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Dietary intakes of fat soluble vitamins as predictors of mortality from heart failure in a large prospective cohort study

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ABSTRACT

Objectives: A few reports have investigated the association of dietary vitamin intakes with risk of heart failure in Asia. Therefore, we examined the relation between dietary intakes of fat-soluble vitamins A, K, E, and D and mortality from heart failure in the Japanese population.
Methods: A total of 23 099 men and 35 597 women ages 40 to 79 y participated in the Japan Collaborative Cohort Study and completed a food frequency questionnaire from which dietary intakes of vitamins A, K, E, and D were calculated. The Cox proportional hazard model was used to estimate the sex-specific risks of heart failure mortality according to increasing quintiles of fat-soluble vitamin intakes.
Results: During the median 19.3 y follow-up period, there were 567 deaths from heart failure (240 men, 327 women). Dietary vitamin A intake showed no association with heart failure mortality in both sexes; however, the reduced risk was observed in women but not in men with dietary intakes of vitamins K, E, and D. The multivariable hazard ratios (95% confidence interval) in the highest versus the lowest intake quintiles among women were 0.63 (0.45–0.87; P for trend = 0.006) for vitamin K, 0.55 (0.36–0.78; P for trend = 0.006) for vitamin E, and 0.66 (0.48–0.93; P for trend = 0.01) for vitamin D. The association for each vitamin was slightly attenuated but remained statistically significant after mutual adjustment for intakes of the other vitamins.
Conclusions: High dietary intakes of fat-soluble vitamins K, E, and D were associated with a reduced risk of heart failure mortality in Japanese women but not men.

Introduction

Heart failure is a complex syndrome that stands on the activation of numerous biological mechanisms that follow or coincide with myocardial injury and lead to inadequate systematic perfusion [1]. In developed countries with a high proportion of aging population, such as in Japan, heart failure is a notable public health burden [2]. Intakes of seafood and fish [3,4], fermented soybeans [5], and fruits and vegetables [5,6] have been associated with a reduced risk of heart failure. In the Japanese diet, seafood and fish are the main dietary contributors of vitamin D [7], natto (i.e., fermented soybeans) is a major source of vitamin K [8], and vitamins A and E are mainly provided by the consumption of fruits and vegetables [9]. Whether the observed reduced risks with higher intakes of these foods are attributed to the effect of their content of fat-soluble vitamins (i.e., A, K, E, and D) remains unclear.

Dietary antioxidant capacity was inversely associated with the risk of cardiovascular diseases including heart failure [10]. However, the association between dietary intakes of vitamins A and E and cardiovascular mortality is questionable [11–13]. Conflicting observations also exist on the impact of vitamin K intake on cardiovascular health [14–17]. In addition, there is growing

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evidence on the protective effects of vitamin D against cardiovascular disease [18,19] including heart failure [18,20].

When taking these contradictory findings together, the associations between dietary intakes of fat-soluble vitamins and risk of heart failure still need to be investigated, especially in Asian populations. Therefore, we aimed to examine the association between dietary intakes of vitamins A, K, E, and D and the risk of mortality from heart failure among men and women enrolled in the Japan Collaborative Cohort study (JACC), a large prospective study.

Materials and methods

Study population and baseline covariates

With a total of 110 585 Japanese participants including middle-aged (40–79 y) men (n = 46 395) and women (n = 64 190) from 45 communities across Japan, the Ministry of Education, Sports, and Science sponsored the JACC study from 1988 to 1990. A detailed description of the JACC study was published previously [21].

Data on baseline lifestyle and participant characteristics including demographic data, medical history of chronic diseases, diabetes mellitus and hypertension, alcohol consumption habits, smoking, exercise, diet and other items were compiled via a self-administered questionnaire that included a 40 food item/food frequency questionnaire (FFQ). Participants who did not provide answers to ≥4 items of the FFQ or reported a history of either cancer or cardiovascular disease were excluded from the study. Participants with missing information about fat-soluble vitamin intake were also excluded from the study, which left a total of 58 646 individuals with eligible data for the study (23 099 male and 35 547 female participants; Suppl. Fig. 1).

