aggressive periodontitis. Int J Biol Markers 2013;28:108–12.

[18] Nomura Y, Shimada Y, Hanada N, Numabe Y, Kamoi K, Sato T, et al. Salivary biomarkers for predicting the progression of chronic periodontitis. Arch Oral Biol 2012;57:413–20.

[19] Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. Hypertension 2008;52: 652–9.

[20] Ohara T, Kokubo Y, Toyoda K, Watanabe M, Koga M, Nakamura S, et al. Impact of chronic kidney disease on carotid atherosclerosis according to blood pressure category: the Suita study. Stroke 2013;44:3537–9.

[21] Ainamo J, Barmes D, Beagrie G, Cutress T, Martin J, Sardo-Infirri J, et al. Development of the World Health Organization (WHO) community periodontal index of treatment needs (CPITN). Int Dent J 1982;32:281–91.

[22] Yang C, Xiao L, Tongren JE, Sullivan J, Lai AA, Collins WE. Cytokine production in rhesus monkeys infected with Plasmodium coatneyi. Am J Trop Med Hyg 1999;61:226–9.

[23] Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, et al. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2014). Hypertens Res 2014;37:253–387.

[24] Vita JA, Loscalzo J. Shouldering the risk factor burden: infection, atherosclerosis, and the vascular endothelium. Circulation 2002;106:164–6.

[25] Higashi Y, Goto C, Jitsuki D, Umemura T, Nishioka K, Takemoto H, et al. Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. Hypertension 2008;51:446–53.

[26] Epstein SE, Zhou YF, Zhu J. Infection and atherosclerosis: emerging mechanistic paradigms. Circulation 1999;100:e20–8.

[27] Nakashima A, Yorioka N, Asakimori Y, Ito T, Masaki T, Shigemoto K, et al. Different risk factors for the maximum and the mean carotid intima-media thickness in hemodialysis patients. Intern Med 2003;42:1095–9.

[28] Labat C, Temmar M, Nagy E, Bean K, Brink C, Benetos A, et al. Inflammatory mediators in saliva associated with arterial stiffness and subclinical atherosclerosis. J Hypertens 2013;31:2251–8.

[29] Joldersma M, Klein-Nulend J, Oleksik AM, Heyligers IC, Burger EH. Estrogen enhances mechanical stress-induced prostaglandin production by bone cells from elderly women. Am J Physiol Endocrinol Metab 2001;280:436–42.

Rice consumption is not associated with risk of cardiovascular disease morbidity or mortality in Japanese men and women: a large population-based, prospective cohort study[1–3]

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ABSTRACT

Background: Rice consumption has been associated with risk of type 2 diabetes, but its relation with cardiovascular disease (CVD) is limited.
Objective: We examined the association between rice consumption and risk of CVD incidence and mortality in a Japanese population.
Design: This was a prospective study in 91,223 Japanese men and women aged 40–69 y in whom rice consumption was determined and updated from 3 self-administered food-frequency questionnaires, each 5 y apart. Follow-up for incidence was from 1990 to 2009 in cohort I and 1993 to 2007 in cohort II and for mortality was from 1990 to 2009 in cohort I and 1993 to 2009 in cohort II. HRs and 95% CIs of CVD incidence and mortality were calculated according to quintiles of cumulative average rice consumption.
Results: In 15–18 y of follow-up, we ascertained 4395 incident cases of stroke, 1088 incident cases of ischemic heart disease (IHD), and 2705 deaths from CVD. Rice consumption was not associated with risk of incident stroke or IHD; the multivariable HR (95% CI) in the highest compared with lowest rice consumption quintiles was 1.01 (0.90, 1.14) for total stroke and 1.08 (0.84, 1.38) for IHD. Similarly, there was no association between rice consumption and risk of mortality from CVD; the HR (95% CI) for mortality from total CVD was 0.97 (0.84, 1.13). There were no interactions with sex or effect modifications by body mass index for any endpoint.
Conclusion: Rice consumption is not associated with risk of CVD morbidity or mortality.   *Am J Clin Nutr* 2014;100:199–207.

INTRODUCTION

White rice is a major staple food of the Japanese people and central to the Japanese diet. Although rice consumption in Japan has decreased over the past several decades, nearly 29% of total caloric intake for Japanese is still derived from rice (1). Rice consumed by the Japanese is primarily refined white rice and not brown rice. Compared with brown rice, white rice contains less dietary fiber and fewer vitamins and minerals (2), which may be positively associated with greater risk of type 2 diabetes and cardiovascular disease (CVD)[4]. However, white rice is free of cholesterol and has a very low sodium content (3), which was the basis for its use in the traditional Kempner rice diet where it was used as an aid to treat hypertension (4). Therefore white rice consumption might also be considered to be inversely associated with risk of CVD. A meta-analysis showed that white rice consumption was associated with elevated risk of type 2 diabetes

(5). In addition, rice consumption was positively associated with risk of type 2 diabetes in women but not in men in the Japan Public Health Centre-based (JPHC) study (6). However, a recent cohort study in Spain showed an inverse association between rice consumption and risk of type 2 diabetes (7). In some (8–13) but not all (14–19) studies, foods rich in refined carbohydrates, such as white rice, have been associated with increased risk of CVD, especially in women. However, few studies have been conducted in Asian populations, who are known to consume large quantities of rice (12, 13, 18, 19). To our knowledge, associations between rice consumption with risk of incident stroke and ischemic heart disease (IHD) have not been previously investigated. A Japanese study suggested a positive association with mortality from stroke in young women with low BMI (12), whereas another Japanese study showed an inverse association with mortality from IHD in elderly men with high BMI (18).

With the use of data from a large-scale, population-based cohort study in Japan, we aimed to examine the prospective association between white rice consumption and risk of stroke

and IHD incidence and mortality in Japanese men and women both combined and sex specifically. Also, a stratified analysis by BMI (kg/m^2) was conducted because overweight and obesity might represent intermediate endpoints or pathways rather than confounders for rice. In addition, this analysis provided the ability to examine previous studies that yielded different results (12, 18) and evaluate the issue of whether overweight and obese subjects may have changed their rice consumption to lose weight because rice is a major source of caloric intake. Because rice was positively associated with risk of type 2 diabetes in our cohort study (6), it was hypothesized that rice consumption may be associated with higher risk of CVD.

SUBJECTS AND METHODS

Study population

The JPHC study, which is a large, Japanese, nationwide, prospective cohort study, was launched in 5 public health centers (PHCs) for cohort I and 6 PHCs for cohort II. The study population was defined as all inhabitants in study areas aged 40–59 y in cohort I and 40–69 y in cohort II. The study design has been described in detail previously (20) and was approved by the Institutional Review Board of the National Cancer Centre, Tokyo, Japan.

Baseline survey

The baseline was in 1990 for cohort I and 1993 for cohort II; with the use of a self-administered questionnaire, study subjects were asked to provide information regarding personal and familial medical histories, lifestyles, and other health-related information. The dietary habits of subjects were assessed by using a food-frequency questionnaire (FFQ) of 44 items for cohort I (21) and 52 items for cohort II. The response rate for the baseline questionnaire was 77% in men and 83% in women.

Five- and 10-y follow-up surveys

We conducted 5-y follow-up, self-administered questionnaire surveys in 1995 for cohort I and 1998 for cohort II and 10-y surveys in 2000 for cohort I and 2003 for cohort II. FFQs used in 5- and 10-y follow-up surveys were developed to estimate dietary intake from 138 food items and was validated for estimations of various nutrients and food groups (22). Data on demographics, lifestyles, personal and familial medical histories, and other health-related information were also obtained. The response rate for the 5-y questionnaire was 72% in men and 79% in women and, for the 10-y questionnaire, was 70% in men and 78% in women.

Dietary assessment

Frequencies of consumption were reported for the previous month in baseline FFQs. We used the following 4 response choices in the cohort I FFQ: almost never, 1–2 and 3–4 d/wk, and almost daily. Responses of cohort II's baseline FFQ were selected from the following 5 choices: never; <1, 1–2, and 3–4 d/wk; and almost daily. Portion sizes for food items were determined on the basis of 14- to 28-d diet-record data. Data on the daily consumption of standard rice bowls (a standard bowl was equal

to 140 g), with possible answers as "not even one per day" or "approximately XX bowls per day" in cohort I and "almost not" or "approximately XX bowls per day" in cohort II, were also calculated (21, 23).

In 5- and 10-y follow-up surveys, a standard unit and relative portion sizes for each food item were included and were identical for both cohorts. Frequency-response choices were as follows: never; 1–3 times/mo; 1–2, 3–4, and 5–6 times/wk; or 1, 2–3, 4–6, and ≥7 times/d. Relative portion sizes were as follows: small (50% smaller), medium (same as the standard), and large (50% larger). Participants were asked to determine their consumption of rice on the basis of their usual rice bowl sizes [small (110 g), standard (140 g), and large (170 g)] and the number of bowls consumed daily from 9 options that ranged from <1 to ≥10 bowls/d (23). Daily food intakes were computed by multiplying the frequency by relative portions for each food item in FFQs. Daily intakes of nutrients were calculated by using the food-composition table developed for each FFQ on the basis of the fifth revised edition of the Standard Tables of Food Composition in Japan (24). Caloric-adjusted nutrient consumptions were calculated by using the residual method (25). The validity of rice consumption estimated by the 5-y FFQ was assessed in subsamples by using both 14- and 28-d dietary records. Spearman's correlation coefficients between intake values for rice derived from the FFQ and those derived from dietary records were 0.67 in men and 0.55 in women. For reproducibility of estimations between 2 FFQs administered 1 y apart, respective Spearman's correlation coefficients were 0.79 in men and 0.71 in women. The rice consumption from the FFQ (mean ± SD: 439 ± 200 g/d in men and 334 ± 146 g/d in women) did not differ from that for dietary records (480 ± 159 g/d in men and 315 ± 101 g/d in women) (26).

Inclusion and exclusion criteria

Participants who resided in 2 PHCs were excluded because of differences in recruitment criteria. Of the remaining 116, 672 subjects, responses were obtained from 95,405 participants [43,149 subjects in cohort I and 52,256 subjects in cohort II (overall response rate 82%; 80% in cohort I and 84% in cohort II)] and were included in the current study. At baseline, participants who did not respond to rice-intake items ($n = 528$; 98 subjects in cohort I and 430 subjects in cohort II) and participants with implausible energy intakes [outside of the mean ± 3 SD: $n = 744$ subjects; 334 subjects in cohort I and 410 subjects in cohort II) were excluded. Participants who reported a history of stroke, IHD, or cancer ($n = 2910$; 1216 subjects in cohort I and 1694 subjects in cohort II) at baseline were also excluded, which left a total of 91,223 participants (41,501 subjects in cohort I and 49,722 subjects in cohort II) and were ultimately included in our analysis.

Endpoint assessment

Morbidity

A total of 78 major hospitals with the capability of treating patients with IHD and stroke were registered within the administrative districts of JPHC cohorts. Physicians, who were unaware of the patients' lifestyle data, reviewed medical records at each hospital. Incidences of fatal and nonfatal stroke were

determined if the criteria of the National Survey of Stroke (27) were met, specifically, the presence of focal neurologic deficits of sudden or rapid onset that lasted ≥24 h or until death. For each subtype of stroke (ie, hemorrhagic and ischemic strokes), a diagnosis was established on the basis of data collected from computed tomography scans, magnetic resonance images, or autopsy.

Fatal IHD events and nonfatal myocardial infarction were confirmed through medical records according to the criteria of the Monitoring Trends and Determinants of Cardiovascular Disease project (28), which requires evidence from electrocardiograms, cardiac enzymes, or autopsy.

