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paste, 0.544 g for dried or salted fish, 0.929 g for deep-fried foods or *tempura*, 0.357 g for fried vegetables, 0.230 g for boiled beans, and 0.184 g for *miso* soup. The amounts of nutrients consumed were calculated by multiplying the frequency scores and estimated nutrients for each portion and summing across all 33 items. Data on fish oil supplementation were not available in the baseline survey, but supplement use was not common among Japanese adults. The details of the validation study and methods for the estimation of nutrient factors were reported previously (13).

Subjects missing the fresh fish intake item and subjects missing more than 1 of the other 3 fish items were excluded during fish or ω-3 PUFA estimation. Furthermore, subjects with a missing response to more than 4 of the 33 items on the food frequency questionnaire were also excluded, leaving 57,972 eligible for the analyses. Energy adjustments were done for dietary intakes of fish, vegetables, fruit, ω-3 and ω-6 PUFA, saturated fatty acids, and cholesterol, using the nutrient residual model (14).

We previously had performed another validation study of the frequency of fresh fish, steamed fish paste, and dried or salted fish captured by the JACC study questionnaires compared with serum ω-3 PUFA levels in a subsample (n = 1,319) (15). We also tested the validity of dietary intakes of fish and ω-3 PUFA: The age- and gender-adjusted mean plasma ω-3 PUFA levels (weight percent of total fatty acids) across quintiles of energy-adjusted fish intake were 9.5, 9.8, 10.4, 10.5, and 11.2 (p for trend <0.001), and respective values across quintiles of energy-adjusted ω-3 PUFA intake were 9.5, 10.0, 10.4, 10.3, and 11.2 (p for trend <0.001).

The quintiles of energy-adjusted fish intake were 0 to 27, 27 to 39, 39 to 53, 53 to 72, and 72 to 229 g/day, and those of ω-3 PUFA intake were 0.05 to 1.18, 1.18 to 1.47, 1.47 to 1.75, 1.75 to 2.11, and 2.11 to 5.06 g/day. The validation study showed that the estimated mean fish intake in this study compared with dietary records in a subsample (n = 88, mostly female) were one-half that in the dietary record (42.9 vs. 87.2 g/day).

Statistical analysis. Age-adjusted means and proportions of selected cardiovascular risk factors and nutrients were calculated according to quintiles of energy-adjusted dietary intakes of fish and ω-3 PUFA, and the overall difference across the quintiles was tested by analysis of covariance. For each participant, we calculated the person-years of follow-up from baseline in 1988 to 1990 to the first end point: death, moving from the community, or the end of 2003. The mortality rates of each outcome were calculated according to quintiles of intakes of fish or ω-3 PUFA. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated after adjustment of age, gender, and other potential confounding factors with Cox proportional hazards survival models. The confounding factors included body mass index (quintiles), history of hypertension and diabetes mellitus (yes or no), smoking status (never, former smoker, and current smoker of 1 to 19 or ≥20 cigarettes/day), alcohol intake (never, former drinker, and current drinker of ethanol at 1 to 22, 23 to 45, 46 to 68, or ≥69 g/day; 23 g ethanol corresponds to 1 *go*, a Japanese traditional unit for volume), perceived mental stress (low, medium, or high), walking (rarely, 30, 30 to 60, or more than 60 min/day), sports (rarely, or more than 1 h/week), education levels (age of completed education of <13, 13 to 15, 16 to 18, or ≥19 years), and continuous values of total energy and energy-adjusted nutrient intakes (cholesterol, saturated fatty acids, and ω-6 PUFA), and quintiles of energy-adjusted vegetable and fruit intakes. Body mass index was calculated as body weight (kg) divided by the square of height (m^2), where weight and height were obtained from the baseline questionnaire. Histories of hypertension and diabetes were derived from the baseline questionnaire. The linear trend of HRs across the quintiles was tested by using variables with −2, −1, 0, 1, and 2 assigned to successive quintiles. Multiplicative interactions with gender were tested using a cross-product term (16). We excluded monounsaturated fatty acids from the models because of multicolinearity with dietary intakes of cholesterol and saturated fatty acids (Spearman correlation coefficient = 0.72 and 0.82, respectively).

We used SAS version 9.1.3 Service Pack 4 (SAS Institute, Cary, North Carolina) for the analyses. All probability values for statistical tests were two-tailed, and values of $p < 0.05$ were regarded as statistically significant.

Results

During 735,905 person-years of follow-up for 57,972 persons, we documented 419 deaths due to IHD (including 329 myocardial infarctions), 107 due to cardiac arrest, 307 due to heart failure, and 972 due to stroke (including 223 intraparenchymal hemorrhages, 153 subarachnoid hemorrhages, and 319 ischemic strokes); there were 2,045 total cardiovascular deaths and 7,008 total deaths.

As shown in Table 1, several variables, such as age, mean body mass index, history of diabetes, current smoking, mean alcohol intake, high perceived mental stress, and all nutrient factors, were correlated with energy-adjusted fish intake. The Spearman correlation coefficient between energy-adjusted dietary intakes of fish and ω-3 PUFA was 0.84. As a result, we observed similar correlations between dietary intake of ω-3 PUFA and the preceding variables (not shown in the table).

Because no interactions with gender were observed for the association of fish or ω-3 PUFA intake with any end point, we combined men and women for further analyses. Table 2 shows the HRs of cardiovascular diseases according to dietary intake of fish. Fish intake tended to be inversely associated with age- and gender-adjusted risks of IHD, myocardial infarction, and heart failure. Risk of cardiac arrest tended to be higher in the second and third quintiles of fish intake but to be lower in the higher quintiles with no

Table 1 Baseline Characteristics of Cardiovascular Risk Factors and Selected Dietary Variables in a Cohort of 22,881 Men and 35,091 Women to Quintile of Fish Intakes

	Men						Women					
	Quintiles of Fish Intake*						Quintiles of Fish Intake*					
	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	p Value†	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	p Value†
Median intake*, g/day	20	33	45	62	86		21	33	46	62	85	
Number at risk	4,845	4,608	4,345	4,446	4,637		6,749	6,987	7,249	7,149	6,957	
Age at baseline, yrs	54.7	55.2	55.7	56.1	57.8	<0.001	56.5	55.6	55.7	56.5	56.9	<0.001
Mean body mass index‡, kg/m^2	22.6	22.7	22.7	22.8	22.7	0.03	22.8	22.9	22.9	23.0	23.1	<0.001
History of hypertension‡, %	18	17	18	18	18	0.39	19	20	19	19	20	0.61
History of diabetes mellitus‡, %	5	5	6	5	7	0.006	3	3	3	3	4	0.08
Current smoker‡, %	55	52	51	51	51	<0.001	6	5	4	4	4	<0.001
Mean alcohol intake‡, g/day	35.6	33.9	33.5	35.8	31.0	<0.001	12.6	9.8	9.2	10.1	8.7	<0.001
Sports 5 h/week or more‡, %	6	7	7	7	7	0.19	4	4	4	4	4	0.51
Walking 1 h/day or more‡, %	47	47	47	48	46	0.70	48	48	47	49	47	0.29
College or higher education‡, %	17	17	17	16	19	0.01	10	10	10	10	10	0.56
High perceived mental stress‡, %	23	25	24	24	26	0.01	22	21	20	21	20	0.12
Mean energy intake‡, Kcal/day	1,624	1,623	1,659	1,746	1,591	<0.001	1,306	1,328	1,340	1,396	1,274	<0.001
Dietary cholesterol‡, mg/day	186	219	242	272	291	<0.001	192	220	243	270	276	<0.001
Saturated fatty acids‡, g/day	7.9	8.7	9.3	9.9	10.0	<0.001	8.2	9.0	9.4	10.0	9.4	<0.001
Monounsaturated fatty acids‡, g/day	7.4	8.7	9.6	10.6	11.1	<0.001	7.8	9.0	9.7	10.7	10.5	<0.001
Polyunsaturated fatty acids‡, g/day	6.7	7.6	8.2	9.0	9.1	<0.001	6.5	7.3	7.9	8.7	8.5	<0.001
ω-3 polyunsaturated fatty acids‡, g/day	1.0	1.3	1.6	2.0	2.3	<0.001	1.1	1.4	1.6	2.0	2.2	<0.001
ω-6 polyunsaturated fatty acids‡, g/day	5.7	6.2	6.6	7.0	6.8	<0.001	5.5	6.0	6.3	6.7	6.3	<0.001
Fish intake‡, g/day	19	33	46	65	86	<0.001	19	33	46	66	84	<0.001
Vegetable intake‡, g/day	71	83	93	104	110	<0.001	87	96	106	116	120	<0.001
Fruit intake‡, g/day	101	110	117	126	132	<0.001	131	139	145	153	148	<0.001

*Energy-adjusted values by nutrient residual model; †p values for overall difference among quintiles based on analysis of covariance; ‡age-adjusted.

significant trend. No associations were observed for total stroke or its subtypes. Inverse associations were observed for total cardiovascular disease, and less prominently, for total death. After further adjustment for cardiovascular risk factors and dietary variables, these inverse associations were generally weakened but were not altered substantially.

Similarly, Table 3 shows the HRs of cardiovascular diseases according to dietary intake of ω-3 PUFA. The results were essentially the same as those for fish intake. However, the associations of ω-3 PUFA with heart failure were more prominent than with fish intake. An inverse trend was also observed for intraparenchymal hemorrhage but was no longer significant after adjustment for cardiovascular risk factors. Our results were essentially the same when analyzed for long-chain ω-3 PUFA (a sum of eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids), although the association for heart failure became weaker: the multivariable HR (95% CI) for the highest versus lowest quintiles was 0.80 (0.55 to 1.17), p for trend was 0.13.

There were no differences between genders in any associations shown in Tables 2 and 3. For example, the gender-specific multivariable HRs (95% CIs) for the highest versus lowest quintiles of fish intake for total cardiovascular disease were 0.84 (0.69 to 1.04) for men and 0.83 (0.68 to 1.02) for women, and respective HRs for ω-3 PUFA were 0.83 (0.63 to 1.08) for men and 0.84 (0.64 to 1.10) for women.

