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Consumption of flavonoid-rich fruits and risk of CHD: a prospective cohort study

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Abstract

Although the association between fruit consumption and CHD risk has been well studied, few studies have focused on flavonoid-rich fruits (FRF), in particular strawberries and grapes. We aimed to verify the association of total and specific FRF consumption with risk of CHD by a large prospective cohort study. A total of 87 177 men and women aged 44–75 years who were free of CVD and cancer at study baseline were eligible for the present analysis. FRF consumption was assessed using a FFQ. Cox proportional hazards regression models were used to estimate the hazard ratios (HR) of CHD in relation to FRF consumption with adjustment for potential risk factors and confounders. During a mean follow-up of 13·2 years, we identified 1156 incident CHD cases. After full adjustment for covariates including demographics, lifestyles and dietary factors, the HR were 0·93 (95 % CI 0·77, 1·11), 0·91 (95 % CI 0·75, 1·11), 0·84 (95 % CI 0·67, 1·04) and 0·78 (95 % CI 0·62, 0·99) for the second, third, fourth and fifth quintiles compared with the lowest quintile of FRF consumption. Regarding specific fruits, we observed a significant inverse association for citrus fruit consumption and a borderline inverse association for strawberry consumption, while no association was observed for apple/pear or grape consumption. Although the associations appeared to be stronger in women, they were not significantly modified by sex. Higher consumption of FRF, in particular, citrus fruits, may be associated with a lower risk of developing CHD.

Key words: **Fruits: Flavonoids: CHD: Incidence: Prospective cohort studies**

As population ageing advances in many countries, chronic diseases such as CVD are having an enormous impact on society. CVD has become the leading cause of death worldwide, with an estimated 17·9 million deaths (31 % of all deaths), attributed to it in 2016[1]. CHD was the number two cause of death among people aged ≤59 years and number one among those aged ≥60 years[2]. Accumulating evidence suggests higher fruit consumption is inversely associated with the risk of CHD[3]. Fruits are rich in vitamins, minerals and dietary fibre. Also, flavonoids in fruit may contribute beneficial cardiovascular effects because of their antioxidant properties[4,5]; this probably occurs through suppressing the formation and progress of atherosclerosis, the major pathology of CHD[6,7].

Flavonoids are a large class of polyphenols widely present in many common foods, including fruits, tea, chocolate, nuts and red wine[8]. They are classified into multiple subgroups, including anthocyanidins, flavanones, flavanonols, flavans and isoflavones[9]. These non-energy, non-nutrient polyphenols are secondary metabolites that humans cannot synthesise[9]. They are, however, regarded as indispensable dietary components for humans because of their antioxidative property related to prevention of various diseases associated with oxidative stress[9]. A review of prospective cohort studies showed that dietary flavonoid consumption was inversely associated with mortality from CHD[10].

Although the association between total fruits and CHD risk was well studied, few studies have focused on flavonoid-rich fruits (FRF), in particular strawberries and grapes. Understanding the role of FRF in the development of CHD may have implications in the prevention practice. We, therefore, aimed to verify the association of total and specific FRF consumption with CHD risk, through use of a large prospective cohort study.

Materials and methods

Participants

The Japan Public Health Center-based Prospective Study (JPHC Study) aims to provide evidence on the prevention of

Abbreviations: FRF, flavonoid-rich fruits; HR, hazard ratio.