To confirm and verify nonfatal stroke and myocardial infarction, for subjects who reported the occurrence of coronary or stroke events in the 10-y follow-up questionnaire but who were not registered in the stroke or IHD registry, contact attempts were made by letter or telephone to obtain permission to review relevant medical records. Of 653 subjects who reported an unregistered stroke, 582 subjects (89%) were successfully contacted, and 245 subjects provided information that was consistent with suspected strokes. Of these 245 subjects, 213 participants (87%) provided written informed consent for their records to be reviewed by physicians. In these subjects, a diagnosis of stroke was verified for 165 subjects, and these cases were, therefore, included in the registry. Of 288 subjects who reported an unregistered myocardial infarction, 252 subjects (88%) were contacted, and 119 subjects provided information that was consistent with suspected myocardial infarctions. Of these 119 subjects, 102 participants (86%) provided written informed consent for their medical records to be reviewed by physicians. In these subjects, myocardial infarction was confirmed for 51 individuals and subsequently included in the registry. Similarly, cases identified by the 5-y follow-up questionnaire and confirmed by hospital records were also included in the registry. As a result, an additional 225 strokes and 93 myocardial infarction cases were identified and reported. Of these cases, 172 additionally identified stroke and 71 additionally identified myocardial infarction subjects were included in the current analyses. A systematic search for additional fatal stroke and IHD subjects was also conducted by reviewing death certificates. Deaths that were a result from stroke (International Classification of Diseases, 10th Revision codes I60–I69), IHD, or acute heart failure (codes I21–23, I46, and I50) that were listed on the death certificate but had not been registered were reviewed.

Mortality

The underlying cause of death was defined according to the International Classification of Diseases, 10th Revision. All death certificates were forwarded centrally to the Ministry of Health, Welfare and Labor and coded for the National Vital Statistics. Registration of death is required by the Family Registration Law; therefore, accurate reporting was assumed for the purposes of this study.

Statistical analysis

Participants were classified into quintiles of rice consumption. Age-adjusted mean values and proportions of updated cardiovascular risk factors and population characteristics were presented according to quintiles of rice consumption. CVD incidence and mortality were analyzed separately. For the analysis of CVD incidence, person-years of follow-up were calculated from the date of the starting point 1 January 1990 in cohort I and 1 January 1993 in cohort II until the obtainment 1 of 4 possible endpoints as follows: 1) incidence of a first stroke or first IHD event, 2) relocation from the study area, 3) the end of the study on 31 December 2009 for cohort I and 31 December 2007 for cohort II, 4) or death. For the analysis of CVD mortality, person-years of follow-up were censored at the date of death, emigration from Japan, or end of the study (31 December 2009 in both cohort I and cohort II), whichever came first. For persons who were lost to follow-up, the last confirmed date of their presence in the study area was used as the date of censoring.

Because there were no interactions by sex for any endpoint (P-interaction > 0.05), analyses were done for both men and women combined; however, we also investigated associations separately for men and women by using Cox proportional hazard modeling to assess the association between quintiles of rice consumption with risk of CVD. For the multivariate analysis, we adjusted for age (continuous), sex, PHC, history of hypertension, and diabetes or the use of a lipid-lowering drug (yes or no); BMI (quintiles); smoking status (never, ex-smoker, and current smoker of 1–19, 20–29, or ≥30 cigarettes/d); ethanol intake (nondrinkers, former drinkers, and weekly ethanol intake <150, 150 to <300, 300 to <450, or ≥450 g/wk); leisure-time sports activity (≤3 d/mo, 1–2 d/wk, and ≥3 d/wk); job status (white-collar job, blue-collar job, and unemployed); and quintiles of energy-adjusted dietary intakes of selected foods and nutrients (seafood, meat, fruit, vegetables, soy, SFAs, and sodium); and total caloric intake. For women, we also adjusted for menopausal status and postmenopausal hormone use. We conducted tests for trends across quintiles of rice consumption by assigning median values for each quintile and testing the significance of this variable.

We updated rice consumption and confounding variables by using the baseline and 5- and 10-y follow-up questionnaire surveys except for age, sex, and PHC. Data on nondietary variables were updated from each questionnaire. To reduce within-subject variation and best represent a long-term diet, cumulative averages of quintiles of total calories and energy-adjusted rice and other dietary variables from the 3 questionnaires were ranked on the basis of the sum of these quintile averages. Cumulative averages of continuous dietary variables themselves were not used because of a large drift in mean amounts of caloric and nutrient intakes between baseline and follow-up questionnaires. We made the last observation carried forward to impute missing values. For example, data from the baseline questionnaire was used to replace missing values in the 5-y follow-up questionnaire, and values in the 5-y follow-up questionnaire were used to replace missing values in the 10-y follow-up questionnaire.

With the use of the cumulative average method, the incidence of and mortality from CVD between each 5-y questionnaire cycle were related to the cumulative average of rice consumptions calculated from all preceding dietary measures. Sensitivity analyses were conducted twice as follows: 1) by reanalyzing with the use of baseline data only and 2) by relating CVD events to most-recent dietary data. Furthermore, associations between total dietary carbohydrate intakes and risk of CVD were also investigated.

A stratified analysis by BMI (<25 or ≥25) was also conducted, and an interaction term generated by multiplying the median of each quintile of rice consumption by BMI was used to test an effect modification by BMI. Multiple sensitivity analyses were also conducted by excluding participants with a past history of diabetes at baseline, ceasing updating rice consumption and other dietary variables if participants reported disease history in follow-up questionnaires (type 2 diabetes, hypertension, cancer, or liver or kidney disease), and restricting the age of participants to a middle-aged group (40–59 y).The analysis was conducted with SAS version 9.3 software (SAS Institute Inc). All P values were 2-sided, and $P < 0.05$ was regarded as statistically significant.

RESULTS

During 1,401,401 person-years of follow-up of 92,223 men and women, 4395 incident cases of stroke (1777 hemorrhagic and 2590 ischemic strokes) and 1088 incident cases of IHD were diagnosed, and during 1,428,544 person-years of follow-up, 2705 deaths that were a result of CVD (1153 stroke, 605 IHD, and 947 other CVD) were reported. Characteristics of study participants according to quintiles of rice consumption are shown in **Table 1**. Compared with participants who consumed less rice, participants with a high consumption of rice tended to be older, less likely to practice sports daily, and more likely to have a blue-collar job. An increased consumption of rice was associated with a lower consumption of alcohol, seafood, vegetables, fruit, meat, soy, SFAs, and sodium.

HRs and 95% CIs for risk of incident stroke and IHD associated with rice consumption are shown in **Table 2**. In both age- and multivariable-adjusted models, rice consumption was not associated with risk of stroke, either hemorrhagic or ischemic stroke, or risk of IHD. Multivariable HRs (95% CIs) in the quintile with the highest rice consumption compared with the quintile with the lowest rice consumption were 1.01 (0.90, 1.14; P-trend = 0.72) for risk of incident stroke and 1.08 (0.84, 1.38; P-trend = 0.56) for risk of incident IHD. Similarly, rice consumption was not associated with risk of mortality from CVD (stroke, IHD, other CVD, or total CVD). The multivariable HR (95% CI) for mortality from total CVD in the quintile with the highest rice consumption compared with quintile with the lowest consumption was 97 (0.84, 1.13; P-trend = 0.33) (**Table 3**). Results did not change materially after several sensitivity analyses (data not shown in tables) including the relation of risk of CVD to the baseline rice consumption, relation of risk of CVD to the most recent rice consumption, exclusion of participants with a past history of diabetes at baseline, ceased updating of rice consumption and other dietary variables if participants reported a disease history in follow-up questionnaires, or restriction of the age of the participants to a middle-aged group (40–59 y). Moreover, a sex-specific analysis revealed similar results; multivariable HRs (95% CIs) in men were 0.88 (0.67–1.11; P-trend = 0.26) for risk of incident stroke, 0.94 (0.71–1.24; P-trend = 0.65) for risk of incident IHD, and 0.89 (0.65–1.15; P-trend = 0.47) for mortality from total CVD, and those in women were 1.26 (0.91–1.66; P- trend = 0.91), 1.38 (0.84–2.28; P-trend = 0.58), and 1.26 (0.87–1.64; P-trend = 0.83), respectively.

TABLE 1
Age-adjusted means and proportions of updated lifestyle, health, and dietary characteristics in Japanese men and women according to quintiles of rice consumption

| | Quintiles of rice consumption | | | | | |
	1 (low)	2	3	4	5 (high)	P-trend[1]
Participants at risk (n)	16,882	16,911	18,090	23,543	15,797	—
Median rice consumption (g/d)	251 ± 83[2]	326 ± 89	377 ± 88	430 ± 89	542 ± 127	—
Men (%)	49	47	46	43	55	—
Age at baseline (y)	50.8 ± 7.7	51.6 ± 7.9	52.1 ± 7.9	52.5 ± 8.0	52.4 ± 7.9	—
BMI (kg/m²)	23.5 ± 3.2	23.7 ± 3.3	23.7 ± 3.2	23.6 ± 3.2	23.4 ± 3.1	0.97
History of hypertension (%)	20	21	23	24	20	0.03
History of diabetes (%)	7	7	8	7	6	0.05
Ethanol intake (g/wk)	407 ± 396	298 ± 305	266 ± 306	261 ± 284	240 ± 264	<0.0001
Current smokers (%)	23	20	19	18	23	0.06
Practicing sports daily (%)	14	13	13	11	9	<0.0001
Blue-collar workers (%)	16	15	20	30	24	<0.0001
Use of lipid-lowering drugs (%)	6	5	5	6	4	0.02
Energy consumption (kcal/d)	2062 ± 1157	2018 ± 1064	2002 ± 921	1901 ± 778	2015 ± 807	<0.0001
Seafood consumption (g/d)	84 ± 104	82 ± 78	85 ± 67	79 ± 67	69 ± 59	0.001
Vegetable consumption (g/d)	509 ± 429	534 ± 455	536 ± 436	532 ± 391	450 ± 354	0.02
Fruit consumption (g/d)	222 ± 242	217 ± 229	216 ± 208	205 ± 184	166 ± 184	<0.0001
Meat consumption (g/d)	70 ± 88	70 ± 86	66 ± 73	64 ± 62	50 ± 52	<0.0001
Soy consumption (g/d)	96 ± 166	94 ± 148	97 ± 168	91 ± 150	71 ± 122	0.0003
Carbohydrate consumption (g/d)	234 ± 73	252 ± 63	264 ± 57	275 ± 48	301 ± 50	<0.0001
Total dietary fiber consumption (g/d)	15.3 ± 12.8	13.6 ± 8.4	14.4 ± 9.2	12.6 ± 6.7	11.9 ± 7.1	<0.0001
Saturated fatty acid consumption (g/d)	19 ± 10	18 ± 9	17 ± 8	16 ± 7	13 ± 6	<0.0001
Protein consumption (g/d)	75 ± 25	74 ± 21	74 ± 22	73 ± 17	66 ± 16	0.0004
Sodium consumption (mg/d)	4552 ± 2153	4671 ± 2065	4704 ± 1971	4731 ± 1807	4274 ± 1800	0.03

[1] Chi-square test was used for categorical variables; ANOVA was used for continuous variables.
[2] Mean ± SD (all such values).

