Table 1. Sex-Specific Baseline Characteristics According to the Keith-Wagener-Barker Classification of Funduscopy Among 29 917 Men and 57 973 Women in Ibaraki, Japan, 1993

	Normal	Grade 1	Grade 2	*P* for Difference*
Men				
Participants, n	22 444	6117	1356	
Age, y	58.5±10.1	64.7±7.9	66.2±7.3	<0.001
Body mass index, kg/m^2	23.3±2.9	23.3±3.1	23.5±3.0	0.050
Systolic blood pressure, mm Hg	133.7±16.6	142.5±17.0	151.2±18.2	<0.001
Diastolic blood pressure, mm Hg	80.0±10.3	83.1±10.8	88.0±11.9	<0.001
Antihypertensive medication use, %	15.3	29.5	43.7	<0.001
Serum total cholesterol level, mmol/L	5.0±0.9	5.0±0.9	4.9±0.9	<0.001
Serum high-density lipoprotein cholesterol level, mmol/L	1.4±0.4	1.4±0.4	1.4±0.4	<0.001
Antidyslipidemic medication use, %	1.1	1.3	1.8	0.063
Diabetes mellitus, %	5.2	6.3	8.3	<0.001
Antidiabetic medication use, %	3.3	4.2	7.2	<0.001
Atrial fibrillation, %	0.5	1.0	1.2	<0.001
ST-T abnormality, %	1.5	2.1	4.1	<0.001
Smoking status, %				
Never smoker	22.1	21.8	23.1	<0.001
Ex-smoker	25.4	30.0	30.1	
Currently smoking <20 cigarettes/d	14.5	17.8	18.4	
Currently smoking ≥20 cigarettes/d	38.0	30.4	28.4	
Alcohol intake, %				
Never	34.2	34.2	29.4	<0.001
Sometimes	14.2	12.8	12.0	
Almost every day <44 g/d	22.6	23.6	25.1	
Almost every day ≥44 g/d	29.0	29.4	33.5	
Women				
Participants, n	45 821	9939	2213	
Age, y	55.8±10.0	63.7±8.2	65.0±8.0	<0.001
Body mass index, kg/m^2	23.5±3.2	24.0±3.3	24.5±3.4	<0.001
Systolic blood pressure, mm Hg	129.1±17.1	139.9±16.9	148.6±17.5	<0.001
Diastolic blood pressure, mm Hg	76.7±10.2	80.9±10.4	85.5±11.5	<0.001
Antihypertensive medication use, %	14.5	33.5	50.0	<0.001
Serum total cholesterol level, mmol/L	5.3±0.9	5.5±0.9	5.5±0.9	<0.001
Serum high-density lipoprotein cholesterol level, mmol/L	1.5±0.4	1.4±0.4	1.4±0.3	<0.001
Antidyslipidemic medication use, %	2.8	4.3	4.8	<0.001
Diabetes mellitus, %	2.3	3.7	5.2	<0.001
Antidiabetic medication use, %	1.8	2.8	4.9	<0.001
Atrial fibrillation, %	0.1	0.2	0.3	0.030
ST-T abnormality, %	1.8	3.3	6.4	<0.001
Smoking status, %				
Never smoker	94.2	95.2	94.4	<0.001
Ex-smoker	0.7	0.7	0.9	
Currently smoking <20 cigarettes/d	3.2	3.0	3.2	
Currently smoking ≥20 cigarettes/d	1.8	1.1	1.5	
Alcohol intake, %				
Never	89.9	91.6	92.6	<0.001
Sometimes	6.5	5.1	3.9	
Almost every day <44 g/d	3.1	3.0	3.1	
Almost every day ≥44 g/d	0.5	0.4	0.3	

*Calculated by ANOVA for age, body mass index, systolic blood pressure, diastolic blood pressure, serum total cholesterol level, and serum high-density lipoprotein cholesterol level and by χ^2 text for antihypertensive medication use, antidyslipidemic medication use, diabetes mellitus, antidiabetic medication use, atrial fibrillation, ST-T abnormality, smoking status, and alcohol intake. Values are mean±SD when appropriate.

Table 2. Hazard Ratios of All-Cause and Cause-Specific Mortality According to the Keith-Wagener-Barker Classification of Ophthalmoscopy Among 29 917 Men and 57 973 Women in Ibaraki, Japan, 1993–2008

	Normal	Grade 1	Grade 2	*P* for Trend*
Men				
Person-years	311 233	79 764	17 011	
All-cause				
Deaths, n	4487	1977	522	
Death rate (per 100 000 person-y)	1442	2479	3069	
Age-adjusted HR	1	1.12	1.26	<0.001
95% CI		1.07–1.19	1.15–1.38	
Multivariable HR†	1	1.09	1.17	<0.001
95% CI		1.04–1.15	1.06–1.28	
Total cardiovascular disease				
Deaths, n	1059	580	155	
Death rate (per 100 000 person-y)	340	727	911	
Age-adjusted HR	1	1.34	1.50	<0.001
95% CI		1.21–1.48	1.26–1.77	
Multivariable HR†	1	1.24	1.23	<0.001
95% CI		1.12–1.38	1.03–1.47	
Total stroke				
Deaths, n	480	279	79	
Death rate (per 100 000 person-y)	154	350	464	
Age-adjusted HR	1	1.39	1.63	<0.001
95% CI		1.20–1.61	1.29–2.08	
Multivariable HR†	1	1.31	1.38	<0.001
95% CI		1.13–1.53	1.08–1.77	
Cerebral infarction				
Deaths, n	304	182	58	
Death rate (per 100 000 person-y)	98	228	341	
Age-adjusted HR	1	1.32	1.70	<0.001
95% CI		1.10–1.59	1.28–2.26	
Multivariable HR†	1	1.25	1.45	0.003
95% CI		1.04–1.51	1.08–1.94	
Intracerebral hemorrhage				
Deaths, n	122	67	17	
Death rate (per 100 000 person-y)	39	84	100	
Age-adjusted HR	1	1.44	1.56	0.011
95% CI		1.06–1.95	0.93–2.60	
Multivariable HR†	1	1.36	1.29	0.082
95% CI		1.00–1.84	0.76–2.18	
Ischemic heart disease				
Deaths, n	310	157	43	
Death rate (per 100 000 person-y)	100	197	253	
Age-adjusted HR	1	1.30	1.51	0.001
95% CI		1.07–1.58	1.10–2.09	
Multivariable HR†	1	1.17	1.18	0.126
95% CI		0.96–1.42	0.84–1.64	

(*Continued*)

Table 2. Continued

	Normal	Grade 1	Grade 2	*P* for Trend*
Women				
Person-years	657 768	139 730	30 227	
All-cause				
Deaths, n	3836	1610	477	
Death rate (per 100 000 person-y)	1233	2018	2804	
Age-adjusted HR	1	1.05	1.33	<0.001
95% CI		0.99–1.11	1.21–1.47	
Multivariable HR†	1	1.02	1.23	0.001
95% CI		0.96–1.08	1.11–1.35	
Total cardiovascular disease				
Deaths, n	1107	583	203	
Death rate (per 100 000 person-y)	356	731	1193	
Age-adjusted HR	1	1.19	1.71	<0.001
95% CI		1.07–1.32	1.47–1.99	
Multivariable HR†	1	1.12	1.44	<0.001
95% CI		1.01–1.24	1.24–1.68	
Total stroke				
Deaths, n	499	299	105	
Death rate (per 100 000 person-y)	160	375	617	
Age-adjusted HR	1	1.38	2.00	<0.001
95% CI		1.19–1.59	1.61–2.47	
Multivariable HR†	1	1.30	1.70	<0.001
95% CI		1.12–1.50	1.36–2.11	
Cerebral infarction				
Deaths, n	233	151	59	
Death rate (per 100 000 person-y)	75	189	347	
Age-adjusted HR	1	1.30	2.06	<0.001
95% CI		1.06–1.60	1.55–2.75	
Multivariable HR†	1	1.27	1.93	<0.001
95% CI		1.03–1.56	1.44–2.59	
Intracerebral hemorrhage				
Deaths, n	140	76	30	
Death rate (per 100 000 person-y)	45	95	176	
Age-adjusted HR	1	1.35	2.23	<0.001
95% CI		1.02–1.80	1.50–3.33	
Multivariable HR†	1	1.24	1.77	0.006
95% CI		0.93–1.66	1.17–2.68	
Ischemic heart disease				
Deaths, n	283	123	39	
Death rate (per 100 000 person-y)	91	154	229	
Age-adjusted HR	1	0.98	1.28	0.370
95% CI		0.79–1.21	0.91–1.79	
Multivariable HR†	1	0.92	1.07	0.901
95% CI		0.74–1.14	0.76–1.51	

HR indicates hazard ratio; CI, confidence interval.

*Calculated by Cox proportional hazard models with continuous variables of the Keith-Wagener-Barker classification.

†Adjusted for age, body mass index, systolic blood pressure, antihypertensive medication use (yes or no), serum total cholesterol level, serum high-density lipoprotein cholesterol level, antidyslipidemic medication use (yes or no), blood glucose level (normal, prediabetes, and diabetes mellitus), antidiabetic medication use (yes or no), atrial fibrillation (yes or no), ST-T abnormality (yes or no), smoking status (never smoker, ex-smoker, currently smoking <20 cigarettes a day, currently smoking ≥20 cigarettes a day), and alcohol intake (never, sometimes, <44 g/d almost every day, and ≥44 g/d almost every day).