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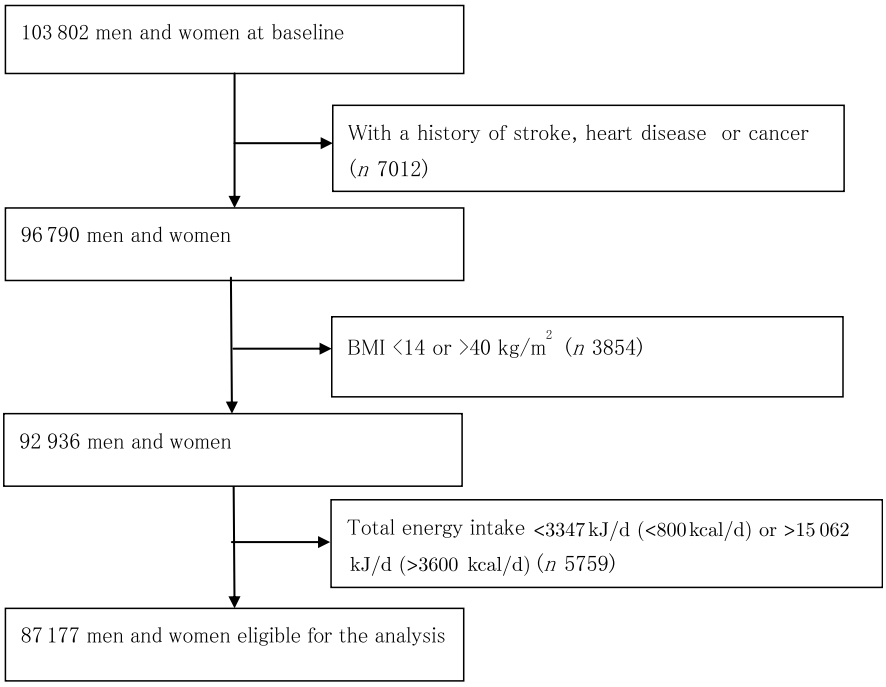

Fig. 1. Flow chart for participant selection.

non-communicable diseases and on health promotion. Details of the study design have been published[11]. Briefly, in 1990, participants aged 40–59 years from five public health centres (cohort I) and, in 1993, participants aged 40–69 years from six public health centres (cohort II) were recruited. At the fifth year after the first survey, a second follow-up survey was carried out. As consumption of pears, grapes and strawberries was not assessed in the first survey, we treated the second survey that assessed 138 food and beverage items as the study baseline for the present analysis (i.e. 1995 for cohort I and 1998 for cohort II). A total of 103 802 men and women answered the questionnaire at study baseline. We excluded 16 625 of them because they had a previous history of CVD or cancer (*n* 7012), had an extreme BMI (<14 or >40 kg/m^2, *n* 3854) or had an implausible energy intake (<3347 kJ/d (<800 kcal/d) or >15062 kJ/d (>3600 kcal/d), *n* 5759). Ultimately, 87 177 men and women were eligible for the present analysis on FRF consumption and CHD risk (Fig. 1). The present study was approved by the institutional review boards of the National Cancer Center and Osaka University. Informed consents were obtained from individuals or from community leaders in some areas.

Dietary assessment

Dietary assessment was based on a validated FFQ[12,13]. Participants were asked to report their frequencies of food and beverage consumption during the preceding 12 months. The FFQ included fourteen fruit items: apples, pears, oranges, other citruses, strawberries, grapes, papayas, Japanese persimmons, melons, watermelons, peaches, kiwifruits, pineapples and bananas. FRF, defined as fruits with high content of total flavonoids >50 mg/100 g[8], included apples, pears, oranges, other citruses, strawberries and grapes in the present study. Total FRF consumption was defined as the total intakes of the above fruits. Other fruits were defined as the remaining fruits in FFQ (papayas, Japanese persimmons, melons, watermelons, peaches, kiwifruits, pineapples and bananas). The question about fruit consumption included nine predefined frequency categories ranging from never to ≥7 times per d. Each respondent's fruit intake was calculated based on the frequency and portion size (85 g for apples, 80 g for pears, 140 g for oranges, 75 g for strawberries, 100 g for grapes and 50–130 g for other fruits). The FFQ was previously found to have acceptable reproducibility and validity[12,13].

