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α-Linolenic acid, linoleic acid and heart failure in women

Emily B. Levitan[1]*, Alicja Wolk[2], Niclas Håkansson[2] and Murray A. Mittleman[3,4]

[1]*Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, RPHB 230K, 1530 3rd Avenue S, Birmingham, AL 35294-0022, USA*
[2]*Division of Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden*
[3]*Cardiovascular Epidemiology Research Unit, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA*
[4]*Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA*

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Abstract

α-Linolenic acid (18 : 3*n*-3) intake and linoleic acid (18 : 2*n*-6) intake have been associated with lower rates of CHD, though results have not been consistent. The relationship of these fatty acids with incident heart failure (HF) is not well established. We examined the hypothesis that women with higher intakes of 18 : 3*n*-3 and 18 : 2*n*-6 would have lower rates of HF hospitalisation and mortality. We measured 18 : 3*n*-3 and 18 : 2*n*-6 intake in 36 234 Swedish Mammography Cohort participants aged 48–83 years using FFQ and followed participants through Swedish inpatient and cause-of-death registers from 1 January 1998 until 31 December 2006. Cox models were used to calculate incidence rate ratios (RR) and 95 % CI. Because of multicollinearity, 18 : 3*n*-3 and 18 : 2*n*-6 were examined separately. Over 9 years, 596 women were hospitalised and fifty-five died due to HF. In models accounting for age and other covariates, the RR for HF comparing the top quintile of 18 : 3*n*-3 (median 1·50 g/d) with the bottom quintile (median 0·88 g/d) was 0·91 (95 % CI 0·71, 1·17, $P_{trend} = 0·41$). The RR comparing the top quintile of 18 : 2*n*-6 (median 7·8 g/d) with the bottom quintile (median 4·6 g/d) was 1·14 (95 % CI 0·88, 1·46, $P_{trend} = 0·36$). We did not find evidence for the interaction of 18 : 3*n*-3 and 18 : 2*n*-6 with each other or with long-chain *n*-3 fatty acids. In conclusion, these data do not support our hypothesis that 18 : 3*n*-3 and 18 : 2*n*-6 are associated with HF. However, these results may not be generalisable to populations with higher intakes of 18 : 3*n*-3.

Key words: Heart failure: α-Linolenic acid: Linoleic acid

Heart failure (HF) is an end-stage CVD with a lifetime risk of approximately 20 %[1]. Although treatment for HF has improved, death rates are still high; mortality is more than 20 % within 1 year of diagnosis[2]. In order to reduce the public health impact of HF, prevention strategies are needed[3]. One non-pharmacological target for intervention is diet. However, the relationship of diet with the development of HF is largely unknown, and existing dietary strategies to prevent or ameliorate HF risk factors such as hypertension and diabetes are underutilised[3].

Supplementation with the long-chain *n*-3 PUFA EPA and DHA, found primarily in fish, may reduce mortality in patients with myocardial infarction (MI) and HF[4,5], and dietary intake is associated with lower rates of CVD including sudden death[6], CHD[7] and HF[8–11]. The plant-derived *n*-3 fatty acid α-linolenic acid (18 : 3*n*-3) is more abundant in the food supply than long-chain *n*-3 fatty acids, and 18 : 3*n*-3 can be metabolised into the long-chain *n*-3 fatty acids, although at a low rate[12]. This rate is even lower in people with a substantial dietary intake of long-chain *n*-3 fatty acids[12]. A higher intake of 18 : 3*n*-3 has been associated with a lower rate of CHD in some populations[13–15], but a recent study did not find an association with HF[16]. Overall, supplementation with neither 18 : 3*n*-3 nor long-chain *n*-3 fatty acids significantly reduced major cardiovascular events in a recent trial in people with a history of MI[17]. However, among the women in the trial, those who received 18 : 3*n*-3 had a 27 % lower rate of major cardiovascular events, which approached statistical significance ($P = 0·07$)[17].