Diet with food item/food frequency questionnaire

The usual consumption frequency for each food item over the past 12 mo without specification of the portion size was obtained from participants through a choice from five frequency responses: rarely, 1 to 2 times/mo, 1 to 2 times/wk, 3 to 4 times/wk, and almost every day [21]. These frequencies were transformed to weekly consumption scores of 0, 0.38, 1.5, 3.5, and 7.0 per wk, respectively. Dietary intakes of fat-soluble vitamins (A, K, E, and D) were calculated using the Japan Food Tables, Fifth Edition to determine the amount of fat-soluble vitamins in each food. These contents were multiplied by participants' frequency score for each food item in the FFQ, followed by a summing of the contents.

A validation study among 85 individuals using four 3-d weighed dietary records (DRs) over a 1-yr period as a reference standard determined the portion size for each food and validated the FFQ intakes. The Spearman rank correlation coefficients for vitamins A, K, E, and D intake between the FFQ and the four 3-d DRs were 0.37, 0.40, 0.38, and 0.39, respectively. The mean ± standard deviation intakes in mg/d from the FFQ were 967 ± 446 for vitamin A, 180 ± 64 for vitamin K, 4.9 ± 1.5 for vitamin E, and 7.8 ± 3.7 for vitamin D, whereas the respective intakes from the DRs were 1089 ± 543, 279 ± 104, 9.1 ± 1.9, and 10.6 ± 4.5 mg/d [22].

Mortality surveillance

As part of the mortality surveillance in each resident area, investigators conducted a systematic review of death certificates, which were centralized at the Ministry of Health and Welfare. International Classification for Diseases, 10th Revision, codes were used to specify the underlying causes of deaths and the code for our primary outcome (heart failure) was 150. This death certificate ascertainment was applied to all deaths within our cohort except for deaths that occurred outside of the original resident areas, which were treated as censored cases.

Statistical analysis

A calorie adjustment with the residual method [23] was made to the dietary intakes of our exposure variables, which were then modeled as categorical (five quintiles) groups in the main analysis. The significance of the differences in proportion and mean of participants' characteristics and known cardiovascular risk factors across calorie-adjusted quintiles of fat-soluble vitamin intakes were tested by $\chi 2$ test and analysis of covariance. Person-years of follow-up were calculated as the period from submission of the questionnaire to either departure of a participant from his or her original residential area, death, or termination of follow-up at the end of 2009, whichever came first. Follow-up was terminated in two study areas in 2008, in four areas in 2003, and in another four areas in 1999.

Sex-specific age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals for risk of mortality from heart failure across increasing intake quintiles of each vitamin were calculated using the Cox proportional model. The hypothesized confounders were history of diabetes and hypertension (yes/no), use of multivitamin supplementation (yes/no), hours of walking (almost never, 0.5, 0.6–0.9, ≥1 h/d), hours of sports (almost never, 1–2, 3–4, ≥5 h/wk), smoking category (never, ex-smoker, current smoker of 1–19, ≥20 cigarettes/d), quintiles of body mass index, years of education (≤15, 16–18, >18 y), perceived mental stress (low, medium, high), and ethanol intake (never, ex-drinker, current drinker of 0.1–22.9, 23.0–45.9, 46.0–68.9, ≥69.0 g ethanol/d), calorie-adjusted quintiles of calcium, sodium, potassium, saturated fatty acids, n-3 fatty acids, total dietary fiber and vitamin C intakes, and total calorie intakes.

The impact of mutual adjustment for each fat-soluble vitamin intake was tested in an additional model. We conducted tests for trends across quintiles of vitamin intake by assigning median values to each quintile and testing the significance of this variable. We further analyzed the data after the exclusion of persons who died within the first 3, 5, and 10 y of follow-up to examine a potential effect of as-yet-undiagnosed diseases at baseline. Two-tailed statistical tests with $P < 0.05$ were regarded as statistically significant and applied by the use of the SAS statistical package (Version 9.4; SAS Institute Inc., Cary, NC).