Covariate assessment

Data on socio-demographic information, self-rated physical and mental health, disease history, medication use, smoking status, drinking status and physical activities were obtained through self-administered questionnaires. BMI was calculated using self-reported height and weight (BMI = weight (kg)/(height (m))^2).

Outcome assessment

The outcome of this analysis was the first incidence of CHD. Cases of CHD, including nonfatal myocardial infarction and coronary deaths, were diagnosed in accordance with the criteria of the Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) project[14], with the use of electrocardiograms, cardiac enzymes and/or autopsy. Cases were diagnosed in hospitals that were registered within the study areas. A total of 3194 participants (3·7 %) who moved out of the registered study areas were not able to follow and they were treated as loss to follow-up. Physicians, hospital workers or investigators, who

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were not aware of the baseline data, were responsible for identifying CHD cases by reviewing the medical records.

Statistical analysis

Person-years of follow-up were calculated from the date of the return of the second survey questionnaire until the date of CHD incidence, death or 31 December 2009, for cohort I, and 31 December 2012, for cohort II, whichever came first. We used a Cox proportional hazards regression model to compute hazard ratios (HR) for CHD incidence based on the quintiles of FRF consumption. We combined men and women in the main analysis and conducted a stratified analysis by sex. We treated the group with the lowest consumption as the reference. All HR were age-adjusted in model 1. In model 2, we further adjusted for study areas, sex, occupation (unemployed, white-collar worker, blue-collar worker, other or missing), BMI (<18·5, 18·5–20·9, 21–22·9, 23–24·9, 25–29·9 or ≥30 kg/m^2), use of medication for hypertension and hypercholesterolaemia (yes or no), history of diabetes (yes or no), smoking status (never, past, current <1 or ≥1 pack/d or missing), alcohol use (never, 0–22·9, 23–45·9, 46–68·9, ≥69 g/d or missing) and physical exercise (never, 1–3 times/month, 1–2, 3–4, ≥5 times/week or missing). In model 3, we further adjusted for dietary factors including coffee intake (never, 1–2, 3–6 cups/week, 1, ≥2 cups/d or missing), green tea intake (never, 1–2, 3–6 cups/week, 1, 2–3, ≥4 cups/d or missing) and quintile intakes of total energy, seafood, red meat, processed meat, milk, soya foods, vegetables and other fruits. We conducted trend tests by treating FRF consumption as a continuous variable. We also examined the associations between specific FRF intake and CHD risk. Apples and pears were combined as apples/pears and oranges and other citrus were combined as citrus fruits. As strawberry and grape consumptions were relatively lower, participants were divided into quartile groups. A sensitivity analysis was performed to examine the association of energy-adjusted FRF consumption with CHD risk by using the residual method. All analyses were performed using SAS 9.4 software (SAS Institute Inc.). All *P* values were two-sided, with $P < 0{\cdot}05$ considered statistically significant.

Results

Table 1 shows the baseline characteristics of the study population based on the quintiles of FRF consumption. Median FRF intakes were 13·4, 43·0, 85·4, 143·4 and 289·8 g/d for the quintiles. People with higher consumption were slightly older, more likely to be women and less likely to smoke and drink than those in the lowest quintile. Additionally, higher FRF consumption was associated with higher intakes of seafood, vegetables, soya foods, green tea, other fruits and total energy.

