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ORIGINAL ARTICLE

Fatty fish, marine ω-3 fatty acids and incidence of heart failure

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Background/Objectives: Marine ω-3 fatty acids have beneficial effects on cardiovascular risk factors. Consumption of fatty fish and marine ω-3 has been associated with lower rates of cardiovascular diseases. We examined the association of fatty fish and marine ω-3 with heart failure (HF) in a population of middle-aged and older women.
Subjects/Methods: Participants in the Swedish Mammography Cohort aged 48–83 years completed 96-item food-frequency questionnaires. Women without any history of HF, myocardial infarction or diabetes at baseline ($n = 36\,234$) were followed from 1 January 1998 until 31 December 2006 for HF hospitalization or mortality through Swedish inpatient and cause-of-death registers; 651 women experienced HF events. Cox proportional hazards models accounting for age and other confounders were used to calculate incidence rate ratios (RR) and 95% confidence intervals (CI).
Results: Compared with women who did not eat fatty fish, RR were 0.86 (95% CI: 0.67, 1.10) for <1 serving per week, 0.80 (95% CI: 0.63, 1.01) for 1 serving per week, 0.70 (95% CI: 0.53, 0.94) for 2 servings per week and 0.91 (95% CI: 0.59, 1.40) for ⩾3 servings per week ($P_{trend} = 0.049$). RR across quintiles of marine ω-3 fatty acids were 1 (reference), 0.85 (95% CI: 0.67, 1.07), 0.79 (95% CI: 0.61, 1.02), 0.83 (95% CI 0.65, 1.06) and 0.75 (95% CI: 0.58, 0.96) ($P_{trend} = 0.04$).
Conclusion: Moderate consumption of fatty fish (1–2 servings per week) and marine ω-3 fatty acids were associated with a lower rate of first HF hospitalization or death in this population.
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Keywords: heart failure; fatty acids; ω-3; diet

Introduction

Fatty fish and marine ω-3 fatty acids have been shown to have beneficial effects on the cardiovascular system which could slow or stop the development of heart failure (HF), a downstream consequence of many types of injury to the heart (Hunt *et al*., 2005). HF is the most common reason for hospitalization in the US Medicare population (Kozak *et al*., 2006). It causes substantial mortality and morbidity, and although treatment is improving, prognosis is still poor, which makes prevention of HF a public health priority (Schocken *et al*., 2008; Jhund *et al*., 2009). Cardiovascular effects of marine ω-3 fatty acids including reductions in blood pressure, heart rate, triacylglycerol concentration, and platelet aggregation and increases in heart rate variability (Bays, 2006; Mozaffarian *et al*., 2006; Mozaffarian *et al*., 2008; Harris *et al*., 2008). High intake seems to reduce propensity to arrhythmia (Leaf *et al*., 2005; Brouwer *et al*., 2006; Den Ruijter *et al*., 2008; Chrysohoou *et al*., 2007; Metcalf *et al*., 2008). In post-myocardial infarction (MI) and HF patients, supplementation with marine ω-3 fatty acids improved survival (GISSI-Prevenzione, 1999; GISSI-HF Investigators, 2008). In addition, ω-3 fatty acids improve endothelial function (Morgan *et al*., 2006) and may reduce inflammation (Lennie *et al*., 2005) in patients with HF.

Several previous studies in a variety of populations with different fish consumption habits have examined the association of fish and ω-3 consumption with incidence of HF events with mixed results. In a study of older US men and

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women, increasing tuna or other baked or broiled fish intake and marine ω-3 intake was associated with a lower rate of HF, but fried fish was not (Mozaffarian *et al*., 2005). Total fish consumption, including fried fish, was not associated with HF incidence in a cohort of white and African–American men and women (Nettleton *et al*., 2008). However, total fish consumption, included tempura fried fish, and total ω-3 fatty acid intake were associated with reduced mortality from HF in a cohort of Japanese adults (Yamagishi *et al*., 2008). In a population of middle-aged and elderly men from central Sweden, moderate consumption of fatty fish and marine ω-3 fatty acids was associated with a lower rate of HF events, but rates of HF events were similar among the highest and lowest consumers (Levitan *et al*., 2009).

