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

Running head: Fat soluble vitamins and heart failure death.

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Authors' contributions

Hiroyasu Iso and Akiko Tamakoshi made a design of this research; Eshak S. Ehab conducted the analyses; Eshak S. Ehab wrote the manuscript; Hiroyasu Iso, Kazumasa Yamagishi, Renzhe Cui and Akiko Tamakoshi made critical revision for the manuscript. All authors read and approved the final manuscript.

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Abstract

Objective: A few reports have investigated the association of dietary vitamin intakes with risk of heart failure in Asia. Therefore, we examined the relation of dietary intakes of fat-soluble vitamins A, K E, and D with mortality from heart failure in Japanese population.

Research Methods and Procedures: A total of 23,099 men and 35,597 women aged 40-79 years participated in the Japan Collaborative Cohort Study and completed a food frequency questionnaire, from which dietary intakes of vitamin A, K, E and D were calculated. Cox proportional hazard model was used to estimate the sex-specific risk of heart failure mortality according to increasing quintiles of fat soluble vitamin intakes.

Results: During median 19.3-year follow-up, there were 567 deaths from heart failure (395 men and 307 women). Dietary vitamin A intake showed no association with heart failure mortality in both genders; contrary, the reduced risk was observed in women but not in men with dietary intakes of vitamin K, E and D. The multivariable HRs (95% CI) 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 other vitamins.

Conclusions: High dietary intakes of fat soluble vitamins K, E and D were associated with reduced risk of heart failure mortality in Japanese women but not men.

Highlights

* Intakes of fish, natto, fruits and vegetables associated with low heart failure risk.

*These foods are major sources of vitamin D, K, A and E in Japanese diet.

*Intakes of vitamins K, E and D were associated with reduced death from heart failure. *The reduced risk of heart failure mortality was evident in Japanese women but not men.

Keywords: dietary vitamin A, dietary vitamin K, dietary vitamin E, dietary vitamin D, heart failure mortality, Japanese.

Introduction

Heart failure is complex syndrome stands on activation of numerous biological mechanisms that follow or coincide with myocardial injury and leads to inadequate systematic perfusion. (1) In developed countries with high proportion of aging society, like in Japan, heart failure resembles a notable public health burden. (2) Intakes of seafood and fish, (3,4) fermented soybeans (5) and fruits and vegetables (5,6) were associated with lower risk of heart failure. In Japanese diet, seafood and fish are main dietary contributors of vitamin D; (7) natto (fermented soybeans) is a major source to vitamin K, (8) while vitamins A and E are mainly provided by fruit and vegetables. (9) It remains unclear whether the observed reduced risks with higher intakes of these foods are attributed to the effect of their content of fat soluble vitamins (A, K, E and D).

Dietary antioxidant capacity was inversely associated with risk of cardiovascular diseases including heart failure. (10) However, the association of dietary intakes of vitamin A and E with cardiovascular mortality is questionable.(11-13) There is also some conflicting observations for the impact of vitamin K intake on cardiovascular health. (14-17) In addition there is growing evidence on the protective effects of vitamin D against cardiovascular disease (18,19) including heart failure. (18,20)

Taking together these controvert findings, the associations between the dietary intakes of the fat soluble vitamins and risk of heart failure still need investigation, especially in Asian population. Therefore, we thought to examine the association between dietary intakes of vitamins A, K, E and D with risk of mortality from heart failure among men and women of the Japan Collaborative Cohort study (JACC), a large prospective study.

Participants and Methods

Study Population and baseline covariates

With a total of 110,585 middle aged (40-79 years) Japanese men (n= 46,395) and women (n=64,190) from 45 communities across Japan, the Ministry of Education, Sports and Science started in 1988 to 1990 to sponsor the JACC Study. Detailed description for the JACC Study was published previously. (21)

Baseline lifestyle and participants' characteristics including demographic data; medical histories of chronic diseases, diabetes mellitus and hypertension; habits of ethanol drinking, smoking, exercise, diet and others were inquired via a self-administered questionnaire that included a 40 food-item food frequency questionnaire (FFQ). If participants did not give answers to ≥4 items of FFQ or reported histories of either cancer or CVD they were excluded. We also excluded from analysis participants with missing information about fat soluble vitamin intake which left a total of 58,646 eligible individuals for the study (23,099 males and 35,547 females) **(Supplemental Figure I)**.