During a mean follow-up of 13·2 years, we identified 1156 incident CHD cases from the 87 177 participants (1·3 %). In the age-adjusted model, participants in the highest quintile of FRF consumption (median 289·8 g/d), compared with those in the lowest (median 13·4 g/d), had a lower risk of developing CHD (age-adjusted HR = 0·58 (95 % CI 0·48, 0·70)) (Table 2). The association was attenuated but remained significant after adjusting for potential risk factors including study area, sex, BMI, occupation, smoking, physical exercise, drinking, hypertension and hypercholesterolaemia medication use, and diabetes history (model 2). Further adjustment for dietary factors yielded similar results to those with model 2; the fully multivariable-adjusted HR were 0·93 (95 % CI 0·77, 1·11), 0·91 (95 % CI 0·75, 1·11), 0·84 (95 % CI 0·67, 1·04) and 0·78 (95 % CI 0·62, 0·99) for the second through fifth quintiles, respectively. In the analyses for specific FRF consumption associated with CHD risk, we observed a significant inverse association for higher citrus fruit consumption and a borderline significantly inverse association for higher strawberry consumption, though no association for higher apple/pear or grape consumption after adjustment for all covariates in model 3. Sensitivity analyses using energy-adjusted data yielded similar results, for example, the fully adjusted HR of the highest group were 0·81 (95 % CI 0·66, 0·995) for total FRF and 0·82 (95 % CI 0·68, 0·98) for citrus fruits.

In the subgroup analysis stratified by sex, significant associations of total FRF consumption and citrus fruit consumption with CHD risk were observed in women but not in men (Fig. 2). However, the differences were not statistically significant (all $P_{\text{for interaction}} \geq 0{\cdot}15$).

As for total fruits, the fully adjusted HR of CHD were 1·07 (95 % CI 0·89, 1·27), 1·06 (95 % CI 0·88, 1·29), 1·12 (95 % CI 0·91, 1·38) and 0·98 (95 % CI 0·78, 1·23) for the second, third, fourth and fifth quintiles compared with the lowest quintile.

Discussion

In this large prospective cohort study, we examined the association of total and specific FRF consumption with CHD risk. We observed that higher FRF consumption, particularly consumption of citrus fruits, was associated with a lower risk of developing CHD. Although the associations appeared to be stronger in women, they were not significantly modified by sex.

The potential cardiovascular effects of FRF may be partially attributed to the antioxidative features of flavonoids and their endothelial control of inflammation, vasodilatation, vascular homeostasis and thrombosis[15]. Flavonoids have been shown to resist oxidative stress by modifying the function of enzymes that modulates superoxide anion production, such as with xanthine oxidase[16] and protein kinase C[17]. They also work as a free radical scavenger of superoxide[18]. The process both inhibits oxidised LDL *in vitro*[19] and antagonises the effect of nitric oxide inactivation[20]. Flavonoids may also protect nitric oxide from superoxide-driven inactivation or they can directly scavenge nitric oxide molecules under certain conditions[21]. Moreover, flavonoids exert an anti-inflammatory effect mediated through signal transduction pathways rather than antioxidant capacity, which has shifted focus from antioxidant effects to enzyme-induced pathways[22]. For example, the flavonols quercetin and myricetin may inhibit NF-κB activity through down-regulating NF-κB pathway signalling[23,24], thus reducing the inflammatory reaction in cells[25].

In addition to flavonoids, other nutrients in fruits, vitamin C in particular, may have contributed to the observed association.

Table 1. Baseline characteristics according to quintiles (Q) of flavonoid-rich fruit consumption*
(Numbers and percentages; mean values and standard deviations)