The most prevalent PUFA in the food supply is *n*-6 linoleic acid (18 : 2*n*-6)[18]. 18 : 2*n*-6 competes with 18 : 3*n*-3 for elongation enzymes, and the intake of one fatty acid may modify the effect of the other[12]. Because 18 : 2*n*-6 is a metabolic precursor to inflammatory eicosanoids, there has been concern that too much 18 : 2*n*-6 or an imbalance in the ratio of *n*-6:*n*-3 fatty acids may increase the risk of CVD[19]. However, in studies of human subjects, higher 18 : 2*n*-6 was not associated with an increase in inflammation[20]. Substituting

Abbreviations: HF, heart failure; MI, myocardial infarction; RR, rate ratio.

* **Corresponding author:** E. B. Levitan, fax +1 205 934 8665, email elevitan@uab.edu

18 : 2*n*-6 for carbohydrate decreases LDL-cholesterol and increases HDL-cholesterol, which is expected to result in lower cardiovascular risk[21]. In addition, 18 : 2*n*-6 consumption has been inversely associated with the rate of CHD in some studies[14,20,22], though many studies have found no significant association[19,20].

We hypothesised that a higher intake of both 18 : 3*n*-3 and 18 : 2*n*-6 would reduce the risk of HF. We examined the associations of 18 : 3*n*-3 and 18 : 2*n*-6 with HF hospitalisation and mortality in a population of middle-aged and older women. Because some studies have suggested that the health effects of 18 : 3*n*-3 may depend on the intake of long-chain *n*-3 fatty acids and 18 : 2*n*-6[12,14], we examined whether the associations varied by the intake of other PUFA.

Methods

Participants

The present study included participants in the Swedish Mammography Study. The recruitment process, characteristics of the cohort and study methods have previously been described in detail[23]. Women born between 1914 and 1948 and living in Västmanland and Uppsala counties in central Sweden received a questionnaire between 1 March 1987 and 14 December 1990. Of the 90 303 women identified in the population register, 66 651 (74 %) returned a completed questionnaire. In September 1997, a second questionnaire was sent to 56 030 participants who were still alive and residing in the study area; 39 227 (70 %) returned a questionnaire. Because information on cardiovascular risk factors such as cigarette smoking was collected on the second questionnaire, only women who completed the 1997 questionnaire were included in the present study. The present study is based on information from the 1997 questionnaire.

Participants who did not provide or provided incorrect national identification numbers, who reported implausible energy intakes (>3 standard deviations from the natural logarithm-transformed mean), who had a previous diagnosis of cancer (other than non-melanoma skin cancer) or HF were excluded (*n* 1126). Because patients with diabetes or MI are often counselled to alter their diets and diabetes and MI are risk factors for HF, only women with no baseline history of MI or diabetes were included (*n* 36 234). History of HF and MI was determined through record linkage to the Swedish inpatient register, and diabetes was determined using self-report and record linkage. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Regional Ethical Review Board at Karolinska Institute, Stockholm, Sweden. Completion and return of the self-administered questionnaire was assumed to imply consent.

Diet assessment

Self-administered food-frequency items on the questionnaires asked participants to report usual frequency of consumption of ninety-six items over the previous year. For foods and beverages such as milk, coffee, cheese and bread that are commonly eaten in Sweden, participants reported their consumption in servings per d or per week. For other foods and beverages, there were eight predefined responses ranging from never to ≥3 times/d. For each food and beverage, total consumption was calculated by multiplying the frequency of consumption by age-specific portion sizes which were determined using weighed dietary records. Nutrient values were calculated by multiplying the food or beverage intake by the nutrient composition obtained from the Swedish National Food Administration[24] and summing over foods and beverages. Nutrient intakes were adjusted for energy using the residual method[25]. Among 239 women included in a study of the questionnaire performance, correlations between FFQ and adipose tissue biopsies were 0·34 for 18 : 3*n*-3 and 0·36 for 18 : 2*n*-6 (A Wolk, unpublished results).

Heart failure follow-up

Participants were followed from 1 January 1998 until 31 December 2006 through record linkage to the Swedish inpatient and cause-of-death registers. The inpatient register captures more than 99 % of inpatient care in Sweden. HF events were defined as hospitalisations for or deaths from HF identified by codes 428 (International Classification of Disease-9), I50 or I11·0 (International Classification of Disease-10) listed as the primary diagnosis. In a previous study, 95 % of people with these codes as the primary diagnosis had confirmed HF on medical record review using the European Society of Cardiology criteria[26]. We included the first HF event recorded in the registers for each individual.

