NUTRITION EPIDEMIOLOGY HIGHLIGHTS ORIGINAL ARTICLE

Fruit and vegetable intake and mortality from cardiovascular disease in Japan: a 24-year follow-up of the NIPPON DATA80 Study

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BACKGROUND/OBJECTIVES: There have been few studies on the association of fruit and vegetable (FV) intake with cardiovascular disease (CVD) risk in Asian populations where both dietary habits and disease structure are different from western countries. No study in Asia has found its significant association with stroke. We examined associations of FV intake with mortality risk from total CVD, stroke and coronary heart diseases (CHDs) in a representative Japanese sample.
METHODS: A total of 9112 participants aged from 24-year follow-up data in the NIPPON DATA80, of which baseline data were obtained in the National Nutrition Survey Japan in 1980, were studied. Dietary data were obtained from 3-day weighing dietary records. Participants were divided into sex-specific quartiles of energy adjusted intake of FV. Multivariate-adjusted hazard ratios (HRs) were calculated between strata of the total of FV intake, fruit intake and vegetable intake. The adjustment included age, sex, smoking, drinking habit and energy adjusted intakes of sodium and some other food groups.
RESULTS: Participants with higher FV intake were older, ate more fish, milk and dairy products and soybeans and legumes and ate less meat. Multivariate-adjusted HR (95% confidence interval; P; P for trend) for the highest versus the lowest quartile of the total of FV intake was 0.74 (0.61–0.91; 0.004; 0.003) for total CVD, 0.80 (0.59–1.09; 0.105; 0.036) for stroke and 0.57 (0.37–0.87; 0.010; 0.109) for CHD.
CONCLUSIONS: The results showed that higher total intake of FVs was significantly associated with reduced risk of CVD mortality in Japan.

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INTRODUCTION

Cardiovascular diseases (CVDs) are among the leading causes of death in most developed countries.[1-3] An increasing number of cohort studies, many of them from western countries, have reported beneficial effects of increased intake of fruits and vegetables on coronary heart diseases (CHDs), stroke and CVD mortality.[4–9] In contrast, there have been few studies in Asian populations[10–13] and these effects need to be examined, especially as food intake pattern differs in several aspects from that in western countries: a lower intake of fat, and a higher intake of salt and fish, because salted fish and salted vegetables are common.[14–19] Frequency of obesity is lower in Asia,[2,18] and the distribution of disease also differs: a higher incidence and mortality from stroke than from CHD in Asia.[2,18,20] In addition to there having been few studies from Asia on the relationship between fruit and vegetable intake and the risk of CVD, the findings have also been inconclusive.[10-13] None of the studies reported significant association between vegetable intake and CVD mortality, whereas two cohort studies in Japan found a

significant inverse association of fruit intake with CVD mortality.[10,11] We know of no studies that have found associations between fruit and vegetable intake with stroke mortality in other countries in Asia.

NIPPON DATA80[21,22] is a cohort study based on the National Survey on Circulatory Disorders (NSCDs)[23] and the National Nutrition Survey (NNS) in Japan in 1980,[24] both surveys were originally conducted by the Ministry of Health and Welfare of Japan. Participants were enrolled from 300 survey districts selected from throughout Japan. In light of the limited reports and equivocal findings in Asia, we used data from the NIPPON DATA80 to investigate more fully the associations of fruit and vegetable (FV) intake with mortality from total CVD, stroke and CHD.

METHODS

NIPPON DATA80

Cohort studies based on the NSCD[23] have been named the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA).[21,22,25] The present

study analyzed data from the NIPPON DATA80, for which baseline surveys were undertaken in 1980 with integration of dietary data from the NNS. Further details are provided elsewhere.[21,26]

In summary, 300 survey districts throughout Japan were randomly selected for the NSCD. Overall, there were 13 771 residents aged 30 years and older in the survey districts, and they were invited to participate in the NSCD in 1980. Among them, 10 546 agreed to participate (76.6% of the target sample) in the NSCD. They were also invited to participate in the NNS conducted in the same year and 3-day dietary record data were obtained. We used both results from NSCD and NNS with permission from the Ministry of Health and Welfare. A total of 10 422 were identified as the same individual by comparing NSCD data and NNS data. Follow-up was made possible through linkage with registration records from municipal governments with updates that were made available as participants move between localities. We excluded those without a residential address, which was needed for linkage to vital statistical records (n = 872).