	Q1			Q2			Q3			Q4			Q5				Total		
Median intakes (g/d)...	13·4			43·0			85·4			143·4			289·8				83·9		
No. of participants...	17 437			17 405			17 464			17 429			17 442				87 177		
	Mean	%	SD	Mean	%	SD	Mean	%	SD	Mean	%	SD	Mean	%	SD	$P_{for\ trend}$	Mean	%	SD
Age (years)	55·9		8·0	56·1		7·8	56·8		7·9	56·8		7·7	57·2		7·6	< 0·001	56·6		7·8
Age distribution (years)																			
<50		26·9			25·3			22·2			20·4			18·8		< 0·001		22·7	
50–59		39·0			41·2			40·8			42·1			41·8		< 0·001		41·0	
60–69		26·8			26·6			29·3			30·3			31·6		< 0·001		28·9	
≥70		7·2			6·9			7·7			7·2			7·8		0·01		7·3	
Male		63·8			53·9			44·9			37·7			29·6		< 0·001		45·7	
BMI (kg/m^2)	23·8		3·1	23·7		3·1	23·6		3·0	23·5		3·0	23·5		2·9	< 0·001	23·5		3·0
History of diabetes		4·6			5·2			4·8			4·2			3·5		< 0·001		4·5	
Use of hypertension drug		18·5			19·2			18·2			18·8			17·6		0·004		18·5	
Use of hypercholesterolaemia drug		3·7			4·7			5·6			6·1			6·7		< 0·001		5·3	
Current smoker		36·9			28·2			22·8			17·5			13·9		< 0·001		23·8	
Never drinker		41·0			47·3			52·4			57·0			64·9		< 0·001		53·0	
Sports ≥ 3 times/week		9·2			10·2			10·9			11·1			12·0		< 0·001		10·6	
White collar		33·9			35·1			32·6			30·7			26·9		< 0·001		31·5	
Alcohol (g/d)	24·1		35·2	17·5		29·2	13·0		24·2	10·4		21·2	7·0		17·0	< 0·001	13·9		26·8
Seafood (g/d)	64·9		56·0	81·0		56·2	92·5		61·4	106·9		67·7	115·9		72·4	< 0·001	90·2		65·6
Red meat (g/d)	43·0		44·5	42·8		40·9	41·7		37·5	42·4		36·5	41·9		35·3	0·01	42·3		39·1
Processed meat (g/d)	6·5		10·3	6·5		8·7	6·5		9·4	6·6		9·4	6·7		8·4	0·04	6·5		9·2
Milk (g/d)	101		189	127		201	144		198	164		210	173·4		212	< 0·001	142		204
Vegetables (g/d)	142		120	177		124	209		130	251		146	318		189	< 0·001	215		156
Soya food (g/d)	51·7		68·5	57·3		57·3	62·4		58·8	69·4		56·7	75·6		63·5	< 0·001	62·1		61·7
Coffee (cups/d)	1·5		1·3	1·2		1·2	1·2		1·1	1·1		1·1	1·1		1·1	< 0·001	1·2		1·1
Green tea (cups/d)	2·3		2·5	2·4		2·6	2·7		2·7	3·0		2·9	3·5		3·1	< 0·001	2·6		2·8
Apples/pears (g/d)	4·6		3·5	14·1		9·6	25·5		17·9	42·8		24·4	79·5		68·9	< 0·001	33·4		43·4
Citrus fruits (g/d)	7·4		1·6	25·5		4·7	48·3		8·4	81·2		13·9	206·4		40·3	< 0·001	12·9		23·1
Grapes (g/d)	1·0		1·3	2·8		3·4	5·1		5·9	9·7		10·2	21·9		27·2	< 0·001	7·9		15·2
Strawberries (g/d)	1·4		1·8	3·9		4·2	6·4		6·8	11·0		10·7	21·9		27·0	< 0·001	8·7		15·2
Other fruits (g/d)	50·8		71·0	74·0		75·9	85·5		79·3	106·4		88·6	149·5		122·6	< 0·001	91·5		95·2
Total energy (kcal/d)†	1774		570	1876		553	1968		553	2090		553	2276		561	< 0·001	1963		584

* Values are age-adjusted. Continuous variables are expressed as mean values and standard deviations and categorical variables are expressed as percentages. Flavonoid-rich fruit consumption is calculated as the total consumption of apples, pears, citrus fruits, strawberries and grapes. Other fruits included papayas, Japanese persimmons, melons, watermelons, peaches, kiwifruits, pineapples and bananas. The percentages of missing data were as follows: 3·6 % for occupation, 3·5 % for smoking, 0·1 % for drinking, 3·9 % for physical exercise, 3·6 % for green tea consumption and 4·9 % for coffee consumption.
† To convert energy values from kcal to kJ, multiply by 4·184.