Statistical analysis

Because some participants were missing data on weight or height to calculate BMI (1·7 %) and physical activity (22·4 %), we used Markov chain Monte Carlo multiple imputation to simulate five complete datasets. Statistical analyses were performed in each of the datasets separately, and the results were then averaged and the CI and *P* values calculated accounting for uncertainty in the imputed estimates[27].

We computed means and percentages of demographic, behavioural and health covariates by quintiles of intake of 18 : 3*n*-3 and 18 : 2*n*-6. To estimate the incidence rate ratios (RR) associated with 18 : 3*n*-3 and 18 : 2*n*-6, we used Cox proportional hazards models that accounted for age by allowing the baseline hazard to vary[28]. We adjusted for BMI (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fibre consumption (linear), Na consumption (linear), education (less than high school, high school or university), family history of myocardial infarction at <60 years (yes or no), cigarette smoking (current, past or never), living alone (yes or no), postmenopausal hormone use (yes or no), self-reported history of hypertension (yes or no) and self-reported history of high cholesterol (yes or no). Nutrient replacement models that additionally adjusted for all but one of the macronutrients demonstrated multicollinearity (highest condition index = 378), suggesting that results of the models

could be severely biased. We tested for linear trend by entering the median 18 : 3*n*-3 or 18 : 2*n*-6 in each quintile as a continuous variable. Assuming a HF rate of two cases per 1000 person-years based on preliminary data and setting the significance level to 0·05, we estimated that there would be at least 80 % power to detect a RR of 0·72 or lower and 1·47 or higher comparing top with bottom quintiles using the Schoenfeld & Richter approach[29].

We examined the associations with 18 : 3*n*-3 and 18 : 2*n*-6 modelled as continuous exposures, expressed as percentage of total fat. We explored the effect of measurement error in 18 : 3*n*-3 and 18 : 2*n*-6 using the regression calibration approach[25] and additional data from the 239 women with fat biopsies. We examined whether the association between 18 : 3*n*-3 and the incidence of HF hospitalisation or mortality varied by long-chain *n*-3 intake above or below the median (0·30 g/d) and by 18 : 2*n*-6 above or below the median (5·9 g/d). We tested for interaction by including the product of the median in each quintile for 18 : 3*n*-3 and an indicator for being above the median intake of long-chain *n*-3 or 18 : 2*n*-6 in the models. Similarly, we examined whether the relationship between 18 : 2*n*-6 intake and the incidence of HF hospitalisation or mortality varied by long-chain *n*-3 intake and 18 : 3*n*-3 intake above or below the median. We examined the relationship between the major food sources of variability in 18 : 3*n*-3 and 18 : 2*n*-6 intake and the incidence of HF hospitalisation or mortality. Because symptoms of HF occurring before hospitalisation or death may influence dietary behaviour, we performed a sensitivity analysis excluding cases occurring during the first 2 years of follow-up. We tested for violations of the proportional hazards assumption by entering the product of 18 : 3*n*-3 or 18 : 2*n*-6 and the natural logarithm of time in the model. The proportional hazards assumption did not appear to be violated.

Statistical analyses were performed using SAS version 9.1. A two-sided P value $<0{\cdot}05$ was considered statistically significant.

Results

Over 9 years of follow-up, 651 of the 36 234 women were hospitalised for HF (*n* 596) or died of HF (*n* 55). Intake of 18 : 3*n*-3 and 18 : 2*n*-6 was highly correlated (*r* 0·79). On average, 2 % of fat consumed was 18 : 3*n*-3 and 10 % was 18 : 2*n*-6. Compared with women in the lowest quintile of 18 : 3*n*-3 intake, women in the highest quintile were more likely to be current smokers (Table 1). On average, they consumed more fibre, Na, saturated fat and long-chain *n*-3 fatty acids, and less alcohol, protein and carbohydrate. Foods that contributed to the variability in 18 : 3*n*-3 intake included soya products, mayonnaise and salad dressing; however, the absolute intake of these foods was low. Compared with women in the lowest quintile of 18 : 2*n*-6 intake, women in the highest quintile were on average younger, more likely to be current