In Sweden, intake of fish high in ω-3 fatty acids including salmon, herring and mackerel is common compared with other regions where the association has been evaluated (Becker *et al*., 2007). In addition, studies to date have examined populations of men or populations including both men and women. We therefore examined the association of fatty fish and ω-3 fatty acids with the rate of HF hospitalization or mortality in a large population of Swedish women.

Participants and methods

Participants

This study included participants in the Swedish Mammography Study. The recruitment process, characteristics of the cohort, and study methods have been previously described (Wolk *et al*., 2006). Briefly, all women in the Swedish population register 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 of the additional information collected on the second questionnaire, such as cigarette smoking, only women who completed the 1997 questionnaire were included in this study.

Participants who did not provide or provided incorrect national identification numbers, who reported implausible energy intakes (>3 s.d. from the natural logarithm-transformed mean), who had a previous diagnosis of cancer (other than non-melanoma skin cancer) or HF were excluded ($n=1126$). As patients with diabetes or MI are often counseled 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 complies with the Declaration of Helsinki and was 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 96 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 day or per week. For other foods and beverages there were eight predefined responses ranging from never to $\geqslant 3$ times per day. The questionnaires queried five types of fish intake: herring/mackerel, salmon/whitefish/char, cod/saithe/fishfingers, caviar and shellfish including shrimp. The reported frequency of consumption of herring/mackerel and salmon/whitefish/char was summed to calculate frequency of fatty fish consumption.

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 diet records. Nutrient values were calculated by multiplying the food or beverage intake by the nutrient composition obtained from the Swedish National Food Administration (Bergström *et al*., 1991) and summing over foods and beverages. Nutrient intakes were adjusted for energy using the residuals method (Willett, 1998). As a secondary exposure, we also adjusted fatty fish intake as for energy using the residuals method. Participants also reported consumption of fish oil supplements in capsules per week. Marine ω-3 fatty acids were calculated as the sum of eicosapentaenoic acid (C20: 5n-3) and docosahexaenoic acid (C22: 6n-3) from food sources. In a validation study of the food-frequency questionnaire among 129 middle-aged and older women from central Sweden, the correlation between the food frequency questionnaire and 41-week weighted diet records was 0.5 for measurement of fatty fish (Wolk *et al*., 2006). Correlations between food-frequency questionnaires and weighed diet records were 0.58 for eicosapentaenoic acid and 0.56 for docosahexaenoic acid, and correlations between food-frequency questionnaires and adipose tissue content were 0.46 for eicosapentaenoic acid and 0.44 for docosahexaenoic acid (Wolk *et al*., 1998).

We collapsed responses and categorized study participants into categories of no consumption of fatty fish, <1 serving per week, 1 serving per week, 2 servings per week and $\geqslant 3$ servings per week for both reported frequency and energy-adjusted frequency. We categorized participants into quintiles of marine ω-3 intake.

HF 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 (National Board of Health and Welfare, 2005). HF events were defined as hospitalizations 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. A secondary definition of an HF event included the codes in any diagnosis position. Ingelsson *et al*. (2005) found that 95% of people with these codes as primary diagnosis and 82% of people with the codes in any diagnosis position had confirmed HF on medical record review using European Society of Cardiology criteria. We included only 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 body mass index (1.7%) and physical activity (22.4%), we used Markov chain Monte-Carlo multiple imputation to simulate five complete datasets. The percentage of participants missing data on the composite physical activity measure was relatively high because this measure could only be calculated for participants who completed all six questions related to physical activity. Statistical analyses were performed in each of datasets separately, and the results were then averaged and the confidence intervals (CI) and *P* values calculated accounting for the uncertainty in the imputed estimates (Schafer, 1997). Results from complete-case analyses were similar, so only the multiple imputation estimates are shown.