Table 3. Multivariable Hazard Ratios of All-Cause and Cause-Specific Mortality According to the Keith-Wagener-Barker Classification of Ophthalmoscopy, Stratified by Hypertensive Status in Ibaraki, Japan, 1993–2008

	Normal	Grade 1	Grade 2	*P* for Trend*
Men				
Hypertensives				
Person-years	147 065	56 191	15 094	
All-cause				
Deaths, n	2683	1478	449	
Multivariable HR†	1	1.10	1.11	0.002
95% CI		1.04–1.18	1.01–1.23	
Total cardiovascular disease				
Deaths, n	710	466	131	
Multivariable HR†	1	1.27	1.14	0.003
95% CI		1.13–1.43	0.94–1.38	
Total stroke				
Deaths, n	318	223	68	
Multivariable HR†	1	1.36	1.32	0.001
95% CI		1.14–1.62	1.01–1.73	
Ischemic heart disease				
Deaths, n	212	127	35	
Multivariable HR†	1	1.17	1.03	0.385
95% CI		0.93–1.46	0.71–1.49	
Nonhypertensives				
Person-years	164 168	23 573	1917	
All-cause				
Deaths, n	1804	499	73	
Multivariable HR†	1	1.05	1.56	0.007
95% CI		0.95–1.16	1.23–1.98	
Total cardiovascular disease				
Deaths, n	349	114	24	
Multivariable HR†	1	1.11	2.30	
95% CI		0.90–1.38	1.51–3.51	0.004
Total stroke				
Deaths, n	162	56	11	
Multivariable HR†	1	1.14	2.09	0.058
95% CI		0.83–1.55	1.12–3.90	
Ischemic heart disease				
Deaths, n	98	30	8	
Multivariable HR†	1	1.12	2.96	0.046
95% CI		0.74–1.70	1.41–6.20	
Women				
Hypertensives				
Person-years	244 275	93 560	26 295	
All-cause				
Deaths, n	2164	1190	423	
Multivariable HR†	1	1.03	1.20	0.004
95% CI		0.96–1.10	1.08–1.34	

(*Continued*)

Table 3. Continued

	Normal	Grade 1	Grade 2	*P* for Trend*
Total cardiovascular disease				
Deaths, n	730	461	179	
Multivariable HR†	1	1.13	1.41	<0.001
95% CI		1.00–1.27	1.19–1.66	
Total stroke				
Deaths, n	325	236	92	
Multivariable HR†	1	1.30	1.64	<0.001
95% CI		1.10–1.54	1.29–2.07	
Ischemic heart disease				
Deaths, n	184	98	36	
Multivariable HR†	1	0.96	1.12	0.782
95% CI		0.75–1.23	0.78–1.60	
Nonhypertensives				
Person-years	413 493	46 170	3932	
All-cause				
Deaths, n	1672	420	66	
Multivariable HR†	1	1.00	1.39	0.175
95% CI		0.89–1.11	1.08–1.78	
Total cardiovascular disease				
Deaths, n	377	122	24	
Multivariable HR†	1	1.08	1.68	0.049
95% CI		0.88–1.34	1.11–2.56	
Total stroke				
Deaths, n	174	63	13	
Multivariable HR†	1	1.25	2.15	0.001
95% CI		0.93, 1.68	1.21–3.83	
Ischemic heart disease				
Deaths, n	99	25	3	
Multivariable HR†	1	0.83	0.74	0.356
95% CI		0.53–1.30	0.23–2.35	

HR indicates hazard ratio; CI, confidence interval.

*Calculated by Cox proportional hazard models with continuous variables of the Keith-Wagener-Barker classification.

†Adjusted for age, body mass index, systolic blood pressure, antihypertensive medication use (yes or no), serum total cholesterol level, serum high-density lipoprotein cholesterol level, antidyslipidemic medication use (yes or no), blood glucose level (normal, prediabetes, and diabetes mellitus), antidiabetic medication use (yes or no), atrial fibrillation (yes or no), ST-T abnormality (yes or no), smoking status (never smoker, ex-smoker, currently smoking <20 cigarettes a day, currently smoking ≥20 cigarettes a day), and alcohol intake (never, sometimes, <44 g/d almost every day, and ≥44 g/d almost every day).

findings regarding the association between hypertensive retinopathy and risk for stroke mortality.

The potential mechanism of the independent association between hypertensive retinopathy and stroke disease is unclear. However, a significant association between "masked hypertension" and risk of cardiovascular mortality and stroke incidence has been reported.[18] Masked hypertension, which may be considered nonhypertension, may yield both hypertensive retinopathy and cardiovascular disease. Retinal arteriolar narrowing has been shown to precede the development of hypertension, which was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the combination of a self-reported diagnosis of high blood pressure and use of antihypertensive drugs.[19] Hypertensive retinopathy may predict future hypertension, and future hypertension may lead to cardiovascular disease. Ophthalmoscopy may identify masked hypertension or future hypertension among a normotensive population. Furthermore, retinal microvascular changes have been reported to be associated with future cerebral ventricular enlargement after adjustment for 6-year mean arterial blood pressure.[20]

The strength of the present study is the use of a large population-based cohort in which sex-stratified and cause-specific analyses were available, compared with previous studies.[5,9–17] In addition, all blood samples were measured by the same device, reagents, and quality control program.

On the other hand, our study had several limitations. First, we did not have incidence data for cardiovascular disease. Previous studies, however, provided evidence that

death certificate diagnosis of stroke subtypes is valid as a result of the high prevalence of computed tomography scans or magnetic resonance imaging use in hospitals in Japan.[21,22] Moreover, in the present study sample, a validation study confirmed the validity of stroke.[22,23] In addition, previous studies reported that three fourths of death certificate diagnoses of ischemic heart disease have been found to be correct in Japan.[24,25] Second, subjects of this study were participants of health checkup for residents with an ≈40% response rate, so a "healthy" participant effect cannot be negated. Third, direct ophthalmoscopy was not performed to identify the grade of retinopathy. Retinopathy beyond the 45 ° photograph might have been missed. However, the nonmydriatic camera is the preferred method of screening because retinal photography with interpretation by an ophthalmologist is more sensitive than direct ophthalmoscopy by general physicians.[26] Fourth, despite a previous study that provided the predictive value of arteriovenous nicking and focal arteriolar narrowing,[10] those variables were not examined in the present study. Finally, parental history of cardiovascular disease was not available. Further study is warranted to clarify the generalizability and effect of family history of cardiovascular disease.

Conclusion

Even a mild degree of hypertensive retinopathy classified by the Keith-Wagener-Barker classification is a risk factor for cardiovascular mortality independently of cardiovascular risk factors among men and women with and without hypertension.

Acknowledgments

We thank the Ibaraki Health Service Association for supplying the health checkup data.

Sources of Funding

This research was supported by grant-in-aids from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan (Research on Health Services: H17-Kenkou-007; Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H18-Junkankitou[Seishuu]-Ippan-012; Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H20-Junkankitou[Seishuu]-Ippan-013; Intractable Diseases Conquest Research: H21-Nanchi-Ippan-059; and Comprehensive Research on Cardiovascular and Life-Style Related Diseases: H23-Junkankitou[Seishuu]-Ippan-005).

Disclosures

None.

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CLINICAL PERSPECTIVE

Previous studies have suggested that moderate and severe hypertensive retinopathy is associated with an increased risk of cardiovascular disease. The present study extends the evidence of an association between mild retinopathy and cardiovascular risk among populations with and without hypertension. We show an association between grade 1 or 2 retinopathy graded by the Keith-Wagener-Barker classification and increased risk of death resulting from cardiovascular disease in the general population. The present findings suggest that mild retinopathy can be an independent predictor for cardiovascular disease even in a normotensive population.

Preventive Medicine 54 (2012) 32–37

Contents lists available at SciVerse ScienceDirect

Preventive Medicine

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Salt preference and mortality from stroke and coronary heart disease for Japanese men and women: The JACC study

Satoyo Ikehara [a,*], Hiroyasu Iso [a], Chigusa Date [b], Shogo Kikuchi [c], Yoshiyuki Watanabe [d], Yutaka Inaba [e], Akiko Tamakoshi [c] and The JACC Study Group [1]

[a] Public Health, Department of Social and Environmental Medicine, Osaka University, Graduate School of Medicine, Osaka, Japan
[b] Department of Food Science and Nutrition, School of Human Science and Environment, University of Hyogo, Hyogo, Japan
[c] Department of Public Health, Aichi Medical University School of Medicine, Nagoya, Japan
[d] Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Sciences, Kyoto, Japan
[e] Division of Public Health, Department of Food & Health Sciences, Faculty of Human Life Sciences, Jissen Women's University, Tokyo, Japan

ARTICLE INFO

Article history:
Received 23 May 2011
Received in revised form 4 October 2011
Accepted 9 October 2011
Available online 28 October 2011

Keywords:
Salt preference
Stroke
Coronary heart disease
Cardiovascular disease
Mortality
Follow-up study

ABSTRACT

Objective: The study aims to examine the association between salt preference and mortality from stroke and coronary heart disease (CHD).
Methods: Between 1988 and 1990, 35515 men and 49275 women aged 40–79 years completed a self-administered questionnaire in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by Monbusho. During a median duration of 16.4 years, 1970 stroke and 922 CHD deaths were observed. Salt preference was divided into three groups: low, moderate and high.
Results: Mortality rates per 1000 person-year from stroke were 2.0 for men, 1.3 for women and 1.6 for total subjects. The respective mortality from CHD was 1.1, 0.5 and 0.8, and that from total cardiovascular disease was 4.6, 2.9 and 3.6. Salt preference was positively associated with mortality from stroke for both sexes. The multivariable hazard ratios of stroke mortality for high versus low salt preference were 1.21(0.99–1.49) for men, 1.22(1.00–1.49) for women and 1.23(1.06–1.41) for total subjects. That positive association was primarily observed among male heavy drinkers (≥46.0 g ethanol/day). Salt preference tended to be inversely associated with mortality from CHD.
Conclusion: Salt preference was associated with increased mortality from stroke for both sexes, particularly for male heavy drinkers.

Introduction

Several studies have shown that a higher sodium intake is associated with increased incidence of and mortality from cardiovascular disease, especially stroke (He et al., 1999; Umesawa et al., 2008).

Salt preference may be useful for the qualitative evaluation of salt intake and it can be assumed that this measure is reflective of an individual's attitude and response to salty foods, while the assessment of sodium intake is more difficult because of the use of seasoning and table salt (Clark and Mossholder, 1986; Caggiula et al., 1985; Wakai, 2009). Therefore, salt preference is often inquired during clinical assessment of hypertension management and prevention. High salt preference may result in a high long-term sodium intake, because it is considered that salt preference is formed by food selection which was influenced by socio-environmental factors such as family use of salt and seasoning (Mattes, 1997; Contreras, 1978).

However, the association between salt preference and mortality from stroke, coronary heart disease (CHD) and cardiovascular disease (CVD) in the general population has been rarely examined. Our priority hypothesis was that levels of salt preference would be positively associated with stroke mortality, since salt preference influences long-term sodium intake.

We also examined the joint effect of salt preference and alcohol intake for mortality from stroke because alcohol drinking influences risk of CVD and often accompanied by high sodium intake. The combination of high salt preference and heavy alcohol drinking could lead to the higher mortality from stroke. We therefore analyzed these hypotheses using follow-up data from a large-scale prospective study of approximately 84,000 middle-aged Japanese men and women.