Participants aged 80 years and older were also excluded (n = 150), as were subjects with missing data on body mass index (BMI), smoking and drinking habit, use of hypertensive medication or on a history of diabetes mellitus (DM), CHD or stroke (n = 274). Additional exclusions were made when total energy intake fell below 500 kcal/day or was 5000 kcal/day or higher (n = 14).[27] The remaining sample that is used in this report comprises 9112 participants (4000 men and 5112 women).

Baseline examinations

The NSCD consisted of history taking, physical examinations, blood tests and a self-administered questionnaire on lifestyle. The survey was conducted at public health centers according to a standardized manual. BMI was calculated as weight (kg) divided by the square of height (m). In the lifestyle questionnaire, participants were asked about their alcohol drinking habit (never, past, occasional or daily drinker), smoking habit (never, past or current smoker), use of antihypertensive medications and their history of DM, CHD and stroke. Questionnaires were administered during face-to-face interviews by trained public health nurses.

Dietary survey

In the NNS, dietary records for an entire household were collected for 3 consecutive days, excluding Saturday, Sunday and national holidays.[28] Participants were asked to weigh and record all food and beverages with the amounts that were consumed by any household member. Trained dietitians reviewed and confirmed the accuracy of the data and assigned food codes using standard food tables.[29] The dietary records were then used to calculate nutrient and food group intakes per household. Although data on only household intake are available in the NNS in 1980, estimates of individual intake were derived by taking the total intake for a household divided by the number of household members. Refinements in the individual intake values were further made by accounting for differences in proportional amounts consumed by age and sex as reported in the NNS in 1995 when information became available on how food or dishes were shared by family members.[26,30] On the basis of the NNS report, total food intake within a household was proportionally distributed among family members according to a member's age and sex. Further details on the estimation of individual dietary intake are provided elsewhere.[26]

End point determination

For the present study, the participants were followed for 24 years until 2004. The procedure used for end point determination in our study has been reported elsewhere.[21] Briefly, deaths are identified every 5 years through a search of the National Vital Statistics database with permission from the Management and Coordination Agency, Government of Japan. Collected information included the subject's residence and cause of death. The underlying causes of death were assigned centrally according to the International Classification of Diseases, Ninth Revision (ICD-9), through the end of 1994 and according to the International Classification of Diseases, Tenth Revision (ICD-10), from the beginning of 1995. Deaths from total CVD (ICD-9: 393–459 and ICD-10: I00 to I99), stroke (ICD-9: 430–438 and ICD-10: I60.0–I69.8) and CHD (ICD-9: 410–414 and ICD-10: I20.0–I25.9) were identified. Approval for the study was obtained from the institutional review board of Shiga University of Medical Science (No. 12–18, 2000).

Statistical analysis

Vegetable intake was calculated as the total of yellow-green and other vegetables (including salted vegetables) and mushrooms. Potatoes were not included in this calculation. Fruit intake was calculated as the total from all fruit (including fruit juice and canned fruit). Food group intake per 1000 kcal, nutrient intake per 1000 kcal and nutrient densities (%kcal) for protein, total fat and carbohydrates were also derived. For the current report, participants were divided into quartiles of total intake of fruits and vegetables, fruits alone and vegetables alone. Quartiles were defined separately for men and women. Differences in baseline characteristics and means of nutritional variables across the quartiles were compared by analysis of variance or the χ^2 test.