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Table 2 Multivariate HRs and 95% CIs of Mortality From Ischemic Heart Disease, Cardiac Arrest, Heart Failure, Stroke, Total Cardiovascular Disease, and Total Death According to Quintiles of Fish Intake, 22,881 Men and 35,091 Women

	Quintiles of Fish Intake*					
	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	p Value for Trend
Person-years	144,903	146,244	147,322	148,797	148,639	
Ischemic heart disease, n	89	79	88	79	84	
Age- and gender-adjusted	1.0	0.93 (0.69–1.26)	1.00 (0.75–1.35)	0.85 (0.63–1.15)	0.78 (0.58–1.06)	0.09
Multivariable†	1.0	0.99 (0.73–1.34)	1.11 (0.82–1.51)	0.98 (0.71–1.34)	0.86 (0.62–1.19)	0.41
Myocardial infarction, n	74	59	73	59	64	
Age- and gender-adjusted	1.0	0.83 (0.59–1.17)	1.00 (0.72–1.38)	0.76 (0.54–1.07)	0.72 (0.52–1.01)	0.05
Multivariable†	1.0	0.87 (0.62–1.23)	1.10 (0.79–1.54)	0.87 (0.61–1.24)	0.77 (0.53–1.10)	0.22
Cardiac arrest, n	19	25	27	18	18	
Age- and gender-adjusted	1.0	1.39 (0.77–2.53)	1.44 (0.80–2.59)	0.89 (0.47–1.70)	0.74 (0.39–1.42)	0.15
Multivariable†	1.0	1.44 (0.79–2.62)	1.49 (0.81–2.72)	0.90 (0.46–1.76)	0.73 (0.36–1.46)	0.16
Heart failure, n	77	59	46	56	69	
Age- and gender-adjusted	1.0	0.82 (0.59–1.16)	0.62 (0.43–0.89)	0.71 (0.50–1.00)	0.77 (0.55–1.06)	0.07
Multivariable†	1.0	0.83 (0.59–1.17)	0.63 (0.43–0.91)	0.72 (0.50–1.03)	0.76 (0.53–1.09)	0.10
Total stroke, n	208	179	178	191	216	
Age- and gender-adjusted	1.0	0.91 (0.75–1.11)	0.87 (0.71–1.07)	0.88 (0.72–1.07)	0.87 (0.72–1.06)	0.17
Multivariable†	1.0	0.95 (0.78–1.16)	0.93 (0.76–1.14)	0.92 (0.75–1.14)	0.91 (0.74–1.13)	0.40
Intraparenchymal hemorrhage, n	53	43	41	37	49	
Age- and gender-adjusted	1.0	0.84 (0.56–1.26)	0.78 (0.52–1.17)	0.67 (0.44–1.01)	0.80 (0.54–1.18)	0.13
Multivariable†	1.0	0.93 (0.62–1.40)	0.91 (0.60–1.39)	0.78 (0.50–1.21)	0.95 (0.62–1.47)	0.58
Subarachnoid hemorrhage, n	30	33	27	33	30	
Age- and gender-adjusted	1.0	1.12 (0.68–1.83)	0.89 (0.53–1.49)	1.04 (0.63–1.70)	0.91 (0.55–1.51)	0.64
Multivariable†	1.0	1.18 (0.71–1.94)	0.96 (0.57–1.65)	1.12 (0.67–1.89)	0.96 (0.55–1.68)	0.84
Ischemic stroke, n	67	57	58	64	73	
Age- and gender-adjusted	1.0	0.92 (0.64–1.30)	0.89 (0.63–1.26)	0.93 (0.66–1.30)	0.89 (0.64–1.24)	0.56
Multivariable†	1.0	0.96 (0.67–1.37)	0.97 (0.68–1.40)	0.98 (0.68–1.40)	0.93 (0.65–1.34)	0.78
Total cardiovascular disease, n	453	384	383	389	436	
Age- and gender-adjusted	1.0	0.90 (0.78–1.03)	0.86 (0.75–0.99)	0.82 (0.72–0.94)	0.81 (0.71–0.92)	<0.001
Multivariable†	1.0	0.93 (0.81–1.06)	0.91 (0.79–1.05)	0.86 (0.75–1.00)	0.82 (0.71–0.95)	0.007
Total death, n	1,429	1,288	1,328	1,397	1,566	
Age- and gender-adjusted	1.0	0.94 (0.87–1.01)	0.94 (0.87–1.01)	0.93 (0.87–1.00)	0.93 (0.86–1.00)	0.06
Multivariable†	1.0	0.96 (0.89–1.04)	0.98 (0.90–1.05)	0.96 (0.89–1.04)	0.92 (0.85–1.00)	0.08

*Energy-adjusted quintiles by nutrient residual model. †Further adjusted for history of hypertension and diabetes mellitus, smoking status, alcohol consumption, body mass index, mental stress, walking, sports, education levels, total energy, and dietary intakes of cholesterol, saturated and ω-6 polyunsaturated fatty acids, vegetables, and fruit.
CI = confidence interval; HR = hazard ratio.

Discussion

In this large, community-based, prospective cohort study, we observed generally inverse associations of fish and dietary ω-3 PUFA intakes with risks of mortality from IHD, myocardial infarction, heart failure, and total cardiovascular disease. These inverse associations were more evident between dietary ω-3 PUFA intake and heart failure. However, inverse associations with IHD or myocardial infarction were attenuated after adjustment for potential risk factors. As for stroke, neither fish nor ω-3 PUFA dietary intakes were associated with mortality risk. Compared with the lowest quintile, dietary intakes of fish and ω-3 PUFA in the highest quintile were associated with 18% to 19% lower mortality rates of total cardiovascular disease.

Previous Asian reports (2,4,5) have shown that fish or ω-3 PUFA was associated inversely with the risk of IHD. The relatively weak association in the present study may be partly due to the use of mortality, rather than incidence, data. A previous prospective study of a national representative sample of 8,879 Japanese men and women (NIPPON DATA 80) did not show a significant association between fish intake and coronary mortality (3). The Japan Public Health Center-based prospective study (4), a cohort study of 41,578 men and women, showed a strong inverse association primarily for nonfatal coronary events but not for fatal events. Furthermore, the JELIS (Japan EPA Lipid Intervention Study), a recent Japanese intervention trial of 18,645 hypercholesterolemic patients (5), demonstrated a protective effect of eicosapentaenoic acid supplementation on nonfatal coronary events, but an effect on fatal coronary

Table 3 Multivariate HRs and 95% CIs of Mortality From Ischemic Heart Disease, Cardiac Arrest, Heart Failure, Stroke, Total Cardiovascular Disease, and Total Death According to Quintiles of ω-3 PUFA Intake, 22,881 Men and 35,091 Women

	Quintiles of ω-3 PUFA Intake*					
	Q1 (Low)	Q2	Q3	Q4	Q5 (High)	p Value for Trend
Person-years	143,208	145,552	148,548	149,359	149,237	
Ischemic heart disease, n	75	86	78	81	99	
Age- and gender-adjusted	1.0	1.06 (0.78–1.45)	0.86 (0.62–1.18)	0.84 (0.61–1.15)	0.82 (0.61–1.11)	0.07
Multivariable†	1.0	1.17 (0.84–1.62)	0.98 (0.69–1.40)	1.00 (0.68–1.45)	0.95 (0.62–1.43)	0.58
Myocardial infarction, n	65	65	60	60	79	
Age- and gender-adjusted	1.0	0.93 (0.66–1.31)	0.77 (0.54–1.09)	0.73 (0.51–1.03)	0.78 (0.56–1.08)	0.05
Multivariable†	1.0	0.97 (0.67–1.40)	0.81 (0.54–1.20)	0.77 (0.51–1.18)	0.75 (0.47–1.19)	0.14
Cardiac arrest, n	14	18	38	17	20	
Age- and gender-adjusted	1.0	1.14 (0.57–2.29)	2.05 (1.11–3.79)	0.87 (0.43–1.77)	0.78 (0.40–1.56)	0.33
Multivariable†	1.0	1.07 (0.51–2.22)	1.86 (0.92–3.74)	0.76 (0.33–1.73)	0.64 (0.26–1.59)	0.24
Heart failure, n	68	53	50	58	78	
Age- and gender-adjusted	1.0	0.73 (0.51–1.04)	0.61 (0.42–0.88)	0.68 (0.48–0.96)	0.73 (0.53–1.01)	0.07
Multivariable†	1.0	0.69 (0.47–1.01)	0.56 (0.37–0.85)	0.60 (0.39–0.92)	0.58 (0.36–0.93)	0.03
Total stroke, n	159	166	201	186	260	
Age- and gender-adjusted	1.0	0.97 (0.78–1.20)	1.04 (0.85–1.28)	0.92 (0.74–1.14)	1.04 (0.85–1.26)	0.93
Multivariable†	1.0	0.95 (0.75–1.19)	1.00 (0.79–1.26)	0.87 (0.67–1.12)	0.93 (0.70–1.22)	0.46
Intraparenchymal hemorrhage, n	49	44	42	39	49	
Age- and gender-adjusted	1.0	0.85 (0.56–1.27)	0.74 (0.49–1.12)	0.65 (0.43–0.99)	0.69 (0.47–1.03)	0.03
Multivariable†	1.0	0.87 (0.56–1.35)	0.77 (0.48–1.24)	0.68 (0.41–1.14)	0.70 (0.40–1.24)	0.16
Subarachnoid hemorrhage, n	28	28	33	32	32	
Age- and gender-adjusted	1.0	0.94 (0.56–1.59)	1.04 (0.63–1.72)	0.98 (0.59–1.63)	0.91 (0.55–1.52)	0.80
Multivariable†	1.0	0.98 (0.56–1.70)	1.08 (0.61–1.93)	1.02 (0.55–1.89)	0.90 (0.44–1.81)	0.83
Ischemic stroke, n	43	50	71	62	93	
Age- and gender-adjusted	1.0	1.07 (0.71–1.61)	1.32 (0.91–1.93)	1.10 (0.75–1.63)	1.27 (0.88–1.83)	0.22
Multivariable†	1.0	1.06 (0.69–1.63)	1.31 (0.85–2.01)	1.07 (0.68–1.69)	1.17 (0.71–1.92)	0.58
Total cardiovascular disease, n	360	367	412	388	518	
Age- and gender-adjusted	1.0	0.94 (0.81–1.09)	0.94 (0.82–1.08)	0.84 (0.73–0.97)	0.90 (0.79–1.04)	0.04
Multivariable†	1.0	0.93 (0.80–1.09)	0.91 (0.78–1.07)	0.81 (0.68–0.96)	0.81 (0.67–0.98)	0.01
Total death, n	1,252	1,262	1,328	1,415	1,751	
Age- and gender-adjusted	1.0	0.95 (0.88–1.02)	0.90 (0.84–0.98)	0.91 (0.84–0.98)	0.93 (0.87–1.00)	0.03
Multivariable†	1.0	0.97 (0.90–1.06)	0.94 (0.86–1.02)	0.94 (0.85–1.03)	0.92 (0.84–1.02)	0.10

*Energy-adjusted quintiles by nutrient residual model. †Further adjusted for history of hypertension and diabetes mellitus, smoking status, alcohol consumption, body mass index, mental stress, walking, sports, education levels, total energy, and dietary intakes of cholesterol, saturated and ω-6 PUFA, vegetables, and fruit.
PUFA = polyunsaturated fatty acids; other abbreviations as in Table 2.

events was not confirmed because of the small numbers (n = 60).