TABLE 2
Multivariable HRs (95% CIs) of incident cardiovascular disease according to quintiles of rice consumption

	Quintiles of daily rice consumption					
	1 (low)	2	3	4	5 (high)	P-trend[1]
Participants at risk (n)	16,882	16,911	18,090	23,543	15,797	—
Person-years	250,899	253,985	279,828	371,990	244,699	—
Total stroke						
Cases (n)	789	985	777	1033	838	—
HR (95% CI)[2]	1.00 (reference)	1.15 (0.98, 1.27)	0.82 (0.75, 1.01)	0.81 (0.74, 1.09)	0.95 (0.86, 1.14)	0.36
HR (95% CI)[3]	1.00 (reference)	1.07 (0.93, 1.17)	0.94 (0.85, 1.08)	0.93 (0.84, 1.13)	1.01 (0.90, 1.14)	0.72
Hemorrhagic stroke						
Cases (n)	336	388	318	426	309	—
HR (95% CI)[2]	1.00 (reference)	1.11 (0.96, 1.29)	0.81 (0.70, 1.05)	0.81 (0.70, 1.03)	0.90 (0.84, 1.11)	0.43
HR (95% CI)[3]	1.00 (reference)	1.05 (0.90, 1.22)	0.95 (0.81, 1.12)	0.95 (0.81, 1.11)	0.96 (0.79, 1.15)	0.51
Ischemic stroke						
Cases (n)	450	563	452	604	512	—
HR (95% CI)[2]	1.00 (reference)	1.08 (0.94, 1.26)	0.93 (0.79, 1.04)	0.92 (0.79, 1.12)	0.98 (0.88, 1.13)	0.27
HR (95% CI)[3]	1.00 (reference)	1.07 (0.92, 1.23)	0.99 (0.81, 1.07)	0.99 (0.81, 1.16)	1.05 (0.90, 1.22)	0.34
Ischemic heart disease						
Cases (n)	185	210	208	258	227	—
HR (95% CI)[2]	1.00 (reference)	1.09 (0.90, 1.33)	0.96 (0.78, 1.17)	0.90 (0.74, 1.09)	1.06 (0.87, 1.29)	0.61
HR (95% CI)[3]	1.00 (reference)	0.93 (0.76, 1.14)	0.99 (0.80, 1.22)	0.95 (0.77, 1.19)	1.08 (0.84, 1.38)	0.56

[1] Median values of the cumulative averages of rice consumption in each quintile were used to test for a linear trend across quintiles. P values for interaction terms generated by multiplying the median value of each quintile of rice consumption by sex were >0.05 for all endpoints.
[2] Estimated by using Cox's proportional hazard model adjusted for age and sex.
[3] Estimated by using Cox's proportional hazard model adjusted for age; sex; public health center area; history of hypertension; history of diabetes; use of lipid-lowering drugs; BMI; smoking status; ethanol intake; leisure-time sports activity; occupation; intakes of seafood, meat, fruit, vegetables, soy, SFAs, and sodium; total energy intake; and, for women, menopausal status and hormone use.

Furthermore, associations between dietary intake of total carbohydrate and risk of CVD were examined. In a multivariable model adjusted for age, sex, PHC, history of hypertension, history of diabetes, use of cholesterol-lowering drugs, BMI, smoking status, alcohol intake, leisure-time sports activity, occupation, and intakes of SFAs, total protein, and sodium, and total caloric

TABLE 3
Multivariable HRs (95% CIs) of mortality from cardiovascular disease according to quintiles of rice consumption

	Quintiles of daily rice consumption					
	1 (low)	2	3	4	5 (high)	P-trend[1]
Participants at risk (n)	16,838	16,802	18,168	23,675	15,740	—
Person-years	255,254	258,247	285,966	379,863	249,212	—
Total stroke						
Cases (n)	202	237	221	276	217	—
HR (95% CI)[2]	1.00 (reference)	1.09 (0.91, 1.32)	0.89 (0.73, 1.07)	0.91 (0.68, 1.07)	0.93 (0.77, 1.13)	0.64
HR (95% CI)[3]	1.00 (reference)	1.07 (0.88, 1.30)	1.07 (0.88, 1.32)	1.00 (0.82, 1.23)	1.03 (0.82, 1.30)	0.71
Ischemic heart disease						
Cases (n)	113	108	112	147	125	—
HR (95% CI)[2]	1.00 (reference)	0.89 (0.69, 1.16)	0.80 (0.62, 1.04)	0.78 (0.61, 1.09)	0.94 (0.73, 1.22)	0.55
HR (95% CI)[3]	1.00 (reference)	0.81 (0.61, 1.06)	0.93 (0.70, 1.23)	0.85 (0.64, 1.12)	0.93 (0.68, 1.27)	0.42
Other cardiovascular disease						
Cases (n)	172	187	182	218	188	—
HR (95% CI)[2]	1.00 (reference)	1.01 (0.82, 1.24)	0.85 (0.69, 1.12)	0.83 (0.64, 1.09)	0.94 (0.76, 1.15)	0.33
HR (95% CI)[3]	1.00 (reference)	0.93 (0.75, 1.16)	0.96 (0.77, 1.20)	0.85 (0.67, 1.14)	0.91 (0.71, 1.17)	0.71
Total cardiovascular disease						
Cases (n)	487	532	515	641	530	—
HR (95% CI)[2]	1.00 (reference)	1.02 (0.90, 1.15)	0.86 (0.76, 1.07)	0.78 (0.69, 1.06)	0.94 (0.83, 1.10)	0.19
HR (95% CI)[3]	1.00 (reference)	0.96 (0.85, 1.09)	1.00 (0.88, 1.15)	0.81 (0.80, 1.11)	0.97 (0.84, 1.13)	0.33

[1] Median values of the cumulative averages of rice consumption in each quintile were used to test for a linear trend across quintiles. P values for interaction terms generated by multiplying the median value of each quintile of rice consumption by sex were >0.05 for all endpoints.
[2] Estimated by using Cox's proportional hazard model adjusted for age and sex.
[3] Estimated by using Cox's proportional hazard model adjusted for age; sex; public health center area; history of hypertension; history of diabetes; use of lipid-lowering drugs; BMI; smoking status; ethanol intake; leisure-time sports activity; occupation; intakes of seafood, meat, fruit, vegetables, soy, SFAs, and sodium; total energy intake; and, for women, menopausal status and hormone use.

intake, HR (95% CIs) in the quintile with the highest carbohydrate consumption compared with the quintile with the lowest consumption were 0.89 (0.78, 1.12; P-trend = 0.33) for risk of incident stroke, 1.30 (0.88, 1.87; P-trend = 0.19) for risk of incident IHD, and 0.88 (0.69, 1.12; P-trend = 0.26) for mortality from total CVD (data not shown in tables).

Associations of rice consumption with risk of incident stroke and IHD and mortality from stroke, IHD, and other CVD after BMI (<25 or ≥25) stratification was investigated (**Table 4**). There was no interaction with BMI for any endpoint, and results did not change materially in both BMI strata regarding the incidence of and mortality from CVD.

DISCUSSION

In this large Japanese cohort, no significant lower or higher risk of CVD incidence or mortality with higher rice consumption was observed. In addition, there was no clear evidence of differences in risk of CVD incidence or mortality between lean and overweight men or women.

There has been a great deal of speculation about the association of white rice with risk of type 2 diabetes, stroke, and IHD (5–7, 12, 17–19, 29, 30). Similar to the current study, 2 previous Japanese-cohort studies did not associate rice consumption with mortality from total or ischemic stroke in men or women (12, 18). However, in an age-only adjusted model, a positive trend was seen for hemorrhagic stroke in Japanese women in the study of Oba et al (12), with an HR (95% CI) in the quartile with the highest rice consumption of 2.36 (0.92, 6.03; P-trend = 0.03). However, in that study, the follow-up period was short (only 6 y), the sample size in rice-consumption quartile groups was limited (6 cases in the reference group), and the model did not address possible confounding factors, which may have contributed to an inaccurate measure of real risk.

In the current study, no association between rice consumption and risk of IHD incidence or mortality was shown, which was consistent with findings that were based on studies in Italian men and women (17). In contrast, rice was inversely associated with risk of mortality from IHD in men in another Japanese study [the Japan Collaborative Cohort (JACC) study (18)], whereas in a recent Chinese study; a combination of refined rice and wheat products were positively associated with the incidence of IHD (13). Differences between current study findings and those of the JACC or Chinese study may have been attributed to the lack of multiple measurements of dietary variables. Dietary and non-dietary variables were measured once at baseline in the JACC and Chinese studies, whereas in this current study, data were updated through the use of 3 questionnaires, each 5 y apart. The use of data at only one point of time may tend to underestimate or overestimate associations, particularly when follow-up years are extensive. Moreover, the mean rice consumption (389 g/d) in the current study differed from that (511 g/d) in the JACC study. An additional factor to be considered was that rice in the current study provided 42% of total carbohydrate intake and 25% of total caloric intake, whereas 70% of carbohydrate and 60–70% of all caloric intakes in the Chinese study came from rice (13).

Rice consumption in the JPHC study was positively associated with risk of type 2 diabetes in women (6). However, on the basis of a recent Spanish cohort study, an inverse association between rice consumption and a 6-y incidence of type 2 diabetes was also

shown (7). Because diabetic patients are often advised to reduce carbohydrate intake, they might change their rice consumption habits. However, in a sensitivity analysis that excluded participants in the current cohort who reported a history of diabetes at baseline (n = 2046), we showed no evidence of an association between rice consumption and risk of CVD. Multivariable HRs (95% CIs) for risk of incident stroke and IHD were 1.09 (0.84, 1.16; P-trend = 0.47) and 0.99 (0.79, 1.44; P-trend = 0.66), respectively.

Previously, Japanese men and women of different ages and BMIs showed different associations between rice consumption and mortality from CVD (12, 18). Overweight and obese individuals and those who developed some diseases may have changed their dietary habits as a result of diagnoses and treatments. However, results of the current study did not change materially when we restricted participants' ages to a middle-age group (40–59 y) or stratified groups by BMI. In a sensitivity analysis that ceased updating rice consumption and other dietary variables if participants reported a disease history in the 5- or 10-y follow-up questionnaire (type 2 diabetes, hypertension, cancer, or liver or kidney diseases), rice consumption was still not associated with risk of CVD incidence or mortality. In the current study, there were no interactions with sex for any endpoint, and results did not change materially when men and women were analyzed separately. However, trends tended to be inverse in men, whereas the same trends tended to be positive in women. Lipoprotein changes in response to low-fat and high-carbohydrate diets differ according to sex, with greater increases in triglycerides and VLDL-cholesterol concentrations and greater decreases in HDL-cholesterol concentrations in women than in men (31). However, we should interpret these trends carefully because of the lack of clear explanations on the basis of biology or plausible mechanisms for previously observed sex differences in associations between rice consumption and risk of type 2 diabetes or CVD.

Possible reasons to explain why white rice consumption might not be associated with risk of CVD despite its positive association with risk of type 2 diabetes may be because, during the refining process, white rice loses much of its content of insoluble fiber, magnesium, vitamins, lignans, phytoestrogens, and phytic acid (2, 5), and deficiencies of these nutrients are more related to diabetes risk (32). In addition, because white rice is free of cholesterol (3) and low in sodium, its consumption, contrary to providing risk of CVD, was actually used as an aid to treat hypertension (4). In a Chinese follow-up study, there were no associations between rice consumption and plasma triglycerides concentrations or risk of metabolic syndrome. There was a 42% decrease in risk of hypertension with high rice consumption (19). These effects on lipid profiles and blood pressure are expected not to increase CVD risk in the Japanese population (33).