* Corresponding author at: Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan. Fax: +81 6 6879 3919.
E-mail address: s-ikehara@pbhel.med.osaka-u.ac.jp (S. Ikehara).
[1] See acknowledgements for the investigators (name and affiliation) involved in the JACC Study.

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doi:10.1016/j.ypmed.2011.10.013

Methods

Study population

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by Monbusho (JACC Study) was conducted between 1988 and 1990, during which 110,792 subjects (46,465 men and 64,327 women) aged 40–79 years and living in 45 areas across Japan participated in municipal health screening examinations and completed self-administered questionnaires pertaining to lifestyle and past medical histories of CVD and cancer at baseline. In 22 of 45 areas, all noninstitutionalized residents living in a given target area were regarded as study subjects. In 20 areas, those who had undertaken a basic health examination conducted under the Health and Medical Service Law for the Aged were invited to participate in the study. In two areas, the study subjects consisted of health examinees plus volunteers. In one area, subjects were defined on the basis of the health check-up for atomic bomb survivors. Response rates were obtainable from 17 of 22 areas, where all noninstitutionalized residents were recruited as the subjects; the average response rate was 83%. Details of the study procedure (Ohno and Tamakoshi, 2001; Tamakoshi et al., 2005) and the reproducibility and validity for dietary intake (Date et al., 2005) have been described previously. In most areas, informed consent was obtained individually and directly from members of the cohort, while in several areas, informed consent was obtained at the community level after the purpose of the study and confidentiality of the data had been explained to community leaders and mayors. Of the 110,792 cohort participants, 5864 subjects (2576 men and 3288 women) who reported a history of CVD and cancer were excluded. Then, 20,138 subjects (8374 men and 11,764 women) were excluded because of missing information on salt preference. In total, 35,515 men and 49,275 women were included in the study.

Mortality surveillance

For mortality surveillance in each of the communities, investigators conducted a systematic review of death certificates, all of which had been forwarded to the public health center in the area of residency. Mortality data were then centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded for the National Vital Statistics according to the 10th revision of the *International Classification of Diseases* (ICD-10). Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who had died after moving from their original community, in which case such subjects were censored. Cause-specific mortality was determined separately in terms of stroke (ICD-10 codes I60 to I69), CHD (I20 to I25) and total CVD (I01 to I99). The follow-up is believed to be complete and accurate because of systematic examination of death certificates and residency status. By December 31, 2006 (by 1999 in 4 areas, and by 2003 in 5 areas), 14,915 subjects had been censored because they had died, and 4140 subjects because they had moved out of the study area. The median follow-up period for the participants was 16.4 years. This study was approved by the ethics committees of the Nagoya University School of Medicine and the University of Tsukuba.

Baseline survey

The baseline data was collected by means of a self-administered questionnaire, with items relating to salt preference, demographic characteristics, hypertension, diabetes mellitus and other chronic diseases, as well as habits related to smoking, alcohol consumption, diet, and exercise. Salt preference was ascertained with the question: 'Do you like salty foods (salted fish, foods boiled in soy sauce, or pickled vegetables)?' Participants chose from one of five graded responses: 'hate', 'not like', 'moderate', 'like', or 'love'. Salt preference was then classified into three categories based on this response, with 'low' (hate or not like), 'moderate' and 'high' (like or love) categories, because of the small proportion that chose 'hate' and 'love' (the proportion = 2% and 8%, respectively). We calculated nutritional intakes for subjects who completed a food frequency questionnaire (n = 55,342). The methods for calculation of sodium intake have been described in detail previously (Umesawa et al., 2008). The Spearman rank correlation coefficient for sodium intake between the food-frequency questionnaire (FFQ) and four 3-d dietary records was 0.37. We asked the subjects about salt modification of intake, 'Have you changed the selection of salty foods since 30 years of age?' The subjects selected one of three answers: 'decreased', 'unchanged' or 'increased'. The answer for 'decreased' was defined as the presence of salt intake modification. Alcohol drinking status was established by asking the subjects whether they were nondrinkers, ex-drinkers, or current drinkers. Ex-drinkers and current drinkers were also asked about the age at which they started drinking, frequency of alcohol intake per week during the previous year (less than once/week, 1 to 2 times/week, 3 to 4 times/week, and almost every day), type of beverage (sake [rice wine], shochu [a type of brandy], beer, whiskey, or wine), and the amount consumed per occasion. The unit of amount consumed per occasion was "gou", which is the equivalent of 23 g of alcohol. The amount of ethanol per day was calculated as follows: the unit of amount consumed per occasion multiplied by the frequency of alcohol consumption per week divided by 7 (Ikehara et al., 2008).

Statistical analysis

Statistical analyses were based on sex-specific mortality rates of stroke during the follow-up period from 1988–1990 to 2006 (to 1999 for 4 areas and to 2003 for 5 areas). The person-years of follow-up were calculated from the date of filling out the baseline questionnaire to death, moving out of the area, or the end of follow-up, whichever came first.

Sex-specific age-adjusted mean values and prevalence of cardiovascular risk factors were calculated according to the categories of salt preference. Sex-specific hazard ratios with 95% confidence intervals (CIs) for mortality from stroke, CHD and total CVD were calculated with reference to the risk for low salt preference. These estimates were adjusted for age and other potential confounding factors by means of the Cox proportional hazards model. The other potential confounding factors included a history of diabetes, body mass index (sex-specific quintiles), smoking status (never, ex-smoker, current smoker of 1 to 19 and ≥20 cigarettes per day), alcohol consumption (nondrinker, ex-drinker, current drinker of 1 to 22.9, 23.0 to 45.9, 46.0 to 68.9 and ≥69.0 g ethanol per day), frequency of exercise (almost never, 1 to 2, 3 to 4 and ≥5 h per week), hours of walking (almost never, 0.5, 0.6–0.9 and ≥1 h per day), perceived mental stress (low, moderate and high), education level (<13, 13–15, 16–18, and ≥19 years), fresh fish intake (almost never, 1 to 2 times per month, 1 to 2 times per week, 3 to 4 times per week and almost every day). Another multivariate model was used after further adjustments were made for a history of hypertension. We also examined the joint effect of salt preference and alcohol intake. Statistical interactions were checked by using cross-product terms of salt preference and alcohol consumption categories in the fully-adjusted model. SAS (version 9.13) was used for all statistical analyses.

Results

During a median follow-up of 16.4 years, 1970 stroke deaths (1023 men and 947 women), 922 CHD deaths (543 men and 379 women) and 4417 total CVD deaths (2318 men and 2099 women) were observed. Mortality rates per 1000 person-year from stroke were 2.0 for men, 1.3 for women and 1.6 for total subjects. The respective mortality from CHD was 1.1, 0.5 and 0.8, and that from total CVD was 4.6, 2.9 and 3.6.

Table 1 shows sex-specific age-adjusted mean values or prevalence of risk characteristics at baseline according to salt preference. Compared with low-salt preference subjects, those with high-salt preference tended to be younger, less educated and smokers, and had a higher body mass index, and higher alcohol consumption. Mean values of sodium, other nutritional parameters and the frequency of salty food intakes were higher in subjects with high-salt preference in both sexes, with the exception of calcium and saturated fatty acid intake.

Table 2 shows sex-specific, age-adjusted and multivariable hazard ratios for mortality from stroke, CHD and total CVD according to salt preference. Salt preference was associated with increased mortality from stroke for both sexes. The multivariable hazard ratios of mortality from stroke for high versus low salt preference were 1.21 (0.99–1.49) for men, 1.22 (1.00–1.49) for women and 1.23 (1.06–1.41) for total subjects adjusted for sex. For CHD, reduced risks of mortality was observed for moderate and/or high salt preference compared

with low salt preference , but the trend did not reach statistical significance for men, women and total subjects.

Among 55,342 persons who were obtained information about sodium intake (65.3% of total subjects), the multivariable hazard ratios of stroke among total subjects adjusting for sex were 1.32 (1.09–1.58) for moderate-salt preference and 1.37 (1.13–1.66) for high-salt preference compared with low salt preference (p for trend = 0.005). After adjustment further for sodium intake, these associations were slightly attenuated but remained statistically significant; the corresponding multivariable hazard ratios of stroke were 1.28 (1.06–1.54) and 1.32 (1.08–1.60) (p for trend = 0.01).

We also examined the joint effect of salt preference and alcohol intake on mortality from stroke (Table 3). In male heavy drinkers (≥46.0 g ethanol/day), the multivariable hazard ratios (95% CI) for stroke were 1.93 (1.23–3.04) for moderate salt preference and 2.19 (1.40–3.44) for high salt preference compared with low salt-preferred nondrinkers (p for interaction = 0.18 for moderate preference and 0.05 for high preference). For total subjects, the corresponding multivariable hazard ratios of stroke were 1.70 (1.30–2.23) and 2.01 (1.54–2.61) (p for interaction = 0.33 and 0.08, respectively). The multivariable hazard ratio of stroke for high salt-preferred current drinkers were 1.56 (1.01–2.40, p for interaction = 0.94 and 0.79, respectively) among men, 1.32 (0.89–1.95, p for interaction = 0.77 and 0.20, respectively) among women and 1.35 (1.08–1.69, p for interaction = 0.86 and 0.44, respectively) among total subjects compared with low salt-preferred nondrinkers. For men and total subjects, there was a similar excess mortality from stroke among ex-drinkers in all categories of salt preference. In other word, there was no association between salt preference and stroke mortality among ex-drinkers.

Discussion

The results from this large prospective cohort study of middle-aged men and women indicated that high salt preference was associated with a 20% increased risk of mortality from stroke compared with low salt preference. These associations were not changed dramatically after adjustment for cardiovascular risk factors including history of hypertension. To our knowledge, ours is the first prospective study to provide evidence on the association of salt preference with increased mortality from stroke, although several prospective cohort studies have shown an association of sodium intake with stroke mortality and incidence (He et al., 1999; Umesawa et al., 2008).

High salt preference may result in a high long-term sodium intake, leading to high blood pressures and an increased stroke risk. The ability to sense the taste of salt is generally acquired during early infancy, after which the selection of salty foods may be influenced by environmental factors such as cultural and social factors including family use of salt and seasoning (Mattes, 1997; Contreras, 1978). In the present study, persons with high salt preference were more likely to have salty foods and a smaller proportion of salt modification since 30 years of age for both sexes (p for trend = <0.001). Even after

Table 1
Age-adjusted mean values or prevalence of risk characteristics at baseline according to salt preference, Japan, 1988–1990.