Results

As shown in Table 1, participants in the highest quintile of fat-soluble vitamin intake were older; more educated; less likely to smoke; and consumed more sodium, potassium, calcium, saturated fat, n-3 fatty acids, and dietary fiber compared with those in the lowest quintile but they consumed less alcohol. Moreover, men in the highest intake quintiles of vitamins A, K, and D and women in the highest intake quintiles of vitamin A and K were more likely to be hypertensive and diabetic.

During 965 970 person-years of follow-up, there were 567 deaths (240 men, 327 women) from heart failure. Dietary intake of vitamin A was not associated with heart failure mortality in either sex. Higher intakes of dietary vitamins K, E, and D were associated with a lower mortality risk of heart failure among women but not men. The multivariable HRs (95% CI) of heart failure mortality in the highest versus lowest intake quintiles among women were 0.63 (0.45–0.87; *P* for trend = 0.006) for vitamin K, 0.55 (0.36–0.78; *P* for trend = 0.006) for vitamin E, and 0.66 (0.48–0.93; *P* for trend = 0.01) for vitamin D. The respective HRs (95% CIs) among men were 1.02 (0.67–1.56; *P* for trend = 0.61), 1.10 (0.73–1.86; *P* for trend = 0.81), and 1.04 (0.72–1.51; *P* for trend = 0.26; Table 2, Model 2). No material changes were observed in the reported associations after mutual adjustment for the intakes of fat-soluble vitamins (Table 2, Model 3) or after exclusion of heart failure mortalities that occurred with the first 3, 5, and 10 y of follow-up (Suppl. Table 1).

Discussion

Analysis of data from 58 646 Japanese men and women with a median follow-up period of 19.3 y in a large prospective cohort study revealed that higher dietary intakes of vitamins K, E, and D were associated with a reduced risk of heart failure mortality in women only. Dietary intake of vitamin A was not related to heart failure mortality in either sex. These associations remained statistically significant even after controlling for known cardiovascular risk factors, mutual adjustment of fat-soluble vitamins, and excluding early events within 3 to 10 y of the follow-up.

The major dietary sources of fat-soluble vitamins in a Japanese diet are seafood/fish, soybeans, and fruit and vegetables [7–9], and dietary recommendations to prevent heart failure suggest increased intakes of these foods [3–6]. Higher intakes of

Table 1
Participant characteristics in accordance with energy-adjusted quintiles of dietary intake of fat soluble vitamins