Although epidemiologic evidence has shown positive associations between glycemic load (GL) and glycemic index (GI) with risk of CVD (9–13) and type 2 diabetes (34), overall carbohydrate intake is less strongly related to these diseases, with studies that showed no association (9, 12, 17, 34), a positive association (10, 11, 13), and an inverse association (35, 36). Furthermore, adverse metabolic effects of high carbohydrate intake or dietary GL have been greatly exaggerated in the presence of an underlying insulin resistance (9). Greater BMI has strongly been associated with insulin resistance (37).

TABLE 4
Multivariable HRs (95% CIs) of incidence of and mortality from cardiovascular disease according to quintiles of rice consumption stratified by BMI[1]

	BMI <25 kg/m^2 (n = 68,780)						BMI ≥25 kg/m^2 (n = 22,443)					
	Quintile 1 (low)	Quintile 2	Quintile 3	Quintile 4	Quintile 5 (high)	P-trend[2]	Quintile 1 (low)	Quintile 2	Quintile 3	Quintile 4	Quintile 5 (high)	P-trend[2]
Participants at risk (n)	13,071	12,632	13,403	17,484	12,190		3811	4279	4687	6059	3607	—
Person-years	194,444	189,164	206,466	275,269	188,456		56,455	64,822	73,363	96,721	56,243	—
Incident stroke												
Cases (n)	581	673	581	715	623		208	285	196	318	215	—
HR (95% CI)	1.00 (reference)	1.02 (0.91, 1.15)	0.97 (0.86, 1.10)	0.89 (0.79, 1.01)	0.97 (0.85, 1.12)	0.47	1.00 (reference)	1.20 (0.89, 1.44)	0.87 (0.70, 1.06)	1.04 (0.85, 1.27)	1.10 (0.87, 1.39)	0.75
Incident IHD												
Cases (n)	138	146	145	194	166		47	64	63	64	61	—
HR (95% CI)	1.00 (reference)	0.91 (0.71, 1.16)	0.99 (0.77, 1.27)	1.01 (0.79, 1.30)	1.09 (0.82, 1.45)	0.83	1.00 (reference)	1.04 (0.70, 1.54)	1.00 (0.66, 1.50)	0.82 (0.53, 1.26)	1.07 (0.66, 1.73)	0.82
Total stroke mortality												
Cases (n)	172	188	181	216	182		30	49	40	60	35	—
HR (95% CI)	1.00 (reference)	1.01 (0.82, 1.25)	1.05 (0.82, 1.25)	0.93 (0.75, 1.17)	0.99 (0.76, 1.28)	0.33	1.00 (reference)	1.49 (0.83, 2.39)	1.17 (0.71, 1.93)	1.36 (0.83, 2.25)	1.33 (0.74, 2.39)	0.79
IHD mortality												
Cases (n)	93	81	87	125	97		20	27	25	22	28	—
HR (95% CI)	1.00 (reference)	0.79 (0.58, 1.07)	0.91 (0.67, 1.25)	0.92 (0.68, 1.25)	0.93 (0.66, 1.32)	0.26	1.00 (reference)	1.05 (0.53, 2.06)	1.06 (0.53, 2.11)	0.69 (0.33, 1.42)	1.03 (0.48, 2.23)	0.91
Other CVD mortality												
Cases (n)	155	158	154	169	155		17	29	28	49	33	—
HR (95% CI)	1.00 (reference)	0.85 (0.64, 1.14)	0.83 (0.61, 1.13)	0.86 (0.63, 1.16)	0.80 (0.56, 1.15)	0.78	1.00 (reference)	2.16 (0.88, 3.76)	2.00 (0.88, 3.55)	2.59 (0.90, 4.85)	2.62 (0.85, 5.56)	0.29

[1] HRs (95% CIs) were estimated by using Cox's proportional hazard model adjusted for age; sex; public health center area; history of hypertension; history of diabetes; use of lipid-lowering drugs; BMI; smoking status; ethanol intake; leisure-time sports activity; occupation; intakes of seafood, meat, fruit, vegetables, soy, SFAs, and sodium; total energy intake; and, for women, menopausal status and hormone use. CVD, cardiovascular disease; IHD, ischemic heart disease.

[2] Median values of the cumulative averages of rice consumption in each quintile were used to test for a linear trend across quintiles. P values for an interaction term generated by multiplying the median of each quintile of rice consumption by BMI were >0.05 for all endpoints.

Japanese populations have a relatively lower BMI than that of Chinese or Western populations, which may explain the null association between total carbohydrate intake and risk of CVD in our cohort. The use of GI and GL were considered better indicators for the relation of the quantity and quality of carbohydrates to risk of chronic disease (9). Regrettably, data on GI and GL were not yet available for the current study.

To the best of our knowledge, this is the first prospective cohort study of white rice consumption and incident risk of CVD. Some strengths of the current study were its population-based prospective design involving a large sample size as well as the use of a validated FFQ. Analyses contained in the current study were based on caloric-adjusted measures of rice consumption. Changes in rice consumption over time were considered, and enhanced data from follow-up surveys were able to capture consumed amounts more accurately. Furthermore, dietary data of the Japanese population allowed an assessment of any potential associations at relatively high amounts of rice consumption. Several sensitivity analyses were conducted that yielded similar results.

Limitations to this study included a potential misclassification that arose from gathering self-reported data. However, self-reported data such as height, weight, and blood pressure may have been reasonably accurate because nationwide annual health screenings conducted since 1992 in Japan produced similar results (38). We included 1405 subjects with missing information on rice consumption on follow-up surveys in our analysis after the imputation of their rice consumption from the preceding questionnaire which may have raised a source of selection bias. However, in addition to the small number (1.1% of the total sample), there were no significant differences in CVD risk profiles between subjects with or without missing data. Last, because FFQs did not contain data on the consumption of whole grain or brown rice, an isocaloric analysis describing results when total caloric intake is fixed could not be conducted. However, because brown rice or other whole grains are not commonly used in Japan, whether risk would be lower if the white rice was replaced by these foods would not have easily been determined.

In conclusion, contrary to various expectations that an inverse or a positive association between rice consumption with risk of CVD may exist, our large Japanese cohort showed that rice consumption is not associated with risk of CVD incidence or mortality in Japanese men and women. Despite the growing evidence for a positive association between white rice consumption and risk of type 2 diabetes, rice consumption adds no additional risk of CVD in Japanese men and women.

REFERENCES

1. Kenko Eiyo Joho Kenkyukai. The National Health and Nutrition Survey in Japan, 2006. Tokyo, Japan: Daiichi-shuppan, 2009 (in Japanese).
2. Science and Technology Agency. Standard tables of food composition in Japan. 5th rev and enlarged ed. Tokyo, Japan: Printing Bureau of the Ministry of Finance, 2005 (in Japanese).
3. Kik MC. The nutritive value of rice and its by-products. Arkansas Agricultural Experiment Station Bulletin 1957:589.
4. Cirillo M, Del Guidice L, Bilancio G, Franzese MD, De Santo NG. Low salt diet and treatment of hypertension: an old story. J Nephrol 2009;22(suppl 14):136–8.
5. Hu EA, Pan A, Malik V, Sun Q. White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review. BMJ 2012;344: e1454.
6. Nanri A, Mizoue T, Noda M, Takahashi Y, Kato M, Inoue M, Tsugane S; Japan Public Health Center-based Prospective Study Group. Rice intake and type 2 diabetes in Japanese men and women: the Japan Public Health Centre-based Prospective Study. Am J Clin Nutr 2010; 92:1468–77.
7. Soriguer F, Colomo N, Olveira G, García-Fuentes E, Esteva I. White rice consumption and risk of type 2 diabetes. Clin Nutr 2013;32:481–4.
8. Liu S, Stampfer MJ, Hu FB, Giovannucci E, Rimm E, Manson JE, Hennekens CH, Willett WC. Whole-grain consumption and risk of coronary heart disease: results from the Nurses' Health Study. Am J Clin Nutr 1999;70:412–9.
9. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71:1455–61.
10. Oh K, Hu FB, Cho E, Rexrode KM, Stampfer MJ, Manson JE, Liu S, Willett WC. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. Am J Epidemiol 2005;161:161–9.
11. Sieri S, Korgh V, Berrino F, Evangelista A, Angoli C, Brighenti F, Pellegrini N, Palli D, Masala G, Sacerdote C, et al. Dietary glycemic load and index and risk of coronary heart disease in a large Italian cohort: the EPICOR Study. Arch Intern Med 2010;170:640–7.

12. Oba S, Nagata C, Nakamura K, Fuji K, Kawachi T, Takatsuka N, Shimizu H. Dietary glycemic index, glycemic load, and intake of carbohydrate and rice in relation to risk of mortality from stroke and its subtypes in Japanese men and women. Metabolism 2010;59:1574–82.

13. Yu D, Shu XO, Li H, Xiang YB, Yang G, Gao YT, Zheng W, Zhang X. Dietary carbohydrates, refined grains, glycemic load and risk of coronary heart disease in Chinese adults. Am J Epidemiol 2013;178: 1542–9.

14. Jacobs DR, Meyer KA, Kushi LH, Folsom AR. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. Am J Clin Nutr 1998;68:248–57.

15. Jacobs DR, Meyer KA, Kushi LH, Folsom AR. Is whole grain intake associated with reduced total and cause-specific death rates in older women? The Iowa Women's Health Study. Am J Public Health 1999;89:322–9.

16. Liu S, Manson JE, Stampfer MJ, Rexrode KM, Hu FB, Rimm E, Rimm EB, Willett WC. Whole grain consumption and risk of ischemic stroke in women: a prospective study. JAMA 2000;284:1534–40.

17. Tavani A, Bosetti C, Negri E, Augustin LS, Jenkins DJA, La Vecchia C. Carbohydrates, dietary glycemic load and glycemic index, and risk of acute myocardial infarction. Heart 2003;89:722–6.

18. Eshak ES, Iso H, Date C, Yamagishi K, Kikuchi S, Watanabe Y, Wada Y, Tamakoshi A; JACC Study Group. Rice intake is associated with reduced risk of mortality from cardiovascular disease in Japanese men but not women. J Nutr 2011;141:595–602.

19. Shi Z, Taylor AW, Hu G, Gill T, Wittert GA. Rice intake, weight change and risk of the metabolic syndrome development among Chinese adults: the Jiangsu Nutrition Study (JIN). Asia Pac J Clin Nutr 2012;21:35–43.

20. Tsugane S, Sobue T. Baseline survey of JPHC study-design and participation rate. Japan Public Health Centre-based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol 2001;11:S24–9.

21. Tsubono Y, Kobayashi M, Sasaki S, Tsugane S. Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC Study Cohort I. J Epidemiol 2003; 13:S125–33.

22. Tsubono Y, Sasaki S, Kobayashi M, Akabane M, Tsugane S. Food composition and empirical weight methods in predicting nutrient intakes from food frequency questionnaire. Ann Epidemiol 2001;11:213–8.

23. Sasaki S, Kobayashi M, Ishihara J, Tsugane S. Self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study: questionnaire structure, computation algorithms, and area-based mean intake. J Epidemiol 2003;13:S13–22.

24. Science and Technology Agency, ed. Standard tables of food composition in Japan. 5th rev ed. Tokyo, Japan: Printing Bureau, Ministry of Finance, 2000 (in Japanese).

25. Willett W, Stampfer MJ. Total energy intake: implication for epidemiologic analysis. Am J Epidemiol 1986;124:17–27.

26. Nanri A, Shimazu T, Ishihara J, Takachi R, Mizoue T, Inoue M, Tsugane S; JPHC FFQ Validation Study Group. Reproducibility and validity of dietary patterns assessed by a food frequency questionnaire used in the Japan Public Health Centre-Based Prospective Study. J Epidemiol 2012;22:205–15.