	Salt preference					
	Men			Women		
	Low	Moderate	High	Low	Moderate	High
No. of subjects	4328	16239	14948	9174	27081	13020
Age, years	58.5	57.9†	55.7†	58.1	57.3†	56.9†
Mean body mass index, kg/m^2	22.5	22.6	22.7†	22.5	22.8†	23.2†
History of hypertension, %	20.9	19.4	19.8	22.1	21.0	23.6*
History of diabetes, %	6.8	6.1	6.7	4.3	3.6†	4.2
Current smokers, %	46.7	52.0†	58.4†	4.9	4.4	7.2†
Alcohol consumption, g/day	31.8	32.1	37.1†	9.4	9.7	12.5†
Education ≥19 years, %	19.6	17.5†	17.7*	12.1	9.8†	9.5†
Exercise 5 h or more/week, %	7.1	7.1	7.8	5.1	4.6	5.0
Walking 1 h or more/day, %	49.3	49.9	50.0	50.9	51.8	51.6
High mental stress, %	24.8	19.7†	26.3	21.1	17.9†	24.0†
Fresh fish intake, times/week	3.4	3.3*	3.5	3.5	3.5	3.5
Miso soup, times/day	2.1	2.2†	2.2†	1.8	1.9†	2.0†
Salted fish, no. of days/week	1.6	1.9†	2.3†	1.7	2.0†	2.3†
Foods boiled in soy sauce, no. of days/week	1.2	1.4†	1.6†	1.1	1.5†	1.7†
Pickled vegetables, no. of days/week	3.9	4.8†	5.4†	4.2	5.2†	5.7†
No. of subjects with nutrient data	2612	9736	9511	6061	18321	9101
Total energy, kcal/day	1684	1746†	1804†	1376	1428†	1459†
Sodium, mg/day	1878	2083†	2151†	1725	1950†	2022†
Potassium, mg/day	2039	2100†	2105†	2091	2140†	2161†
Protein, g/day	52.9	54.4†	55.1†	51.0	52.6†	53.0†
Calcium, mg/day	449	460†	455	461	466	464
Saturated fatty acid, g/day	9.7	9.8	9.7	10.0	10.0	9.9
Monounsaturated fatty acid, g/day	10.0	10.2*	10.2*	10.2	10.4†	10.4†
Polyunsaturated fatty acid, g/day	7.5	7.8†	7.9†	7.1	7.5†	7.6†
N-3 fatty acid, mg/day	1.4	1.5†	1.5†	1.4	1.5†	1.5†
Total dietary fiber, g/day	12.0	12.5†	12.5†	11.7	12.2†	12.4†
Vitamin B6, mg/day	1.1	1.2†	1.2†	1.1	1.2†	1.2†
Dietary cholesterol, mg/day	224	227	230†	223	227*	227*
Systolic blood pressure, mm Hg (men = 8858, women = 15762)	134.0	133.9	135.2	130.5	130.6	131.5*
Diastolic blood pressure, mm Hg (men = 8855, women = 15755)	80.9	80.5	81.1	77.8	77.6	78.1
Medication use for hypertension, %	12.6	12.8	13.9	13.7	12.8	14.4
Serum total cholesterol, mg/dl (men = 8905, women = 15891)	189.9	188.3	186.8*	203.9	203.9	202.8
Serum total cholesterol ≥220 mg/dl, %	19.4	17.0	16.1*	31.9	31.0	29.7
Serum HDL-cholesterol, mg/dl (men = 3515, women = 5711)	52.5	52.5	53.4	55.6	55.1	54.3*

* $p<0.05$ test for difference from the low salt preference group.
† $p<0.01$ test for difference from the low salt preference group.

Table 2
Age-adjusted and multivariable hazard ratio (HR) and 95% confidence interval (95% CI) of mortality from stroke, CHD and total CVD according to salt preference, Japan, 1988–2006.

	Salt preference			*P* for trend
	Low	Moderate	High	
Men				
Person-years	59903	230090	214563	
Stroke				
No. of deaths	125	492	406	
Age-adjusted HR (95% CI)	1.00	1.10 (0.90–1.34)	1.22 (1.00–1.49)	0.03
Multivariable HR (95% CI)[a]	1.00	1.13 (0.93–1.38)	1.20 (0.98–1.47)	0.08
Multivariable HR (95% CI)[b]	1.00	1.14 (0.93–1.38)	1.21 (0.99–1.49)	0.07
CHD				
No. of deaths	84	247	212	
Age-adjusted HR (95% CI)	1.00	0.80 (0.63–1.03)	0.89 (0.69–1.15)	0.75
Multivariable HR (95% CI)[a]	1.00	0.78 (0.60–1.00)	0.83 (0.64–1.07)	0.38
Multivariable HR (95% CI)[b]	1.00	0.78 (0.61–1.01)	0.84 (0.65–1.09)	0.45
Total CVD				
No. of deaths	306	1117	895	
Age-adjusted HR (95% CI)	1.00	1.01 (0.89–1.15)	1.08 (0.95–1.23)	0.15
Multivariable HR (95% CI)[a]	1.00	1.02 (0.89–1.15)	1.04 (0.91–1.19)	0.50
Multivariable HR (95% CI)[b]	1.00	1.02 (0.90–1.16)	1.05 (0.92–1.20)	0.38
Women				
Person-years	131986	399263	188299	
Stroke				
No. of deaths	161	523	263	
Age-adjusted HR (95% CI)	1.00	1.16 (0.97–1.38)	1.28 (1.05–1.55)	0.02
Multivariable HR (95% CI)[a]	1.00	1.17 (0.98–1.40)	1.24 (1.02–1.51)	0.04
Multivariable HR (95% CI)[b]	1.00	1.17 (0.98–1.40)	1.22 (1.00–1.49)	0.06
CHD				
No. of deaths	92	191	96	
Age-adjusted HR (95% CI)	1.00	0.74 (0.58–0.95)	0.82 (0.61–1.09)	0.20
Multivariable HR (95% CI)[a]	1.00	0.74 (0.58–0.95)	0.79 (0.59–1.05)	0.13
Multivariable HR (95% CI)[b]	1.00	0.74 (0.58–0.95)	0.78 (0.58–1.04)	0.10
Total CVD				
No. of deaths	415	1108	576	
Age-adjusted HR (95% CI)	1.00	0.95 (0.85–1.07)	1.09 (0.96–1.23)	0.14
Multivariable HR (95% CI)[a]	1.00	0.96 (0.86–1.08)	1.06 (0.93–1.20)	0.30
Multivariable HR (95% CI)[b]	1.00	0.96 (0.86–1.08)	1.05 (0.92–1.19)	0.40
Total subjects				
Person-years	191888	629353	402862	
Stroke				
No. of deaths	286	1015	669	
Age, sex-adjusted HR (95% CI)	1.00	1.13 (0.99–1.29)	1.26 (1.09–1.45)	<0.001
Multivariable HR (95% CI)[a]	1.00	1.15 (1.01–1.32)	1.23 (1.06–1.41)	0.007
Multivariable HR (95% CI)[b]	1.00	1.16 (1.01–1.32)	1.23 (1.06–1.41)	0.007
CHD				
No. of deaths	176	438	308	
Age, sex-adjusted HR (95% CI)	1.00	0.77 (0.65–0.92)	0.88 (0.73–1.06)	0.44
Multivariable HR (95% CI)[a]	1.00	0.76 (0.63–0.90)	0.82 (0.68–0.99)	0.12
Multivariable HR (95% CI)[b]	1.00	0.76 (0.64–0.91)	0.82 (0.68–0.99)	0.12
Total CVD				
No. of deaths	721	2225	1471	
Age, sex-adjusted HR (95% CI)	1.00	0.98 (0.90–1.06)	1.09 (1.00–1.19)	0.02
Multivariable HR (95% CI)[a]	1.00	0.98 (0.90–1.07)	1.05 (0.96–1.15)	0.18
Multivariable HR (95% CI)[b]	1.00	0.99 (0.91–1.07)	1.05 (0.96–1.15)	0.19

[a] Multivariable adjustment: age, body mass index, history of diabetes, smoking, ethanol intake, education level, sport, walking, mental stress and fresh fish intake.
[b] Further adjusted for history of hypertension.

further adjustment for sodium intake from FFQ at baseline, excess mortality from stroke remained. In the present analysis, high salt preference was associated with less education and smoking behavior. Therefore, subjects with high salt preference may have a low socioeconomic status and health risk behaviors, leading to higher risk of stroke. Genetic predispositions associated with salt preference, although not investigated extensively (Birch, 1999), might also increase risk of stroke through mechanisms other than a long-term high salt intake. Further studies are necessary to clarify mechanisms in the relation between salt preference and stroke.

Since alcohol intake is another major determinant of high blood pressure (Marmot et al., 1994) and stroke risk (Iso et al., 2004; Ikehara et al., 2008), we examined the joint effect of salt preference and alcohol intake on mortality from stroke. Increased stroke risks were observed in salt-preferred male heavy drinkers and female current drinkers compared with low salt-preferred nondrinkers. These findings suggest the need to encourage low-salt diets, especially for those with high alcohol and salt intakes for the prevention of stroke.