Sex- and age-adjusted mortalities were calculated by direct method using Japanese model population in 1985 for each quartile. To examine the association of FV intake with a mortality end point, Cox proportional hazards models were used. Results from the models provided estimates of the hazard ratio (HR) of a fatal event in the top three quartiles of FV intake versus the lowest quartile (the reference). Three models were investigated. Model 1 included sex and age as covariates. In model 2, additional covariates included BMI, smoking and drinking behavior and sodium intake (mg/1000 kcal). In model 3, further adjustments were made for the intakes of meat, fish and shellfish, milk and dairy products and soybeans and legumes. For each model, interaction effects between sex and FV intake were also examined. Separate analyses were conducted for total FV intake, fruit intake alone and vegetable intake alone. In model 3, vegetable intake alone and fruit intake alone were modeled jointly to help determine whether either intake variable had an effect on a mortality end point that was independent of the other intake variable. Trend analyses were also performed using the Cox proportional hazards model, with fruit and vegetable intake quartiles analyzed as a continuous variable.

Sex-specific models were also derived, as were models according to hypertension and diabetes status. Additional models were examined for subjects >60 years old and models for those who were younger. Hypothesis testing was two-sided with a 0.05 level of significance. SPSS v.21.0 for Windows (IBM Corporation, Chicago, IL, USA) was used throughout the analyses.

RESULTS

Characteristics of the study participants across the quartiles of fruit and vegetable intake are shown in Table 1. Approximately 56% percent of participants were women in each quartile. From the bottom to top quartiles, median intake (g/1000 kcal) increased from 113 to 249 in men and from 148 to 332 in women. For both sexes combined, the average age in bottom quartile was 46.1 years and 55.2 years in the top. Moving from low to high fruit and vegetable quartiles, mean intakes (g/1000kcal) of fish and shellfish (49–56), milk and dairy products (34–43) and soybeans and legumes (32–42) increased. Intakes of potassium (1136 –1638 mg/1000 kcal), sodium (2288–2971) and dietary fiber (6.7–10.6 g/1000 kcal) also increased. Conversely, meat intake declined from 30 to 27 g/1000 kcal with rising intake of fruits and vegetables. Use of medications to treat hypertension (7.1–16.0%) and the presence of diabetes (2.3–3.8%) rose with increasing intake of fruits and vegetables.

During the 24-year course of follow-up, there were 823 total CVD deaths, 385 stroke deaths and 165 CHD deaths (Table 2). Table 2 provides sex- and age-adjusted person-year mortalities, and results from the Cox analyses on the association of fruit and vegetable intake with the risk of mortality due to each cause are shown. More numbers of death were included in higher quartiles, but adjusted mortalities tended to be lower because more elderly participants were included in the higher quartiles and age distribution of the standard model population differed from that of the study population.

From Cox analyses, increased intake of fruits and vegetables was significantly associated with a lower risk of mortality for total CVD in all models. The multivariate-adjusted HR (95% confidence interval; P for the HR; P for trend) for the top versus bottom quartiles was 0.77 (0.64–0.93; 0.008; 0.006) in model 1 and 0.74 (0.61–0.91; 0.004; 0.018) in model 3. For stroke mortality, the

Table 1. Baseline characteristics of participants by quartiles of fruit and vegetable intake (g/1000 kcal), 4000 men and 5112 women aged 30–79 years, NIPPON DATA80