Table 2. Flavonoid-rich fruit consumption and risk of CHD among the Japanese population (Hazard ratios (HR) and 95 % confidence intervals)

	Q1	Q2		Q3		Q4		Q5		
		HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	$P_{for\ trend}$
Flavonoid-rich fruits										
Median intakes (g/d)	13·4	43·0		85·4		143·4		289·8		
Person-years	220 144	222 509		223 858		227 010		228 322		
No. of cases	295	235		240		200		186		
HR, model 1	1·00	0·85	0·72, 1·01	0·76	0·63, 0·90	0·63	0·52, 0·76	0·58	0·48, 0·70	< 0·001
HR, model 2	1·00	0·93	0·78, 1·11	0·91	0·76, 1·09	0·83	0·69, 1·01	0·80	0·66, 0·98	0·03
HR, model 3	1·00	0·93	0·77, 1·11	0·91	0·75, 1·11	0·84	0·67, 1·04	0·78	0·62, 0·99	0·04
Apples and pears										
Median intakes (g/d)	2·7	7·0		17·1		40·7		79·9		
Person-years	199 099	220 375		234 845		237 713		229 810		
No. of cases	261	247		252		209		187		
HR, model 1	1·00	0·97	0·81, 1·15	0·92	0·77, 1·10	0·75	0·62, 0·90	0·71	0·59, 0·86	< 0·001
HR, model 2	1·00	1·03	0·86, 1·24	1·04	0·86, 1·24	0·94	0·77, 1·13	0·93	0·76, 1·14	0·22
HR, model 3	1·00	1·06	0·88, 1·28	1·08	0·88, 1·31	0·99	0·80, 1·23	0·98	0·78, 1·24	0·46
Citrus fruits										
Median intakes (g/d)	4·8	17·8		43·6		79·3		182·4		
Person-years	219 660	223 337		222 787		219 160		236 899		
No. of cases	293	237		229		205		192		
HR, model 1	1·00	0·82	0·69, 0·98	0·73	0·62, 0·88	0·63	0·53, 0·76	0·55	0·46, 0·66	< 0·001
HR, model 2	1·00	0·92	0·77, 1·09	0·88	0·73, 1·05	0·84	0·69, 1·01	0·77	0·63, 0·93	0·009
HR, model 3	1·00	0·92	0·77, 1·10	0·88	0·73, 1·06	0·83	0·68, 1·02	0·76	0·61, 0·94	0·01
Strawberries										
Median intakes (g/d)	0·0	2·4		7·7		18·0				
Person-years	291 256	252 093		294 129		284 365				
No. of cases	396	257		288		215				
HR, model 1	1·00	0·87	0·74, 1·02	0·87	0·74, 1·01	0·68	0·58, 0·81			<0·001
HR, model 2	1·00	0·91	0·77, 1·07	0·97	0·82, 1·14	0·83	0·69, 0·99			0·06
HR, model 3	1·00	0·94	0·79, 1·11	0·99	0·83, 1·17	0·84	0·69, 1·02			0·09
Grapes										
Median intakes (g/d)	0·0	2·0		6·4		15·0				
Person-years	225 151	342 581		256 588		297 522				
No. of cases	275	383		257		241				
HR, model 1	1·00	1·03	0·88, 1·21	0·96	0·80, 1·14	0·79	0·66, 0·94			0·001
HR, model 2	1·00	1·09	0·93, 1·29	1·07	0·90, 1·28	0·96	0·80, 1·15			0·25
HR, model 3	1·00	1·13	0·95, 1·34	1·12	0·92, 1·35	0·99	0·81, 1·23			0·36

Q, quintile.