The present study has several limitations. Firstly, the misclassification may have been unavoidable because we defined salt preference via a single item in the self-administered questionnaires. In the present study, however, the frequency of salty foods intake were correlated with the intensity of salt preference in both men and women. The misclassification of salt preference was likely nondifferential and would have lead to the underestimation of real associations. Secondly, the data for hypertension were self-reported in the present study. However, a previous validation study showed that self-reported blood pressure values were reasonably accurate probably because of national-wide blood pressure screening in Japan (Kawada and Suzuki, 2005). Thirdly, although we adjusted for selected cardiovascular risk factors, socioeconomic status and psychosocial factors such as education level and mental stress, we cannot exclude the possible influence of other confounding factors including nutrient factors such as dietary protein intake (Okiyama et al., 1996). However, after further adjustment for sodium and dietary protein among subsamples who completed the FFQ, the result did not change. The multivariable hazard ratios of stroke were 1.27 (1.06–1.53) for moderate salt preference and 1.31 (1.08–1.59) for high salt preference compared with low salt preference. Fourthly, although 19% persons of the cohort subjects were excluded from the present analyses because of missing data on salt preference, that exclusion was unlikely to affect the results because of no material differences in baseline characteristics between those included and those excluded. For example, sex-adjusted mean age was 57.2 versus 58.1 years; age and sex-adjusted mean body mass index was 22.7 versus 23.1 kg/m^2; age and sex-adjusted history of hypertension was 21.1 versus 23.4%; history of diabetes was 5.0 versus 5.7%; current smokers was 26.8 versus 27.7%. Finally, the reason why salt preference tended to be inversely associated with CHD mortality is not fully explained. However, the Japanese dietary pattern associated with high salt preference may affect the risk of mortality from CHD. That dietary pattern was also characterized by high intakes of n3 polyunsaturated fatty acids and isoflavones which have been associated with reduced risk of CHD (Iso et al., 2006; Kokubo et al., 2007). Finally, we used mortality data rather than incidence data as endpoints, which may be affected by survival, and liable to misclassification in the diagnosis of stroke and CHD. However, the widespread use of computed tomography in local hospitals since the 1980s has probably made the diagnosis of stroke reported on death certificates sufficiently accurate (Iso et al., 1990; Sankai et al., 1991). For CHD, approximately one fourth to one third of deaths attributed to CHD on the death certificate is misdiagnosed, according to validation studies (Yamashita et al., 1997; Baba et al., 1994).

The strength of the present study lies in its prospective design and large sample size, which was sufficient to detect sex-specific associations of salt preference with mortality from stroke, CHD and total CVD. In addition, the findings of this study can be generalized to Japanese populations because our subjects were selected from the general population and a high response rate.

The findings of this study indicate that salt preference is associated with increased mortality from stroke for both men and women. The association between salt preference and stroke mortality was particularly evident among male heavy drinkers. Salt preference is easily assessed in clinical and public settings, and useful for dietary intervention when individuals report to like salt. Our findings support

Table 3
Multivariable hazard ratio (HR) and 95% confidence interval (95% CI) of mortality from stroke according to salt preference stratified by drinking status, Japan, 1988–2006.

	Salt preference								
	Men			Women			Total subjects		
	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Nondrinkers									
Person-years	13547	43390	32392	95979	283737	122976	109526	327127	155368
No. of deaths	23	96	60	120	391	171	143	487	231
Multivariable HR (95% CI)[a]	1.00	1.33 (0.84–2.10)	1.29 (0.80–2.10)	1.00	1.23 (1.00–1.51)	1.16 (0.92–1.47)	1.00	1.24 (1.03–1.50)	1.18 (0.96–1.46)
Ex-drinkers									
Person-years	3714	11084	8200	1916	4497	3079	5630	15581	11279
No. of deaths	18	53	34	1	8	3	19	61	37
Multivariable HR (95% CI)[a]	2.27 (1.22–4.22)	2.39 (1.46–3.92)	2.48 (1.45–4.23)	0.40 (0.06–2.84)	1.52 (0.74–3.13)	0.73 (0.23–2.30)	1.55 (0.95–2.52)	1.93 (1.41–2.65)	1.81 (1.25–2.63)
Current drinkers									
Person-years	33854	143457	145565	15464	49241	31571	49318	192698	177136
No. of deaths	57	267	235	8	33	33	65	300	268
Multivariable HR (95% CI)[a]	1.24 (0.76–2.02)	1.45 (0.94–2.23)	1.56 (1.01–2.40)	0.67 (0.33–1.37)	0.93 (0.63–1.38)	1.32 (0.89–1.95)	1.00 (0.74–1.36)	1.21 (0.97–1.50)	1.35 (1.08–1.70)
Drinkers of 0.1–45.9g ethanol per day									
Person-years	21424	88281	75789	14955	47239	29634	36380	135520	105423
No. of deaths	38	151	99	8	33	29	46	184	128
Multivariable HR (95% CI)[a]	1.27 (0.75–2.14)	1.24 (0.80–1.94)	1.16 (0.73–1.83)	0.69 (0.34–1.41)	0.97 (0.66–1.44)	1.22 (0.81–1.83)	1.02 (0.72–1.43)	1.08 (0.85–1.37)	1.08 (0.84–1.39)
Drinkers of ≥46.0g ethanol per day									
Person-years	12429	55176	69776	509	2003	1937	12938	57178	71713
No. of deaths	19	116	136	0	0	4	19	116	140
Multivariable HR (95% CI)[a]	1.24 (0.67–2.29)	1.93 (1.23–3.04)	2.19 (1.40–3.44)	–	–	3.26 (1.19–8.92)	1.11 (0.68–1.81)	1.70 (1.30–2.23)	2.01 (1.54–2.61)

[a] Multivariable adjustment: age, body mass index, history of hypertension, history of diabetes, smoking, education level, sport, walking, mental stress and fresh fish intake (further adjusted for sex among total subjects).

the need for education in dietary modification to reduce salt intake and reduce stroke incidence and mortality.

Study investigators

Dr. Akiko Tamakoshi (present chairperson of the study group), Aichi Medical University School of Medicine; Drs. Mitsuru Mori & Fumio Sakauchi, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Osaka University School of Medicine; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Michiko Kurosawa, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences; Dr. Naohito Tanabe, Niigata University School of Medicine; Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Science; Dr. Kenji Wakai, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, National Institute of Health and Nutrition; Dr. Koji Suzuki, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Yasuhiko Wada, Faculty of Human Life and Environmental Science, Kochi Women's University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Kotaro Ozasa, Radiation Effects Research Foundation; Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Nara Women's University; Dr. Kiyomi Sakata, Iwate Medical University; Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine; Dr. Takesumi Yoshimura, Fukuoka Institute of Health and Environmental Sciences; Dr. Yoshihisa Fujino, University of Occupational and Environmental Health; Dr. Akira Shibata, Kurume University School of Medicine; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; and Dr. Hideo Shio, Moriyama Municipal Hospital.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Acknowledgments

The JACC Study (Japan Collaborative Cohort Study) was supported by grants-in-aid for scientific research from the Ministry of Education, Science, Sports and Culture of Japan (Monbusho); 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011 and 20014026. The authors thank all staff members involved in this study for their valuable help in conducting the baseline survey and follow-up.

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European Heart Journal (2012) **33**, 467–477
doi:10.1093/eurheartj/ehr429

Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: the Japan collaborative cohort study

Eri Eguchi[1], Hiroyasu Iso[1]*, Naohito Tanabe[2], Yasuhiko Wada[3], Hiroshi Yatsuya[4], Shogo Kikuchi[5], Yutaka Inaba[6], and Akiko Tamakoshi[5], on behalf of the Japan Collaborative Cohort Study Group

[1]Department of Social and Environmental Medicine, Public Health, Osaka University Graduate School of Medicine, 2-2, Yamadaoka, Suita, Osaka, Japan; [2]Division of Health Promotion, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [3]Department of Nutrition, Kochi Women's University, Kochi, Japan; [4]Health/Health Information Dynamics, Nagoya University Graduate School of Medicine, Aichi, Japan; [5]Department of Public Health, Aichi Medical University School of Medicine, Aichi, Japan; and [6]Division of Public Health, Department of Food and Health Sciences, Faculty of Human Life Sciences, Jissen Women's University, Tokyo, Japan

Received 16 May 2011; revised 12 October 2011; accepted 26 October 2011

See page 428 for the editorial comment on this article (doi:10.1093/eurheartj/ehr446)

Aims To examine the combined impacts of healthy lifestyle behaviours on cardiovascular disease (CVD) in Asians.

Methods and results A total of 18 747 men and 24 263 women aged 40–79 without a history of stroke or coronary heart disease (CHD) at baseline in 1988–90 were followed up until 2006. Participants scored one point for each following lifestyle behaviour: consumption of fruits ≥1 intake per day, fish ≥1 intake per day, milk almost every day, exercise ≥5 h per week and/or walking ≥1 h per day, body mass index (BMI) of 21–25 kg/m^2, alcohol intake <46.0 g per day, non-smoking, and sleep duration of 5.5–7.5 h per day. During 16.5 years of follow-up, there were 1907 deaths from total CVDs including 849 strokes and 402 CHDs. For both genders, persons with the highest scores had the lowest CVD mortality. The multivariable hazard ratios (95% confidence interval, population-attributable fraction) for the highest (7–8) vs. lowest (0–2) score categories were 0.35 (0.25–0.49, 52.3%) in men, and 0.24 (0.16–0.36, 44.6%) in women. Similar associations were found for stroke: 0.36 (0.22–0.58, 45.0%) in men and 0.28 (0.15–0.53, 43.4%) in women, and for CHD: 0.19 (0.08–0.50, 76.2%) and 0.20 (0.09–0.47, 34.5%), respectively.

Conclusion Mortality from stroke, CHD, and CVD in the highest healthy lifestyle score category was one-third in men and one-fourth in women of those in the lowest scores, suggesting that a large fraction of CVD could be prevented through lifestyle modification.

Keywords Mortality • Stroke • Coronary heart disease • Cardiovascular disease • Lifestyle and risk factor

Introduction

Lifestyle behaviours such as the consumption of fruits,[1] fish[2] and milk[3], moderate physical activity,[4] having a normal body mass index (BMI),[5] moderate alcohol intake,[6] not currently smoking,[7] and moderate sleep duration[8] were associated with lower mortality from cardiovascular disease (CVD) in the Japan Collaborative Cohort (JACC) study. We have also documented that the associations between a combination of these healthy lifestyle behaviours lead to a lower mortality from total death,[9] and a longer life expectancy.[10] While many studies have shown inverse associations between these lifestyle behaviours and CVD mortality,[11–18] few studies have investigated the impact of the *combination* of these behaviours on CVD risk until now. These results emphasize the importance of public health campaigns targeting lifestyle modification in CVD prevention.

Stampfer *et al.*[19] showed that a combination of five healthy lifestyle behaviours was associated with a 83% reduction in the incidence of coronary heart disease (CHD), and a 75% reduction in the incidence of CVD among American women. Similarly, Chiuve

* Corresponding author. Tel: +81 6 6879 3911, Fax: +81 6 6879 3919, Email: iso@pbhel.med.osaka-u.ac.jp

et al.[20] have shown a 69–79% reduction in the incidence of stroke among American men and women; and Myint *et al.*[21] demonstrated that a combination of four bad lifestyle behaviours was associated with a 45–240% increase in the incidence of stroke among European men and women.