	Vitamin A			Vitamin K			Vitamin E			Vitamin D		
	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5	Q1	Q3	Q5
Men, n	4619	4620	4620	4619	4620	4620	4619	4620	4620	4619	4620	4620
Age, y	53.9 ± 9.2*	55.8 ± 10.1	57.9 ± 9.8	53.5 ± 9.2	56.1 ± 10.0	58.7 ± 9.9	53.5 ± 9.2	54.7 ± 9.7	58.8 ± 9.9	54.3 ± 9.6	56.0 ± 10.2	57.9 ± 9.4
History of hypertension, %	18	19	20	17	19	21	18	19	19	17	19	20
History of diabetes, %	4	7	7	5	6	7	5	6	7	5	7	7
Body mass index, kg/m^2	22.8 ± 2.8	22.8 ± 2.7	22.5 ± 2.7	22.8 ± 2.8	22.7 ± 2.8	22.6 ± 2.7	22.8 ± 2.8	22.7 ± 2.8	22.7 ± 2.7	22.7 ± 2.8	22.6 ± 2.7	22.7 ± 2.8
Current smoker, %	59	54	51	60	54	48	62	53	47	57	53	53
Ethanol intake, g/d	40.1 ± 24.6	32.7 ± 21.3	33.2 ± 21.5	39.6 ± 24.9	32.3 ± 21.6	30.4 ± 19.8	41.2 ± 25.2	32.5 ± 20.9	28.2 ± 19.2	37.1 ± 24.1	32.1 ± 21.3	33.4 ± 21.2
Sports ≥5 h/wk, %	18	21	20	19	20	21	19	20	20	19	21	20
Walking ≥5 h/wk, %	51	48	52	49	49	53	49	49	53	51	48	51
>18 y education,%	14	17	17	14	17	18	14	18	19	15	17	18
High mental stress,%	25	25	22	26	25	22	26	25	22	24	25	24
Vitamin supplementation, %	3	3	4	3	4	4	3	4	4	3	4	4
Sodium intake, mg/d	1763 ± 765	2229 ± 690	2478 ± 775	1515 ± 611	2286 ± 644	2746 ± 657	1433 ± 572	2231 ± 569	2893 ± 645	1741 ± 751	2191 ± 663	2674 ± 691
Calcium intake, mg/d	383 ± 132	510 ± 130	581 ± 162	369 ± 129	505 ± 127	626 ± 137	352 ± 119	504 ± 116	463 ± 130	419 ± 147	507 ± 143	578 ± 152
Potassium intake, mg/d	1794 ± 448	2354 ± 450	2721 ± 626	1710 ± 412	2328 ± 401	2955 ± 475	1653 ± 372	2313 ± 337	3025 ± 443	1910 ± 524	2332 ± 500	2748 ± 574
Saturated fat intake, mg/d	7.5 ± 2.7	9.7 ± 2.7	11.2 ± 3.4	7.7 ± 2.9	9.7 ± 2.9	11.3 ± 3.3	7.0 ± 2.5	9.6 ± 2.5	12.3 ± 3.0	7.8 ± 3.0	9.7 ± 2.9	11.2 ± 3.2
N-3 fatty acids intake, mg/d	1.3 ± 0.5	1.7 ± 0.5	2.0 ± 0.6	1.1 ± 0.4	1.7 ± 0.5	2.1 ± 0.6	1.0 ± 0.3	1.6 ± 0.3	2.4 ± 0.5	1.0 ± 0.4	1.6 ± 0.3	2.4 ± 0.4