We computed means and percentages of demographic, behavioral, and health covariates by intake of fatty fish. We tested for differences using linear regression for continuous variables and χ^2 tests for categorical variables. To estimate the incidence rate ratios (RR) associated with fish consumption, we used Cox proportional hazards models that accounted for age by allowing the baseline hazard to vary (Collett, 2003). We adjusted for body mass index (linear), physical activity (linear), energy intake (linear), alcohol consumption (linear), fiber consumption (linear), sodium consumption (linear), daily servings of red or processed meat (linear), education (less than high school, high school and university), family history of MI at <60 years (yes, no), cigarette smoking (current, past and never), living alone (yes, no), postmenopausal hormone use (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no). The covariates were selected based on the associations between the variables and fish intake and the variables and incident HF in the literature and in our data. For example, in our data women who lived alone were more likely to be at the extremes of fatty fish intake and being unmarried has been associated with a higher rate of HF (Ingelsson *et al*., 2006).

We calculated the RR associated with quintiles of marine ω-3 fatty acids and explored the potentially nonlinear shape of the association between marine ω-3 fatty acids and incidence of HF using a restricted cubic spline with 3 knots (Durrleman and Simon, 1989) using models adjusted as described above. For the spline, we excluded individuals with values below the 2.5th and above the 97.5th percentiles to avoid modeling where data were sparse. We created an additional model, which adjusted the RR associated with quintiles of marine ω-3 fatty acids for protein (linear), saturated fat (linear), monounsaturated fat (linear), non-marine ω-3 fatty acids (linear) and ω-6 fatty acids (linear). We examined the effect of excluding women with self-reported prevalent hypertension at baseline using models as described above. We additionally examined HF events defined as HF listed in any diagnosis position. As symptoms of HF occurring before hospitalization or death may influence dietary behavior, 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 fish intake or marine ω-3 intake and the natural logarithm of time in the model. The proportional hazards assumption did not appear to be violated for any of the models.

Statistical analyses were performed using SAS version 9.1 (Cary, NC, USA) and Stata version 10.0 (College Station, TX, USA). A two-sided *P*-value <0.05 was considered statistically significant.

Results

Over 9 years of follow-up, 651 of 36 234 women were hospitalized for HF ($n=596$) or died of HF ($n=55$), corresponding to a rate of 20 cases per 10 000 person-years. A total of 12% of the women did not consume fatty fish, 25% ate <1 serving per week, 44% ate 1 serving per week, 17% ate 2 servings per week and 3% ate 3 or more servings per week. The women who ate the most fatty fish were, on average, older and heavier, less likely to be current smokers, more likely to have a history of hypertension and high cholesterol, and consumed more sodium and more red and processed meat (Table 1).

Compared with women who did not consume fatty fish, women who consumed <1 serving per week had a 14% lower rate of HF events, women who consumed 1 serving per week had a 20% lower rate, women who consumed 2 servings per week had a 30% lower rate, and women who consumed $\geqslant 3$ servings per week had a 9% lower rate after accounting for age and adjusting for dietary, demographic and lifestyle factors (Table 2). A test for linear trend was significant ($P=0.049$) and a test of quadratic trend was not statistically significant ($P=0.21$). Results were similar when examining energy-adjusted fatty fish intake. Compared with women who never consumed fatty fish, women who consumed <1 serving per week had a multivariable-adjusted RR of 0.81 (95% CI: 0.62, 1.06), women who consumed 1 serving per week has an RR of 0.83 (95% CI: 0.66, 1.05), women who consumed 2 servings per week had an RR

Table 1 Baseline characteristics of 36 234 Swedish mammography cohort participants by intake of fatty fish[a]