	Quartiles of vegetable and fruit intake, g/1000 kcal								P[a]	P for trend
	Q1 (low)		Q2		Q3		Q4 (high)			
Fruit and vegetable intake (g/1000 kcal), median (range)										
Men	113	(0, 137)	154	(137, 170)	190	(170, 213)	249	(213, 576)		
Women	148	(11, 178)	201	(178, 225)	251	(225, 282)	332	(282, 748)		
Number at risk	2278		2278		2278		2278			
	Mean	(s.d.)	Mean	(s.d.)	Mean	(s.d.)	Mean	(s.d.)		
Age at baseline (years)	46.1	(12.3)	48.0	(12.4)	50.7	(12.3)	55.2	(11.7)	< 0.001	< 0.001
Body mass index (kg/m^2)	22.6	(3.2)	22.6	(3.2)	22.8	(3.1)	22.9	(3.1)	< 0.001	< 0.001
Fruit (g/1000 kcal)	38	(24)	63	(30)	86	(39)	132	(66)	< 0.001	< 0.001
Vegetables (g/1000 kcal)	90	(26)	118	(28)	139	(34)	179	(54)	< 0.001	< 0.001
Fish and shellfish (g/1000 kcal)	49	(25)	49	(24)	52	(24)	56	(26)	< 0.001	< 0.001
Meat (g/1000 kcal)	30	(17)	29	(16)	28	(16)	27	(15)	< 0.001	< 0.001
Milk and dairy products (g/1000 kcal)	34	(29)	39	(30)	41	(33)	43	(36)	< 0.001	< 0.001
Soybeans and legumes (g/1000 kcal)	32	(22)	35	(21)	37	(21)	42	(23)	< 0.001	< 0.001
Total energy (kcal/day)	2145	(496)	2175	(483)	2163	(488)	2096	(486)	< 0.001	0.001
Protein (%kcal)	14.7	(2.1)	15.1	(1.9)	15.4	(2.0)	16.0	(2.1)	< 0.001	< 0.001
Total fat (%kcal)	20.6	(5.7)	21.2	(5.4)	20.9	(5.3)	20.5	(5.5)	< 0.001	0.404
Carbohydrate (%kcal)	61.2	(6.8)	60.8	(6.3)	61.1	(6.5)	61.7	(6.8)	< 0.001	0.012
Sodium (mg/1000 kcal)	2288	(699)	2495	(750)	2642	(782)	2971	(1016)	< 0.001	< 0.001
Potassium (mg/1000 kcal)	1136	(179)	1288	(175)	1409	(190)	1638	(257)	< 0.001	< 0.001
Total dietary fiber (g/1000 kcal)	6.7	(1.3)	7.9	(1.3)	8.8	(1.4)	10.6	(1.9)	< 0.001	< 0.001
Current smoker, n (%)	841	(36.9)	777	(34.1)	720	(31.6)	662	(29.1)	< 0.001	
Ex-smoker, n (%)	179	(7.9)	177	(7.8)	233	(10.2)	242	(10.6)		
Daily drinker, n (%)	593	(26.0)	539	(23.7)	497	(21.8)	457	(20.1)	< 0.001	
Use of antihypertensive medication, n (%)	161	(7.1)	180	(7.9)	234	(10.3)	364	(16.0)	< 0.001	
History of diabetes mellitus, n (%)	52	(2.3)	62	(2.7)	76	(3.3)	86	(3.8)	0.033	

Abbreviation: s.d., standard deviation. [a]Obtained from analysis of variance or the χ^2 test.

Table 2. Multivariate-adjusted HRs and 95% CIs of mortality from total CVD, stroke and CHD according to quartiles of fruit and vegetable intake, 4000 men and 5112 women aged 30–79 years, NIPPON DATA80 Study

	Quartiles of fruit and vegetable intake, g/1000 kcal							
		Q2		Q3		Q4 (high)		
	Q1 (low)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	P for trend
Person-years	49930	49253		48031		46443		
Total CVD								
Number of deaths (adjusted mortality[a])	169 (483)	181 (419)		188 (363)		285 (398)		
Model 1	1	0.86 (0.70, 1.06)	0.150	0.73 (0.59, 0.90)	0.003	0.77 (0.64, 0.93)	0.008	0.006
Model 2	1	0.85 (0.69, 1.05)	0.123	0.71 (0.58, 0.88)	0.002	0.74 (0.60, 0.90)	0.003	0.002
Model 3	1	0.85 (0.69, 1.05)	0.135	0.72 (0.58, 0.89)	0.002	0.74 (0.61, 0.91)	0.004	0.003
Stroke								
Number of deaths (adjusted mortality)	71 (202)	97 (225)		90 (174)		127 (174)		
Model 1	1	1.09 (0.81, 1.49)	0.564	0.83 (0.61, 1.13)	0.243	0.81 (0.61, 1.09)	0.167	0.042
Model 2	1	1.08 (0.80, 1.47)	0.609	0.81 (0.59, 1.11)	0.194	0.77 (0.57, 1.05)	0.102	0.022
Model 3	1	1.10 (0.81, 1.50)	0.602	0.83 (0.60, 1.13)	0.199	0.80 (0.59, 1.09)	0.105	0.036
CHD								
Number of deaths (adjusted mortality)	42 (121)	21 (48)		44 (85)		58 (82)		
Model 1	1	0.41 (0.24, 0.68)	0.001	0.70 (0.46, 1.08)	0.104	0.66 (0.44, 0.98)	0.040	0.298
Model 2	1	0.39 (0.23, 0.66)	< 0.001	0.65 (0.43, 1.00)	0.051	0.57 (0.38, 0.87)	0.010	0.107
Model 3	1	0.39 (0.23, 0.66)	< 0.001	0.65 (0.43, 1.00)	0.052	0.57 (0.37, 0.87)	0.010	0.109