27. Walker AE, Robins M, Weinfeld FD. The National Survey Of Stroke. Clinical findings. Stroke 1981;12(suppl 1):I13–44..

28. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates and case fatality in 38 populations from 21 countries in 4 continents. Circulation 1994;90:583–612.

29. Neal B. White rice and risk of type 2 diabetes-New study highlights old challenges of nutritional epidemiology. BMJ 2012;344:e2021.

30. Kadoch MA. White rice and risk of type 2 diabetes-In defence of white rice. BMJ 2012;344:e3099.

31. Knopp RH, Paramsothy P, Retzlaff BM, Fish B, Walden C, Dowdy A, Tsunehara C, Aikawa K, Cheung MC. Gender differences in lipoprotein metabolism and dietary response: basis in hormonal differences and implications for cardiovascular disease. Curr Atheroscler Rep 2005;7:472–9.

32. Schulze MB, Schulz M, Heidemann C, Schienkiewitz A, Hoffmann K, Boeing H. Fiber and magnesium intake and incidence of type 2 diabetes: a prospective study and meta-analysis. Arch Intern Med 2007; 167:956–65.

33. Iso H. Changes in coronary heart disease risk among Japanese. Circulation 2008;118:2725–9.

34. Greenwood DC, Threapleton DE, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, Burley VJ. Glycemic index, glycemic load, carbohydrates, and type 2 diabetes: systematic review and dose-response meta-analysis of prospective studies. Diabetes Care 2013;36:4166–71.

35. McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program: relationship to nutrient intake. Am J Epidemiol 1984;119:667–76.

36. Garcia-Palmieri MR, Sorlie P, Tillotson J, Costas R Jr, Cordero E, Rodriguez M. Relationship of dietary intake to subsequent coronary heart disease incidence: The Puerto Rico Heart Health Program. Am J Clin Nutr 1980;33:1818–27.

37. Guilherme A, Virbasius JV, Puri V, Czech MP. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat Rev Mol Cell Biol 2008;9:367–77.

38. Kawada T, Suzuki S. Validation study on self-reported height, weight, and blood pressure. Percept Mot Skills 2005;101:187–91.

Sleep-disordered breathing is associated with elevated human atrial natriuretic peptide levels in a Japanese urban population: The Suita study

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Human atrial natriuretic peptide (hANP) and brain natriuretic peptide (BNP) are cardiac hormones that are released when the walls of the atria are stretched [1] or in response to end-diastolic pressure overload and ventricular volume expansion [2]. HANP and BNP are expected to be related to sleep-disordered breathing (SDB), because SDB also leads to changes in cardiac structures [3]. Although some small case–control studies showed that hANP and BNP were higher in patients with SDB [4,5], a larger cross-sectional, community-based population study failed to demonstrate such a relationship after adjusting for confounding factors [6]. However, that study may have a limitation in that it included subjects with a prior history of myocardial infarction, whose data may have confounded the results. The aim of the present study was to elucidate the associations of SDB with hANP and BNP using a large Japanese urban population without a prior history of cardiovascular disease (CVD).

The Suita study is a population-based cohort study; the details of which have been described elsewhere [7]. Briefly, from 1989, 6485 residents, aged 30 to 79 years, were enrolled as study participants, randomly selected from the community of Suita City. A total of 790 subjects in the Suita study was selected at random and underwent in-home pulse oximetry from June 2006 to March 2008. Of these, 24 individuals were excluded: 18 with a prior history of myocardial infarction or angina pectoris, and 6 with stroke or transient ischemic attack. Finally, 766 subjects (452 women, mean age 59.3 ± 7.1 years, mean body mass index [BMI] 23.0 ± 3.3 kg/m^2) were included in the study. Informed consent was obtained from all participants. This study was approved by the institutional review board of the National Cerebral and Cardiovascular Center.

The baseline survey included questionnaires, anthropometric measurements, and blood sample tests. The systolic and diastolic blood pressures were the averages of two measurements, and subjects were categorized into 4 groups according to the criteria of ESH-ESC 2007 [8]. Hyperlipidemia was defined as total serum cholesterol levels ≥ 5.7 mmol/L (220 mg/dL) and/or current use of anti-hyperlipidemic medications. Diabetes was defined as fasting plasma glucose levels ≥ 7.0 mmol/L (126 mg/dL) and/or current use of antidiabetic medications.

The baseline questionnaires asked about the presence of snoring or cessation of breathing during sleep, as noticed by family or bed partners. In addition, all patients assessed their daytime sleepiness with the Epworth Sleepiness Scale (ESS) [9]. The severity of SDB was evaluated with equipment including a digital pulse oximeter (PULSOX-3Si, Minolta Co., Osaka, Japan) to measure arterial oxygen saturation at home when they were in bed. Data were downloaded to a personal computer through an interface (PULSOX IF-3, Minolta) and analyzed by proprietary software (DS-3 ver. 2.0a, Minolta). The severity of SDB was expressed by the 3% oxygen desaturation index (3%ODI), defined as the number of apneas associated with a drop in blood oxygen by 3% or more per hour. Patients were divided into 3 groups according to this index: 3%ODI < 5, 3%ODI 5–15, and 3%ODI $\geq$ 15.

First, mean values and frequencies were compared with analyses of variances and chi-square tests. Next, the values of hANP and BNP in each SDB category were assessed by analysis of covariance to adjust for age, sex, and other potential confounding factors (Table 2). All statistical analyses were performed using the SAS statistical package (release version 8.2; SAS Institute Inc., Cary, NC). Results were considered significant at $p < 0.05$.

Table 1 shows the baseline characteristics of the study participants stratified by 3%ODI category. Overall, 57% individuals had 3%ODI < 5, 33% had 3%ODI 5–15, and 10% had 3%ODI $\geq$ 15. The ESS did not differ among the 3 groups ($p = 0.285$). Moreover, there was no difference in either the hANP or BNP levels among the 3 groups on univariate analyses.

Table 2 demonstrated the results of analysis of covariance for hANP. The mean hANP level was significantly higher in subjects with 3%ODI 5–15 (13.6 pg/mL; 95% confidence intervals [CI], 12.1–15.1 pg/mL) than in those with 3%ODI < 5 (11.1; 10.0–12.2 pg/mL, $p = 0.011$), even with adjustment for multiple confounding factors. The mean BNP level tended to be higher in individuals with 3%ODI $\geq$ 15 (28.6; 21.7–35.6 pg/mL) than in those with 3%ODI < 5 (21.3; 18.4–24.3 pg/mL) when adjusted for confounders among the 3 groups (Table 2), but no significant association was observed ($p = 0.064$).

HANP was significantly higher and BNP was marginally higher in individuals with SDB in the present study. This finding was partly in line with previous case–control studies that showed that hANP and BNP levels were elevated in patients with SDB [4,5]. However, few studies have demonstrated the relationship between SDB and natriuretic hormones in a community-based study [6]. One of the characteristics of SDB is excessive negative intrathoracic pressure [3], and periodic negative intrathoracic pressure causes cyclic changes in left atrial volume and diastolic function of the left ventricle, even in healthy individuals [10]. Since these changes are also strong triggers for secreting hANP [1] and BNP [2], higher levels of hANP and BNP in individuals with SDB are physiologically plausible. HANP is elevated in subjects with SDB, even in community-dwelling people without a prior history of CVD.

This is the largest study to date to investigate the relationship between SDB and natriuretic hormones in community-dwelling people, in which individuals with a prior history of CVD were excluded. However, there are some limitations that need to be addressed. First, a simple piece of equipment consisting of a pulse oximeter without an electroencephalograph was used to evaluate the

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Table 1

Baseline characteristics according to the severity of sleep-disordered breathing in 2006–2008.

Variables	Total	3%ODI < 5	3%ODI 5–15	3%ODI ≥ 15	p
	n = 766	n = 435	n = 252	n = 79	
Female sex, %	59	74	44	29	<0.001
Age, years	59.3 ± 7.1	58.5 ± 7.3	59.9 ± 6.3	60.4 ± 7.9	0.006
Body mass index, kg/m²	23.0 ± 3.3	22.0 ± 3.0	23.9 ± 2.9	25.2 ± 3.5	<0.001
Epworth Sleepiness Scale	8.8 ± 4.4	8.6 ± 4.4	8.9 ± 4.5	9.4 ± 4.2	0.285
Snoring during asleep, %	42	30	52	75	<0.001
Cessation of breathing during sleep, %	4	1	6	11	<0.001
Blood pressure category, %					<0.001
Optimal	51	58	46	30	
Normal	20	17	23	20	
High-normal blood pressure	14	13	15	19	
Hypertension	15	12	16	30	
Hyperlipidemia	42	45	37	42	0.139
Diabetes mellitus	8	6	8	17	0.003
Smoking status, %					<0.001
Current	16	14	19	22	
Quit	16	11	22	27	
Never	67	75	59	52	
Current drinkers, %	50	57	39	43	<0.001
Total cholesterol, mg/dL	209.6 ± 32.7	213.1 ± 31.9	205.0 ± 32.4	209.1 ± 31.5	0.072
HDL cholesterol, mg/dL	61.7 ± 15.8	64.4 ± 16.5	59.6 ± 14.3	56.1 ± 15.1	<0.001
HbA1c, %	5.9 ± 0.8	5.8 ± 0.6	5.9 ± 0.8	6.1 ± 1.1	0.001
hANP, pg/mL	12.2 ± 11.3	11.5 ± 8.7	13.5 ± 14.7	12.0 ± 12.4	0.099
BNP, pg/mL	23.5 ± 33.0	22.5 ± 32.7	22.8 ± 29.8	26.8 ± 31.3	0.508

ODI, oxygen desaturation index; HDL, high density-lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HANP, atrial natriuretic peptide; BNP, brain natriuretic peptide.

Table 2

Confounders-adjusted mean and 95% confidence interval of human atrial natriuretic (ANP) and brain natriuretic (BNP) peptide.

	3%ODI < 5	3%ODI = 5–15		3%ODI > 15	
	n = 435	n = 252	pᵃ	n = 79	pᵃ
hANP					
Model 1ᵇ	11.1 (10.0–12.3)	13.6 (12.1–15.1)	0.011	12.8 (10.2–15.4)	0.249
Model 2ᶜ	11.0 (9.9–12.2)	13.7 (12.2–15.2)	0.006	13.1 (10.5–15.8)	0.160
Model 3ᵈ	11.0 (9.9–12.1)	13.7 (12.2–15.2)	0.006	13.1 (10.5–15.8)	0.161
BNP					
Model 1ᵇ	21.5 (18.5–24.4)	23.4 (19.5–27.3)	0.451	28.1 (21.2–35.0)	0.087
Model 2ᶜ	21.2 (18.2–24.2)	23.7 (19.8–27.6)	0.332	28.9 (21.9–36.0)	0.054
Model 3ᵈ	21.1 (18.1–24.1)	23.9 (20.0–27.8)	0.285	28.6 (21.6–35.7)	0.061

ᵃ vs. 3%ODI < 5.
ᵇ Adjusted for age and sex.
ᶜ Adjusted for age, sex, and body mass index.
ᵈ Adjusted for age, sex, body mass index, smoking status, drinking status, hypertension, diabetes mellitus, and high density-lipoprotein cholesterol.

presence and severity of SDB in this study. Therefore, the presence and severity of SDB may be underestimated with such equipment. Second, the equipment used in this study cannot distinguish obstructive sleep apnea (OSA) from central sleep apnea (CSA). Third, men and women were not analyzed separately in the present study due to the relatively small sample size. Fourth, since this was a cross-sectional study, cause–effect reversal may have occurred. Further research is awaited.