As for stroke, 3 previous observational studies have examined the associations between fish and stroke mortality among Asian populations (2,3,17). A study of 18,244 men in Shanghai, China (2), showed no association; the multivariable-adjusted HR (95% CI) for fish/shellfish intake of ≥200 g/week compared with <50 g/week was 1.11 (0.83 to 1.47). The NIPPON DATA 80 (3) reported a HR (95% CI) for fish intake of twice a day or more of 1.26 (0.70 to 2.29) and for intake of once a day of 1.20 (0.82 to 1.75) compared with once or twice a week. That study also showed no association with cerebral hemorrhage or infarction, separately. Another study of 40,349 men and women in Hiroshima and Nagasaki, Japan (17), showed 15% lower mortality from total stroke among persons with intake of fish products of ≥46 g/day compared with persons consuming ≤18 g/day. In that study, the risk reduction was primarily observed for intraparenchymal hemorrhage (HR: 0.70 [95% CI: 0.54 to 0.92]) but not for ischemic stroke (HR: 0.94 [95% CI: 0.77 to 1.14]). We observed a similar and nonsignificant inverse association with intraparenchymal hemorrhage. Taken together, dietary intakes of fish and ω-3 PUFA seem unlikely to have a protective effect on mortality from ischemic stroke and a harmful effect on mortality from intraparenchymal hemorrhage among Asian populations. As for incident stroke, a nested case-control study in a Japanese community cohort of approximately 10,000 subjects (18) showed no association between serum ω-3 PUFA (eicosapentaenoic, docosapentaenoic, or docosahexaenoic acid) concentrations and risk of stroke and its subtypes (HR for 1 SD changes ranged 1.01 to 1.17 for total stroke, 0.99 to 1.21 for ischemic stroke, and 0.87 to 1.09 for intraparenchymal hemorrhage; none of these reached sta-

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tistical significance). The JELIS trial (5) showed no protective effect of eicosapentaenoic acid supplementation on risk of incident total stroke (HR: 1.02 [95% CI: 0.91 to 1.13]), ischemic stroke (HR: 0.97 [95% CI: 0.85 to 1.10]), or hemorrhagic stroke (HR: 1.12 [95% CI: 0.91 to 1.39]) among Japanese hypercholesterolemic patients. Yet, to date, there are no reports on inverse associations between fish or ω-3 PUFA and the incidence of stroke among general populations of Asia. By contrast, inverse associations between fish or ω-3 PUFA and the incidence of total or ischemic stroke have been reported for Western populations, for example, Dutch (19) or Americans (20–23). However, consistent with the present study, such an association was not observed with stroke mortality in the Chicago Western Electric Study (24) or the Iowa Women's Health Study (25).

We did not observe clear inverse associations between dietary intake of fish or ω-3 PUFA with the risk of mortality from cardiac arrest, although a tendency of lower risk was observed in the top 2 quintiles of fish intake. Despite growing evidence of an antiarrhythmic effect of fish oil (26), a number of trials have shown that ω-3 PUFA supplements have little effect on the rate of defibrillator firings in patients with implantable cardioverter-defibrillators (27). The JELIS trial (5) did not find that eicosapentaenoic acid supplementation reduced sudden death (HR: 1.06 [95% CI: 0.55 to 2.07]), probably because of a small number of cases (n = 35) and the high background fish consumption among Japanese. It has been suggested that the slope of the dose-response curve for the antiarrhythmic effect of ω-3 PUFA is steep at modest levels (<750 mg eicosapentaenoic plus docosahexaenoic acid) but plateaus thereafter (28).

Few studies have examined the association of fish and ω-3 PUFA intakes with the incidence of congestive heart failure. The Cardiovascular Health Study, involving 4,738 men and women ages ≥65 years (8), found an inverse association of baked/broiled fish intake with congestive heart failure; the HR (95% CI) for baked/broiled fish intake of ≥5 times a week versus <1 time a month was 0.68 (0.45 to 1.03), and the trend across the frequency categories was statistically significant (p = 0.009). A similar inverse association was observed for quintiles of long-chain ω-3 PUFA (eicosapentaenoic and docosahexaenoic acids). This result was supported by a recent report from the ARIC (Atherosclerosis Risk in Communities) study, showing an inverse association between plasma long-chain ω-3 PUFA and incident heart failure among women (29). Our findings are in line with these studies. On the other hand, another ARIC study (9) found no association between dietary fish intake ascertained by food frequency questionnaire and incident heart failure, probably because fried fish could not be differentiated from other fish. The Cardiovascular Health Study (8) reported that fried fish, unlike baked/broiled fish, increased the risk of incident heart failure. Our questionnaire did not directly ask about fried fish intake, but when we excluded the estimated amount of deep-fried fish from the present analysis for fish intake, the inverse association with heart failure did not change materially: the multivariate HR (95% CI) for the highest versus lowest quintiles of fish intake was 0.78 (0.55 to 1.10), p for trend was 0.14. This finding may reflect a cultural difference in fried fish intake between Western and far-Eastern countries, namely, that fried fish in Japan is usually rich in ω-3 PUFA, unlike the white fish used in the United States. Japanese also use less cooking oil containing trans fats.

For heart failure, however, the accuracy of death certificate diagnosis in Japan is a concern. It is generally believed that death certificate diagnosis for heart failure before 1994 was not necessarily accurate, because Japanese physicians were inclined to diagnose deaths of unknown origin or deaths occurring during the end stages of chronic diseases as "unspecified heart failure" (I50.9 for ICD-10) (30). Sudden death of unknown origin, such as cardiac arrest or arrhythmic death, was especially likely to be classified as heart failure, whereas these deaths have been mainly diagnosed as IHD in the U.S. (31). Sudden death was reported to account for 27% to 50% of diagnosed heart failure as the underlying cause of death in Japan (30). Therefore, we speculate that one-fourth to one-half of the heart failure in this study was contaminated with cardiac arrest, and that may have affected the association of fish or ω-3 PUFA intake with heart failure.

It has been speculated that docosahexaenoic acid is most important for cardioprotection (10), because sudden cardiac deaths were not reduced by eicosapentaenoic acid supplementation in the JELIS trial (5). The aforementioned ARIC study reported that higher plasma docosahexaenic, but not eicosapentaenoic, acid was inversely associated with incident heart failure among white women (29). In the present study, however, eitacopentaenoic and docosahexaenoic acids were highly correlated with each other (r = 0.99), and therefore dietary intakes of these were similarly associated with cardiovascular outcomes (not shown).

The JACC study is a large, nationwide, community-based Japanese cohort, which allowed us to examine the associations of fish and ω-3 PUFA intakes with heart failure for the first time in Asian populations. Another advantage of the present study was the wider distribution of fish intake than that in Western studies. Therefore, we could test the potential effect of very high intake of fish or ω-3 PUFA, which cannot be studied in Western populations.

Study limitations. Dietary intakes in this study were based on a food frequency questionnaire. Although this questionnaire has been previously validated (13,15), there are several limitations. First, for people who picked the highest categories of frequency, namely, almost every day, we could not estimate how many times they ate fish in a day. A previous

study (3) showed approximately 6% of Japanese men and women eat fish twice or more in a day. In the present study, 73% of people who responded "almost every day" for fish frequency fell into the highest quintile of nonenergy-adjusted fish intake, and 27% of them were in the second highest quintile of fish intake. Thus, the impact of misclassification may weaken the association to some extent but not substantially. Yet, it should be noted that the absolute amount of fish or ω-3 PUFA intake in the present study is probably underestimated; the estimated mean fish intake in the present study (49.5 g/day) was much lower than in a National Nutrition Survey in 1990 (95.3 g/day). Indeed, the estimated fish intake in this study was one-half that using dietary records in a subsample. Second, we excluded 23,339 subjects because of incomplete dietary information. Excluded subjects were older (60.8 vs. 56.1 years) and more likely to be men than women (45% vs. 39%) compared with included subjects, but there were only slight differences between them in other baseline characteristics, thus suggesting bias is unlikely. Lastly, we cannot negate the possibility of residual confounding by other factors, healthy life-styles, or socioeconomic status.

Conclusions

We found an inverse association between fish and ω-3 PUFA dietary intakes and cardiovascular mortality, especially for heart failure in a large, nationwide, community-based Japanese cohort. This finding, taken together with those from prior studies, suggests a protective effect of fish intake on cardiovascular diseases.

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Fruit, vegetable and bean intake and mortality from cardiovascular disease among Japanese men and women: the JACC Study

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To examine the association of plant-based food intakes with CVD and total mortality among Japanese. In the Japan Collaborative Cohort Study for Evaluation of Cancer Risk, 25 206 men and 34 279 women aged 40–79 years, whose fruit, vegetable and bean intakes were assessed by questionnaire at baseline in 1988–90, were followed for 13 years. Deaths from total stroke, stroke subtypes, CHD and total CVD, according to the International Classification for Diseases 10th Revision, were registered. During 756 054 person-years of follow-up, there were 559 deaths from total stroke, 258 from CHD, 1207 from total CVD and 4514 from total mortality for men, and for women, 494, 194, 1036 and 3092, respectively. Fruit intake was inversely associated with mortality from total stroke (the multivariable hazard ratio (HR (95 % CI)) in the highest *v.* lowest quartiles = 0·67 (0·55, 0·81)), total CVD (HR = 0·75 (0·66, 0·85)) and total mortality (HR = 0·86 (0·80, 0·92)). Vegetable intake was inversely associated with total CVD (HR = 0·88 (0·78, 0·99)). Bean intake was inversely associated with other CVD (HR = 0·79 (0·64, 0·98)), total CVD (HR = 0·84 (0·74, 0·95)) and total mortality (HR = 0·90 (0·84, 0·96)). Further adjustment for other plant-based foods did not alter the association of fruit intake with mortality from total stroke, total CVD and total mortality, but attenuated the associations of vegetables and beans with mortality risk. In conclusion, intakes of plant-based foods, particularly fruit intake, were associated with reduced mortality from CVD and all causes among Japanese men and women.

Fruits: Vegetables: Beans: CVD: Mortality

Protective effects of plant-based foods against CVD have been suggested by prospective cohort studies in Western countries[1–6]. Fruit and vegetable intakes were associated with reduced risks of stroke and CHD[1,2], and nut intake was associated with a reduced risk of CHD[3–6]. These potential effects of plant-based foods need to be examined for Japanese, because of their different profiles of CVD and diet. In Japan, the incidence of stroke is higher than that of CHD, and the proportion of haemorrhagic stroke among the stroke subtypes is higher than in Western countries[7,8]. The Japanese habitually consume more beans than the Westerners, and soyabeans, in particular, have recently been highlighted as a protective factor for CVD in Western countries[9,10].

So far, several Japanese studies have shown inverse associations of the fruit, vegetable or bean intake with the risk of stroke[11–14]. The Hiroshima/Nagasaki Life Span Study showed a protective association of both fruit and vegetable intakes with mortality from both ischaemic stroke and intra-parenchymal haemorrhage[11]. The Shibata Study showed a protective association of vegetable intake with the incidence of total stroke[12].

Abbreviation: HR, hazard ratio.

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The Japan Public Health Center-based Prospective Study showed a protective association of fruit intake with the incidence of CVD for Japanese men and women combined[13], and also showed a protective association of soya intake with the incidence of cerebral infarction and mortality from CVD for women[14]. The Takayama Study also showed a protective association of vegetable intake with mortality from CVD for Japanese women[15]. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk previously reported the association between plant-based food intakes and mortality from CVD, cancer and all causes[16], but these associations were not adjusted for major confounding factors.

Therefore, no study has examined whether plant-based foods were associated with CVD, their subtypes and total mortality systematically in Japan. Such a study in Japanese is also of value because plant-based food intakes are positively correlated with saturated fat intake in Japanese[15] unlike Western populations[17,18], and confounding factors may be different from Western studies. We hypothesised that higher plant-based food intake had beneficial effects for the prevention of CVD and their subtypes in general Japanese populations, and we comprehensively examined the associations of the fruit, vegetable and bean intake with mortality from stroke, stroke subtypes, CHD, total CVD and all causes in a 13-year cohort study of approximately 60 000 Japanese men and women.