	Fatty fish intake					
	Never (N = *4344*)	*<1 servings/week* (N = *8988*)	*1 serving/week* (N = *15 932*)	*2 servings/week* (N = *6026*)	*⩾3 servings/week* (N = *944*)	*P*[b]
Age (years)	61.9 ± 9.8[c]	61.6 ± 9.4	60.8 ± 8.9	62.9 ± 8.9	66.1 ± 9.2	<0.001
Physical activity (MET h/d)	42.4 ± 5.0	42.4 ± 4.8	42.3 ± 4.6	42.8 ± 4.8	42.8 ± 5.1	<0.001
Body mass index (kg/m^2)	24.9 ± 4.0	25.0 ± 4.0	24.8 ± 3.7	25.2 ± 4.0	25.5 ± 4.4	0.009
Cigarette smoking						<0.001
Current	1129 (26.0)[d]	2119 (23.6)	3617 (22.7)	1221 (20.3)	184 (19.5)	
Past	899 (20.7)	1912 (21.3)	3791 (23.8)	1392 (23.1)	180 (19.1)	
Never	2316 (53.3)	4957 (55.1)	8524 (53.5)	3413 (56.6)	580 (61.4)	
Living alone	1391 (32.0)	2324 (25.9)	3220 (20.2)	1271 (21.1)	297 (31.5)	<0.001
Postmenopausal hormone use	1994 (45.9)	4159 (46.3)	8113 (50.9)	3197 (53.1)	450 (47.7)	<0.001
Education						<0.001
Less than high school	3405 (78.4)	6887 (76.6)	11 214 (70.4)	4419 (73.3)	772 (81.8)	
High school	337 (7.8)	659 (7.3)	1374 (8.6)	447 (7.4)	54 (5.7)	
University	602 (13.9)	1442 (16.0)	3344 (21.0)	1160 (19.3)	118 (12.5)	
Family history of myocardial infarction	550 (12.7)	1144 (12.7)	2204 (13.8)	863 (14.3)	141 (14.9)	0.008
History of hypertension	796 (18.3)	1820 (20.3)	3002 (18.8)	1362 (22.6)	253 (26.8)	<0.001
History of high cholesterol	287 (6.6)	626 (7.0)	1240 (7.8)	607 (10.1)	96 (10.2)	<0.001
Energy intake (kcal/day)	1562 ± 541	1651 ± 493	1748 ± 483	1898 ± 519	2234 ± 796	<0.001
Alcohol (g/day)	2.9 ± 4.5	3.5 ± 5.0	4.7 ± 5.3	4.8 ± 5.5	3.6 ± 5.8	<0.001
Sodium (g/day)[e]	2443 ± 460	2451 ± 353	2519 ± 347	2620 ± 345	3087 ± 655	<0.001
Fiber (g/day)[e]	21.6 ± 6.6	21.6 ± 5.5	22.1 ± 5.2	23.0 ± 5.2	22.6 ± 5.8	<0.001
Red/processed meat (servings per day)	0.9 ± 0.8	1.0 ± 0.6	1.1 ± 0.7	1.2 ± 0.7	1.7 ± 1.7	<0.001
Marine ω-3 (g/day)[e]	0.13 ± 0.11	0.22 ± 0.08	0.34 ± 0.10	0.55 ± 0.14	1.26 ± 0.73	<0.001

[a]MET, metabolic equivalent task; s.d., standard deviation.
[b]Derived from tests of linear trend for continuous variables or χ^2 tests for categorical variables.
[c]Mean ± s.d. (all such values).
[d]N (percent) (all such values).
[e]Adjusted for energy using the residuals method.

Table 2 Fatty fish intake and incidence of heart failure hospitalization or mortality[a]

Fatty fish intake	*Cases*	*Person-years*	*Model 1*[b]		*Model 2*[c]	
			RR	*95% CI*	*RR*	*95% CI*
Never	104	37 086	1.00	Reference	1.00	Reference
<1 serving per week	177	77 451	0.88	0.69, 1.13	0.86	0.67, 1.10
1 serving per week	237	1 38 614	0.79	0.62, 0.99	0.80	0.63, 1.01
2 servings per week	101	52 189	0.69	0.53, 0.91	0.70	0.53, 0.94
⩾3 servings per week	32	7879	0.96	0.64, 1.42	0.91	0.59, 1.40
P for linear trend			0.03		0.049	