In conclusion, the plasma hANP level was elevated in individuals with SDB among a large Japanese urban population.

References

[1] Kuroski-de Bold ML, de Bold AJ. Stretch-secretion coupling in atrial cardiocytes. Dissociation between atrial natriuretic factor release and mechanical activity. Hypertension 1991;18:III169–78.
[2] Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998;135:825–32.
[3] Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 2003;290:1906–14.
[4] Ichioka M, Hirata Y, Inase N, et al. Changes of circulating atrial natriuretic peptide and antidiuretic hormone in obstructive sleep apnea syndrome. Respiration 1992;59:164–8.
[5] Rao A, Georgiadou P, Francis DP, et al. Sleep-disordered breathing in a general heart failure population: relationships to neurohumoral activation and subjective symptoms. J Sleep Res 2006;15:81–8.
[6] Patwardhan AA, Larson MG, Levy D, et al. Obstructive sleep apnea and plasma natriuretic peptide levels in a community-based sample. Sleep 2006;29:1301–6.
[7] Kokubo Y, Kamide K, Okamura T, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. Hypertension 2008;52:652–9.
[8] Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105–87.
[9] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.
[10] Orban M, Bruce CJ, Pressman GS, et al. Dynamic changes of left ventricular performance and left atrial volume induced by the Mueller maneuver in healthy young adults and implications for obstructive sleep apnea, atrial fibrillation, and heart failure. Am J Cardiol 2008;102:1557–61.

Blood Pressure, Low-Density Lipoprotein Cholesterol, and Incidences of Coronary Artery Disease and Ischemic Stroke in Japanese: The Suita Study

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BACKGROUND

Blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) are risk factors for coronary artery disease (CAD) and ischemic stroke. However, the hazards of their coexistence are not fully understood in Asian populations. We investigated whether the relationship between BP and cardiovascular disease (CVD) outcomes are modified by LDL-C level in a Japanese population.

METHODS

Individuals aged 30–79 years (n = 5,151) were classified into 6 groups according to LDL-C levels (<140 and ≥140 mg/dL or lipid medication) and BP levels (optimal BP, prehypertension, and hypertension; reference: low LDL-C and optimal BP). Hazard ratios (HRs) were calculated after adjusting for age, high-density lipoprotein cholesterol, diabetes, smoking status, and alcohol consumption. The effect modification of LDL-C on BP–CVD association was assessed using likelihood ratio tests.

RESULTS

There were 264 CAD and 215 ischemic stroke events during 13 years of follow-up. With low LDL-C, the HRs of prehypertension and hypertension for CAD were 2.01 and 4.71, respectively. Similar trends of HRs were observed with high LDL-C (optimal BP = 2.09, prehypertension = 3.45, hypertension = 5.94). However, the HRs for ischemic stroke did not differ between normal and high LDL-C levels at the same BP level. The apparent effect modification of LDL-C was not observed in the BP–CVD association in either CAD (P = 0.48) or ischemic stroke (P = 0.39).

CONCLUSIONS

The HRs for CAD in prehypertensive and hypertensive groups were higher than those in the optimal BP group at the same LDL-C levels in a Japanese population; however, there was no statistical effect modification of LDL-C on the BP–CAD association.

Keywords: Asian; blood pressure; cohort study; coronary artery disease; hypertension; incidence; ischemic stroke; low-density lipoprotein cholesterol; Suita Study.

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Cardiovascular disease is a leading cause of mortality and morbidity in Asian countries.[1] Elevated blood pressure (BP)[1-5] and hypercholesterolemia[1,6-10] are well-established independent cardiovascular risk factors. Moreover, the combination of these risk factors is a better predictor of the risk of cardiovascular disease in Western populations.[11,12] In Japan, the Japan Lipid Intervention Trial (J-LIT) study showed that Japanese hypercholesterolemia patients with high systolic BP (SBP; ≥130 mm Hg) and high total cholesterol

levels (≥220 mg/dl) treated with low-dose simvastatin had an increased risk of cardiovascular disease events.[14] In Asia, the Asia Pacific Cohort Studies Collaborations (APCSC) demonstrated that the combination of high SBP (≥130 mm Hg) and high total cholesterol (≥212 mg/dl) increased the risks of fatal and nonfatal cardiovascular disease among both Western and Asian populations.[14] However, the J-LIT and APCSC studies have some drawbacks, including relatively short follow-up periods (mean follow-up period

of approximately 6 years) and lipid profiles based on total cholesterol and not low-density lipoprotein cholesterol (LDL-C). Furthermore, the J-LIT study was a patient-based clinical trial,[13] and the APCSC study[14] did not exclusively involve Asian populations, which have a higher incidence of stroke and lower incidence of coronary artery disease (CAD) than Western populations.[1]

The purpose of our study was to examine whether the relationship between BP and CVD outcomes (CAD and ischemic stroke) is modified by LDL-C levels in a community-based cohort study in a Japanese population.

METHODS

Population

The Suita Study, a cohort study evaluating cardiovascular disease risk in an urban Japanese population, was established in 1989. This cohort study has been extensively used to evaluate risk factors associated with the incidences of CAD and stroke.[4,15–18] The details of this study have been described previously.[4,15–18] Briefly, 6,483 men and women aged 30–79 years underwent a baseline survey at the National Cerebral and Cardiovascular Centre (Japan) between September 1989 and March 1994. Subjects older than 80 years were excluded because it remains unconfirmed whether LDL-C is a risk factor for cardiovascular disease in the elderly population (aged ≥80 years).[19] A total of 1,332 participants were excluded for the following reasons: history of CAD or stroke (n = 208); loss to follow-up (n = 535); lack of participation in the baseline survey (n = 78); nonfasting visit (n = 239); triglyceride level >400 mg/dl (n = 86); LDL-C ≤0 (n = 1); missing total cholesterol, high-density lipoprotein cholesterol (HDL-C), or triglyceride data (n = 30); aged ≥80 years (n = 12); and other missing data (n = 145). Therefore, data from the remaining 5,151 participants (men: n = 2,399; women: n = 2,752) were included in our analysis.

This study was approved by the institutional review board of the National Cerebral and Cardiovascular Centre. Informed consent was obtained from all participants by health professions at the baseline examination. The collected data were anonymized.

Baseline examination

Blood samples were collected at the National Cerebral and Cardiovascular Centre after the participants had fasted for at least 10 hours. The samples were immediately centrifuged, and a routine blood examination that included serum total cholesterol, HDL-C, triglyceride, and glucose levels was performed. LDL-C was estimated for both men and women using the Friedewald formula.[20] Participants with triglyceride levels >400 mg/dl were excluded because LDL-C estimates are inaccurate among such persons.[19,21,22]

BP was measured by well-trained physicians using a standard mercury sphygmomanometer. After the participant had been in the seated position for 5 minutes, BP was measured 3 times on the right arm, and the average of the second and third measurements was used in the analyses to avoid bias due to white coat hypertension. Because HbA1c data from

before 1995 were unavailable, diabetes was defined according to the American Diabetes Association 2013 guidelines as a fasting serum glucose level ≥126 mg/dl, the use of diabetes medication, or both.[23,24] Height and weight were measured while the subjects wore socks and light clothing. Public health nurses obtained information about smoking status, alcohol consumption, and medical history of the participants.

The information about smoking and alcohol consumption have been reported previously.[4,15–18] Well-trained nurses obtained information on smoking and alcohol consumption. Smoking status was classified as never, ex-smoker, or current smoker. If a participant responded yes to "current smoker," the number of cigarettes smoked per day was ascertained. Alcohol consumption was categorized as never drinker, ex-drinker, or current drinker (i.e., >1 time per week).

Endpoint determination

The endpoint determination in the Suita Study has been described previously.[4,15–18] The Suita Study is an ongoing cohort study, and the latest endpoint determination was performed on 31December 2007. The endpoints in our follow-up study were as follows: (i) the date of the first CAD or stroke event, (ii) the date of death, (iii) the date of leaving Suita City, and (iv) 31 December 2007.

The first step in the CAD and stroke survey involved checking the health status of all participants at biennial clinical visits every 2 years and through annual questionnaires sent by mail or administered by telephone. The second step involved the review of the in-hospital medical records of participants suspected of having had CAD or stroke; the reviews were performed by registered hospital physicians or research physicians blinded to the baseline information. The diagnosis of stroke was based on the US National Survey of Stroke criteria.[25] Stroke subtypes, including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, were diagnosed on the basis of computed tomography, magnetic resonance imaging, or autopsy results. Definite and probable acute myocardial infarction were defined according to the criteria of the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) Project.[26] In addition to acute myocardial infarction, the criteria for CAD diagnosis included sudden cardiac death within 24 hours from symptom onset or CAD followed by coronary artery bypass or angioplasty. Furthermore, myocardial infarction and stroke fatalities were recorded by searching for systematic death certificates.

Statistical analysis

BP was categorized into 3 groups; optimal BP (SBP <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg), prehypertension (SBP = 120–139 mm Hg, DBP = 80–89 mm Hg, or both), and hypertension (SBP ≥140 mm Hg, or DBP ≥90 mm Hg, or the use of antihypertensive agents). LDL-C was categorized into 2 groups; normal (LDL-C <140 mg/dl) or high (LDL-C ≥140 mg/dl or lipid medication) according to the diagnostic criteria for screening of the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases.[19]

This guideline has set the cutoff point of LDL-C to 140 mg/dl as diagnostic criteria of dyslipidemia. Using the abovementioned BP and LDL-C categories, combinations of BP and LDL-C (3×2 groups) were made to estimate hazard ratios (HRs) with optimal BP and normal LDL-C as the reference group. Analysis of variance and the Bonferroni test were used to compare continuous variables, and the χ^2 test was used to compare dichotomous variables.

Sex-stratified Cox proportional hazard models, accounting for different baseline hazards in men and women, were used to estimate the HRs of the combination of BP and LDL-C on cardiovascular disease outcomes. Age, HDL-C, smoking status, alcohol consumption, and diabetes were included in the models as confounders. For the primary analysis, HRs and 95% confidence intervals (CIs) were estimated for CAD and stroke events by analyzing BP as a categorical variable within each LDL-C group. Moreover, the association between BP and LDL-C was examined by comparing the HRs for CAD and stroke events across the 6 groups, adjusting for age, HDL-C, diabetes, smoking status, and alcohol consumption. The interaction between BP and LDL-C on cardiovascular outcomes was assessed using likelihood ratio tests.[27] The level of significance was set at $P < 0.05$. All statistical analyses were performed using STATA release 12 (Stata Corp LP, College Station, TX).

RESULTS

Overall, 5,151 individuals (men: n = 2,399; women: n = 2,752) were analyzed. Table 1 shows the baseline characteristics of groups with BP and LDL-C combination in men. In both LDL-C groups, men with hypertension had the highest mean age, body mass index, and fasting blood glucose, as well as the most cases of diabetes and medications. There were fewer current drinkers in the high LDL-C group than the normal LDL-C group ($P < 0.001$). Moreover, there were more current smokers in the normal LDL-C group than the high LDL-C group ($P < 0.001$).

Table 2 shows the means and prevalence of baseline characteristics with respect to BP and LDL-C groups in women. As with the men, in both LDL-C groups, women with hypertension had the highest mean age, body mass index, and fasting blood glucose, as well as the most cases of diabetes and medications. There were fewer current drinkers in the high LDL-C group than the normal LDL-C group ($P < 0.001$). Moreover, there were more current smokers in the normal LDL-C group than in high LDL-C group ($P < 0.001$).