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular diseases; HR, hazard ratio. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, body mass index (kg/m^2), smoking habit (current-, ex-, never), drinking habit (daily drinkers and others) and sodium intake (mg/1000 kcal). Model 3: adjusted for age, sex, body mass index (kg/m^2), smoking habit (current-, ex-, never), drinking habit (daily drinkers and others), sodium intake (mg/1000 kcal) and intakes of meat (g/1000 kcal), fish and shellfish (g/1000 kcal), milk and dairy products (g/1000 kcal) and soybeans and legumes (g/1000 kcal). [a]Person-year mortality per 100 000 person-years, adjusted for age and sex using standard model population of Japan in 1985.

inverse associations with FVs were less significant. The P value for the HR for the top versus bottom quartile was 0.105 in model 3, whereas risk lowering trend was significant (P for trend = 0.036). For CHD, although result of trend analysis was not significant (P for trend = 0.109), Q2, Q3 and Q4 were associated with lower risk of mortality with significance or borderline significance. The P values for the HRs were < 0.001, 0.052 and 0.010 for the Q2, Q3 and Q4 quartiles versus the bottom quartile, respectively, in model 3. The multivariate-adjusted HR using model 3 for the total of Q2 to Q4 versus Q1 was 0.55 (P = 0.001; data not shown).

Results from the Cox analyses using fruit intake alone and vegetable intake alone are shown in Tables 3 and 4, respectively. In both instances, adjustments were made for the other intake variable. The association of increased fruit intake with risk of CVD mortality was similar to that of vegetable intake. Significant inverse associations with the risk of total CVD mortality were observed for each intake variable in model 3. The multivariate-adjusted HR (95% confidence interval; P for the HR; P for trend) for the top versus bottom quartiles in model 3 was 0.79 (0.65–0.96; 0.018; 0.029) for fruit (Tables 3) and 0.81 (0.66–1.00; 0.046; 0.021) for vegetable (Table 4). Although fruit intake was significantly and inversely associated with the risk of stroke mortality, the association with the risk of CHD mortality was less clear. The P values for the HR for the top versus bottom quartile in model 3 were 0.020 for stroke and 0.596 for CHD. Results of analyses using quartiles of vegetable intake also yielded similar results to those using quartiles of total FV intake (Table 4). Significance, however, was weaker for mortality from stroke and CHD. The P values for HR for the top versus bottom quartile in model 3 were 0.165 for stroke and 0.060 for CHD.

Results of sex-specific analyses are shown in Supplementary Table 1. The overall trends were similar for men and women, with some loss of significance for women. The interaction effect of sex with FV intake was not significant (P = 0.167 for total CVD, P = 0.608 for stroke and P = 0.213 for CHD in model 3; data not shown). In Supplementary Table 2, results from stratifying participants according to the use of antihypertensive medication and a history of DM are shown. In the absence of antihypertensive treatment and a history of DM, intake of fruits and vegetables was significantly and inversely associated with risk of mortality from total CVD, stroke and CHD. The association was less clear for participants receiving treatment for hypertension or who had a history of DM. Dichotomizing participants by age (< 60 versus ≥ 60 years) yielded similar results for the younger participants and the elderly, with some loss of significance for both groups (Supplementary Table 3).