* Model 1: adjusted for age (87 177 participants without missing data). Model 2: model 1 and further adjusted for the study area, sex, BMI, smoking, drinking, physical exercise, occupation, medication use for hypertension and hypercholesterolaemia, and history of diabetes (79 507 participants without missing data). Model 3: model 2 and further adjusted for dietary intakes of seafood, red meat, processed meat, milk, soya food, green tea, coffee, vegetables, other fruits and total energy (75 519 participants without missing data). Flavonoid-rich fruit consumption is calculated as the total consumption of apples, pears, citrus fruits, strawberries and grapes. Other fruits included papayas, Japanese persimmons, melons, watermelons, peaches, kiwifruits, pineapples and bananas.

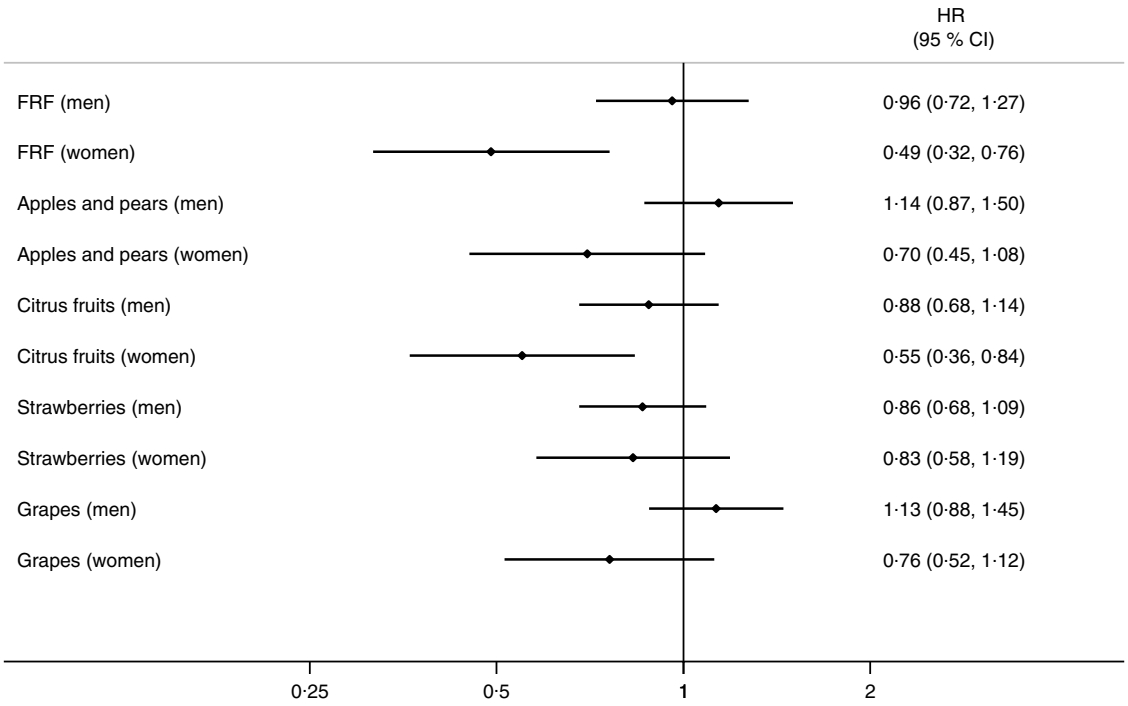

Fig. 2. Associations between consumptions of total and specific flavonoid-rich fruits (FRF) and risk of CHD stratified by sex. Hazard ratios (HR, highest *v.* lowest group) were adjusted for age, study area, BMI, smoking, drinking, physical exercise, occupation, medication use for hypertension and hypercholesterolaemia, history of diabetes and dietary intakes of seafood, red meat, processed meat, milk, soya food, green tea, coffee, vegetables, other fruits and total energy. All $P_{\text{for interaction}} \geq 0{\cdot}15$.