Table 1. Characteristics of 36 234 women aged 48–83 years by α-linolenic acid consumption

(Mean values and standard deviations; percentages)

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	62·5	9·4	61·7	9·1	61·4	9·0	61·4	9·1	61·1	9·2
BMI (kg/m^2)	25·0	3·9	25·1	3·8	25·0	3·9	25·0	3·9	24·8	4·0
Physical activity (metabolic equivalent h/d)	42·3	4·9	42·6	4·7	42·4	4·7	42·5	4·7	42·4	4·8
Cigarette smoking (%)										
Current	20·7		21·1		21·8		23·3		27·2	
Past	22·8		22·4		23·2		21·9		22·5	
Never	56·5		56·5		55·0		54·8		50·3	
Education (%)										
Less than high school	72·8		75·1		75·2		74·0		71·3	
High school	8·1		7·7		7·9		7·9		8·0	
University	19·1		17·2		16·9		18·1		20·7	
Living alone (%)	26·1		22·2		22·5		22·4		24·2	
History of hypertension (%)	20·8		20·9		20·1		19·1		18·9	
History of high cholesterol (%)	8·1		8·4		8·2		7·4		7·3	
Postmenopausal hormone therapy (%)	49·1		49·6		49·3		49·5		49·7	
Family history of myocardial infarction (%)	13·6		13·8		13·4		13·3		13·6	
Energy intake (kJ/d)	7326	2318	7230	2134	7226	2109	7272	2100	7326	2305
Alcohol (g/d)	4·4	6·5	4·1	4·9	4·1	4·9	4·2	4·8	4·1	4·8
Fibre (g/d)	21·1	5·8	21·9	5·3	22·1	5·2	22·2	5·2	22·9	5·8
Na (g/d)	2385	387	2499	350	2547	360	2574	364	2618	441
Protein (g/d)	72·8	14·0	71·5	11·0	70·7	10·4	69·7	10·0	67·6	10·6
Carbohydrate (g/d)	220·8	30·0	215	25	211	24	207	23	200	24
Saturated fat (g/d)	26·1	7·0	26·7	6·1	27·3	5·9	27·9	5·9	28·7	6·5
Linoleic acid (g/d)	4·7	0·7	5·5	0·7	6·0	0·8	6·5	0·9	7·9	2·1
α-Linolenic acid (g/d)	0·86	0·09	1·03	0·04	1·15	0·03	1·28	0·04	1·56	0·22
Long-chain *n*-3 PUFA (g/d)	0·30	0·20	0·33	0·21	0·36	0·25	0·36	0·26	0·37	0·31
Soya products (servings/week)	0·1	0·2	0·2	0·3	0·2	0·4	0·3	0·5	0·6	1·7
Nuts (servings/week)	0·3	0·6	0·3	0·7	0·3	0·7	0·4	0·7	0·4	1·1
Mayonnaise (servings/week)	0·3	0·4	0·3	0·4	0·4	0·5	0·5	0·6	0·7	1·65
Salad dressing (servings/week)	0·5	0·8	0·7	1·1	0·9	1·3	1·2	1·7	2·1	2·7

smokers, more likely to have a university education, less likely to live alone and less likely to self-report a history of hypertension or high cholesterol (Table 2). The mean intake of alcohol, fibre, Na and long-chain *n*-3 was higher and the mean intake of protein and carbohydrate was lower in women in the top quintile of 18 : 2*n*-6 intake compared with the bottom quintile. Foods that accounted for variability in 18 : 2*n*-6 intake included soya products, nuts, mayonnaise and salad dressing.

We did not find a significant association between 18 : 3*n*-3 intake and the incidence of HF hospitalisation or mortality in models accounting for age and other covariates (Table 3). The relationships did not vary by intake of long-chain *n*-3 (*P* for interaction=0·29) or by intake of 18 : 2*n*-6 (*P* for interaction=0·81). The RR for a 1 standard deviation difference in 18 : 3*n*-3 as the percentage of total fat (0·4 % of total fat) was 1·00 (95 % CI 0·91, 1·10) before adjustment for measurement error and 1·01 (95 % CI 0·55, 1·85) after adjustment for measurement error.