DISCUSSION

We found a significant inverse association of increased FV intake with the risk of mortality from total CVD in men and women recruited from 300 general population samples from all over Japan. The findings were independent of other confounding factors including age, sex, BMI, smoking and drinking habit, sodium intake and intake of several other food groups. For stroke mortality, the overall trends were similar to total CVD mortality. For CHD, the trend analysis was not significant, but the HR comparing the combined top 3 quartiles with the bottom quartile was significant. This suggests that benefits from consuming fruits and vegetables to lower CHD risk can occur at lower levels of intake than it does for stroke. The associations were similar for both men and women and also evident when the participants were limited to those without antihypertensive medication and a history of DM.

Table 3. Multivariate-adjusted HRs of mortality from total CVD, stroke and CHD by quartiles of fruit intake, 4000 men and 5112 women aged 30–79 years, NIPPON DATA80 Study

| | | Quartiles of fruit intake, g/1000 kcal | | | | | | |
| | | Q2 | | Q3 | | Q4 (high) | | |
	Q1 (low)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	P for trend
Fruit intake (g/1000 kcal), median (range)								
Men	20 (0, 32)	42 (32, 52)		63 (52, 78)		99 (78, 323)		
Women	35 (0, 54)	70 (54, 86)		105 (86, 127)		163 (127, 551)		
Person-years	48 809	49 635		48 231		46 388		
Total CVD								
Number of deaths (adjusted mortality[a])	187 (540)	170 (392)		203 (393)		263 (368)		
Model 1	1	0.83 (0.68, 1.03)	0.088	0.84 (0.69, 1.02)	0.085	0.76 (0.63, 0.92)	0.005	0.009
Model 2	1	0.86 (0.69, 1.05)	0.140	0.86 (0.70, 1.05)	0.130	0.78 (0.65, 0.94)	0.010	0.016
Model 3	1	0.85 (0.69, 1.05)	0.140	0.86 (0.70, 1.05)	0.138	0.79 (0.65, 0.96)	0.018	0.029
Stroke								
Number of deaths (adjusted mortality)	96 (277)	75 (173)		97 (187)		117 (165)		
Model 1	1	0.72 (0.53, 0.97)	0.029	0.78 (0.59, 1.03)	0.082	0.66 (0.50, 0.86)	0.002	0.008
Model 2	1	0.73 (0.54, 0.99)	0.043	0.80 (0.60, 1.06)	0.124	0.68 (0.52, 0.89)	0.005	0.017
Model 3	1	0.75 (0.55, 1.01)	0.058	0.82 (0.62, 1.09)	0.180	0.72 (0.54, 0.95)	0.020	0.049
CHD								
Number of deaths (adjusted mortality)	37 (107)	29 (66)		40 (77)		59 (82)		
Model 1	1	0.72 (0.44, 1.18)	0.191	0.85 (0.54, 1.33)	0.475	0.90 (0.60, 1.36)	0.621	0.903
Model 2	1	0.75 (0.46, 1.22)	0.255	0.87 (0.55, 1.36)	0.537	0.91 (0.60, 1.39)	0.673	0.917
Model 3	1	0.74 (0.46, 1.21)	0.236	0.87 (0.55, 1.36)	0.534	0.89 (0.58, 1.36)	0.596	0.839

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular diseases; HR, hazard ratio. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, body mass index (kg/m^2), smoking habit (current-, ex-, never), drinking habit (daily drinker or others) and sodium intake (mg/1000 kcal). Model 3: adjusted for age, sex, body mass index (kg/m^2), smoking habit (current-, ex-, never), drinking habit (daily drinker or others), sodium intake (mg/1000 kcal) and intakes of vegetables (g/1000 kcal), meat (g/1000 kcal), fish and shellfish (g/1000 kcal), milk and dairy products (g/1000 kcal) and soybeans and legumes (g/1000 kcal). [a]Person-year mortality per 100 000 person-years, adjusted for age and sex, using standard model population of Japan in 1985.

