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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

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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.

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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

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 <0.05 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 >0.05). 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

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

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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