Experimental methods

Subjects

The Japan Collaborative Cohort Study sponsored by Monbusho, the Ministry of Education, Science, Sports and Culture, began in 1988–90 when 110 792 individuals (46 465 men and 64 327 women) aged 40–79 years living in forty-five communities across Japan participated in municipal health screening examinations and completed a self-administered questionnaire about their lifestyles (habits of smoking and drinking, physical activity, hours of sleep, education and mental stress) and medical histories (hypertension, diabetes, CVD and cancer). Informed consent was obtained before completing the questionnaire. We excluded 2576 men and 3288 women from the analysis because of previous history of stroke, CHD or cancer at baseline. Persons (18 683 men and 26 760 women) with missing information regarding the intake of fruits, vegetables and beans were also excluded, and a total of 25 206 men and 34 279 women were used for the analysis. There was no substantial difference in mortality rates between persons who gave the valid dietary information and those who did not; the multivariable hazard ratios (HR (95 % CI)) for respondents *v.* non-respondents were 1·08 (0·98, 1·21) for total stroke, 0·98 (0·83, 1·14) for CHD, 1·04 (0·97, 1·12) for total CVD and 1·02 (0·98, 1·07) for all causes. No material differences were also found between the respondents and non-respondents for BMI, history of hypertension, history of diabetes, smoking, ethanol intake and other cardiovascular risk characteristics.

Dietary assessment

The self-administered FFQ was conducted to estimate the consumption of thirty-three foods during the past year[19]. The food items were beef, pork, ham or sausage, chicken, liver, eggs, milk, yogurt, cheese, butter, margarine, deep-fried foods or tempura, fried vegetables, fresh fish, steamed fish paste, dried fish or salted fish, spinach or garland chrysanthemum, carrot or pumpkin, tomatoes, cabbage or head lettuce, Chinese cabbage, edible wild plants, fungi, potatoes, algae, pickles, preserved foods using soya sauce, boiled beans, tofu, citrus fruits, fruits excluding citrus varieties, fresh fruit juice in summer and sweets. Each food had a five-level precoded answer: 'rarely eat'; 'once or twice per month'; 'once or twice per week'; 'three or four times per week'; 'almost daily'. Then, we converted the answers 'rarely eat' to 0, 'once or twice per month' to 0·375, 'once or twice per week' to 1·5, 'three or four times per week' to 3·5 and 'almost daily' to 7 servings per d to estimate the average weekly intake of each fruit (citrus fruits, fruits excluding citrus varieties and fresh fruit juice in summer), vegetable (spinach or garland chrysanthemum, carrot or pumpkin, tomatoes, cabbage or head lettuce and Chinese cabbage) and beans (tofu, i.e. soyabean curd, and boiled beans) for each participant. The average weekly intakes of individual foods were combined to compute the total fruit, vegetable and bean intakes.

The reproducibility of the dietary data was confirmed by comparing two questionnaires administered 1 year apart for eighty-five subjects (eight men and seventy-seven women)[19]. The median (range) values of the Spearman correlation coefficients were 0·57 (0·55, 0·58) for three items of fruits, 0·63 (0·43, 0·66) for five items of vegetables and 0·62 (0·59, 0·64) for two items of beans. The validity of the data was confirmed by comparing the data from the questionnaire with those from four 3-d dietary records for the eighty-five subjects, collected approximately 3–4 months apart[19]. The median values of the Spearman correlation coefficients were 0·26 (0·24, 0·39) for three items of fruits, 0·33 (0·18, 0·45) for five items of vegetables and 0·40 (0·30, 0·50) for two items of beans. The intakes of selective nutrients, i.e. cholesterol, saturated, *n*-3 polyunsaturated and sodium intake, were calculated and adjusted using the residual method, and used as potential confounding factors for the analysis.

Mortality surveillance

For mortality surveillance in each community, investigators systematically reviewed death certificates, all of which were filed in the public-health centre in the area of residency. Mortality data were sent centrally to the Ministry of Health and Welfare and the underlying causes of deaths were coded for the National Vital Statistics according to the International Classification for Diseases, 9th Revision from 1988 to 1994 and 10th Revision from 1995 to 2003. Registration of death is required by the Family Registration Law in Japan, and is believed to be completed across the country. Therefore, all deaths that occurred in the cohort were ascertained by death certificates from the public-health centres, except for subjects who died after they moved from their original community, in which case the subject was treated as censored. The follow-up was conducted until the end of 2003 and the average follow-up period for the participants was 12·7 years.

Cause-specific mortality was defined separately for total stroke (International Classification for Diseases-9 codes

Table 1. Age- and sex-adjusted mean values or prevalence of cardiovascular risk factors according to quartiles of the frequency of the fruit, vegetable and bean intakes*

	Quartiles of fruit intake				*P* for trend	Quartiles of vegetable intake				*P* for trend	Quartiles of bean intake				*P* for trend
	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
Servings per week	0·9	2·3	3·9	5·9	–	1·2	2·3	3·4	5·2	–	0·8	1·8	3·0	4·5	–
Number of subjects	14 967	14 066	17 607	12 845	–	14 768	15 213	14 142	15 362	–	15 212	15 573	12 321	16 379	–
Age (years)	55·9	56·4	56·6	56·1	<0·001	55·3	55·5	56·4	57·8	<0·001	54·9	55·5	57·0	57·7	<0·001
Women (%)	43·8	55·6	63·3	68·2	<0·001	46·3	56·8	61·4	65·9	<0·001	51·5	56·3	57·3	64·7	<0·001
BMI (kg/m^2)	22·8	22·8	22·8	22·9	0·07	22·9	22·8	22·8	22·9	0·16	22·8	22·8	22·8	22·9	0·24
History of hypertension (%)	20·4	20·0	19·6	19·5	0·04	20·0	20·3	19·8	19·4	0·08	19·9	20·7	20·0	19·1	0·01
History of diabetes (%)	4·9	4·9	4·7	3·9	<0·001	4·4	4·6	4·7	4·7	0·29	4·5	4·7	4·6	4·6	0·95
Current smoking (%)	31·1	26·3	24·7	23·7	<0·001	30·1	26·1	25·4	24·4	<0·001	29·5	26·9	25·8	23·8	0·14
Ethanol intake (g/d)	31·1	27·6	26·9	26·4	<0·001	29·3	28·1	28·2	27·6	<0·001	28·6	28·4	28·4	28·0	<0·001
Walk 30 min or more/ week (%)	68·3	69·9	71·2	73·2	<0·001	65·8	70·6	72·1	74·1	<0·001	68·6	70·2	72·2	71·9	<0·001
Sports 1 h or more/ week (%)	22·1	25·2	29·1	30·5	<0·001	22·5	25·8	27·8	30·7	<0·001	23·9	25·8	27·8	29·4	<0·001
Hours of sleep (h/d)	7·3	7·2	7·2	7·2	0·01	7·2	7·2	7·2	7·3	<0·001	7·2	7·2	7·2	7·3	<0·001
College or higher education (%)	10·4	12·2	14·6	16·3	<0·001	11·4	13·1	13·5	15·4	<0·001	12·3	12·9	14·0	14·3	<0·001
High perceived mental stress (%)	22·3	22·4	22·2	23·1	0·23	23·5	22·4	22·0	22·0	0·004	23·2	22·3	22·4	22·0	0·04
Total energy intake (kJ)	5640	5933	6243	6636	<0·001	5427	5958	6272	6728	<0·001	5498	5929	6314	6669	<0·001
Cholesterol intake (mg)	219	237	250	258	<0·001	208	233	250	271	<0·001	215	235	250	264	<0·001
SFA intake (g)	8·4	9·0	9·5	9·9	<0·001	8·2	9·0	9·4	10·0	<0·001	8·5	9·0	9·5	9·8	<0·001
n-3 Fatty acid intake (g)	1·5	1·6	1·7	1·8	<0·001	1·4	1·6	1·7	1·9	<0·001	1·4	1·6	1·7	1·9	<0·001
Sodium intake (mg)	2065	2110	2141	2167	<0·001	1902	2058	2166	2345	<0·001	1929	2057	2175	2316	<0·001

*Nutrient intakes were adjusted for total energy intake by the residual method.

Table 2. Risk of mortality from stroke, CHD, total CVD and all causes according to quartiles of the frequency of fruit intake (Hazard ratio (HR) values and 95 % CI)

	Quartiles of fruit intake							
		Q2		Q3		Q4		
	Q1	HR	95 % CI	HR	95 % CI	HR	95 % CI	*P* for trend
Person-years	187 700		178 625		223 683		166 046	
Total stroke								
Number	348		258		284		163	
Age- and sex-adjusted HR	1·00	0·77	0·66, 0·91	0·68	0·58, 0·80	0·57	0·48, 0·69	<0·001
Multivariable HR*	1·00	0·83	0·71, 0·98	0·79	0·67, 0·92	0·67	0·55, 0·81	<0·001
Multivariable HR†	1·00	0·81	0·69, 0·96	0·76	0·64, 0·90	0·65	0·53, 0·80	<0·001
Haemorrhagic stroke								
Number	130		93		108		62	
Age- and sex-adjusted HR	1·00	0·73	0·56, 0·96	0·67	0·52, 0·87	0·55	0·40, 0·74	<0·001
Multivariable HR*	1·00	0·79	0·60, 1·03	0·76	0·59, 0·99	0·63	0·46, 0·87	0·004
Multivariable HR†	1·00	0·76	0·58, 1·00	0·72	0·55, 0·95	0·59	0·42, 0·82	0·002
Ischaemic stroke								
Number	121		82		102		57	
Age- and sex-adjusted HR	1·00	0·71	0·54, 0·95	0·72	0·55, 0·94	0·60	0·44, 0·82	0·002
Multivariable HR*	1·00	0·77	0·58, 1·03	0·85	0·65, 1·12	0·72	0·52, 1·00	0·070
Multivariable HR†	1·00	0·76	0·57, 1·01	0·83	0·63, 1·11	0·71	0·50, 1·00	0·081
CHD								
Number	146		116		117		73	
Age- and sex-adjusted HR	1·00	0·84	0·66, 1·07	0·69	0·54, 0·88	0·63	0·47, 0·83	<0·001
Multivariable HR*	1·00	0·92	0·72, 1·18	0·79	0·62, 1·02	0·74	0·55, 0·99	0·015
Multivariable HR†	1·00	0·97	0·75, 1·24	0·84	0·65, 1·10	0·79	0·58, 1·08	0·061
Other CVD								
Number	205		173		229		131	
Age- and sex-adjusted HR	1·00	0·88	0·72, 1·08	0·94	0·78, 1·14	0·78	0·63, 0·98	0·060
Multivariable HR*	1·00	0·95	0·77, 1·17	1·06	0·87, 1·29	0·89	0·71, 1·12	0·553
Multivariable HR†	1·00	0·99	0·80, 1·22	1·13	0·92, 1·38	0·96	0·76, 1·23	0·988
Total CVD								
Number	699		547		630		367	
Age- and sex-adjusted HR	1·00	0·82	0·73, 0·91	0·76	0·68, 0·85	0·65	0·57, 0·73	<0·001
Multivariable HR*	1·00	0·88	0·79, 0·99	0·87	0·78, 0·97	0·75	0·66, 0·85	<0·001
Multivariable HR†	1·00	0·90	0·80, 1·00	0·89	0·79, 0·99	0·77	0·67, 0·88	<0·001
All causes								
Number	2284		1824		2158		1340	
Age- and sex-adjusted HR	1·00	0·86	0·81, 0·91	0·83	0·79, 0·89	0·76	0·71, 0·81	<0·001
Multivariable HR*	1·00	0·91	0·86, 0·97	0·93	0·87, 0·99	0·86	0·80, 0·92	<0·001
Multivariable HR†	1·00	0·92	0·86, 0·98	0·93	0·87, 0·99	0·86	0·80, 0·93	<0·001

* Adjusted for sex, age, BMI, smoking status, alcohol intake, hours of walking, hours of sleep, education years, perceived mental stress, cholesterol intake, SFA intake, *n*-3 fatty acids intake, sodium intake and histories of hypertension and diabetes.
† Adjusted further for vegetable and bean intakes.