[a]CI, confidence interval; RR, incidence rate ratio.
[b]Cox proportional hazards model accounting for age.
[c]Cox proportional hazards model accounting for age and additionally adjusted for education (less than high school, high school and university), body mass index (linear term), physical activity (linear term), cigarette smoking (current, past and never), living alone (yes, no), postmenopausal hormone use (yes, no), total energy intake (linear term), alcohol intake (linear term), fiber intake (linear term), sodium intake (linear term), intake of red or processed meat (linear term), family history of myocardial infarction before 60 years (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).

of 0.70 (95% CI: 0.52, 0.94), and women who consumed ⩾3 servings per week had an RR of 1.00 (95% CI: 0.66,1.52).

The highest quintile of marine ω-3 fatty acid intake was associated with a 25% lower rate of HF events compared with the lowest quintile in multivariable-adjusted models (Table 3). The dose-response analysis using a restricted cubic spline suggested that the rate of HF declined with increasing marine ω-3 fatty acids up to approximate 0.4 g day^{-1}; above

Table 3 Marine ω-3 intake and incidence of heart failure hospitalization or mortality[a]

Marine ω-3 fatty acids	*Median (g/day)*	*Range (g/day)*	*Cases*	*Person-years*	*Model 1*[b]		*Model 2*[c]	
					RR	*95% CI*	*RR*	*95% CI*
Quintile 1	0.14	0.01–0.19	168	61 959	1.00	Reference	1.00	Reference
Quintile 2	0.23	0.20–0.27	123	62 897	0.87	0.69, 1.10	0.85	0.67, 1.07
Quintile 3	0.30	0.28–0.33	99	63 153	0.80	0.62, 1.02	0.79	0.61, 1.02
Quintile 4	0.38	0.34–0.45	120	63 064	0.84	0.67, 1.07	0.83	0.65, 1.06
Quintile 5	0.57	0.46–7.15	141	62 146	0.77	0.61, 0.96	0.75	0.58, 0.96
P for linear trend					0.03		0.04	

[a]CI, confidence interval; RR, incidence rate ratio.
[b]Cox proportional hazards model accounting for age.
[c]Cox proportional hazards model accounting for age and additionally adjusted for education (less than high school, high school and university), body mass index (linear term), physical activity (linear term), cigarette smoking (current, past and never), living alone (yes, no), postmenopausal hormone use (yes, no), total energy intake (linear term), alcohol intake (linear term), fiber intake (linear term), sodium intake (linear term), intake of red or processed meat (linear term), family history of myocardial infarction before 60 years (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).

$0.4\,g\,day^{-1}$, marine ω-3 fatty acids did not appear to be strongly correlated with rate of HF events (Figure 1). However, the test for deviation from linearity was not statistically significant ($P=0.32$). Further adjusting for macronutrients, including protein, saturated fat, monounsaturated fat, non-marine ω-3 fatty acids and ω-6 fatty acids, slightly attenuated the difference in rates (compared with the lowest quintile, RR for quintile 2 = 0.87, 95% CI: 0.69, 1.11, RR for quintile 3 = 0.83, 95% CI: 0.64, 1.07, RR for quintile 4 = 0.88, 95% CI: 0.69, 1.12, RR for quintile 5 = 0.81, 95% CI: 0.63, 1.05).