18 : 2*n*-6 was also not significantly associated with the incidence of HF. We did not find evidence that the relationship between 18 : 2*n*-6 and HF varied by long-chain *n*-3 intake (*P* for interaction=0·54). The RR for a 1 standard deviation difference in 18 : 2*n*-6 as the percentage of total fat (2·7 % of total fat) was 1·04 (95 % CI 0·95, 1·14) before adjustment for measurement error and 1·20 (95 % CI 0·54, 2·66) after adjustment for measurement error.

In nutrient replacement models, 18 : 3*n*-3 was not significantly associated with HF, but the RR for the top quintile compared with the bottom quintile of 18 : 2*n*-6 was 1·57 (95 % CI 1·06, 2·34). This estimate was greatly attenuated when either carbohydrate or saturated fat was removed from the model, and there was strong evidence of model-fitting problems due to multicollinearity. We did not find significant associations between the consumption of soya products, nuts, mayonnaise or salad dressing one or more times per week and the incidence of HF events (Table 4). Results were not materially different when the first 2 years of follow-up were excluded.

Discussion

In this population of middle-aged and older women, there was no significant association of 18 : 3*n*-3 or 18 : 2*n*-6 or their major foods sources with the incidence of HF hospitalisation or mortality. We did not find evidence that the associations differed by intake of other PUFA. We had hypothesised that both 18 : 3*n*-3 and 18 : 2*n*-6 would have inverse associations with the incidence of HF. However, intake of 18 : 3*n*-3 was relatively

Table 2. Characteristics of 36 234 women aged 48–83 years by linoleic acid consumption
(Mean values and standard deviations; percentages)

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	64·0	9·4	62·6	9·2	61·5	9·0	60·4	8·7	59·5	8·7
BMI (kg/m^2)	24·9	3·9	25·0	3·9	25·0	3·9	25·0	3·9	24·8	3·9
Physical activity (metabolic equivalent h/d)	42·3	4·9	42·5	4·6	42·6	4·7	42·5	4·7	42·3	4·8
Cigarette smoking (%)										
Current	21·8		21·3		21·8		23·3		25·9	
Past	21·0		23·1		21·4		23·2		24·1	
Never	57·2		55·6		56·8		53·5		50·0	
Education (%)										
Less than high school	75·2		75·6		75·4		74·2		68·1	
High school	7·3		7·7		7·9		7·7		9·0	
University	17·5		16·7		16·7		18·1		22·9	
Living alone (%)	29·2		24·8		21·2		21·2		20·8	
History of hypertension (%)	21·7		21·0		19·5		19·2		18·4	
History of high cholesterol (%)	8·2		8·3		8·1		7·6		7·2	
Postmenopausal hormone therapy (%)	49·1		48·8		49·9		49·1		50·3	
Family history of myocardial infarction (%)	13·3		13·4		13·6		13·6		13·6	
Energy intake (kJ/d)	7360	2360	7268	2130	7222	2075	7222	2100	7314	2301
Alcohol (g/d)	4·1	6·2	4·0	5·2	3·9	4·6	4·2	4·7	4·7	5·3
Fibre (g/d)	21·1	6·1	22·0	5·4	22·4	5·2	22·4	5·1	22·4	5·5
Na (g/d)	2308	378	2469	333	2550	328	2627	360	2669	433
Protein (g/d)	72·7	14·7	71·0	11·0	70·3	9·9	69·8	10·0	68·5	10·4
Carbohydrate (g/d)	219	31	214	26	211	24	207	23	202	24
Saturated fat (g/d)	27·1	7·4	27·4	6·3	27·4	6·1	27·4	5·9	27·1	5·9
Linoleic acid (g/d)	4·4	0·5	5·3	0·2	5·9	0·2	6·5	0·2	8·4	1·8
α-Linolenic acid (g/d)	0·92	0·15	1·07	0·14	1·16	0·15	1·26	0·16	1·48	0·27
Long-chain *n*-3 PUFA (g/d)	0·31	0·26	0·33	0·26	0·35	0·24	0·36	0·23	0·37	0·26
Soya products (servings/week)	0·1	0·2	0·1	0·3	0·2	0·3	0·3	0·5	0·7	1·7
Nuts (servings/week)	0·2	0·3	0·2	0·4	0·3	0·4	0·4	0·6	0·6	1·5
Mayonnaise (servings/week)	0·2	0·4	0·3	0·4	0·4	0·4	0·5	0·5	0·8	1·7
Salad dressing (servings/week)	0·5	1·0	0·7	1·1	0·8	1·3	1·1	1·5	2·2	2·6