Vitamin C has the abilities to prevent LDL from atherogenic modification[26] and counteract the damage caused by existing highly bio-reactive-oxidised LDL[27]. Vitamin C can also decrease the bioavailability of superoxide, relieving superoxide-mediated nitric oxide inactivation[28].

A meta-analysis of prospective studies confirmed the inverse association of apple and pear consumption with CHD risk (*n* 10, pooled HR = 0·85 (95 % CI 0·79, 0·93))[3]. The absence of such an association in the Japanese population was, however, not surprising. Database from the United States Department of Agriculture[29] has shown the flavonoid composition of fruits, though the specific compositions of flesh and peel have not been shown. Recent research has shown apple peel possesses more flavonoid than apple flesh[30], thus indicating apple peel's dietary benefit[31,32]. In Japan, unlike in many countries, it is common to peel apples before eating them. The loss of abundant flavonoids and other nutrients in the peel may account for the non-significant association observed in our study.

In line with findings from previous studies, we found higher consumption of citrus fruits was associated with a decreased risk of CHD. The previously mentioned meta-analysis pooled the results of fourteen cohort studies and supported an inverse association between citrus fruit consumption and CHD risk, showing a combined HR of 0·91 (95 % CI 0·86, 0·96)[3]. Moreover, individual study results included in that meta-analysis did not significantly differ ($P_{\text{for heterogeneity}} = 0{\cdot}69$)[3]. Citrus fruits are rich in flavonoids and vitamin C, and they were the most consumed FRF in this Japanese population (Table 1). In the Iowa Women's Health Study with 15 years of follow-up, a significant inverse association was observed between flavanones – the major flavonoid class existing in citrus fruits – and CHD mortality for the highest *v.* the lowest quintile (HR = 0·78 (95 % CI 0·65, 0·94))[33].

To date, the evidence linking strawberry and grape consumption to CHD risk is very limited. We observed a borderline significant association between strawberry consumption and lower CHD risk. Strawberries have abundant vitamin C and polyphenols such as anthocyanin, which are suggested to have antioxidant and anti-inflammatory activity associated with beneficial effects on improving lipid profile, blood pressure, endothelial function and insulin resistance[34,35]. However, two cohort studies found no association of strawberry consumption with myocardial infarction incidence or CHD mortality[33,36]. We observed no association of grape consumption with CHD risk, which was consistent with results from previous studies conducted in Western countries[33,37–39].

Strengths of the present study included its prospective community-based cohort design and a large sample size. Several limitations, however, should also be noted. First, as an observational study, the risk of confounding bias should be considered when interpreting the results. As shown in Table 1, participants with higher FRF consumption were more likely to have a healthier lifestyle, which includes less smoking and higher intakes of vegetables, seafood and other fruits. It was therefore unsurprising that adjustment for age only (model 1) always led to statistically significant HR while further adjustments for covariates in model 2 and model 3 resulted in attenuated associations between FRF consumption and risk of CHD. Other unmeasured factors associated with FRF consumption, such as income and

education level, may at least partly explain the observed associations. Second, because the diet assessment was based on a self-reported questionnaire, the influence of measurement errors cannot be completely ruled out; these were probably non-differential and could attenuate the association towards the null. Third, the questionnaire addressed frequently consumed fruits in Japan but did not include FRF such as blueberries, which have been shown to have potential effects on preventing CVD[37]. Finally, an underestimation of CHD occurrence was inevitable due to 3·7 % of loss to follow-up, yet such a proportion of loss to follow-up was not likely to change our findings materially.

In conclusion, the findings from this prospective cohort study suggest that higher FRF consumption, especially citrus fruits, is associated with a lower risk of developing CHD.

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Members of the JPHC study group are listed in https://epi.ncc.go.jp/en/jphc/781/8233.html

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J.-Y. D. designed the study, analysed the data and edited the manuscript. Y. Y. drafted the manuscript. All authors conducted the technique review and edited the manuscript. J.-Y. D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors declare that there are no conflicts of interest.

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