Total dietary fiber intake, g/d	8.1 ± 2.2	9.5 ± 2.2	11.9 ± 3.1	7.1 ± 1.7	10.4 ± 1.7	13.6 ± 2.2	7.1 ± 1.6	10.2 ± 1.6	13.7 ± 2.2	8.7 ± 2.5	10.4 ± 2.6	11.8 ± 3.0
Total energy intake, kcal/d	1942 ± 486	1666 ± 459	1779 ± 505	1812 ± 495	1674 ± 478	1783 ± 447	1824 ± 498	1687 ± 490	1803 ± 492	1860 ± 464	1640 ± 497	1809 ± 462
Vitamin A intake, mg/d	461 ± 142	920 ± 52	2241 ± 1194	731 ± 656	1071 ± 712	1530 ± 974	695 ± 574	4067 ± 697	1554 ± 1029	826 ± 645	1102 ± 734	1347 ± 1018
Vitamin K intake, mg/d	119 ± 45	185 ± 54	230 ± 73	93 ± 22	175 ± 11	286 ± 27	105 ± 36	179 ± 42	299 ± 48	138 ± 60	185 ± 61	225 ± 68
Vitamin E intake, mg/d	3.6 ± 1.1	5.0 ± 1.1	6.1 ± 1.6	3.2 ± 0.9	5.0 ± 0.9	6.8 ± 1.2	3.0 ± 0.6	4.9 ± 0.2	7.2 ± 0.9	3.9 ± 1.2	5.0 ± 1.1	6.3 ± 1.4
Vitamin D intake, mg/d	6.1 ± 3.2	7.8 ± 3.1	9.1 ± 3.6	5.7 ± 3.0	7.9 ± 3.0	9.9 ± 3.5	4.9 ± 2.4	7.7 ± 2.7	10.9 ± 3.2	3.5 ± 1.1	7.3 ± 0.5	13.0 ± 1.8
Women, *n*	7019	7019	7019	7019	7019	7019	7019	7019	7019	7019	7019	7019
Age, y	55.5 ± 9.8*	56.5 ± 10.1	56.7 ± 9.6	54.7 ± 9.8	56.0 ± 10.0	58.4 ± 9.5	55.7 ± 9.9	56.0 ± 10.0	57.7 ± 9.4	56.1 ± 10.1	55.8 ± 10.0	57.0 ± 9.4
History of hypertension, %	20	22	18	19	20	23	20	21	20	20	20	20
History of diabetes, %	3	4	5	3	3	4	3	4	4	3	3	4
Body mass index, kg/m^2	23.1 ± 3.2	23.0 ± 3.1	22.7 ± 3.0	23.0 ± 3.2	22.9 ± 3.1	23.0 ± 3.1	23.0 ± 3.2	22.9 ± 3.0	22.9 ± 3.0	22.9 ± 3.2	22.9 ± 3.1	23.1 ± 3.1
Current smoker, %	6	4	4	6	4	4	7	5	3	6	5	4
Ethanol intake, g/d	13.8 ± 19.3	9.2 ± 10.8	9.1 ± 11.7	13.8 ± 19.8	8.7 ± 9.7	8.6 ± 10.5	14.9 ± 20.5	8.8 ± 9.6	7.8 ± 8.9	12.5 ± 18.7	9.1 ± 11.3	9.8 ± 11.6
Sports ≥5 h/wk, %	19	21	22	20	21	21	19	22	21	20	22	20
Walking ≥5 h/wk, %	53	50	53	50	50	55	52	51	53	54	50	53
>18 y education, %	7	10	12	8	10	11	8	10	11	9	10	10