To our knowledge, no prospective study has reported a combined effect of healthy lifestyle behaviours among CVD in Asian populations until now. In this large prospective cohort study, we developed a healthy lifestyle score based on eight healthy lifestyle behaviours, and examined the potential magnitude of the combined impact of them on mortality from stroke, CHD, and total CVD among Japanese men and women aged 40–79.

Methods

Study population

A baseline survey of the JACC study was conducted in 1988–90. A total of 110 792 subjects (46 465 men and 64 327 women) aged 40–79 years in 45 areas across Japan completed self-administered questionnaires, including lifestyle information and medical histories pertaining to CVD and cancer. The details of the study procedure have been described previously.[1–8,22–25] Of all subjects, 2576 men and 3288 women were excluded due to positive histories of stroke, CHD or cancer, as were another 25 142 and 36 776, respectively, due to missing information for calculating the healthy lifestyle score. A total of 43 010 men and women (18 747 and 24 263, respectively) were eligible for the study. There was no substantial difference in CVD risk factors between individuals with complete healthy lifestyle scores and those with missing.

Mortality surveillance

The cause and date of death among participants were identified by reviewing all death certificates in each area. According to the *International Classification of Diseases*, the 10th revision, cause-specific mortality was determined in terms of stroke (I60–I69), CHD (I20–I25), and total CVD (I01–I99). By 31 December 2006, except for several areas where follow-up was terminated at the end of 1999 (six areas) and 2003 (five areas), a total of 6644 subjects had been censored because of death, and 2158, because of moving out. The median follow-up period was 16.5 (inter-quartiles: 12.8–17.8) years. This study was approved by the Ethics Committees of the Nagoya University School of Medicine, the University of Tsukuba, and Osaka University.

Healthy lifestyle score

Consumption of fruits, fish and milk

Possible responses were 'rarely, 1–2 days a month, 1–2 days a week, 3–4 days a week and almost every day' during the preceding year. For fruit (citrus fruits, other fruits, and fresh fruit juice) and fish, each frequency weight was set at 0, 0.05 (1.5/30), 0.214 (1.5/7), and 0.5 (3.5/7) with 1.0 signifying the response 'almost every day' and divided by three. We allocated 1 point each for fruits $\geq$1 intake/day ($\geq$7 intakes weekly), fish $\geq$1 intake/day ($\geq$7 intakes weekly), and milk almost every day according to the evidence in a previous report.[1–3] A moderate reliability and validity for these measures have been reported elsewhere.[22]

Walking and sports participation

For walking, possible responses were: 'almost never, 0.5, 0.5–1, and 1 h or more' on average on a daily basis. For sport, possible answers were: 'almost never, 1–2, 3–4, and 5 h or more' on average on weekly basis. We allocated 1 point for those who walk '>0.5 to <1 h', and '1.0 h and more' per day, and/or those who participate sports '5 h or more' per week according to the evidence in previous reports [4]. The reliability and validity for these measures have been mentioned elsewhere.[4,23]

Body mass index

Self-reported weight (kg) was divided by the square of self-reported height (m).

According to the evidence in previous reports,[5] one point was allocated to the category of BMI 21.0 to <25.0 kg/m^2.

Smoking status

Categories were smokers, non-smokers including past smokers. One point was allocated to non-smoker.

Alcohol consumption

Categories were non-drinkers, ex-drinkers, or current drinkers. Drinkers also reported the frequency as 'less than once, 1–2 times, 3–4 times, or almost every day' of alcohol consumption per week and the amount per occasion during the previous year. The daily amount of ethanol consumption was calculated. We allocated 1 point for all of non-drinkers, ex-drinkers, and current drinkers of 1–46.0 g ethanol/day according to the evidence in previous reports.[6]

Sleep duration

Average sleep duration on weekdays during the preceding year was classified into seven categories: <4.5, 4.5–5.4, 5.5–6.4, 6.5–7.4, 7.5–8.4, 8.5–9.4, and $\geq$9.5 h per day.

We allocated 1 point for sleeping duration of 5.5–7.4 h/day according to the evidence in previous reports.[8]

The allocated points of lifestyle behaviours were totalled for a healthy lifestyle score ranging from 0 to 8. We showed the components of the score in Supplementary material online, *Table S1*. The scores were grouped into six categories (0–2, 3, 4, 5, 6, 7–8 points) for analyses to keep the number both in men and women balanced in each category. Also, we ran a sensitivity analysis combining both men and women without categorization of the score.

For consideration of the magnitude of the impact of individual lifestyle behaviour, we also constructed a weighted score according to the magnitude of individual hazard ratios (HRs).

Statistical analysis

We first calculated sex-specific age-adjusted mean values and prevalence of risk factors by analysis of covariance, and examined the linear trend by a regression model for adjusted mean values and by a multiple logistic regression model for adjusted prevalence using the median values of healthy lifestyle score as representative values of the score categories.

To investigate sex-specific effects on CVD, we conducted the analyses among men and women separately. Age- and multivariate-adjusted *individual* impacts and population-attributable fraction (PAF) of the components of the score on mortality from CVD were calculated by Cox proportional hazard models and standard PAF calculation methods[26]. Covariates for multivariable-adjusted analysis were: age (years), histories of hypertension and diabetes mellitus (yes or no), education level (attended school until 13, 13–15, 16–18, or beyond 19 years old), perceived stress (high, medium, or low), and regular employment (yes or no) and components of healthy lifestyle score other than specified variable. Since the effect of smoking is the largest among men, we repeated the analysis

stratified by smoking status: current smoker or non-smoker; and examined the effect modification of each lifestyle behaviour and smoking status using cross-product terms of each lifestyle variable and smoking status in the Cox proportion hazard model.

We calculated age- and multivariable-adjusted HRs and 95% confidence intervals (CI) to determine the sex-specific and smoking status-stratified associations between *combination* of the lifestyle behaviours and the risk of mortality from stroke, CHD, and total CVD during the follow-up period. For multivariable HR, we used the same covariates listed above. Linear trends were examined by a Cox proportional hazard model. We also calculated sex-specific age-adjusted average annual mortality rate for CVD according to score categories using the direct standardization method using the age distribution of national model population in 1990. The smoking status-stratified analysis was conducted using seven healthy lifestyle behaviours, after excluding smoking status. The reference categories were 0–2 for sex-stratified, or 0–1 for smoking status-stratified analysis, respectively. The age-adjusted mortality rate from CVD was also constructed. Effect modifications by sex or smoking status were tested separately by an interaction terms of either sex or smoking status by healthy lifestyle score.

PAF was calculated by the following method[9,26]:

$$\text{PAF}\ (\%) = \sum P_i(\text{HR}_i - \text{HR}_{7-8})/(\text{HR}_{7-8} + \sum P_i(\text{HR}_i - \text{HR}_{7-8})) \times 100,$$

where P_i is the prevalence of score i at baseline, and HR_i is the age-adjusted HR for the score i compared with a category of 7–8. In addition, PAF_{+1} was calculated as

$$\text{PAF}_{+1}(\%) = \sum P_i(\text{HR}_i - \text{HR}_i{+}1)/(\text{HR}_{7-8} + \sum P_i(\text{HR}_i - \text{HR}_i{+}1)) \times 100,$$

where HR_i and HR_{i+1} are the age-adjusted HRs of an category for score i and score $i+1$, respectively, compared with a category of 7–8.

We repeated the same analysis using a weighted score[27]. Each was calculated by:

$$\text{Weight} = \log_2(1/\text{HR}) \times 10,$$

where HR is individual multivariable HRs of CVD mortality according to each lifestyle behaviour. Weights were summed up as total weighted healthy lifestyle score for men and women, and divided into six categories.

Also, we constructed sex- and smoking status-stratified Kaplan–Meier's survival curves for men and women. To examine the possibility of reverse causation, the same analyses were repeated after excluding early deaths that occurred within 5 years from the baseline.

We used the 9.1.3 version of SAS for all statistical analyses. All probability values for statistical tests were two-tailed, and $P < 0.05$ were regarded as statistically significant.

Results

The mean age in years of the participants was 55.6 for men and 56.1 for women. During the 16.5-year follow-up period, there were 849 deaths from stroke (441 men and 408 women), 402 from CHD (240 and 162), and 1907 from total CVD (1012 and 895). In total, men had a 20% higher mortality from CVD than women, with an age-adjusted annual mortality rate of 5.13 deaths per 1000 in men and 4.16 in women. The rate was highest in the healthy lifestyle score category of 0–2 points for both genders (6.47 and 9.19 among men and women), and was lowest in the score category of 7–8 points (2.91 and 2.28 deaths, respectively).

Table 1 shows sex-specific age-adjusted mean values or prevalence of risk factors at baseline by healthy lifestyle score categories. The respective percentages of 0–2, 3, 4, 5, 6, and 7–8 points of the score were 13, 19, 25, 22, 14, and 6% in men and 1, 6, 17, 27, 28, and 20% in women. Compared with people of the reference 0–2 category, those of higher categories were more likely to be older, hypertensive, higher educated, with higher perceived mental stress, and regular job among men, and, more likely to be younger, hypertensive, and higher educated among women.

Table 2 shows sex-specific and smoking-stratified HRs and 95% CIs and prevalence for individual health behaviours. In both sexes, people with each healthy lifestyle behaviour had the lower risk of mortality from total CVD compared with those without it. Multivariable HR was lowest for non-smoker in men and ethanol intake <46.0 g/day, and non-smoker in women. The PAFs and weights calculated according to the corresponding HRs were 3.3% and 1.0 for fruit ≥1/day, 4.4% and 1.0 for fish ≥1/day, 7.5% and 1.8 for milk almost every day, 5.2% and 2.5 habitual exercise or walking, 11.9% and 3.6 for BMI 21–25 kg/m^2, 5.3% and 2.3 for ethanol intake <46.0 g/day, 2.5% and 5.1 for non-smoker, 8.6% and 2.5 for sleep 5.5–7.4 h/day for men, 5.7, 8.1, 2.2, 4.1, 15.9, 0.7, 2.3 and 8.7% for PAFs, and 20.0, 2.9, 2.0, 0.6, 2.2, 4.5, 8.9, 5.8, 3.2 for weights for women, respectively. The total score of weights were 20.0 for men and 30.1 for women.