Diet by FFQ

The usual consumption frequency for each food item over the past 12 months, without specifying portion size was inquired through choosing from five frequency responses: rarely, 1-2 times/m, 1-2 times/wk, 3-4 times/wk, and almost every day. (21) These frequencies were transformed to a weekly consumption scores 0, 0.38, 1.5, 3.5, and 7.0/wk, respectively. Dietary intakes of fat soluble vitamins (A, K, E and D) were calculated by using the Japan Food Tables, Fifth Edition to determine the amount of fat soluble vitamins in each food. These contents were multiplied by the participant's frequency score for each food item in the FFQ, followed by summing the contents. A validation study among 85 individuals using four 3-d weighed dietary records (DR) over a 1-year period as a reference standard determined the portion size for each food and validated the FFQ intakes. The Spearman rank correlation coefficients for vitamin A, K, E and D intakes between the FFQ and four 3-days DR were 0.37, 0.40, 0.38 and 0.39. The mean ± SD intakes in mg/day 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 DR were 1089±543, 279±104, 9.1±1.9 and 10.6 ± 4.5 mg/day.(22)

Mortality surveillance

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

Statistical analysis

Calorie-adjustment by the residual method (23) was done to the dietary intakes of our exposure variables which were then modeled as categorical (5 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 vitamins intakes were tested by $\chi 2$-test and the 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/her original residential area, death or termination of follow-up at the end of 2009, whichever came first. Follow-up was terminated in in two areas in 2008, in four study areas in 2003 and in another four areas in 1999.

By means of Cox proportional model, sex-specific age- and multivariable-adjusted hazard ratios (HRs) their 95% confidence intervals (95% CIs) for risk of mortality from heart failure across increasing quintiles of each vitamin. The hypothesized confounders were history of diabetes and hypertension (yes or no); use of multivitamin supplementation (yes or no); hours of walking (almost never, 0.5, 0.6-0.9, and ≥1 hour/day); hours of sports (almost never, 1-2, 3-4 and ≥5 hours/week); smoking category (never, ex-smoker, current smoker of 1-19 and ≥20 cigarettes/day); quintiles of body mass index (BMI), years of education (≤ 15, 16-18 and >18 years); perceived mental stress (low, medium and high) and ethanol intake (never, ex-drinker, current drinker of 0.1-22.9, 23.0-45.9, 46.0-68.9, and ≥69.0 g ethanol/day); 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 vitamins intake by assigning median values for each quintile and testing the significance of this variable. We further analyzed the data after exclusion of persons who died within first 3, 5 and 10 years of follow-up to examine a potential effect of as-yet-undiagnosed diseases at baseline. Two-tailed statistical tests with $P < 0.05$ regarded as statistically significant were applied by the use of SAS statistical package (version 9.4, SAS).

Results

As shown in **Table 1** participants in the highest quintile of fat soluble vitamins intake compared with those in the lowest quintile were older, more educated, less likely to smoke and consumed more sodium, potassium, calcium, saturated fat, n-3 fatty acids and dietary fibre; but 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 diabetics.

During 965, 970 person-years of follow-up, there were 567 deaths (395 men and 307 women) from heart failure. Dietary intake of vitamin A was not associated with heart failure mortality in either gender. Higher intakes of dietary vitamins K, E and D were associated with 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 were. 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 above reported associations after mutual adjustment for the fat soluble vitamins **(Table 2, model 3)** or after excluding heart failure mortalities that occurred with the first 3, 5 and 10 years of follow-up **(Supplemental Table 1)**.

Discussion

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

The major dietary sources of fat soluble vitamins in Japanese diet are seafood/fish, soybeans and fruit and vegetables;(7-9) dietary recommendations to prevent heart failure suggest increase intakes of these foods.(3-6) Higher intakes of fat soluble vitamins, especially vitamin D may help improving the cardiac function, hypertrophy and contractility.(24,25) Lower intakes of fat soluble vitamins were associated with some evoking factors of heart failure such as diabetes,(26) hypertension,(27) atherosclerosis(28) and coronary heart disease.(29) Moreover, some studies suggested beneficial roles of high dietary intakes of antioxidants 10 and vitamin D status,(18-20) vitamin E supplementation(30) regarding the risk of heart failure. However, other studies showed no benefits of vitamins E and D supplementation (31-33) or even insignificant increased risk of heart failure with higher long-term supplementation of vitamin E.(34)

The observed gender difference regarding the association between dietary fat soluble vitamins intake and 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 investigated the direct associations of water and fat soluble vitamins with cardiovascular mortality.(12, 37) Dietary vitamin C intakes were inversely associated with mortality from cardiovascular diseases in Japanese women but not men; meanwhile, although the associations did not reach a level of significance, the risk of cardiovascular mortality was lower in women than 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; whereas the reduced risk of heart failure was observed in men but not in women.(37) The exact reasons for the gender difference are not clear. The effect of dietary fat soluble vitamins may be suppressed by other factors or was not enough to counteract overwhelming heart failure risk factors in men such as smoking and drinking habits and history of hypertension, which were more prevalent in our men than women as shown in **Table 1**.