430–438 and International Classification for Diseases-10 codes I60–I69), CHD (410–414 and I20–I25), other CVD (390–409, 415–429, 439–459, I01–I19, I26–I59 and I70–I99) and total CVD (390–459 and I01–I99). Total stroke was further divided into haemorrhagic stroke (430–431 and I60–61) and ischaemic stroke (433–434 and I63). Total mortality was also examined as a reference. The present study was approved by the Ethical Committee, the Nagoya University School of Medicine and the University of Tsukuba.

Statistical analysis

Statistical analyses were based on sex-specific mortality during the follow-up period from 1989 to 2003. For each participant, the person-year of follow-up was calculated when they died or moved out of his or her community or the end of 2003, whichever was the first. The age- and sex-adjusted risk of mortality from CVD as well as total mortality was defined as the corresponding death rate among the participants according to quartiles of the fruit, vegetable and bean intakes. The means and proportions of selected cardiovascular risk factors were calculated according to quartiles of those food intakes. We calculated the quartile cut-points among the whole study population and used the lowest quartiles as the reference categories for the analyses of relative risk for the second, third and highest quartiles. The HR and their 95 % CI were calculated after adjustment for age, sex and potential confounding factors using the Cox proportional hazard model. These confounding variables, which were associated with CVD among Japanese, included BMI (sex-specific quintiles), smoking category (never, ex- and current smokers of ≤19 or ≥20 cigarettes per d), alcohol intake category (never, ex- and current ethanol intake of 1–22, 23–45, 46–68 and ≥69 g/d), hours of walking (rarely, 30, 30–60 and ≥60 min per d), sports (<1 and ≥1 h per week), education (<10, 10–12, 13–15 and ≥16 years), perceived mental stress (low, medium and high), history of hypertension or diabetes and sex-specific quartiles of dietary cholesterol, SFA, *n*-3 PUFA and sodium intake (sex-specific quartiles). Since the plant-based foods have little of those nutrients, the

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Table 3. Risk of mortality from stroke, CHD, total CVD and all causes according to quartiles of the frequency of vegetable intake (Hazard ratio (HR) values and 95 % CI)

	Quartiles of vegetable intake							
		Q2		Q3		Q4		
	Q1	HR	95 % CI	HR	95 % CI	HR	95 % CI	*P* for trend
Person-years	185 787		193 546		180 543		196 177	
Total stroke								
Number	258		245		254		296	
Age- and sex-adjusted HR	1·00	0·93	0·78, 1·10	0·97	0·81, 1·15	0·91	0·77, 1·08	0·349
Multivariable HR*	1·00	0·97	0·82, 1·16	1·04	0·87, 1·24	0·97	0·81, 1·16	0·790
Multivariable HR†	1·00	1·02	0·85, 1·22	1·11	0·92, 1·34	1·09	0·90, 1·33	0·256
Haemorrhagic stroke								
Number	98		101		76		118	
Age- and sex-adjusted HR	1·00	0·99	0·75, 1·31	0·76	0·56, 1·02	0·98	0·75, 1·28	0·720
Multivariable HR*	1·00	1·06	0·80, 1·40	0·84	0·62, 1·14	1·10	0·82, 1·48	0·638
Multivariable HR†	1·00	1·09	0·82, 1·45	0·88	0·64, 1·21	1·22	0·89, 1·66	0·235
Ischaemic stroke								
Number	92		74		98		98	
Age- and sex-adjusted HR	1·00	0·79	0·58, 1·07	1·05	0·79, 1·39	0·84	0·63, 1·12	0·492
Multivariable HR*	1·00	0·83	0·61, 1·13	1·14	0·85, 1·54	0·91	0·67, 1·24	0·884
Multivariable HR†	1·00	0·87	0·64, 1·20	1·24	0·91, 1·70	1·03	0·74, 1·43	0·591
CHD								
Number	140		105		96		111	
Age- and sex-adjusted HR	1·00	0·74	0·57, 0·95	0·69	0·53, 0·89	0·65	0·51, 0·84	0·002
Multivariable HR*	1·00	0·79	0·61, 1·02	0·78	0·60, 1·02	0·77	0·58, 1·00	0·079
Multivariable HR†	1·00	0·82	0·63, 1·07	0·83	0·63, 1·10	0·85	0·64, 1·14	0·376
Other CVD								
Number	207		176		156		199	
Age- and sex-adjusted HR	1·00	0·83	0·68, 1·01	0·74	0·60, 0·91	0·76	0·62, 0·92	0·067
Multivariable HR*	1·00	0·88	0·72, 1·08	0·81	0·66, 1·01	0·85	0·69, 1·05	0·138
Multivariable HR†	1·00	0·89	0·72, 1·10	0·82	0·66, 1·03	0·87	0·70, 1·10	0·299
Total CVD								
Number	605		526		506		606	
Age- and sex-adjusted HR	1·00	0·85	0·76, 0·95	0·82	0·73, 0·93	0·80	0·71, 0·89	<0·001
Multivariable HR*	1·00	0·90	0·80, 1·01	0·90	0·80, 1·02	0·88	0·78, 0·99	0·069
Multivariable HR†	1·00	0·93	0·82, 1·05	0·95	0·83, 1·08	0·96	0·84, 1·10	0·835
All causes								
Number	1983		1786		1745		2092	
Age- and sex-adjusted HR	1·00	0·89	0·84, 0·95	0·90	0·84, 0·95	0·90	0·85, 0·96	0·007
Multivariable HR*	1·00	0·93	0·87, 0·99	0·96	0·9, 1·02	0·97	0·91, 1·04	0·762
Multivariable HR†	1·00	0·95	0·89, 1·02	0·99	0·93, 1·06	1·03	0·96, 1·10	0·188

* The same variables as shown in the footnote of Table 2.
† Adjusted further for fruit and bean intakes.

adjustment for them is justified. Further adjustment for other plant-based foods was also conducted for another multivariable model. A test for trend was used to assess statistical significance across exposure categories by including ordinal terms for each of the four categories and entering the variable as a continuous term in the model. A test for effect modification by sex was conducted using an interaction term generated by multiplying the fruit, vegetable and bean intakes by sex. A P value of $<0{\cdot}05$ was considered to be significant.

Results

Among the 25 206 men and 34 279 women followed up for an average of 12·7 years, 1207 men and 1036 women died from CVD, and 4514 men and 3029 women died from all causes. The deaths among men included 559 from stroke (128 intraparenchymal haemorrhages, 52 subarachnoid haemorrhages and 214 ischaemic strokes) and 258 from CHD. The respective numbers of deaths among women were 494 (104, 109 and 148) and 194.

Table 1 shows selected cardiovascular risk factors by fruit, vegetable and bean quartile. The participants with higher fruit intake smoked less, had lower mean ethanol intake, walked more and had higher education. The participants with higher vegetable intake were older, smoked less, had lower mean ethanol intake, walked more and had higher education. The participants with higher bean intake were older, smoked less, walked more and had higher education. The participants with higher intakes of fruit, vegetable and bean had higher mean intakes of total energy, cholesterol, n-3 fatty acids and sodium.

The associations of the fruit, vegetable and bean intakes with mortality from stroke, CHD, total CVD and all causes did not vary by sex (P for interaction $>0{\cdot}05$). Thus, we combined men and women in the present study. Table 2 shows the sex- and age-adjusted and multivariable HR of mortality from stroke, CHD and total CVD, as well as total mortality according to quartiles of fruit intake. There were inverse associations of fruit intake with age- and sex-adjusted mortality from total stroke, haemorrhagic stroke, total CVD and total mortality. After adjustment for cardiovascular risk

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Table 4. Risk of mortality from stroke, CHD, total CVD and all causes according to quartiles of the frequency of bean intake (Hazard ratio (HR) values and 95 % CI)

	Quartiles of bean intake							
		Q2		Q3		Q4		
	Q1	HR	95 % CI	HR	95 % CI	HR	95 % CI	*P* for trend
Person-years	191 279		198 098		156 448		210 229	
Total stroke								
Number	238		266		261		288	
Age- and sex-adjusted HR	1·00	1·01	0·85, 1·21	1·06	0·89, 1·26	0·86	0·73, 1·02	0·046
Multivariable HR*	1·00	1·00	0·84, 1·19	1·10	0·92, 1·32	0·90	0·75, 1·08	0·188
Multivariable HR†	1·00	1·02	0·85, 1·22	1·14	0·95, 1·38	0·95	0·79, 1·16	0·496
Haemorrhagic stroke								
Number	88		100		99		106	
Age- and sex-adjusted HR	1·00	1·05	0·79, 1·40	1·16	0·87, 1·55	0·90	0·68, 1·20	0·400
Multivariable HR*	1·00	1·06	0·80, 1·42	1·26	0·94, 1·69	1·03	0·77, 1·40	0·857
Multivariable HR†	1·00	1·10	0·82, 1·47	1·34	0·98, 1·82	1·11	0·80, 1·52	0·620
Ischaemic stroke								
Number	85		90		84		103	
Age- and sex-adjusted HR	1·00	0·96	0·71, 1·29	0·92	0·68, 1·25	0·85	0·63, 1·13	0·210
Multivariable HR*	1·00	0·94	0·69, 1·26	0·96	0·70, 1·31	0·88	0·64, 1·19	0·389
Multivariable HR†	1·00	0·95	0·70, 1·29	0·98	0·71, 1·35	0·92	0·66, 1·26	0·554
CHD								
Number	123		115		97		117	
Age- and sex-adjusted HR	1·00	0·85	0·66, 1·10	0·78	0·59, 1·01	0·70	0·54, 0·90	0·006
Multivariable HR*	1·00	0·90	0·69, 1·16	0·85	0·65, 1·12	0·80	0·61, 1·05	0·124
Multivariable HR†	1·00	0·93	0·72, 1·21	0·92	0·69, 1·23	0·88	0·66, 1·18	0·407
Other CVD								
Number	195		169		175		199	
Age- and sex-adjusted HR	1·00	0·78	0·64, 0·96	0·86	0·70, 1·06	0·72	0·59, 0·88	0·020
Multivariable HR*	1·00	0·80	0·65, 0·99	0·93	0·75, 1·15	0·79	0·64, 0·98	0·097
Multivariable HR†	1·00	0·82	0·66, 1·01	0·96	0·77, 1·19	0·82	0·65, 1·02	0·196
Total CVD								
Number	556	550			533		604	
Age- and sex-adjusted HR	1·00	0·90	0·80, 1·01	0·93	0·82, 1·05	0·78	0·69, 0·87	<0·001
Multivariable HR*	1·00	0·91	0·81, 1·02	0·99	0·87, 1·12	0·84	0·74, 0·95	0·010
Multivariable HR†	1·00	0·93	0·82, 1·05	1·03	0·91, 1·17	0·89	0·78, 1·01	0·106
All causes								
Number	1883		1868		1741		2114	
Age- and sex-adjusted HR	1·00	0·92	0·86, 0·98	0·94	0·88, 1·01	0·86	0·80, 0·91	<0·001
Multivariable HR*	1·00	0·94	0·88, 1·00	0·99	0·92, 1·06	0·90	0·84, 0·96	0·006
Multivariable HR†	1·00	0·95	0·89, 1·01	1·00	0·94, 1·08	0·92	0·86, 0·98	0·025

* The same variables as shown in the footnote of Table 2.
† Adjusted further for fruit and vegetable intakes.

factors, these associations were attenuated slightly but remained statistically significant. The multivariable HR (95 % CI) of total stroke, haemorrhagic stroke, total CVD and total mortality in the highest *v.* lowest quartiles of fruit intake were 0·67 (0·55, 0·81, *P* for trend<0·001), 0·63 (0·46, 0·87, *P* for trend=0·004), 0·75 (0·66, 0·85, *P* for trend<0·001) and 0·86 (0·80, 0·92, *P* for trend<0·001). These inverse associations did not alter materially when we adjusted further for vegetable and bean intakes.