High mental stress, %	22	22	20	23	21	19	21	21	19	21	22	20
Vitamin supplementation, %	3	3	4	3	3	3	3	3	3	3	3	3
Sodium intake, mg/d	1760 ± 729	2126 ± 623	2202 ± 656	1529 ± 589	2147 ± 595	2506 ± 577	1434 ± 565	2099 ± 519	2612 ± 281	1641 ± 688	2204 ± 569	2493 ± 600
Calcium intake, mg/d	397 ± 134	530 ± 125	587 ± 143	400 ± 136	521 ± 123	618 ± 126	378 ± 129	524 ± 115	627 ± 123	444 ± 152	519 ± 136	575 ± 139
Potassium intake, mg/d	1874 ± 435	1461 ± 43	2730 ± 508	1854 ± 430	2414 ± 370	2928 ± 397	1784 ± 392	2423 ± 316	2961 ± 383	2037 ± 524	2403 ± 444	2741 ± 484
Saturated fat intake, mg/d	7.7 ± 2.9	10.0 ± 2.7	11.3 ± 3.0	8.3 ± 2.0	10.0 ± 2.8	11.0 ± 3.1	7.4 ± 2.7	10.0 ± 2.5	12.0 ± 2.9	8.3 ± 3.2	10.0 ± 2.6	10.9 ± 2.9
N-3 fatty acids intake, mg/d	1.3 ± 0.5	1.7 ± 0.5	1.8 ± 0.5	1.2 ± 0.5	1.7 ± 0.4	2.0 ± 0.5	1.0 ± 0.4	1.6 ± 0.3	2.3 ± 0.4	1.1 ± 0.4	1.6 ± 0.3	2.3 ± 0.4
Total dietary fiber intake, g/d	8.6 ± 2.2	10.9 ± 2.3	11.7 ± 2.5	7.8 ± 1.8	10.7 ± 1.6	13.5 ± 1.9	7.8 ± 1.7	10.7 ± 1.6	13.3 ± 2.1	9.3 ± 2.5	10.6 ± 2.3	11.9 ± 2.5
Total energy intake, kcal/d	1603 ± 399	1379 ± 331	1448 ± 373	1479 ± 404	1391 ± 350	1475 ± 336	1503 ± 422	1380 ± 33	1514 ± 352	1523 ± 381	1358 ± 358	1505 ± 337
Vitamin A intake, mg/d	494 ± 158	942 ± 51	2227 ± 1237	775 ± 726	1093 ± 742	1480 ± 951	747 ± 674	111 ± 743	1489 ± 979	903 ± 772	1127 ± 751	1265 ± 879
Vitamin K intake, mg/d	130 ± 45	201 ± 56	232 ± 63	105 ± 25	186 ± 11	286 ± 22	120 ± 40	191 ± 43	165 ± 44	180 ± 57	193 ± 58	226 ± 62
Vitamin E intake, mg/d	3.9 ± 1.1	5.4 ± 1.1	6.1 ± 1.3	3.7 ± 1.0	5.3 ± 0.8	6.8 ± 1.0	3.4 ± 0.7	5.2 ± 0.2	7.1 ± 0.7	4.1 ± 1.2	5.3 ± 1.0	6.4 ± 1.2
Vitamin D intake, mg/d	6.4 ± 3.3	8.2 ± 3.0	8.9 ± 3.3	6.1 ± 3.0	8.0 ± 2.9	9.7 ± 3.3	5.3 ± 2.5	8.0 ± 2.6	10.8 ± 3.1	3.8 ± 1.2	7.5 ± 0.5	12.9 ± 1.7