Table 4. Multivariate-adjusted HRs of mortality from total CVD, stroke and CHD by quartiles of vegetable Intake, 4000 men and 5112 women aged 30–79 years, NIPPON DATA80 Study

| | Q1 (Low) | Quartiles of vegetable intake, g/1000 kcal | | | | | | | |
| | | Q2 | | Q3 | | Q4 (High) | | | |
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	P for trend
Vegetable intake (g/1000 kcal), median (range)								
Men	76 (0, 90)	103 (90, 115)		128 (115, 144)		168 (144, 449)		
Women	87 (0, 105)	119 (105, 133)		144 (133, 167)		197 (167, 504)		
Person-years	48 943	48 383		48 817		46 914		
Total CVD								
Number of deaths (adjusted mortality[a])	184 (531)	189 (439)		189 (365)		261 (374)		
Model 1	1	0.95 (0.78, 1.17)	0.631	0.83 (0.68, 1.01)	0.066	0.87 (0.72, 1.05)	0.153	0.091
Model 2	1	0.94 (0.77, 1.16)	0.572	0.80 (0.65, 0.98)	0.032	0.80 (0.65, 0.98)	0.029	0.012
Model 3	1	0.95 (0.77, 1.16)	0.611	0.81 (0.66, 1.00)	0.045	0.81 (0.66, 1.00)	0.046	0.021
Stroke								
Number of deaths (adjusted mortality)	84 (244)	91 (211)		90 (174)		120 (185)		
Model 1	1	1.00 (0.74, 0.35)	0.995	0.86 (0.67, 1.16)	0.327	0.88 (0.66, 1.16)	0.350	0.234
Model 2	1	0.99 (0.74, 1.34)	0.966	0.83 (0.61, 1.11)	0.220	0.79 (0.59, 1.07)	0.128	0.068
Model 3	1	1.01 (0.75, 1.36)	0.964	0.85 (0.63, 1.14)	0.278	0.81 (0.60, 1.09)	0.165	0.093
CHD								
Number of deaths (adjusted mortality)	42 (119)	37 (87)		34 (65)		52 (74)		
Model 1	1	0.82 (0.53, 1.27)	0.371	0.65 (0.42, 1.03)	0.066	0.77 (0.51, 1.16)	0.216	0.179
Model 2	1	0.79 (0.51, 1.24)	0.308	0.60 (0.38, 0.95)	0.028	0.63 (0.41, 0.98)	0.039	0.025
Model 3	1	0.79 (0.51, 1.24)	0.304	0.61 (0.38, 0.96)	0.033	0.65 (0.42, 1.02)	0.060	0.041

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular diseases; HR, hazard ratio. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, body mass index (kg/m^2), smoking habit (current-, ex-, never), drinking habit (daily drinker or others) and sodium intake (mg/1000 kcal). Model 3: adjusted for age, sex, body mass index (kg/m^2), smoking habit (current-, ex-, never), drinking habit (daily drinker or others), sodium intake (mg/1000 kcal) and intakes of fruit (g/1000 kcal), meat (g/1000 kcal), fish and shellfish (g/1000 kcal), milk and dairy products (g/1000 kcal) and soybeans and legumes (g/1000 kcal). [a]Person-year mortality per 100 000 person-years, adjusted for age and sex using standard model population of Japan in 1985.

The median intake of fruits and vegetables is 136 g/1000 kcal higher in the top versus bottom quartile for men and 184 g/1000 kcal for women. These excess amounts of intake correspond to an approximate 26% lower risk of CVD. Stroke mortality risk was 20% lower and CHD mortality risk was 43% lower. From meta-analysis by He *et al.*, pooled relative risks for those consuming five or more servings per day compared with fewer than three servings of fruits and vegetables were 0.83 for stroke and 0.74 for CHD mortality.[6,31] In a more recent cohort study on the association of FV intake with CHD mortality, an increase in one serving per day of fruits and vegetables was associated with relative risk of 0.95 for CHD mortality.[7] Only cohort studies in western populations were included in these meta-analyses, and sodium intake was not adjusted for any of the studies involved. Our current results including sodium intake as a covariate may be concordant with the results in western populations.

One of the strengths of this study is that participants were enrolled from 300 survey districts randomly selected from throughout Japan, and thus the effect of regional differences was minimized. Another strength is that we used baseline dietary data obtained from 3-day weighing dietary records, a standardized method applied for NNS.[28] In many cohort study settings, food frequency questionnaires have often been used. In food frequency questionnaires, participants are asked to indicate their average frequency of food consumption listed in the questionnaires, and portion sizes are not fully considered. It is thus generally difficult to evaluate total energy and salt intake from food frequency questionnaires.[32,33] In this study, we used dietary variables obtained from 3-day weighing dietary records and could

use intakes of fruits and vegetables in grams, total energy, sodium intake in mg and other nutrients.