Table 3. α-Linolenic acid, linolenic acid and incidence of heart failure hospitalisation or mortality among 36 234 women aged 48–83 years

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P_{trend}
α-Linolenic acid						
Median	0·88	1·03	1·15	1·28	1·50	
Range	0·34–0·96	0·97–1·09	1·10–1·21	1·22–1·36	1·37–4·85	
Cases	150	143	120	128	110	
Person-years	62 298	62 678	62 655	62 622	62 965	
RR*	1	1·09	0·97	1·01	0·87	0·22
95 % CI*	Reference	0·87, 1·37	0·76, 1·24	0·80, 1·28	0·68, 1·12	
RR†	1	1·10	0·99	1·05	0·91	0·41
95 % CI†	Reference	0·87, 1·38	0·77, 1·26	0·82, 1·33	0·71, 1·17	
Linoleic acid						
Median	4·6	5·3	5·9	6·5	7·8	
Range	1·7–5·0	5·1–5·6	5·7–6·1	6·2–7·0	7·1–31·2	
Cases	180	137	125	100	109	
Person-years	61 664	62 529	62 718	63 036	63 271	
RR*	1	0·91	0·97	0·90	1·07	0·67
95 % CI*	Reference	0·73, 1·14	0·78, 1·23	0·70, 1·15	0·84, 1·35	
RR†	1	0·93	1·03	0·92	1·14	0·36
95 % CI†	Reference	0·74, 1·16	0·81, 1·31	0·71, 1·20	0·88, 1·46	

RR, rate ratio.
* Cox proportional hazards model accounting for age.
† Cox proportional hazards model accounting for age and adjusted for BMI, physical activity, energy intake, alcohol consumption, fibre consumption, Na consumption, education, family history of myocardial infarction at < 60 years, cigarette smoking, living alone, post-menopausal hormone use, self-reported history of hypertension, and self-reported history of high cholesterol.

low; an association between 18 : 3*n*-3 and HF may be evident at higher levels of intake than observed in the Swedish Mammography Cohort. The present results are consistent with a recent large study of women from the USA, which also failed to find an association between 18 : 3*n*-3 and HF[16]. In addition, we were not able to examine independent effects of 18 : 3*n*-3 and 18 : 2*n*-6 because of the correlation between them.

There is strong evidence from numerous randomised, controlled feeding studies that PUFA reduced LDL-cholesterol and increased HDL-cholesterol when substituted for carbohydrate[21]. However, dyslipidaemia is a minor risk factor for HF[3]. Dyslipidaemia can cause CHD, a major risk factor for HF[3]. Intake of both 18 : 3*n*-3 and 18 : 2*n*-6 has been inversely associated with incident CHD, but the results have not been consistent and are not conclusive[13–15,20]. In the present study, we excluded women with prevalent MI, and follow-up may not have been long enough to complete a proposed pathway from low 18 : 3*n*-3 and 18 : 2*n*-6 intake to dyslipidaemia to MI to HF.