* Means ± standard deviation, all such variables.

Table 2
Sex-specific associations between dietary intakes of fat-soluble vitamins and risk of heart failure mortality

	Men						Women					
	Q1 (low)	Q2	Q3	Q4	Q5 (high)	*P*-trend*	Q1 (low)	Q2	Q3	Q4	Q5 (high)	*P*-trend*
Vitamin A												
Person years, n	77 216	75 428	74 935	73 202	71 439		120 743	121 109	118 963	117 672	115 262	
Cases, n	39	34	49	67	51		66	76	70	53	62	
Model 1[†]	1.00	0.75 (0.47–1.18)	0.96 (0.63–1.46)	1.13 (0.76–1.68)	0.86 (0.57–1.31)	0.13	1.00	1.00 (0.72–1.38)	0.87 (0.62–1.21)	0.68 (0.47–0.98)	0.91 (0.64–1.29)	0.47
Model 2[‡]	1.00	0.79 (0.50–1.25)	1.03 (0.67–1.58)	1.27 (0.84–1.91)	0.92 (0.60–1.41)	0.14	1.00	1.00 (0.72–1.39)	0.88 (0.62–1.23)	0.66 (0.46–0.95)	0.92 (0.65–1.31)	0.51
Model 3[§]	1.00	0.83 (0.51–1.36)	1.14 (0.70–1.85)	1.40 (0.85–2.32)	0.96 (0.60–1.62)	0.16	1.00	1.11 (0.77–1.60)	1.05 (0.71–1.55)	0.83 (0.54–1.29)	1.23 (0.80–1.89)	0.33
Vitamin K												
Person years, n	75 354	74 890	75 232	73 719	73 028		117 502	119 317	119 254	118 354	119 321	
Cases, n	35	42	53	46	64		70	60	67	55	75	
Model 1[†]	1.00	0.98 (0.62–1.53)	0.99 (0.64–1.52)	0.82 (0.53–1.28)	0.94 (0.62–1.42)	0.40	1.00	0.70 (0.50–0.99)	0.72 (0.52–1.01)	0.57 (0.40–0.80)	0.62 (0.45–0.86)	0.005
Model 2[‡]	1.00	0.99 (0.63–1.56)	1.06 (0.69–1.63)	0.91 (0.58–1.42)	1.02 (0.67–1.56)	0.61	1.00	0.70 (0.50–1.00)	0.73 (0.52–1.02)	0.57 (0.40–0.81)	0.63 (0.45–0.87)	0.006
Model 3[§]	1.00	1.04 (0.62–1.74)	1.11 (0.67–2.11)	1.06 (0.58–1.94)	1.14 (0.59–2.23)	0.90	1.00	0.68 (0.46–1.00)	0.68 (0.44–1.04)	0.54 (0.33–0.86)	0.63 (0.38–0.94)	0.02
Vitamin E												
Person years, n	74 774	74 358	75 262	74 429	73 380		115 792	118 460	118 288	119 363	121 846	
Cases, n	32	47	50	43	68		76	54	62	76	59	
Model 1[†]	1.00	1.19 (0.76–1.87)	1.07 (0.68–1.67)	0.80 (0.51–1.27)	1.07 (0.70–1.63)	0.38	1.00	0.69 (0.48–0.97)	0.70 (0.50–0.97)	0.82 (0.60–1.03)	0.55 (0.39–0.77)	0.005
Model 2[‡]	1.00	1.28 (0.81–2.01)	1.16 (0.74–1.83)	0.92 (0.58–1.47)	1.10 (0.73–1.86)	0.81	1.00	0.67 (0.47–0.95)	0.70 (0.50–0.98)	0.80 (0.58–1.01)	0.55 (0.36–0.78)	0.006
Model 3[§]	1.00	1.35 (0.74–2.45)	1.11 (0.63–2.34)	0.87 (0.49–1.68)	0.99 (0.64–1.62)	0.20	1.00	0.65 (0.41–1.02)	0.65 (0.39–1.04)	0.76 (0.47–1.04)	0.57 (0.29–0.98)	0.04
Vitamin D												
Person years, n	751 76	73 968	73 847	74 875	74 356		116 251	116 504	117 687	120 157	123 149	
Cases, n	47	36	39	46	72		78	67	65	54	63	
Model 1[†]	1.00	0.65 (0.42–1.01)	0.63 (0.41–0.96)	0.75 (0.50–1.12)	1.00 (0.69–1.45)	0.29	1.00	0.82 (0.59–1.14)	0.82 (0.59–1.15)	0.64 (0.45–0.90)	0.68 (0.49–0.95)	0.01
Model 2[‡]	1.00	0.68 (0.44–1.05)	0.65 (0.43–1.00)	0.77 (0.51–1.16)	1.04 (0.72–1.51)	0.26	1.00	0.77 (0.55–1.07)	0.79 (0.57–1.11)	0.60 (0.42–0.85)	0.66 (0.48–0.93)	0.01
Model 3[§]	1.00	0.67 (0.42–1.08)	0.62 (0.36–1.06)	0.67 (0.37–1.22)	0.85 (0.44–1.65)	0.92	1.00	0.78 (0.55–1.09)	0.83 (0.49–1.17)	0.63 (0.33–0.92)	0.69 (0.39–0.99)	0.05

* Median values of vitamin intakes in each quintile were used to test for a linear trend across quintiles.
† Model 1 Age-adjusted hazard ratio (95% confidence interval) by Cox proportional model.
‡ Model 2 Adjusted further for histories of hypertension and diabetes, smoking status, body mass index, hours of walking, hours of sports, educational status, perceived mental stress and alcohol intake, multivitamin supplementation, quintiles of energy-adjusted sodium, calcium, potassium, saturated fatty acids, n-3 fatty acids, dietary fiber and vitamin C, and total energy intakes.
§ Model 3 Adjusted further mutually for the intakes of the other 3 fat soluble vitamins.

fat-soluble vitamins, especially vitamin D, may help improve the cardiac function, hypertrophy, and contractility [24,25]. Lower intakes of fat-soluble vitamins were associated with some risk factors of heart failure such as diabetes [26], hypertension [27], atherosclerosis [28], and coronary heart disease [29]. Moreover, some studies suggest the beneficial roles of high dietary intakes of antioxidants [10], vitamin D status [18–20], and vitamin E supplementation [30] with regard to the risk of heart failure. However, other studies have shown that there are no benefits of vitamins E and D supplementation [31–33] or even an insignificantly increased risk of heart failure with higher, long-term supplementation of vitamin E [34].