In the smoking status-stratified analysis, the protective effects of each health behaviour were generally larger among non-smokers than smokers in men. Also, for women, most of the associations remained statistically significant among non-smokers. The smoking interactions between each healthy lifestyle behaviour with total CVD mortality were statistically significant for fruit and fish consumptions, and borderline significance for milk consumption, habitual exercise or walking, and sleep duration among men.

Table 3 shows sex-specific age- and multivariable-adjusted HRs of mortality and crude mortality rates from stroke, CHD, and total CVD according to healthy lifestyle score. In both men and women, age-adjusted risks were lower with higher healthy lifestyle score in a graded fashion. These inverse associations remained statistically significant after adjusting for other risk factors. The multivariable HRs (95% CI) of mortality from stroke, CHD, and total CVD for 7–8 point category compared with the 0–2 were 0.36 (0.22–0.58), 0.19 (0.08–0.50), and 0.35 (0.25–0.49), respectively, for men, and were 0.28 (0.15–0.53), 0.20 (0.09–0.47), and 0.24 (0.16–0.36), respectively, for women. The results of sensitivity analysis including both men and women without categorization were not substantially different from the results above. The PAF of stroke, CHD, and total CVD for the 7–8 category was 45.0, 76.2, and 52.3% in men, and 43.4, 34.5, and 44.6% in women. The respective PAF_{+1} towards the 7–8 point category was 25.8, 41.6, 26.4% in men and 25.2, 22.3, 25.9% in women.

For the smoking status-stratified analysis, both crude mortality and HRs were generally higher in smokers (*Table 3*). The

Table 1 Mean age and age-adjusted prevalence of cardiovascular risk factors by healthy lifestyle score

	Healthy lifestyle score (points)						
	0–2	3	4	5	6	7–8	*P* for trend
Men							
No. at risk (%)	2506 (13)	3566 (19)	4664 (25)	4209 (22)	2611 (14)	1191 (6)	
Age (years)	54	55	55	56	57	58	<0.0001
Fruits ≥1/day (%)	13	34	53	71	84	95	—
Fish ≥1/day (%)	13	25	35	47	60	80	—
Milk almost everyday (%)	9	20	36	51	69	87	—
Habitual exercise or walking (%)	45	62	71	79	85	94	—
Body mass index 21–25 kg/m^2 (%)	23	38	50	61	73	88	—
Ethanol intake <46.0 g/day (%)	35	57	68	78	88	95	—
Non-smoker (%)	13	27	41	56	74	89	—
Sleep 5.5–7.4 h/day (%)	19	36	47	56	67	87	—
History of hypertension (%)	21	19	18	18	18	17	0.01
History of diabetes (%)	6	6	6	6	6	6	0.88
College or higher education (%)	16	16	19	19	22	29	<0.0001
High perceived mental stress (%)	26	25	25	25	26	29	0.01
Regular employment (%)	75	77	77	77	79	79	0.002
Women							
No. at risk (%)	325 (1)	1534 (6)	4041 (17)	6552 (27)	6886 (28)	4925 (20)	
Age (years)	57	58	57	56	56	55	<0.0001
Fruits ≥1/day (%)	7	26	48	70	86	97	—
Fish ≥1/day (%)	3	7	16	31	48	77	—
Milk almost everyday (%)	3	9	20	37	58	84	—
Habitual exercise or walking (%)	18	40	58	70	82	93	—
Body mass index 21–25 kg/m^2 (%)	7	14	26	40	57	82	—
Ethanol intake <46.0 g/day (%)	87	97	99	99	100	100	—
Non-smoker (%)	57	82	92	96	98	100	—
Sleep 5.5–7.4 h/day (%)	11	25	42	56	71	88	—
History of hypertension (%)	21	20	21	19	19	18	0.03
History of diabetes (%)	5	4	4	3	3	3	0.26
College or higher education (%)	8	8	9	10	12	13	<0.0001
High perceived mental stress (%)	22	22	21	21	21	21	0.93
Regular employment (%)	36	33	33	34	34	36	0.09

—, Statistical testing was not conducted because of a component of the healthy lifestyle score.

multivariable HRs (95% CI) of mortality from total CVD for the highest category to the lowest was 0.54 (0.34–0.85) among smoking men and was 0.33 (0.21–0.51) among non-smoking men. The respective HRs among women were 0.20 (0.06–0.69) and 0.06 (0.02–0.14), respectively.

Sex-specific survival curves of mortality from total CVD are illustrated in *Figure 1*. The larger decline in survival rate was observed for the lower healthy lifestyle score categories compared with the higher among both men and women. Women showed more divergent curves of mortality from total CVD than did men. However, there were no significant interaction between sex and healthy lifestyle score with stroke, CHD, and total CVD: *P*-value for interaction = 0.58, 0.13, and 0.64, respectively.

Figure 2 illustrates the survival curves of mortality from CVD by smoking status among men. There was not substantial difference between smoker and non-smoker for first 10 years. However, there were significant interaction between the score and smoking status (*P* for interaction = 0.03). Supplementary material online, *Figure S1* illustrates the result for women. The decline of the survival curves seemed more steep in smoking women, but there was no significant difference between smokers and non-smokers (*P* for interaction = 0.80).

After the exclusion of deaths within 5 years from baseline, the associations between the score and mortality did not change materially. The multivariable-adjusted HRs (95% CI) for healthy lifestyle scores of the highest compared with the lowest were 0.37 (0.22–0.63) for stroke, 0.21 (0.08–0.55) for CHD, and 0.38 (0.27–0.55) for total CVD among men, and 0.30 (0.15–0.60), 0.23 (0.10–0.56), and 0.27 (0.17–0.43), respectively, among women.

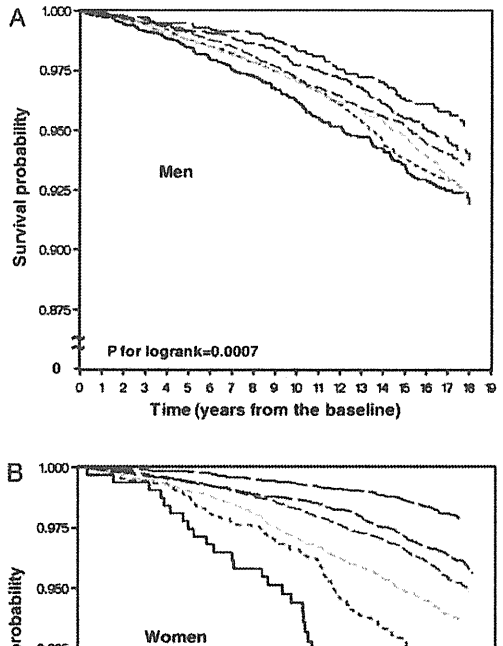

Figure 1 Kaplan–Meier survival curves of mortality from total cardiovascular disease according to the healthy lifestyle score among men (*A*) and among women (*B*). The purple line shows the highest score category, and the black line shows the lowest.

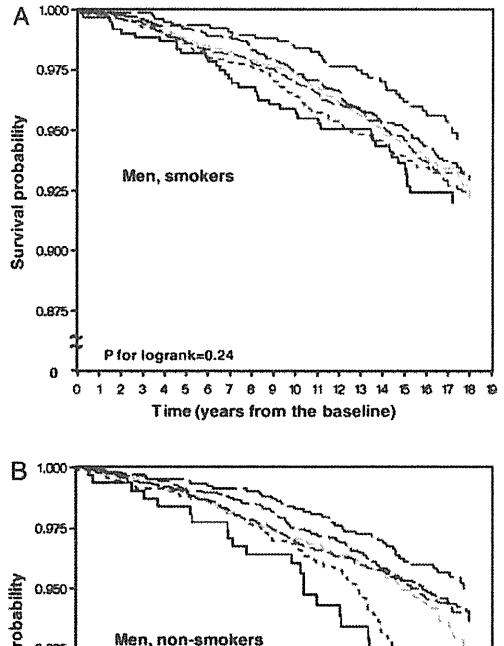

Figure 2 Kaplan–Meier survival curves of mortality from total cardiovascular disease according to the healthy lifestyle score in men for smokers (*A*) and for non-smokers (*B*). The purple line shows the highest score category, and the black line shows the lowest.

Lastly, the repeated analysis of association with CVD mortality conducted according to weighted healthy lifestyle score is shown in Supplementary material online, *Table S2*. The magnitude of impact on the highest score category compared with the lowest was smaller for all stroke, CHD, and CVD, but similar dose response trends with narrower CIs were observed.

Discussion

Findings from this large-scale prospective study of Japanese men and women aged 40–79 years revealed graded inverse associations between the number of healthy lifestyle behaviours and mortality from stroke, CHD, and total CVD.

These associations have been documented previously among Western populations. In the Nurses' Health study, 84 129 women were followed up for 14 years, and the HRs for CHD and CVD incidence were 0.17 (0.07–0.41) and 0.25 (0.14–0.44), respectively, for women who had five healthy lifestyle behaviours compared those with none of them.[19] In the Health Professional Follow-up study, 42 847 men were followed up for 16 years, and the HR of CHD incidence was 0.13 (0.09–0.19) for men who had five healthy lifestyle behaviours when compared with those with none of them.[27] Similarly, in the Nutrition Potsdam study, 23 153 men and women aged 35–65 years were followed up for 8–12 years, and the HRs were 0.81 (0.47–0.93) for myocardial infarction incidence, and 0.36 (0.05–0.57) for stroke for men and women together who had four (no score for alcohol consumption) healthy lifestyle behaviours.[28] The components of the score of lifestyle behaviours of those three studies were more or less similar to those of our study, i.e. (Diet, exercise, BMI, alcohol consumption, and smoking status). Scoring was similar for the Nurse Health study and HPFS as follows, i.e. scoring with in the top 40% of healthy diet, moderate to vigorous exercise for $\geq$30 min per day, BMI of $<$25, alcohol consumption 5–45 g

Table 2 Sex-specific and smoking status-stratified hazard ratios and 95% confidence intervals of cardiovascular disease mortality for individual health behaviours