The associations of alcohol consumption and smoking status with LDL-C levels were similar in both sexes. In addition, the rates of current smokers and drinkers were obviously higher in men than women (Tables 1 and 2).

During the 13-year follow-up (total = 67,287 person-years), 164 CAD cases (men: n = 110; women: n = 54) and 215 stroke cases (ischemic: n = 126; hemorrhagic: n = 48; subarachnoid hemorrhage: n = 22; and unclassified stroke: n = 19) were documented. The adjusted HRs for CAD in hypertension were highest in both the normal and the high LDL-C groups. The high HRs were observed as both BP and LDL-C upgraded in CAD (Figure 1). In

the high LDL-C group, the HRs of CAD with optimal BP, prehypertension, and hypertension were 2.09 (95% CI = 0.88–4.98), 3.45 (95% CI = 1.59–7.51), and 5.94 (95% CI = 2.88–12.27), respectively. In the normal LDL-C group, the HR of CAD with prehypertension (2.01; 95% CI = 0.92–4.42) was almost the same as those with optimal BP and high LDL-C, whereas the HR with hypertension (2.95; 95% CI = 1.45–5.9) was significantly higher (Figure 1). The HR for ischemic stroke was 2.70 (95% CI = 1.37–5.35) in the hypertension and normal LDL-C group and 2.95 (95% CI = 1.47–5.90) in the hypertension and high LDL-C group. No apparent interaction between BP and LDL-C was detected with either CAD ($P = 0.48$) or ischemic stroke ($P = 0.39$).

These results have almost no differences when medication use (lipid-lowering medicine and BP-lowering medicine) is not considered the BP and LDL classification.

DISCUSSION

This study showed that the HRs for CAD in prehypertensive and hypertensive groups were higher than those in the optimal BP group at the same LDL-C levels in the Japanese population; however, 95% CIs for these groups almost overlapped, and no apparent modification by LDL-C was observed in the BP–CVD relationship. Furthermore, the HRs for ischemic stroke were not different between normal and higher LDL-C levels at the same BP levels.

Our results support the results from the APCSC, which demonstrated that the combination of elevated BP and elevated total cholesterol increases the risks of fatal and nonfatal cardiovascular disease in Asian, Australian, and New Zealand populations.[14] The APCSC showed that cardiovascular disease events are particularly increased in individuals with SBP ≥130 mm Hg and the highest total cholesterol levels (≥212 mg/dl). Furthermore, the relative risk of cardiovascular disease events in individuals with an SBP of 130–144 mm Hg and total cholesterol levels of 212–241 mg/dl is similar to that of individuals with an SBP of 145–159 mm Hg and total cholesterol levels <212 mg/dl. The J-LIT study, which was an observational study among Japanese patients that investigated the relationship between total cholesterol and BP on cardiovascular disease, also found that the relative risk of cardiovascular disease events was significantly higher in patients with poorly controlled hypercholesterolemia patients (total cholesterol >220 mg/dl), prehypertension (SBP = 130–139 mm Hg; DBP = 80–89 mm Hg), and hypertension (SBP >140 mm Hg; DBP >90 mm Hg) compared with the reference group (SBP <130 mm Hg; DBP <80 mm Hg).[13] Thus, our findings are concordant with those of the APCSC and J-LIT studies. However, it should be emphasized that our study cohort consisted exclusively of a general Asian population in contrast with the APCSC. In addition, hypercholesterolemia patients in the J-LIT study were treated with low-dose simvastatin.

The HRs for ischemic stroke did not differ between the normal and high LDL-C groups at the same BP levels. However, most cohort studies in Japan report that total cholesterol and LDL-C are not risk factors for total stroke[28] despite their

Table 1. Baseline characteristics of women with respect to blood pressure and serum low-density lipoprotein categories in men

	Normal LDL-C						High LDL-C						P value
	Optimal BP		Prehypertension		Hypertension		Optimal BP		Prehypertension		Hypertension		
No.	543		593		491		232		269		271		
Age, y	49.5	(13.2)	54.8	(13.2)**	61.3	(11.4)**	52.4	(12.5)*	56.2	(11.5)**	60.7	(10.8)**	<0.001
Systolic blood pressure, mm Hg	107.6	(7.5)	126.1	(7.3)**	150.8	(17.6)**	108.3	(7.4)*	126.3	(7.7)**	149.3	(16)**	<0.001
Diastolic blood pressure, mm Hg	67.9	(7)	67.9	(7)**	90.1	(10.6)**	69.3	(6.3)	79.5	(6.8)**	90.1	(10.3)**	<0.001
LDL-C, mg/dl	108.7	(20.5)	109.2	(20.7)*	108.6	(21.6)**	159.9	(18.5)**	159.8	(19.4)**	161.5	(22.5)**	<0.001
Fasting blood glucose, mg/dl	96.5	(13)	100.6	(17.8)*	102.6	(19.4)**	98.0	(20.7)**	102.9	(22.7)**	104.2	(21.2)**	<0.001
Body mass index, kg/m²	21.8	(2.7)	22.7	(2.7)**	23.1	(3)**	22.6	(2.5)*	23.3	(2.6)**	23.8	(2.7)**	<0.001
Diabetes, %	3.5		5.4		7.9		3.4		4.8		10		0.004
Medication for hypertension, %	0		0		49.7		0		0		34.3		
Medication for hypercholesterolemia, %	0		0		0		2.6		5.6		8.5		
Medication for diabetes, %	0.9		2		2		1.3		1.9		5.2		0.001
Smoking, %													<0.001
Current smoker	60.6		49.7		43.6		32.8		44.2		41.7		
Ex-smoker	22.7		29.3		36.9		67.8		32.7		40.6		
Never smoker	16.8		20.9		19.6		43.3		23		17.7		
Alcohol consumption, %													<0.001
Current drinker	74.2		78.8		79.6		65.1		72.9		73.1		
Ex-drinker	2.2		3.9		3.1		3.9		4.8		6.6		
Never drinker	23.6		17.4		17.3		31		22.3		20.3		

Age, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose, and body mass index were analyzed by analysis of variance. The percentages of diabetes, medication for hypertension, medication for hypercholesterolemia, medication for diabetes, smoking, and alcohol consumption were analyzed by the χ^2 test. Data are expressed as mean (SD) or percentages. Optimal BP: systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg. Prehypertension: systolic blood pressure 120–139 mm Hg or diastolic blood pressure 80–89 mm Hg. Hypertension: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication. Normal LDL-C: fasting LDL-C <140 mg/dl. High LDL-C: fasting LDL-C ≥140 mg/dl or the use of medication for hypercholesterolemia. Diabetes: fasting plasma glucose ≥126 mg/dl or the use of antidiabetic medication.

Abbreviations: BP, blood pressure; LDL-C, low-density lipoprotein cholesterol.

*P < 0.05, **P < 0.001: Bonferroni test (with normal LDL-C and optimal BP as the reference).

Table 2. Baseline characteristics of women with respect to blood pressure and serum LDL-C categories in women

	Normal LDL-C						High LDL-C						
	Optimal BP		Prehypertension		Hypertension		Optimal BP		Prehypertension		Hypertension		P value
No.	837		427		311		364		403		410		
Age, y	44.9	(11.3)	53.2	(12.4)**	61.9	(10.4)**	53.3	(10.8)**	57.9	(10.1)**	62.5	(8.9)**	<0.001
Systolic blood pressure, mm Hg	104.8	(8.1)	126.3	(7.1)**	151.8	(16.9)**	106.9	(7.5)	127.5	(6.8)**	151.4	(16.6)**	<0.001
Diastolic blood pressure, mm Hg	66	(6.6)	77.4	(6.8)**	86.3	(11.2)**	67	(6.8)	77.7	(7)**	86.8	(11.3)**	<0.001
LDL-C, mg/dl	108.9	(19.4)	114.2	(18.2)	115.4	(18.1)	163.3	(23.6)**	167.2	(26.6)**	168	(26.3)**	<0.001
Fasting blood glucose, mg/dl	91.3	(8.3)	96.2	(14.7)**	100.1	(20.5)**	93.5	(11.4)	98.6	(22.7)**	101.9	(18.3)**	<0.001
Body mass index, kg/m^2	20.9	(2.65)	22.2	(3.03)**	23.2	(3.81)**	21.7	(2.82)*	22.9	(3.08)**	23.8	(3.43)**	<0.001
Diabetes, %	1.2		2.3		6.1		1.4		4.5		6.3		<0.001
Medication for hypertension, %	0		0		37.6		0		0		39.3		
Medication for hypercholesterolemia, %	0		0		0		3.6		5.2		7.6		
Medication for diabetes, %	0.6		0.9		2.3		0.5		1.5		2		0.09
Smoking, %													<0.001
Current smoker	16.4		9.8		8.7		13.7		10.2		7.6		
Ex-smoker	3.8		3.5		2.3		2.7		3.2		5.6		
Never smoker	79.8		86.7		89.1		83.5		86.6		86.8		
Alcohol consumption, %													<0.001
Current drinker	41.1		33		29.3		26.1		29.3		27.8		
Ex-drinker	2		1.6		1.9		1.6		1.7		1.7		
Never drinker	56.9		65.3		68.8		72.3		69		70.5		

Age, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose, and body mass index were analyzed by analysis of variance. The percentages of diabetes, medication for hypertension, medication for hypercholesterolemia, medication for diabetes, smoking, and alcohol consumption were analyzed by the χ^2 test. Data are expressed as mean (SD) or percentages. Optimal BP: systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg. Prehypertension: systolic blood pressure 120–139 mm Hg or diastolic blood pressure 80–89 mm Hg. Hypertension: systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication. Normal LDL-C: fasting LDL-C <140 mg/dl. High LDL-C: fasting LDL-C ≥140 mg/dl or the use of medication for hypercholesterolemia. Diabetes: fasting plasma glucose ≥126 mg/dl or the use of antidiabetic medication. When mean body mass index was examined in women, there were 836 women with normal blood pressure and normal LDL-C.

Abbreviation: BP, blood pressure.

*P < 0.05, **P < 0.001: Bonferroni test (with normal LDL-C and optimal BP as the reference).