Vegetable consumption is often associated with high salt intake in Japan; some people often use table soy sauce on salted vegetables and vegetables cooked with soy sauce are common in Japan.[34] From Japanese cohort studies, Takachi *et al.* reported a significant inverse association of fruit intake with risk of mortality from total CVD, but not of vegetable intake, in which sodium intake was not adjusted.[10] Nagura *et al.* also reported a significant inverse association of fruit intake with risk or mortality from CVD, but not for vegetable intake, although they adjusted sodium intake.[11] They both used dietary data obtained from food frequency questionnaires. In Japan, 10% of daily salt intake is derived from salted vegetables (tsukemono).[34,35] As salt reduction is well established as the most important factor in explaining the large declines in CVD risk in Japan during the past 30 years,[36] recommendations to encourage the intake of vegetables need to coincide with vigorous recommendations to avoid salty vegetables. Our current results suggest a beneficial effect of increased vegetable intake while avoiding increased salt intake and the importance of considering sodium intake in evaluation of the effects of dietary factors on CVDs, especially in Japan.

The possible protective effect of fruits and vegetables on CVD mortality might be mediated through well-established CVD risk factors. Fruits and vegetables are important sources of potassium, dietary fiber, folate and various antioxidants. In a randomized controlled trial using meals with increased intake of fruits and vegetables, with a subsequent rise in 24-h urinary potassium excretion, blood pressure was decreased effectively.[37,38] Many controlled trials also reported increased potassium intake and decreased blood pressure.[39,40] In a study in which usual salt was

replaced with potassium-enriched salt in meals prepared for the elderly for 31 months, reduced CVD mortality was observed;[41] this effect might have been attributable to both reduced sodium intake and increased potassium intake. Because hypertension is a major risk factor for CVD, the blood-pressure-lowering effect of potassium in fruits and vegetables might be a major mechanism contributing to a reduced risk of CVD. The effects of dietary fiber on CVD and CVD risk factors were also reported elsewhere; the reported beneficial effects with increased intake of dietary fiber were lower serum cholesterol levels and improved glycemia and insulin sensitivity.[42] Fruits and vegetables are rich in antioxidants, and associations of dietary intake or serum concentration of certain antioxidants with CVD outcomes have been examined and beneficial effects have been reported.[43] The protective effect of FV intakes on CVD mortality in this study may be based on the total effect of these factors attributable to fruits and vegetables.

There are some limitations in this study. Subjects in the present data set were followed up to 24 years, and participants in a wide age range were included: 30–79 years of age. As data on only household intake were available, individual intake had to be measured by using estimates of average intake patterns in Japan for an individual's age and sex based on the NNS survey. The dietary intake of an entire household was proportionally distributed among individual household members by accounting for typical sex and age intakes derived from the NNS. Although the way in which foods are shared within and between families is likely to vary, the extent of this variation could not be assessed in this study. Dietary record data were collected only on weekdays. Potential day-of-week effects on food and nutrient intake were also not taken into account.[44] The dietary assessment was carried out only once at baseline, and change of dietary habit over the follow-up period was not accounted for. The status of CVD risk factors and other lifestyle factors may have changed after the baseline survey. There may also be a possibility that we could not adjust for other potential confounding factors. For instance, individuals who eat more fruits and vegetables have higher levels of physical exercise, which was not included in the current study. The inherent measurement error in these assessments could cause bias in the results. However, any bias from measurement error would probably tend to attenuate the identified protective effect of fruits and vegetables, and the sizes of the reductions in stroke and CHD risk seen in our study could have been underestimated.

In summary, the results of the analyses present a beneficial association between increased intake of fruits and vegetables and CVD mortality in Japanese men and women, which supports the recommendation to eat a sufficient amount of fruits and vegetables while avoiding increased sodium intake to prevent CVD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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