	Prevalence of healthy behaviour (%)	Total	Smoking status		*P* for interaction
			Smokers	Non-smokers	
Men					
Person-years		270 105	146 534	123 572	
Fruits ≥1/day vs. others, *n*	55.2	560/452	304/262	256/190	
Age-adjusted HR (95% CI)		0.86 (0.77–0.97)	0.97 (0.82–1.14)	0.77 (0.64–0.94)	0.03
Multivariable HR (95% CI)		0.93 (0.82–1.06)	0.98 (0.83–1.17)	0.87 (0.72–1.06)	0.39
Fish ≥1/day vs. others, *n*	39.2	416/596	239/327	177/269	
Age-adjusted HR (95% CI)		0.91 (0.80–1.03)	0.99 (0.84–1.17)	0.82 (0.68–0.99)	0.03
Multivariable HR (95% CI)		0.93 (0.82–1.05)	1.00 (0.84–1.18)	0.82 (0.68–1.00)	0.15
Milk almost every day vs. others, *n*	40.8	406/606	218/348	188/258	
Age-adjusted HR (95% CI)		0.81 (0.72–0.92)	0.97 (0.82–1.15)	0.70 (0.58–0.85)	0.06
Multivariable HR (95% CI)		0.88 (0.77–1.00)	0.98 (0.83–1.17)	0.76 (0.63–0.92)	0.04
Habitual exercise or walking vs. others, *n*	71.0	726/286	403/163	323/123	
Age-adjusted HR (95% CI)		0.83 (0.72–0.95)	0.78 (0.65–0.94)	0.87 (0.71–1.07)	0.07
Multivariable HR (95% CI)		0.84 (0.73–0.97)	0.79 (0.66–0.96)	0.89 (0.72–1.10)	0.24
Body mass index 21–25 kg/m^2 vs. others, *n*	52.2	444/568	247/319	197/249	
Age-adjusted HR (95% CI)		0.77 (0.68–0.87)	0.81 (0.68–0.95)	0.75 (0.62–0.91)	0.12
Multivariable HR (95% CI)		0.78 (0.69–0.88)	0.80 (0.67–0.94)	0.75 (0.62–0.90)	0.51
Ethanol intake <46.0 g/day vs. others, *n*	68.3	712/300	365/201	347/99	
Age-adjusted HR (95% CI)		0.77 (0.67–0.89)	0.82 (0.69–0.98)	0.80 (0.63–1.00)	0.22
Multivariable HR (95% CI)		0.85 (0.74–0.97)	0.85 (0.71–1.01)	0.86 (0.68–1.08)	0.57
Sleep 5.5–7.4 h/day vs. others, *n*	48.5	363/649	204/362	159/287	
Age-adjusted HR (95% CI)		0.78 (0.69–0.89)	0.82 (0.69–0.98)	0.77 (0.63–0.93)	0.07
Multivariable HR (95% CI)		0.84 (0.73–0.95)	0.85 (0.71–1.01)	0.81 (0.67–0.99)	0.37
Non-smoker vs. others, *n*	45.6	446/566	566	446	
Age-adjusted HR (95% CI)		0.69 (0.61–0.78)			
Multivariable HR (95% CI)		0.70 (0.62–0.80)			
Women					
Person-years		359 197	16 222	342 974	
Fruits ≥1/day vs. others, *n*	72.7	601/294	36/28	565/266	
Age-adjusted HR (95% CI)		0.76 (0.66–0.88)	0.77 (0.47–1.26)	0.77 (0.67–0.89)	0.97
Multivariable HR (95% CI)		0.82 (0.71–0.95)	0.75 (0.45–1.26)	0.83 (0.71–0.96)	0.79
Fish ≥1/day vs. others, *n*	41.0	330/565	21/43	309/522	
Age-adjusted HR (95% CI)		0.81 (0.71–0.93)	1.04 (0.61–1.75)	0.81 (0.70–0.93)	0.27
Multivariable HR (95% CI)		0.87 (0.76–1.00)	0.98 (0.57–1.71)	0.86 (0.74–0.99)	0.40
Milk almost every day vs. others, *n*	47.2	393/502	26/38	367/464	
Age-adjusted HR (95% CI)		0.88 (0.77–1.01)	1.25 (0.76–2.05)	0.87 (0.76–1.00)	0.20
Multivariable HR (95% CI)		0.96 (0.84–1.10)	1.22 (0.72–2.06)	0.95 (0.82–1.09)	0.52
Habitual exercise or walking vs. others, *n*	73,6	637/258	39/25	598/233	
Age-adjusted HR (95% CI)		0.84 (0.73–0.98)	0.53 (0.32–0.87)	0.88 (0.76–1.03)	0.04
Multivariable HR (95% CI)		0.86 (0.74–0.99)	0.51 (0.30–0.86)	0.90 (0.77–1.05)	0.02
Body mass index 21–25 kg/m^2 vs. others, *n*	48.7	315/580	18/46	297/534	
Age-adjusted HR (95% CI)		0.71 (0.62–0.81)	0.77 (0.44–1.34)	0.71 (0.62–0.82)	0.50
Multivariable HR (95% CI)		0.73 (0.64–0.84)	0.65 (0.37–1.17)	0.73 (0.63–0.84)	0.72
Ethanol intake <46.0 g/day vs. others, *n*	99.2	886/9	60/4	826/5	
Age-adjusted HR (95% CI)		0.41 (0.21–0.78)	0.49 (0.17–1.38)	0.54 (0.22–1.30)	0.53
Multivariable HR (95% CI)		0.54 (0.28–1.05)	0.50 (0.17–1.48)	0.63 (0.26–1.52)	0.64
Sleep 5.5–7.4 h/day vs. others, *n*	61.9	358/537	24/40	334/497	
Age-adjusted HR (95% CI)		0.76 (0.66–0.87)	0.66 (0.39–1.11)	0.77 (0.67–0.89)	0.96

Continued

Table 2 ***Continued***

	Prevalence of healthy behaviour (%)	Total	Smoking status		P for interaction
			Smokers	Non-smokers	
Multivariable HR (95% CI)		0.80 (0.69–0.91)	0.58 (0.33–0.99)	0.81 (0.71–0.94)	0.65
Non-smoker vs. others, *n*	95.3	831/64	64	831	
Age-adjusted HR (95% CI)		0.57 (0.44–0.74)			
Multivariable HR (95% CI)		0.67 (0.52–0.87)			

Multivariable adjustment: age, history of hypertension, history of diabetes, education level, regular employment, perceived mental stress, and seven health behaviours other than specified variable.

or 5–30 g per day, and non-smoking.[19,27] For the Nutrition-Potsdam study, healthy behaviours were high consumptions of fruits, vegetables, whole grain bread, and low consumption of meat, physical activity >3.5 h per week, a BMI<30 kg/m^2, and never smoking.[28] However, in our study, we expanded the lifestyle behaviour to include fish and milk consumption and moderate sleep duration because of the emerging evidences on their CVD effects.[2,3,8,12,13,18] The score for diet as a healthy lifestyle behaviour, of many of the previous studies[19,21,27,28] was so widely expanded to include higher consumption of fruit, vegetable, nuts, soy, whole-grain bread, cereal fibre, multivitamin, marine n-3 fatty acids and folate, and polyunsaturated to saturated fat ratio, and lower intakes of meat, trans fat, glycaemic load and allocated one point for those who scored high. However, we allocated one point each for each of the three components of dietary intake, i.e. (fish, milk, and fruits) for practical purposes to be easily applied by the public. The healthy lifestyle score was categorized to 0–2, 3, 4, 5, 6, 7–8 for this study to balance the number in men and women in each category. However, the analysis without categorization did not change the result and the categorization did not seem to alter the results. Also, the results of the relationship between weighted healthy lifestyle score and CVD mortality did not make substantial difference from that of non-weighted score.

Our results showed that each lifestyle behaviours had impacts on CVD mortality as previous studies showed.[1–8,11–18] According to the estimation of PAF for each lifestyle, moderate BMI had the biggest impact on cardiovascular health in the present study.

Although several studies[19,27,28] have focused on the risk for CVD among men only, women only, or men and women combined, few studies have addressed a sex difference in the impacts of lifestyle behaviours. In the study of 43 685 men and 71 243 women from the Health Professional Follow-up study and the Nurses' Health study, the multivariable-adjusted HRs of stroke among people with the highest lifestyle score compared with the lowest were 0.31 (0.19–0.53) in men and 0.21 (0.12–0.36) in women.[20] Moreover, in the EPIC Norfolk study, 20 040 men and women aged 40–79 years followed up for 10–14 years also show a graded inverse association between four lifestyle behaviours (plasma concentration of vitamin C ≥50 μmol/L, regular physical activity, moderate alcohol intake 1–112 g per week, and non-smoking status) and stroke mortality. The HRs were 1.48 (0.62–3.53) for men and 3.49 (1.71–7.12) for women in lowest lifestyle score categories compared with the highest.[21] Both of these two studies[20,21] demonstrated larger magnitude of risk reduction among women compared with men in Western countries. In our study, the HRs of total CVD mortality in each healthy lifestyle score category were 1.2–1.5-fold higher among men than among women. The survival curves of total CVD mortality were also less divergent across the healthy lifestyle score categories among men compared with women. Also, they were less divergent among smokers than non-smokers based on both relative risk and absolute risk analyses among men while smoking was generally associated with the higher crude mortality rate in each of the lifestyle score categories. These findings suggest that the protective effect of healthy lifestyle behaviours on morbidity from CVD was masked by smoking. It has been reported that smoking reduces the beneficial effect of physical activity[29] and that vitamin C is effective to reduce hs-CRP levels, an emerging cardiovascular risk marker, only among non-smokers.[30]

In previous studies that have compared individuals in the low-risk category with the rest of population, the reported PAF has been 35% in men and 47% in women for stroke,[20] 62%[27] in men and 82%[19] in women for CHD, and 74%[19] in women for total CVD. Although a simple comparison of PAF is not satisfactory, because of the different scoring methods of lifestyles among studies, all investigations including our study indicated a large potential for the prevention of CVD by the implementation of healthy lifestyle behaviours. Moreover, in the present study, the result of PAF_{+1} indicated that improving just one of these behaviours may translate into benefits equating to a one-fourth decrease in the mortality from total CVD for both men and women.

The strong points of our study were: first, the large-scale cohort with subjects from all over Japan which included >1900 deaths from total CVD; Second, the long follow-up period with a 16.5 year median; Third, the collection of a number of variables at baseline and the adjustment for potential confounding variables; and fourth, the sensitivity analysis with different categorization of the score, for the use of weighted score, and the exclusion of the first 5 years of death from the baseline. These advantages allowed us to estimate the impacts of healthy lifestyle behaviours on CVD mortality. The healthy lifestyle score we adopted was practical to understand and to calculate, and corresponded to possible lifestyle improvements. Thus, it motivates both individuals and health promoters for lifestyle improvement.