Table 3 shows the sex- and age-adjusted and multivariable HR according to quartiles of vegetable intake. Vegetable intake was inversely associated with sex- and age-adjusted mortality from CHD, total CVD and total mortality; after adjustment for cardiovascular risk factors, these associations were weakened but the association with CHD remained statistically significant, that with CVD was borderline statistically significant, but that with total mortality was no longer statistically significant. The multivariable HR (95 % CI) of CHD and total CVD in the highest *v.* lowest quartiles of vegetable intake were 0·77 (0·58, 1·00, *P* for trend=0·08) and 0·88 (0·78, 0·99, *P* for trend=0·07).

Table 4 shows the sex- and age-adjusted and multivariable HR according to quartiles of bean intake. Bean intake was inversely associated with sex- and age-adjusted mortality from total stroke, CHD, other CVD, total CVD and total mortality. After adjustment for cardiovascular risk factors, these associations were weakened, and were no longer statistically significant except for other CVD, total CVD and total mortality. The respective multivariable HR in the highest *v.* lowest quartiles of bean intake were 0·79 (0·64, 0·98, *P* for trend=0·10), 0·84 (0·74, 0·95, *P* for trend=0·01) and 0·90 (0·84, 0·96, *P* for trend=0·01). After further adjustment for fruit and vegetable intakes, these inverse associations became weak and were of borderline statistical significance.

Discussion

In the present large prospective study of Japanese men and women, we found inverse associations of plant-based food intake with mortality from CVD after adjustment for cardiovascular risk factors. High fruit intake was associated with reduced mortality from haemorrhagic and total stroke, total

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CVD and all causes; vegetable intake tended to be associated with reduced mortality from CHD, total CVD and all causes; bean intake was associated with reduced mortality from total CVD as well as total mortality.

Further adjustment for other plant-based foods did not alter the association of fruit intake with mortality, but attenuated the associations of vegetable and bean intakes with mortality. The weakened associations, however, do not necessarily negate potential protective effects of vegetable and bean intakes, because those intakes were moderately correlated with fruit intake: the Spearman correlation coefficients of vegetable and bean intakes were 0·36 and 0·28, respectively. It is possible that vegetable or bean intake is merely a surrogate for fruit intake in the present study.

The meta-analysis of eight cohort studies showed that vegetable and fruit intakes were associated with a reduced risk of stroke[1], and several Japanese cohort studies also showed that intakes of vegetables, fruits and soya were associated with a reduced risk of stroke[11,12,14]. The present study showed that intakes of fruits, but not vegetables and beans, were associated with a reduced risk of stroke.

The meta-analysis for studies of Western countries showed that vegetable, and fruit intakes were associated with a reduced risk of CHD[2]. The present study added the evidence on fruit intake and reduced mortality from CHD in Japanese.

A recent Japanese study reported that soya intake was associated with a reduced risk of ischaemic stroke and myocardial infarction[14]. The present study extends the evidence that bean intake was associated with reduced mortality from total CVD and all causes.

As for the mechanisms for the inverse association between fruit intake and CVD, vitamin C reduces the lipid oxidation of LDL-cholesterol[20] and enhances the formation of endothelial prostacyclin that decreases vascular tone and inhibits platelet aggregation[21]. Potassium, magnesium, calcium, fibre and folate exert the beneficial effects described previously[22–25].

The protective effects of soyabean intake on CVD are now highlighted in Western countries, based on epidemiological studies that showed a lower incidence of CVD in Asian populations consuming soya foods as a dietary staple compared with those who consumed a typical Western diet[9,10,26,27]. Some clinical trials in Western countries that failed to detect the protective association led to the speculation that only high levels of habitual intake exerted the beneficial effects[10,27], and research into populations with a high level of intake was required. In the Japan Collaborative Cohort Study, we did not ask about the intake of soyabeans specifically, but the present finding of the inverse association between bean intake and mortality from total CVD would suggest a cardio-protective effect of soyabeans, because they are the most common beans eaten in Japan[28].

There are several mechanisms for the inverse association between bean intake and CVD. Potassium, calcium and fibre, which are plentiful in beans, may play a role in lowering blood pressure[23,24]. Potassium also inhibits platelet aggregation[23], and fibre, isoflavones, soya protein and saponins help lower total cholesterol levels[9,24]. Isoflavones also enhance antioxidant activity and improve arterial stiffness[9,25]. Folate, which is also plentiful in beans, lowers serum homocysteine levels, a correlate for arterial endothelial dysfunction[25].

Some limitations warrant discussion. First, the food frequency questionnaire used in the present study had high reproducibility but low-to-moderate validity for the estimation of the fruit, vegetable and bean intakes. Thus, some non-differential misclassification would be to weaken the diet–disease association. Second, a number of subjects were excluded because they did not respond sufficiently to the FFQ. However, a potential selection bias may be small because of no difference in mortality and cardiovascular risk characteristics between persons who responded to the food frequency questionnaire and those who did not.

Healthy behaviours associated with plant-based food intake might confound the association with mortality from CVD. Non-smoking, appropriate alcohol intake, more physical activity and higher education are potential confounders in the present study. However, after adjustment for these confounding variables, the associations with mortality from CVD remained statistically significant, suggesting that independent effects of plant-based foods exist for the prevention of CVD. Residual confounding and the contribution of other unexamined factors, however, were not negated.

In conclusion, fruit intake was inversely associated with mortality from stroke, total CVD and all causes, and bean intake was also inversely associated with mortality from total CVD and all causes among Japanese men and women. The present findings suggest the potential for beneficial effects of plant-based food intake for the prevention of CVD in general populations.

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Relations between dietary sodium and potassium intakes and mortality from cardiovascular disease: the Japan Collaborative Cohort Study for Evaluation of Cancer Risks[1–3]

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ABSTRACT

Background: Limited evidence is available about the relations between sodium and potassium intakes and cardiovascular disease in the general population.

Objective: The objective was to investigate relations between sodium and potassium intakes and cardiovascular disease in Asian populations whose mean sodium intake is generally high.

Design: Between 1988 and 1990, a total of 58 730 Japanese subjects (n = 23 119 men and 35 611 women) aged 40–79 y with no history of stroke, coronary heart disease, or cancer completed a lifestyle questionnaire including food intake frequency under the Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by the Ministry of Education, Sports and Science.

Results: After 745 161 person-years of follow-up, we documented 986 deaths from stroke (153 subarachnoid hemorrhages, 227 intraparenchymal hemorrhages, and 510 ischemic strokes) and 424 deaths from coronary heart disease. Sodium intake was positively associated with mortality from total stroke, ischemic stroke, and total cardiovascular disease. The multivariable hazard ratio for the highest versus the lowest quintiles of sodium intake after adjustment for age, sex, and cardiovascular disease risk factors was 1.55 (95% CI: 1.21, 2.00; P for trend < 0.001) for total stroke, 2.04 (95% CI: 1.41, 2.94; P for trend < 0.001) for ischemic stroke, and 1.42 (95% CI: 1.20, 1.69; P for trend < 0.001) for total cardiovascular disease. Potassium intake was inversely associated with mortality from coronary heart disease and total cardiovascular disease. The multivariable hazard ratio for the highest versus the lowest quintiles of potassium intake was 0.65 (95% CI: 0.39, 1.06; P for trend = 0.083) for coronary heart disease and 0.73 (95% CI: 0.59, 0.92; P for trend = 0.018) for total cardiovascular disease, and these associations were more evident for women than for men.

Conclusions: A high sodium intake and a low potassium intake may increase the risk of mortality from cardiovascular disease. *Am J Clin Nutr* 2008;88:195–202.

INTRODUCTION

Several epidemiologic studies conducted in Western countries have shown that a high sodium intake was associated with an increased incidence of stroke among overweight adults (1), whereas a high potassium intake was associated with a reduced risk of stroke (2–5). A high sodium intake was also associated with an increased risk of mortality from coronary heart disease (1), whereas potassium intake was not associated with the risk of coronary heart disease (5). In Asian countries, a 7-y prospective study of Japanese showed a positive association between sodium intake and mortality from stroke (6), but the associations of sodium and potassium intakes with the risk of coronary heart disease were not reported.

Mean sodium intake has been shown to be higher in the Japanese (7) than in whites (8), probably because traditional Japanese diets are rich in soybean paste, soy sauce, and salty pickles, and the mortality rate from stroke has been shown to be higher in Japan than in many Western countries (9). According to the INTERSALT Study, 24-h urinary sodium excretion is 167–201 mmol/d in the Japanese and is 96–137 mmol/d in Americans, whereas the respective potassium excretion rates are 41–46 and

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23–52 mmol/d, respectively (10). To examine the relations of sodium and potassium intakes with cardiovascular disease in the Japanese is of public health importance.

The aim of the present study was to determine the associations of dietary intakes of sodium and potassium with the mortality risk related to total stroke, stroke subtypes, coronary heart disease, and total cardiovascular disease in a large prospective study of Japanese men and women. Our a priori hypothesis was that sodium intake is positively associated, and potassium intake is inversely associated, with mortality from total stroke, each stroke subtype, coronary heart disease, and total cardiovascular disease.

SUBJECTS AND METHODS

Subjects

The Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risks, sponsored by the Ministry of Education, Sports and Science, was conducted from 1988 to 1990. A total of 110 792 subjects (n = 46 465 men and 64 327 women) aged 40–79 y of age completed self-administered questionnaires about their lifestyles and medical histories related to hypertension, diabetes, stroke, myocardial infarction, and cancer. The population sample was from 45 communities across Japan, and most of the participants underwent questionnaires and municipal health screening examinations according to the Health Law for the Aged in their communities (11, 12). The sampling methods and protocols of the JACC Study were described in detail previously (11). We excluded from analysis 16 109 subjects (n = 4683 men and 11 426 women) with a medical history of stroke, coronary heart disease, or cancer. Of the remaining 94 683 subjects, 58 730 (n = 23 119 men and 35 611 women) provided valid responses to the dietary questionnaires and were enrolled in the present study.