Among women without self-reported hypertension at baseline, 401 HF events occurred during follow-up. The results for fatty fish were similar to the total population. Compared with women who did not consume fatty fish, RR were 0.94 (95% CI: 0.69, 1.29) for <1 serving per week, 0.92 (95% CI: 0.68, 1.24) for 1 serving per week, 0.72 (95% CI: 0.50, 1.05) for 2 servings per week and 1.25 (95% CI: 0.73, 2.14) for ⩾3 servings/week ($P_{trend}=0.37$) in a multivariable-adjusted model. In contrast, there was no apparent association between marine ω-3 intake and HF. RR across quintiles of marine ω-3 fatty acids were 1 (reference), 1.04 (95% CI: 0.77, 1.40), 0.94 (95% CI: 0.68, 1.29), 1.00 (95% CI: 0.73, 1.37) and 0.83 (95% CI: 0.60, 1.15). There were 1 489 events when HF in any diagnosis position was used to define events. Compared with women who did not consume fatty fish, RR were 0.87 (95% CI: 0.73, 1.02) for <1 serving per week, 0.85 (95% CI: 0.73, 1.00) for 1 serving per week, 0.77 (95% CI: 0.64, 0.93) for 2 servings per week and 0.97 (95% CI: 0.73, 1.29) for ⩾3 servings per week ($P_{trend}=0.06$) in a multivariable-adjusted model. RR across quintiles of marine ω-3 intake were 1 (reference), 0.90 (95% CI: 0.76, 1.05), 0.86 (95% CI: 0.73, 1.02), 0.86 (95% CI: 0.73, 1.01) and 0.88 (95% CI: 0.74, 1.03) ($P_{trend}=0.17$). Results were not materially different when the first 2 years of follow-up were excluded or when fatty acids from fish oil supplements were included in the calculation of marine ω-3 consumption.

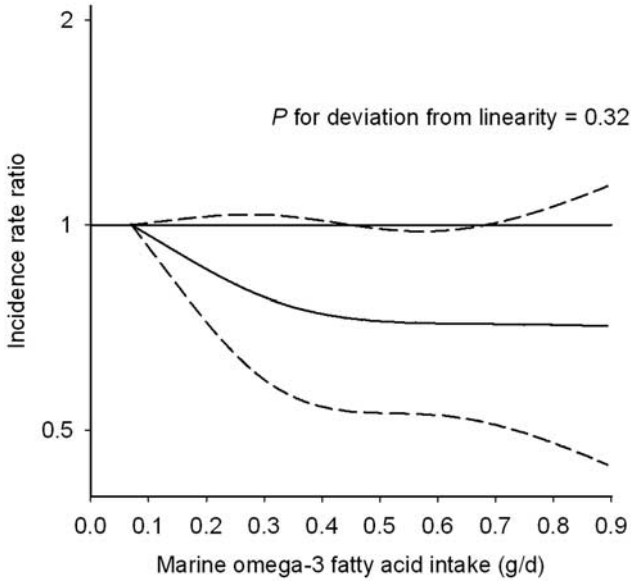

Figure 1 Marine ω-3 intake and incidence rate ratio of heart failure hospitalization or mortality. The solid line represent incidence rate ratio and the dashed line represents the 95% CI. The curve was produced from a Cox proportional hazards model where marine ω-3 intake was modeled as a restricted cubic spline with 3 knots, accounting for age, and adjusted for education (less than high school, high school and university), body mass index (linear term), physical activity (linear term), cigarette smoking (current, past and never), living alone (yes, no), postmenopausal hormone use (yes, no), total energy intake (linear term), alcohol intake (linear term), fiber intake (linear term), sodium intake (linear term), intake of red or processed meat (linear term), family history of myocardial infarction before 60 years (yes, no), self-reported history of hypertension (yes, no) and self-reported history of high cholesterol (yes, no).

Discussion

In this population, women who consumed fatty fish two times per week had a rate of HF events that was 30% lower than that of women who did not consume fatty fish

regularly. Women in the highest fifth of marine ω-3 consumption had a rate of HF that was 25% lower than those in the lowest fifth. A restricted cubic spline analysis suggested a potential threshold in the association with no additional decrease in risk above 0.4 g day^{-1} of marine ω-3 consumption. This is similar to the relationship observed for coronary heart disease death (Mozaffarian and Rimm, 2006), but a test for deviation from linearity was not significant.