18 : 3*n*-3 can be converted into long-chain *n*-3 fatty acids that have a number of beneficial effects, including potentially reducing post-MI mortality and mortality among people with HF[4,5,17], decreasing propensity to arrhythmia in many settings[30], and, at high doses, reducing TAG concentrations[31]. Our previous work and work of others suggested that moderate intake of long-chain *n*-3 fatty acids may decrease the risk of HF[8–11]. In one study, there was an inverse association between dark fish, a major dietary source of long-chain *n*-3 fatty acids, and HF but no association with long-chain *n*-3 fatty acids themselves[16]. Conversion of 18 : 3*n*-3 to long-chain *n*-3 fatty acids is inefficient and seems to be affected by the intake of 18 : 2*n*-6 and long-chain *n*-3 as well as variations in fatty acid desaturase genes[12,32]. Both 18 : 3*n*-3 and 18 : 2*n*-6 are essential fatty acids for humans, which must be obtained from the diet. The present study examined the range of intake reported by a relatively healthy population rather than frank deficiencies in the nutrients. We were not able to examine higher intakes that are consumed in some populations or are possible through supplementation. It is possible that an effect of 18 : 3*n*-3 would be evident in a population with a higher intake of 18 : 3*n*-3 or a lower intake of long-chain *n*-3 fatty acids and 18 : 2*n*-6. We attempted to address this issue by looking for interactions between 18 : 3*n*-3 and the other fatty acids; however, we were limited

Table 4. Intake of high α-linolenic acid or linoleic acid foods and incidence of heart failure hospitalisation or mortality among 36 234 women aged 48–83 years

	Correlation with α-linolenic acid	Correlation with linoleic acid	RR for consumption ≥ 1 time/week*	95 % CI
Soya products	0·29	0·29	1·24	0·80, 1·92
Nuts	0·08	0·23	0·73	0·47, 1·15
Mayonnaise	0·29	0·38	1·08	0·80, 1·44
Salad dressing	0·38	0·41	0·88	0·71, 1·10

RR, rate ratio.
* Cox proportional hazards model accounting for age and adjusted for BMI, physical activity, energy intake, alcohol consumption, fibre consumption, Na consumption, education, family history of myocardial infarction at < 60 years, cigarette smoking, living alone, post-menopausal hormone use, self-reported history of hypertension, and self-reported history of high cholesterol.

to only examining patterns of consumption that exist in this population.

18 : 3*n*-3 and 18 : 2*n*-6 are consumed together in foods and are highly correlated. It is difficult to separate out effects of the two types of polyunsaturated fat, which limits the conclusions we can draw about their biological action. In this population, soya products, mayonnaise and salad dressing contributed importantly to the variability in both 18 : 3*n*-3 and 18 : 2*n*-6. Nutrient replacement models, which are often used when examining the relationships of macronutrients with disease, were not reliable in the present study because of multicollinearity. We therefore could not determine the independent effects of 18 : 3*n*-3 and 18 : 2*n*-6. Feeding studies that directly manipulate specific fatty acids would be able to determine specific effects of 18 : 3*n*-3 and 18 : 2*n*-6. In order to realise any public health benefit from differentially altering 18 : 3*n*-3 and 18 : 2*n*-6 intake, changes to the food supply to provide these fats independent of one another would be necessary. We expect some misclassification of 18 : 3*n*-3 and 18 : 2*n*-6 intake because dietary intake was measured using questionnaires. This misclassification limits our ability to detect moderately sized effects of nutrients. We used regression calibration to try to take the measurement errors into account; however, this technique relies on a number of strong assumptions and does not fully account for the bias towards the null that results from random errors[25]. HF is a clinical syndrome with variable presentation and aetiology, and we did not have information on HF subtype. Although Swedish inpatient and cause-of-death registers are almost complete and the accuracy of HF diagnosis has been shown to be high[26], the registers only captured cases that result in hospitalisation or death. Therefore, the present results may not be generalisable to HF treated on an outpatient basis. While the present study had sufficient power to detect a 30 % decrease in the rate of HF associated with the fatty acids, we did not have power to reliably detect more subtle associations. Finally, as with all observational studies, we were not able to rule out bias due to residual or unmeasured confounding. In particular, it can be difficult to distinguish between the effect of nutrients and the effect of the foods that supply those nutrients.

In summary, we did not find evidence for an association between 18 : 3*n*-3 or 18 : 2*n*-6 intake and the incidence of HF hospitalisation and mortality in this population of women from central Sweden. The present results may not be generalisable to populations with a higher intake of 18 : 3*n*-3 than observed in this population. Further work with other populations and other study designs is needed to determine whether a high intake of 18 : 3*n*-3 can prevent HF and to tease out independent effects of 18 : 3*n*-3 and 18 : 2*n*-6.

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