The observed sex difference with regard to the association between dietary fat-soluble vitamins intake and risk of heart failure in our study was also evident in previous Japanese studies that investigated not only the association of food sources of vitamins with cardiovascular incidence and mortality [35,36] but also in studies that investigated the direct associations of water and fat-soluble vitamins with cardiovascular mortality [12,37]. Dietary vitamin C intake was inversely associated with mortality from cardiovascular diseases in Japanese women but not in men. Although the associations did not reach a level of significance, the risk of cardiovascular mortality was lower in women than in men with higher dietary intakes of vitamins A and E [12]. Another Japanese study showed inverse associations of higher dietary intakes of folate and vitamin B6 with mortality from stroke, coronary heart disease, and total cardiovascular diseases in women but not in men, but the reduced risk of heart failure was observed in men and not in women [37]. The exact reasons for the difference by sex are not clear. The effect of dietary fat-soluble vitamins may be suppressed by other factors or was not sufficient to counteract overwhelming heart failure risk factors in men, such as smoking and drinking habits and history of hypertension, which were more prevalent in men than in women in our study (Table 1).

To the best of our knowledge, this is the first study to show an association between dietary intakes of fat-soluble vitamins and a risk of heart failure in the Japanese population. The strengths of our study include its large sample size from a community-based cohort, the prospective study design, the use of a validated FFQ, and the consistent endpoint determination. Also, the exclusion of participants with known comorbidities before follow-up reduced bias stemming from dietary modifications due to known chronic diseases. Moreover, the associations did not substantially change when we excluded early heart failure mortalities within 3 to 10 y from the baseline survey, which indicates that there are few effects from preexisting unknown illness or reverse causality.

Limitations of our research include the one-time measurement of dietary intakes of fat-soluble vitamins because consumption is likely to change during the long follow-up period. Second, we adjusted for the use of multivitamin supplementation but we have no data about the amounts or types of supplementary vitamins that were used. We believe that this did not affect our results because in the 1980s and 1990s, the use of fat-soluble vitamin supplementation was unpopular among the Japanese population. In our study, only 3.3% of participants reported a daily use of multivitamin supplementation and a sensitivity analysis by excluding those subjects who used multivitamin supplementation did not change the results materially (data not shown in tables).

Another limitation of our study was that only 54% of the potential study participants responded to the FFQ. Those who responded were younger and more educated than the nonrespondents; however, we adjusted for these variables in our examination. In addition, the FFQ underestimated intakes of fat-soluble vitamins by at least a quarter on the basis of a validation study for our cohort, but this systematic underestimation is thought to be non-differential. Last, the use of death certificates to ascertain heart failure deaths in the early years of the study (i.e., prior to 1994) was questionable because most deaths of unknown origin such as cardiac arrest or arrhythmic death, which are classified as ischemic heart disease deaths in the United States [38], were registered as due to “unspecified heart failure” (I50.9 for ICD-10) in Japan. This classification accounted for 27% to 50% of diagnosed heart failure cases [39]. Accordingly, the number of heart failure deaths in this study was contaminated by a number of cardiac arrest deaths and may have affected the association between dietary intakes of fat-soluble vitamins and heart failure; however, sensitivity analyses to exclude heart failure mortalities occurred within 10 y of the follow-up showed similar associations.

Conclusions

In this large, community-based, prospective cohort study, higher dietary intakes of fat-soluble vitamins (K, E, and D) were associated with a reduced risk of mortality from heart failure among Japanese women but not men.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.nut.2017.09.009.

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