Previous studies have examined the association of fish intake and ω-3 fatty acids with HF incidence. Mozaffarian *et al.* (2005) found that tuna and other broiled or baked fish was associated with lower rates of HF in elderly US men and women, as was marine ω-3 intake, but fried fish was associated with higher rates of HF. In contrast, Nettleton *et al.* (2008) found no association between total fish intake and HF incidence in US adults, but they were not able to differentiate between fried fish and baked or broiled fish. In a study of Japanese men and women, total fish and total ω-3 intake were associated with lower HF rates (Yamagishi *et al.*, 2008). We previously reported a U-shaped relationship of fatty fish and marine ω-3 intake and HF in Swedish men (Levitan *et al.*, 2009). These studies varied in the way fish intake was assessed and the types of fish commonly consumed; the method of assessing HF also differed across studies.

Fatty fish and marine ω-3 intake may reduce the propensity to develop HF through several pathways. Elevated blood pressure is a major risk factor for HF, (Hunt *et al.*, 2005) and marine ω-3 fatty acids reduce blood pressure in a dose-dependent manner, though the magnitude of the effect is small (Kris-Etherton *et al.*, 2002). Fatty fish and marine ω-3 fatty acid intake can reduce resting heart rate and improve diastolic filling (Mozaffarian, 2007). In rats with pressure overload, marine ω-3 fatty acids prevented left ventricular hypertrophy and dysfunction (Duda *et al.*, 2009). Marine ω-3 fatty acids have also been shown to improve endothelial function and improve arterial compliance and to reduce inflammatory processes (Kris-Etherton *et al.*, 2002).

In this population, the women who consumed two servings of fatty fish per week appeared to have the lowest rates of HF, although the test for quadratic trend between fatty fish intake and incidence of HF events was not statistically significant. The appearance of a potentially U-shaped relationship could be because of residual or unmeasured confounding by health status or other factors. If women in worse health consumed more fatty fish than those in better health, the rates of HF events in the highest fatty fish consumers could be biased upward. In fact, women with the highest fatty fish intake were more likely to have a history of high cholesterol or hypertension. Although we controlled for self-reported presence of these cardiovascular risk factors, we did not have information on severity or treatment, which could lead to residual confounding. We had limited information on baseline health status and could not control for potential confounding by other indicators of health. Chance could also explain the results, particularly given the small number of women who ate $\geqslant 3$ servings of fatty fish per week and the wide CI around the estimates.

Heart failure is a heterogeneous syndrome, and risk factors may not be identical for all subtypes (Hunt *et al.*, 2005); we did not have information on HF etiology or subtype. If the relationship between fish and HF varied by subtype, we would expect that the observed results would be intermediate between the subtype-specific relationships. We did not have information regarding the duration of HF symptoms before hospitalization or mortality; however, 44% of patients in a Swedish HF registry had new onset HF, defined as HF of <6 months duration (Jonsson *et al.*, 2010). Although Swedish inpatient and cause-of-death registers are almost complete and the accuracy of HF diagnosis has been shown to be high (Ingelsson *et al.*, 2005), the registers only captured cases that result in hospitalization or death. Our results may be only generalizable to the subset of HF cases that result in hospitalization or mortality. We expect that these are the most severe cases. As other investigators have suggested (Ingelsson *et al.*, 2005), we included only cases in which HF was listed as the primary diagnosis for our main analysis. This results in greater specificity of diagnosis at the expense of under-diagnosis of HF, which would be expected to reduce the power of the analysis. It also reduces the likelihood counting hospitalizations for problems other than HF when HF is mentioned in the medical record.

Power was low for some analyses, particularly those limited to women without a history of hypertension at baseline. Fatty fish consumption and marine ω-3 fatty acids intake were measured using food-frequency questionnaires; we expect some misclassification of intake. However, questionnaires have been validated against weighed diet records and adipose tissue biopsies. As with all observational studies, we were not able to rule out bias due to residual or unmeasured confounding.

In conclusion, moderate consumption of fatty fish (1–2 servings per week) and marine ω-3 fatty acids were associated with lower rates of HF in this population of middle-aged and older Swedish women.

Conflict of interest

The authors declare no conflict of interest.

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