Mortality surveillance

For mortality surveillance in each area, investigators unaware of the results of questionnaires reviewed death certificates for target populations in each surveyed area, all of which were forwarded to the public health center in the area of residency. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying cause of death was coded according to the International Classification of Disease (ICD), 9th revision, from 1988 to 1994 or according to the 10th revision from 1995 to 2003 for the National Vital Statistics in Japan. The classifications of stroke subtypes and coronary heart disease were based on the ICD codes. The registration of death is required by the Family Registration Law and is believed to be followed across Japan. Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case the subject was treated as a censored case when they moved out. Of the total of 58 730 subjects, 2487 (4.2%) moved out. The follow-up was conducted until the end of 2003, except for 5 areas (n = 7237 subjects), where follow-up was terminated at the end of 1999. The average follow-up period for the participants was 12.7 y. The present study was approved by the ethics committees of Nagoya University School of Medicine and University of Tsukuba.

Calculation of sodium and potassium intakes

Each participant was asked to record the frequency of the intake of 35 foods. The response was based on the usual food intake for the past year. Five responses were possible for each food item: "rarely," "1–2 d/mo," "1–2 d/wk," "3–4 d/wk," and "almost every day". The consumption of each food item was calculated by multiplying the frequency score of consumption of each food by 0, 0.38, 1.5, 3.5, and 7/wk, respectively. Each portion size was estimated from a validation study conducted in 85 of the baseline participants. The reproducibility and validity of this dietary questionnaire were reported elsewhere (13). The average daily intake of nutrients and total energy was calculated by multiplying the frequency of consumption of each item with its nutrient content and energy per serving and totaling the nutrient intake for all food items. The energy-adjusted nutrient intakes were calculated by the residual method. The Spearman rank correlation coefficients between the food-frequency questionnaire (FFQ) and four 3-d dietary records were 0.36 for sodium intake and 0.43 for potassium intake for 85 individuals in the validation study. The estimated mean sodium intake was 83 mmol/d from the questionnaire and 167 mmol/d from four 3-d dietary records under the validation study. The respective mean values of potassium intake were 55 and 70 mmol/d. Thus, we calculated calibrated intakes of sodium and potassium, multiplied by 2.0 and 1.3, respectively. The Spearman rank correlation coefficients between 2 FFQs conducted 1 y apart were 0.73 for sodium intake and 0.78 for potassium intake.

Statistical analysis

Statistical analysis was based on age- and sex-adjusted mortality rates of stroke and coronary heart disease during the follow-up period from 1989 to 2003. For each participant, the person-years of follow-up were calculated from the date that the baseline questionnaire was completed until the time of death, the participant moved out of the community, or the end of 2003 or 1999, whichever occurred first. Age- and sex-adjusted hazard ratios of mortality from stroke and coronary heart disease were defined as the death rate among participants according to quintiles of sodium and potassium intakes: <62, 62–80, 80–98, 98–118, and >118 mmol/d for uncalibrated sodium intake and <40, 40–48, 48–54, 54–62, and >62 mg/d for uncalibrated potassium intake.

Age- and sex-adjusted median and mean values and proportions of selected cardiovascular disease risk factors were presented according to quintiles of dietary intakes of sodium and potassium. The age- and sex-adjusted and multivariable-adjusted hazard ratios and their 95% CIs were calculated by using the Cox proportional hazard model. We conducted tests for trend across quintiles of sodium and potassium intakes by assigning median values of each quintile and testing the significance of this variable. These confounding variables for the multivariable adjustment included body mass index (BMI; in kg/m^2; sex-specific quintiles), smoking status (never, ex-smoker, and current smokers of 1 to 19 or ≥20 cigarettes/d), alcohol intake category (never, ex-drinker, and current ethanol drinkers of 1 to 22, 23 to 45, 46 to 68, or ≥69 g/d), history of hypertension (yes or no), history of diabetes (yes or no), menopause (yes or no), hormone-replacement therapy (yes or no), time spent in physical activity (never, 1–2, 3–4, and ≥5 h/wk), walking time (never and ≈30, 30–60, or ≥60 min/d), educational status (educated until 12,

13–15, 16–18, and ≥19 y of age), perceived mental stress (low, median, high, or extremely high), and calcium intake (quintiles).

Another multivariable model, after further adjustment for other electrolyte intakes, was constructed to examine an independent effect of sodium or potassium intake on mortality. We tested the interaction of sodium or potassium intake with sex by using an interaction term generated by multiplying the median of each quintile of sodium or potassium intake with sex. There were no significant sex interactions between them except for the association between potassium intake and risk of mortality from coronary heart disease ($P = 0.04$) and total cardiovascular disease ($P = 0.03$). We presented the sex-specific results of these endpoints as well.

We also examined the association between sodium intake and risk of mortality from cardiovascular disease stratified by BMI, because salt sensitivity could be enhanced by overweight (14). We divided subjects into 2 groups: BMI < 25 ($n = 46\,888$ subjects) and BMI ≥ 25 ($n = 11\,842$ subjects) and examined the multivariable hazard ratios associated with a 100-mmol increment in uncalibrated dairy sodium intake.

Cause-specific mortality was determined by total deaths due to stroke (ICD codes 430–438, 9th revision; ICD, 10th revision, codes I60–I69), coronary heart disease (codes 410–414 and I20–I25), and total cardiovascular diseases (codes 390–459 and I01–I99). Stroke was further categorized into subarachnoid hemorrhage (codes 430 and I60), intraparenchymal hemorrhage (codes 431 and code I61), and ischemic stroke (codes 433–434 and I63 and I693). We used SAS version 8.02 software (SAS Institute Inc, Cary) for all analyses. P values < 0.05 were regarded as statistical significance.

RESULTS

Of the cohort followed up for an average 12.7 y, we documented 500 deaths caused by stroke ($n = 47$ subarachnoid hemorrhage, 118 intraparenchymal hemorrhage, 289 ischemic stroke, and 46 undetermined type of stroke) for men and 486 for women ($n = 106$ subarachnoid hemorrhage, 109 intraparenchymal, 221 ischemic stroke, and 50 undetermined type of stroke) and 233 deaths caused by coronary heart disease for men and 191

TABLE 1
Baseline characteristics and risk factors according to quintiles of sodium and potassium intakes

	Quintile of intake				
	1 (low)	2	3	4	5 (high)
Sodium					
No. of subjects	11 746	11 746	11 746	11 746	11 746
Sodium intake (mmol/d)[1,2]	50 ± 15	73 ± 5	90 ± 5	109 ± 6	135 ± 18
Calibrated sodium intake (mmol/d)[1,3]	101 ± 30	146 ± 11	182 ± 11	220 ± 12	272 ± 36
Age (y)[4]	55 ± 10	56 ± 10	56 ± 10	56 ± 10	58 ± 10
Men (%)	55	36	37	36	33
Mean BMI (kg/m^2)[5]	22.8	22.7	22.7	22.9	23.0
Current smokers (%)[5]	28	25	24	24	23
Current drinkers (%)[5]	49	46	45	42	40
History of hypertension (%)[5]	15	15	15	14	13
History of diabetes (%)[5]	3	3	3	3	2
Menopause (% of women)	62	63	63	64	67
Hormone replacement therapy (% of women)	5	5	4	4	4
Energy intake (kcal/d)[1]	1496 ± 452	1287 ± 414	1356 ± 421	1398 ± 397	1466 ± 420
Potassium intake (mmol/d)[1]	39 ± 11	47 ± 10	51 ± 10	55 ± 10	61 ± 11
Calcium intake (mmol/d)[1]	8 ± 3	11 ± 3	12 ± 3	13 ± 3	14 ± 3
Potassium					
No. of subjects	11 746	11 746	11 746	11 746	11 746
Potassium intake (mmol/d)[1,2]	35 ± 6	44 ± 2	51 ± 2	58 ± 2	68 ± 6
Calibrated potassium intake (mmol/d)[1,3]	44 ± 8	56 ± 3	65 ± 2	73 ± 3	86 ± 8
Age (y)[4]	55 ± 10	56 ± 10	56 ± 10	57 ± 10	58 ± 10
Men (%)	67	44	35	29	23
Mean BMI (kg/m^2)[5]	22.8	22.8	22.8	22.9	22.9
Current smokers (%)[5]	30	25	24	23	22
Current drinkers (%)[5]	53	45	43	40	39
History of hypertension (%)[5]	15	15	14	14	13
History of diabetes (%)[5]	2	3	3	3	3
Menopause (% of women)	61	63	64	64	66
Hormone replacement therapy (% of women)	4	4	5	4	5
Energy intake (kcal/d)[1]	1512 ± 496	1308 ± 439	1305 ± 404	1365 ± 380	1501 ± 377
Sodium intake (mmol/d)[1]	60 ± 28	80 ± 26	91 ± 27	103 ± 27	119 ± 29
Calcium intake (mmol/d)[1]	7 ± 2	10 ± 2	12 ± 2	13 ± 2	15 ± 2

[1] All values are medians ± SD.
[2] Values are from food-frequency questionnaires.
[3] Calibrated values are from a validation study.
[4] All values are $\bar{x}$ ± SD.
[5] Age- and sex-adjusted.

for women. In total, there were 986 cases of stroke and 424 cases of coronary heart diseases.

Age- and sex-adjusted selected cardiovascular disease risk factors and cation intakes according to quintiles of dietary intakes of sodium and potassium are shown in **Table 1**. Compared with persons in the lowest quintile of dietary sodium intake, those in the highest quintile were older, had a lower prevalence of current smokers and drinkers, and had a higher prevalence of menopause. On the other hand, persons in the highest quintile of potassium intake were older, had a lower prevalence of current smokers and drinkers, and had a higher prevalence of menopause than did persons in the lowest quintile.

Age- and sex-adjusted and multivariable hazard ratios (and 95% CI) of mortality from total stroke, stroke subtypes, coronary heart disease, and total cardiovascular disease according to quintiles of sodium intake are shown in **Table 2**. Even after adjustment for cardiovascular disease risk factors and potassium intake, sodium intake was positively associated with mortality from total stroke, ischemic stroke, and total cardiovascular disease. These associations were slightly strengthened after further adjustment for potassium intake. The multivariable hazard ratios with highest versus lowest quintiles of sodium intake were 1.55 (95% CI: 1.21, 2.00) for total stroke, 2.04 (95% CI: 1.41, 2.94) for ischemic stroke, and 1.42 (95% CI: 1.20, 1.69) for total cardiovascular disease (Table 2), and those associated with a 100-mmol increment in uncalibrated daily sodium intake were 1.83 (95% CI: 1.45, 2.32), 2.38 (95% CI: 1.71, 3.30), and 1.58 (95% CI: 1.34, 1.87), respectively (data not shown in the table). The association between sodium intake and mortality from intraparenchymal hemorrhage was of borderline statistical significance (P for trend = 0.079).