LDL-C level	Blood pressure level		Hazard ratio (95% CI)	Incidents
Coronary artery disease				
Normal	Optimal BP		1.00	9
	Prehypertension		2.01 (0.92, 4.42)	21
	Hypertension		4.71 (2.28, 9.74)	49
High	Optimal BP		2.09 (0.88, 4.98)	12
	Prehypertension		3.45 (1.59, 7.51)	23
	Hypertension		5.94 (2.88, 12.27)	50
Ischemic stroke				
Normal	Optimal BP		1.00	11
	Prehypertension		1.69 (0.82, 3.48)	23
	Hypertension		2.70 (1.37, 5.35)	41
High	Optimal BP		0.47 (0.13, 1.69)	3
	Prehypertension		1.36 (0.60, 3.11)	12
	Hypertension		2.95 (1.47, 5.90)	36

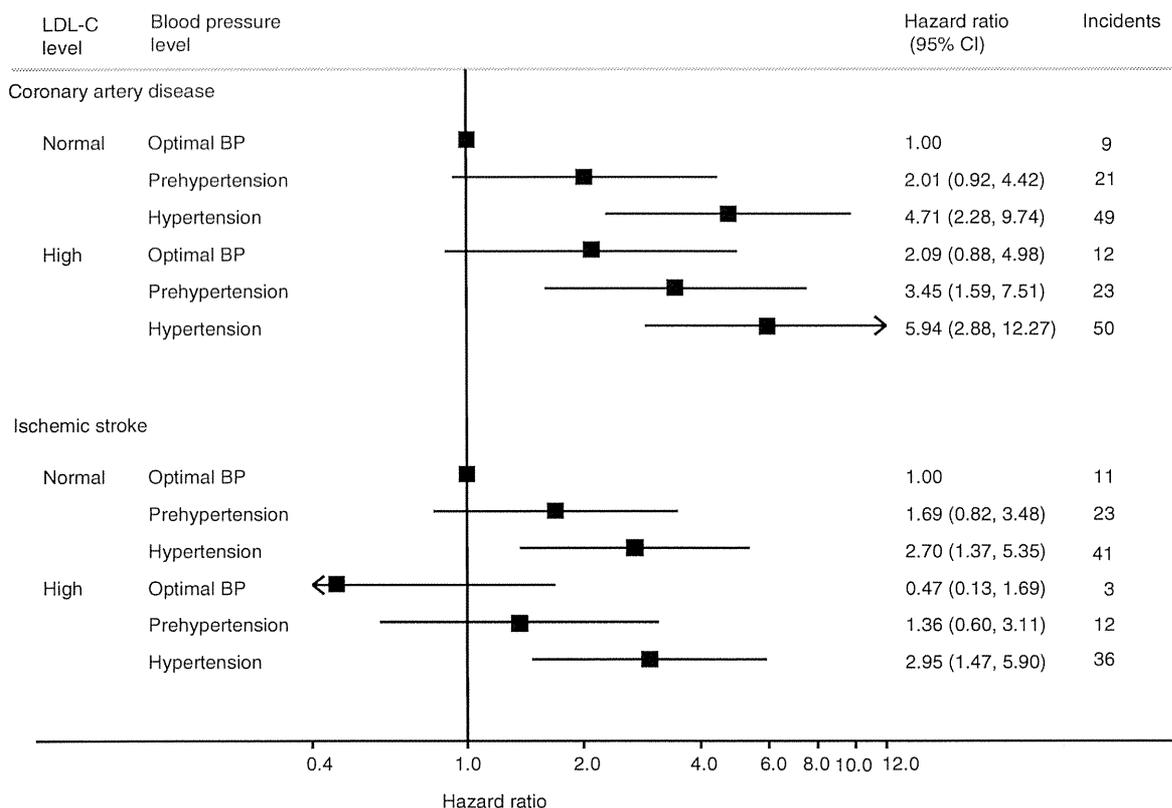Hazard ratio: 0.4 1.0 2.0 4.0 6.0 8.0 10.0 12.0

Figure 1. Hazard ratios (HRs) for coronary artery disease and stroke by blood pressure (BP) group with respect to low-density lipoprotein cholesterol (LDL-C; mg/dl) categories adjusted for age, high-density lipoprotein cholesterol, diabetes, smoking status, and alcohol consumption. ■ indicate HR estimates; ▬ indicate 95% confidence intervals (CIs) by Cox proportional hazard model stratified by sex. The reference group had optimal BP (systolic BP <120 mm Hg and diastolic BP <80 mm Hg) and normal LDL-C levels (LDL-C <140 mg/dl). $P = 0.48$ for CAD; $P = 0.39$ for ischemic stroke.

weak association with ischemic stroke.[29] Given these contradictory results between clinical trials and cohort studies, the effects of statins on the prevention of stroke should be interpreted cautiously. Several studies report cholesterol-lowering statins are beneficial for the prevention of stroke in hypertensive patients.[30,31] The post hoc analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study revealed that pravastatin effectively reduced the incidence of cardiovascular disease, particularly ischemic stroke, in individuals with both hypertension and mildly elevated cholesterol.[30] Meanwhile, the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm showed that atorvastatin significantly reduces CAD, stroke, and cardiovascular disease even in hypertensive patients without dyslipidemia.[31] Although there have been numerous clinical trials for statin therapy, the primary endpoint of these studies was CAD, with ischemic stroke as the secondary endpoint. Furthermore, statins have pleiotropic effects that help prevent cardiovascular disease, including anti-inflammatory effects, improved vascular endothelial function, and plaque stabilization. These factors may explain the significant discrepancy between cohort studies and clinical trials with respect to the efficacy of statins in stroke prevention. Therefore, further investigation is required to clarify

the role of statin therapy in stroke prevention. However, BP management should be the first priority in ischemic stroke prevention irrespective of LDL-C level.

Our study used a stratified Cox model that included 3 BP and 2 LDL-C categories, as well as their interaction terms and confounders. This combined model is statistically appropriate for the investigation of interactions between risk factors and disease outcomes. Furthermore, LDL-C and hypertension, which were the main targets of this study, and the abovementioned confounding factors encompass all major risk factors in the Framingham risk score,[22] the European SCORE chart,[21] and the Japanese Atherosclerosis Society risk chart[19] for predicting future coronary events.

We found that the HRs for CAD in high LDL-C group were higher than those in normal LDL-C at the same BP levels in the Japanese population. However, the apparent effect modification of LDL-C was not detected in the relation between BP and CAD. There are 3 possibilities to explain these results; no interaction, low statistical power, and bias. Our results suggested that BP and LDL-C were mutually independent risk factors and no interaction exist between them. This result was not as similar to other previous studies, and explanations were needed to claim the independence. A second possibility is that lack of statistical power induces

the results; a very small number of events was assigned in each category. The third possibility is that the single assessment of BP and LDL-C at the baseline survey and the fact that we did not evaluate the longitudinal trend for each risk factor may have underestimated the relationship between these conditions and CAD because of regression dilution bias.[32] All of these misclassification diluted the HRs and made the effect modification obscure. We are not quite sure which is the correct answer for this issue, but we believe our description of the BP, LDL-C, and CAD relationship among an Asian population gives important insight to future epidemiological studies.

In conclusion, to the best of our knowledge, this study is the first epidemiological study to examine the combined association between BP and LDL-C on the incidences of cardiovascular disease subtypes in an Asian population only. The results show that risk for CAD due to hypertension or prehypertension in the high LDL-C group was higher than those in the normal LDL-C group, although there were no statistical interaction between BP and LDL-C. Accordingly, BP and LDL-C should be managed for the early prevention of CAD in Japanese and other Asian individuals with hypertension, prehypertension, and high LDL-C levels. Furthermore, large-scale epidemiological studies should carefully assess the association between BP and LDL-C with the incidence of cardiovascular disease subtypes among Asian populations.

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DISCLOSURE

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REFERENCES

1. Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* 2008; 118:2702–2709.
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360:1903–1913.
3. Lawes CM, Bennett DA, Parag V, Woodward M, Whitlock G, Lam TH, Suh I, Rodgers A; Asia Pacific Cohort Studies Collaboration. Blood pressure indices and cardiovascular disease in the Asia Pacific region: a pooled analysis. *Hypertension* 2003; 42:69–75.
4. Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y. Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study. *Hypertension* 2008; 52:652–659.
5. Fujiyoshi A, Ohkubo T, Miura K, Murakami Y, Nagasawa SY, Okamura T, Ueshima H; Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. *Hypertens Res* 2012; 35:947–953.
6. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007; 370:1829–1839.
7. Okamura T. Dyslipidemia and cardiovascular disease: a series of epidemiologic studies in Japanese populations. *J Epidemiol* 2010; 20:259–265.
8. Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, MacMahon S, Woodward M; Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol* 2003; 32:563–572.
9. Patel A, Woodward M, Campbell DJ, Sullivan DR, Colman S, Chalmers J, Neal B, MacMahon S. Plasma lipids predict myocardial infarction, but not stroke, in patients with established cerebrovascular disease. *Eur Heart J* 2005; 26:1910–1915.
10. Nagasawa SY, Okamura T, Iso H, Tamakoshi A, Yamada M, Watanabe M, Murakami Y, Miura K, Ueshima H; Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Relation between serum total cholesterol level and cardiovascular disease stratified by sex and age group: a pooled analysis of 65 594 individuals from 10 cohort studies in Japan. *J Am Heart Assoc* 2012; 1:e001974.
11. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med* 1992; 152:56–64.
12. Marmot M, Elliott P. *Coronary Heart Disease Epidemiology*. 2nd ed. Oxford University Press: New York, 2005.
13. Shimamoto K, Kita T, Mabuchi H, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Itakura H; J-LIT Study Group. The risk of cardiovascular events in Japanese hypertensive patients with hypercholesterolemia: sub-analysis of the Japan Lipid Intervention Trial (J-LIT) Study, a large-scale observational cohort study. *Hypertens Res* 2005; 28:879–887.
14. Asia Pacific Cohort Studies Collaboration. Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region. *Circulation* 2005; 112:3384–3390.
15. Higashiyama A, Wakabayashi I, Ono Y, Watanabe M, Kokubo Y, Okayama A, Miyamoto Y, Okamura T. Association with serum gamma-glutamyltransferase levels and alcohol consumption on stroke and coronary artery disease: the Suita study. *Stroke* 2011; 42:1764–1767.
16. Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Ono Y, Nishimura K, Okayama A, Miyamoto Y. A revised definition of the metabolic syndrome predicts coronary artery disease and ischemic stroke after adjusting for low density lipoprotein cholesterol in a 13-year cohort study of Japanese: the suita study. *Atherosclerosis* 2011; 217:201–206.
17. Watanabe M, Okamura T, Kokubo Y, Higashiyama A, Okayama A. Elevated serum creatine kinase predicts first-ever myocardial infarction: a 12-year population-based cohort study in Japan, the Suita study. *Int J Epidemiol* 2009; 38:1571–1579.
18. Kokubo Y, Okamura T, Watanabe M, Higashiyama A, Ono Y, Miyamoto Y, Furukawa Y, Kamide K, Kawanishi K, Okayama A, Yoshimasa Y. The combined impact of blood pressure category and glucose abnormality on the incidence of cardiovascular diseases in a Japanese urban cohort: the suita study. *Hypertens Res* 2010; 33:1238–1243.
19. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K; Japan Atherosclerosis Society. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan—2012 version. *J Atheroscler Thromb* 2013; 20:517–523.
20. Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the ultracentrifuge. *Clin Chem* 1972; 18:499–502.
21. European Association for Cardiovascular Prevention & Rehabilitation1, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR,

Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008–2010 and 2010–2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011; 32:1769–1818.

22. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143–3421.

23. American Diabetes Association. Executive summary: standards of medical care in diabetes—2013. *Diabetes Care* 2013; 36:S4–S10.

24. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013; 36:S67–S74.

25. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical Findings. *Stroke* 1981; 12:I13–I44.

26. World Health Organization. *Document for Meeting of MONICA Principal Investigators.* WHO: Geneva, Switzerland, 1986.

27. Woodward M. *Epidemiology: Study Design and Data Analysis.* 2nd ed. Chapman & Hall/CRC Press, Boca Raton, FL, 2005.

28. Tanaka T, Okamura T. Blood cholesterol level and risk of stroke in community-based or worksite cohort studies: a review of Japanese cohort studies in the past 20 years. *Keio J Med* 2012; 61:79–88.

29. Amarenco P, Steg PG. The paradox of cholesterol and stroke. *Lancet* 2007; 370:1803–1804.

30. Kushiro T, Mizuno K, Nakaya N, Ohashi Y, Tajima N, Teramoto T, Uchiyama S, Nakamura H; Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study Group. Pravastatin for cardiovascular event primary prevention in patients with mild-to-moderate hypertension in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study. *Hypertension* 2009; 53:135–141.

31. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361:1149–1158.

32. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335:765–774.