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

Limitations of our research include the one-time measurement of dietary fat soluble vitamins; consumption is likely to change during the long follow-up period. Second, we adjusted for the use of multivitamin supplementation, yet we have no data about amounts or types of the used supplementary vitamins. We believe that this did not affect our results because in 1980s-90s the use of fat soluble vitamins supplementation was unpopular among Japanese, only 3.3 % of our participants reported the daily use of multivitamin supplementation, and sensitivity analysis by excluding those subjects who used multivitamin supplementation did not change the results materially (data not shown in tables). Another limitation was that only 54% of potential study participants responded to the FFQ; those respondents were younger and more educated than non-respondents; however, we adjusted these variables in our examination. Last, the FFQ underestimated intakes of fat soluble vitamins by at least a quarter, based on a validation study for our cohort; but, this systematic underestimation is supposed to be non-differential. Last, the use of death certificate to ascertain heart failure deaths in the early years of the study, before 1994, was questionable because most deaths of unknown origin like cardiac arrest or arrhythmic death, which are classified as ischemic heart disease deaths in the U.S.(38) were registered as "unspecified heart failure" (I50.9 for ICD-10) in Japan and accounted for 27% to 50% of diagnosed heart failure.(39) Accordingly, heart failure deaths in this study was contaminated with cardiac arrest, and that may have affected the association between dietary intakes of fat soluble vitamins and heart failure; however, sensitivity analyses by excluding heart failure mortalities occurred within 10 years 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 reduced risk of mortality from heart failure among Japanese women but not men.

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Conflict of interest: none.

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Table 1. Participants' characteristics according to 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, year	53.9 ± 9.2 [a]	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, gm/day	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 hour/week, %	18	21	20	19	20	21	19	20	20	19	21	20
Walking >=5 hour/week, %	51	48	52	49	49	53	49	49	53	51	48	51
>18 years 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/day	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/day	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/day	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/day	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/day	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
Dietary fiber intake, g/day	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/day	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, g/day	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, g/day	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, g/day	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, g/day	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, year	55.5 ± 9.8 [a]	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, gm/day	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 hour/week, %	19	21	22	20	21	21	19	22	21	20	22	20
Walking >=5 hour/week, %	53	50	53	50	50	55	52	51	53	54	50	53
>18 years 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/day	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/day	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/day	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/day	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 ± 2.58	10.9 ± 2.9
N-3 fatty acids intake, mg/day	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/day	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/day	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, g/day	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, g/day	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, g/day	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, g/day	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

[a] 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					
	1(low)	2	3	4	5(high)	*P*-trend [a]	1(low)	2	3	4	5(high)	*P*-trend [a]
Vitamin A												
Person years, n	77213	75429	74935	73202	71439		120743	120743	120743	120743	120743	120743
Cases, n	39	34	49	67	51		66	76	70	53	62	
Model 1 [b]	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 [c]	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 [d]	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	75354	74890	75232	73719	73028		117502	117502	117502	117502	117502	
Cases, n	35	42	53	46	64		70	60	67	55	75	
Model 1 [b]	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 [c]	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 [d]	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	74774	74358	75262	74429	73380		115792	115792	115792	115792	115792	
Cases, n	32	47	50	43	68		76	54	62	76	59	
Model 1 [b]	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 [c]	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 [d]	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	75176	73968	73847	74875	74356		116251	116251	116251	116251	116251	

Cases, n	47	36	39	46	72		78	67	65	54	63	
Model 1 [b]	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 [c]	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 [d]	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

[a] Median values of vitamins intakes in each quintile were used to test for a linear trend across quintiles.

[b] Model 1 Age-adjusted hazard ratio (95% CI) by Cox proportional model.

[c] 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.

[d] Model 3 Adjusted further mutually for the other 3 fat soluble vitamins.