Age- and sex-adjusted and multivariable hazard ratios (and 95% CIs) of mortality from total stroke, stroke subtypes, coronary heart disease, and total cardiovascular disease according to quintiles of potassium intake are shown in **Table 3**. Potassium intake was inversely associated with age- and sex-adjusted mortality from total stroke, intraparenchymal hemorrhage, coronary heart disease, and total cardiovascular disease; however, after adjustment for cardiovascular disease risk factors, these associations were no longer statistically

TABLE 2
Hazard ratios (HRs) and 95% CIs of mortality from stroke, coronary heart disease, and total cardiovascular disease according to quintiles of sodium intake

	Quintile of sodium intake					P for trend[1]
	1 (low)	2	3	4	5 (high)	
No. of subjects	11 746	11 746	11 746	11 746	11 746	
Person-years	144 328	145 123	149 572	153 158	152 980	
Total stroke						
n	154	144	193	230	265	
Age- and sex-adjusted HR	1.00	0.88 (0.70, 1.11)	1.10 (0.89, 1.36)	1.19 (0.97, 1.46)	1.18 (0.97, 1.45)	0.009
Multivariable HR[2]	1.00	0.94 (0.75, 1.19)	1.23 (0.98, 1.54)	1.39 (1.10, 1.75)	1.51 (1.18, 1.92)	<0.001
Multivariable HR[3]	1.00	0.96 (0.76, 1.22)	1.26 (1.00, 1.59)	1.42 (1.12, 1.80)	1.55 (1.21, 2.00)	<0.001
Intraparenchymal hemorrhage						
n	48	32	46	44	57	
Age- and sex-adjusted HR	1.00	0.66 (0.42, 1.04)	0.88 (0.59, 1.33)	0.78 (0.52, 1.18)	0.91 (0.62, 1.35)	0.969
Multivariable HR[2]	1.00	0.73 (0.46, 1.16)	1.07 (0.69, 1.66)	1.03 (0.65, 1.63)	1.38 (0.85, 2.23)	0.088
Multivariable HR[3]	1.00	0.73 (0.46, 1.17)	1.08 (0.69, 1.68)	1.04 (0.65, 1.66)	1.40 (0.86, 2.23)	0.079
Subarachnoid hemorrhage						
n	28	24	27	39	35	
Age- and sex-adjusted HR	1.00	0.76 (0.44, 1.32)	0.81 (0.48, 1.38)	1.09 (0.67, 1.78)	0.90 (0.54, 1.49)	0.823
Multivariable HR[2]	1.00	0.73 (0.41, 1.28)	0.77 (0.44, 1.36)	1.06 (0.61, 1.84)	0.97 (0.54, 1.77)	0.585
Multivariable HR[3]	1.00	0.74 (0.42, 1.32)	0.79 (0.45, 1.41)	1.09 (0.62, 1.92)	1.01 (0.54, 1.86)	0.530
Ischemic stroke						
n	61	73	106	125	145	
Age- and sex-adjusted HR	1.00	1.11 (0.79, 1.56)	1.49 (1.09, 2.04)	1.57 (1.15, 2.13)	1.51 (1.11, 2.04)	0.002
Multivariable HR[2]	1.00	1.23 (0.86, 1.74)	1.73 (1.24, 2.43)	1.94 (1.37, 2.74)	2.00 (1.40, 2.87)	<0.001
Multivariable HR[3]	1.00	1.25 (0.88, 1.77)	1.76 (1.25, 2.49)	1.97 (1.39, 2.80)	2.04 (1.41, 2.94)	<0.001
Coronary heart disease						
n	83	72	82	88	99	
Age- and sex-adjusted HR	1.00	0.84 (0.61, 1.15)	0.88 (0.65, 1.20)	0.86 (0.63, 1.16)	0.84 (0.62, 1.13)	0.338
Multivariable HR[2]	1.00	0.89 (0.64, 1.23)	0.99 (0.71, 1.37)	1.01 (0.72, 1.43)	1.10 (0.77, 1.58)	0.428
Multivariable HR[3]	1.00	0.92 (0.66, 1.28)	1.05 (0.75, 1.46)	1.09 (0.77, 1.54)	1.19 (0.82, 1.73)	0.230
Total cardiovascular disease						
n	338	344	402	463	540	
Age- and sex-adjusted HR	1.00	0.96 (0.83, 1.12)	1.04 (0.90, 1.20)	1.08 (0.94, 1.25)	1.09 (0.95, 1.25)	0.073
Multivariable HR[2]	1.00	1.02 (0.87, 1.19)	1.15 (0.98, 1.34)	1.24 (1.06, 1.46)	1.35 (1.14, 1.60)	<0.001
Multivariable HR[3]	1.00	1.04 (0.89, 1.22)	1.19 (1.01, 1.39)	1.29 (1.10, 1.52)	1.42 (1.20, 1.69)	<0.001

[1] Based on tests for trend across quintiles of sodium intake by assigning the median value of each quintile.

[2] Cox proportional hazard models adjusted further for BMI (sex-specific quintiles), smoking status (4 categories), ethanol intake (6 categories), history of hypertension (yes or no), history of diabetes (yes or no), menopause (yes or no), hormone replacement therapy (yes or no), time spent on sports activity (4 categories), walking time (4 categories), educational status (4 categories), perceived mental stress (4 categories), and calcium intake (quintiles).

[3] Cox proportional hazard models adjusted as noted in footnote 2 and for potassium intake (quintiles).

TABLE 3
Hazard ratios (HRs) and 95% CIs of mortality from stroke, coronary heart disease, and total cardiovascular disease according to quintiles of potassium intake

	Quintile of potassium intake					
	1 (low)	2	3	4	5 (high)	*P* for trend[1]
No. of subjects	11 746	11 746	11 746	11 746	11 746	
Person-years	146 012	147 127	148 963	149 811	153 248	
Total stroke						
n	202	195	184	208	197	
Age- and sex-adjusted HR	1.00	0.88 (0.72, 1.08)	0.84 (0.69, 1.03)	0.88 (0.72, 1.07)	0.77 (0.63, 0.94)	0.021
Multivariable HR[2]	1.00	0.93 (0.74, 1.17)	0.91 (0.70, 1.19)	1.01 (0.77, 1.34)	0.96 (0.70, 1.31)	0.967
Multivariable HR[3]	1.00	0.89 (0.71, 1.13)	0.84 (0.65, 1.10)	0.91 (0.69, 1.22)	0.83 (0.60, 1.14)	0.355
Intraparenchymal hemorrhage						
n	54	50	40	43	40	
Age- and sex-adjusted HR	1.00	0.89 (0.60, 1.31)	0.72 (0.48, 1.09)	0.74 (0.49, 1.11)	0.64 (0.42, 0.97)	0.024
Multivariable HR[2]	1.00	1.02 (0.65, 1.59)	0.93 (0.55, 1.57)	1.07 (0.60, 1.90)	0.99 (0.51, 1.92)	0.987
Multivariable HR[3]	1.00	1.02 (0.65, 1.60)	0.91 (0.53, 1.55)	1.02 (0.56, 1.84)	0.89 (0.45, 1.76)	0.756
Subarachnoid hemorrhage						
n	26	30	29	36	32	
Age- and sex-adjusted HR	1.00	1.00 (0.59, 1.69)	0.91 (0.53, 1.57)	1.05 (0.63, 1.77)	0.85 (0.50, 1.45)	0.614
Multivariable HR[2]	1.00	0.86 (0.47, 1.58)	0.75 (0.38, 1.48)	0.91 (0.44, 1.87)	0.85 (0.38, 1.91)	0.845
Multivariable HR[3]	1.00	0.88 (0.47, 1.64)	0.76 (0.38, 1.53)	0.91 (0.43, 1.91)	0.83 (0.36, 1.91)	0.774
Ischemic stroke						
n	99	94	98	112	107	
Age- and sex-adjusted HR	1.00	0.84 (0.64, 1.12)	0.91 (0.69, 1.21)	0.94 (0.71, 1.24)	0.85 (0.64, 1.12)	0.430
Multivariable HR[2]	1.00	0.95 (0.68, 1.32)	1.06 (0.73, 1.54)	1.15 (0.78, 1.71)	1.12 (0.72, 1.75)	0.450
Multivariable HR[3]	1.00	0.86 (0.61, 1.19)	0.92 (0.63, 1.34)	0.97 (0.65, 1.46)	0.91 (0.58, 1.44)	0.907
Coronary heart disease						
n	105	89	80	77	73	
Age- and sex-adjusted HR	1.00	0.79 (0.59, 1.05)	0.72 (0.54, 0.97)	0.65 (0.48, 0.88)	0.57 (0.42, 0.77)	<0.001
Multivariable HR[2]	1.00	0.81 (0.58, 1.13)	0.74 (0.51, 1.09)	0.69 (0.45, 1.06)	0.69 (0.43, 1.12)	0.127
Multivariable HR[3]	1.00	0.80 (0.57, 1.11)	0.72 (0.49, 1.07)	0.66 (0.43, 1.03)	0.65 (0.39, 1.06)	0.083
Total cardiovascular disease						
n	445	409	395	437	401	
Age- and sex-adjusted HR	1.00	0.84 (0.73, 0.96)	0.82 (0.72, 0.94)	0.84 (0.73, 0.96)	0.71 (0.62, 0.81)	<0.001
Multivariable HR[2]	1.00	0.88 (0.75, 1.02)	0.86 (0.72, 1.03)	0.91 (0.75, 1.10)	0.82 (0.66, 1.02)	0.153
Multivariable HR[3]	1.00	0.84 (0.72, 0.99)	0.81 (0.67, 0.97)	0.84 (0.69, 1.02)	0.73 (0.59, 0.92)	0.018

[1] Based on tests for trend across quintiles of potassium intake by assigning the median value of each quintile.
[2] Cox proportional hazard models adjusted further for variables listed in the footnote of Table 2.
[3] Cox proportional hazard models adjusted further for sodium intake (quintiles).

significant. However, when adjusted further for sodium intake, the inverse association with potassium intake became significant for total cardiovascular disease and marginally significant for coronary heart disease. The inverse association between potassium intake and mortality from coronary heart disease was marginally significant. The multivariable hazard ratios for the highest versus the lowest quintiles of potassium intake were 0.83 (95% CI: 0.60, 1.14) for total stroke, 0.65 (95% CI: 0.39, 1.06) for coronary heart disease, and 0.73 (95% CI: 0.59, 0.92) for total cardiovascular disease.

Sex-specific multivariable hazard ratios of mortality from coronary heart disease and total cardiovascular disease, according to quintiles of potassium intake, are shown in **Table 4**. For women, potassium intake was significantly and inversely associated with mortality from coronary heart disease and total cardiovascular disease; the multivariable hazard ratios for the highest versus the lowest quintiles of potassium intake were 0.40 (95% CI: 0.20, 0.80) and 0.67 (95% CI: 0.49, 0.90), and those associated with a 10-mmol increment in uncalibrated daily potassium intake were 0.80 (95% CI: 0.65, 0.99) and 0.93 (95% CI: 0.86, 1.02), respectively (data not shown in the table). These inverse associations were not significantly different for men.

The joint impact of sodium and potassium intakes, indicated by hazard ratios of mortality from total stroke, ischemic stroke, coronary heart disease, and total cardiovascular disease (with low sodium and high potassium intakes as the reference), is shown in **Table 5** by low and high (less than and greater than or equal to the median of) sodium and potassium intakes. We found a significantly higher mortality rate from total stroke, ischemic stroke, and total cardiovascular disease in those with a high sodium and a low potassium intake and in those with a high sodium and a high potassium intake, but not in those with a low sodium and a low potassium intake. We also calculated hazard ratios with the reference being a high sodium and low potassium intake and found a significantly lower mortality from coronary heart disease in those with a high sodium and a high potassium intake and a lower mortality from total stroke, ischemic stroke, and total cardiovascular disease in those with a low sodium and a low potassium intake.

We also examined the association between sodium intake and mortality from cardiovascular disease, stratified by BMI <25.0