# Plasma and dietary omega-3 fatty acids, fish intake, and heart failure risk in the Physicians' Health Study[1–3]

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## ABSTRACT

**Background:** Data on the relation of plasma and dietary omega-3 (n–3) fatty acids (FAs) with heart failure (HF) risk have been inconsistent.

**Objective:** We evaluated the relation of n−3 FAs with HF in US male physicians.

**Design:** We used nested case-control (*n* = 1572) and prospective cohort study designs (*n* = 19,097). Plasma phospholipid n−3 FAs were measured by using gas chromatography, and food-frequency questionnaires were used to assess dietary n−3 FAs and fish intake. Incident HF was ascertained via annual follow-up questionnaires and validated in a subsample.

**Results:** The mean age was 58.7 y at blood collection. In a multivariable model, plasma α-linolenic acid (ALA) was associated with a lower risk of HF in a nonlinear fashion (*P*-quadratic trend = 0.02), and the lowest OR was observed in quintile 4 (0.66; 95% CI: 0.47, 0.94). Plasma EPA and DHA were not associated with HF, whereas plasma docosapentaenoic acid (DPA) showed a nonlinear inverse relation with HF for quintile 2 (OR: 0.55; 95% CI: 0.39, 0.79). Dietary marine n−3 FAs showed a trend toward a lower risk of HF in quintile 4 (HR: 0.81; 95% CI: 0.64, 1.02) and a nonlinear pattern across quintiles. Fish intake was associated with a lower risk of HF, with RRs of ∼0.70 for all categories of fish consumption greater than one serving per month.

**Conclusions:** Our data are consistent with an inverse and nonlinear relation of plasma phospholipid ALA and DPA, but not EPA or DHA, with HF risk. Fish consumption greater than once per month was associated with a lower HF risk. *Am J Clin Nutr* 2012;96: 882–8.

## INTRODUCTION

Heart failure (HF)[4] is a substantial public health burden in the United States, and several studies have been published suggesting that the dietary marine omega-3 (n−3) fatty acids (FAs) EPA, docosapentaenoic acid (DPA), and DHA and fish consumption may lower the risk of HF. The most recent study in the Women's Health Initiative showed a lower risk of HF with consumption of ≥5 servings baked or broiled fish/wk but was unable to show an association with EPA+DHA concentrations (1). A Swedish study, also among women, was able to show a lower risk of HF for only 2 servings fish/wk and for the highest quintile of marine n−3 intake (2). A Swedish study among men (3) and the Rotterdam Study (4) were both unable to show significant inverse associations between fish consumption and HF. In contrast, the Cardiovascular Health Study cohort reported dose-related inverse associations for 1–2 servings and 3–4 servings fish/wk (5).

Studies of plasma omega-3 FA concentrations and incident HF have been undertaken in an attempt to overcome inconsistencies related to measurement error in food-frequency questionnaire (FFQ)–based studies. Unfortunately, these studies of plasma concentrations have also been inconsistent. In the Minneapolis subset of the Atherosclerosis Risk in Communities cohort, long-chain n−3 FAs were associated with a lower risk of HF among women but not men. The lowest HR was identified for DHA with an estimated 80% lower risk of the highest compared with the lowest quintile of plasma concentration (6). In contrast, a recent report from the Cardiovascular Health Study found the lowest risk of HF with plasma phospholipid EPA concentrations, with an estimated 50% lower risk of the highest compared with the lowest quintile. Additionally, plasma phospholipid DPA showed a trend toward a lower risk across the quintiles (7). α-Linolenic acid (ALA) was not associated with HF in the Cardiovascular Health Study (8). A recent meta-analysis suggested beneficial effects of n−3 FAs on HF (9).

In the current study, we sought to prospectively examine whether plasma phospholipid n−3 FAs were inversely associated with HF risk. In addition, we examined the relation of

fish intake and dietary n−3 FAs with the risk of HF in US male physicians

## SUBJECTS AND METHODS

### Study population

We examined data from the Physicians' Health Study (PHS) I—a completed randomized, double-blind, placebo-controlled trial designed to study low-dose aspirin and β-carotene for the primary prevention of cardiovascular disease and cancer that began in 1982. PHS II began in 2001 and recruited new physicians to add to re-enrolling members of the PHS I. A detailed description of the PHS I+II was published previously (10–12). Only physicians enrolled at baseline in the PHS I were eligible to be included in the nested case-control study of plasma phospholipid n−3 FAs ($n = 1576$). All physicians responding to the FFQ were eligible for inclusion in the dietary study of n−3 FAs ($n = 19,649$). Each participant signed an informed consent, and the Institutional Review Board at Brigham and Women's Hospital approved the study protocol.

The current ancillary study of the PHS used a prospective nested case-control design to evaluate the relation of plasma phospholipid n−3 FAs and HF. Specifically, each participant who provided a blood sample in 1982 and subsequently developed HF was eligible to be selected as a case. For each case of HF, we used a risk set technique to randomly select a control among participants who were alive and free of HF at the time of the index HF diagnosis and matched on age, time of blood collection, year of birth, race, and randomization arm. Each case was allowed to serve as a control before the HF occurrence. Baseline blood samples obtained between 1982 and 1983 were stored at −82°C until measurement of plasma FAs in 2011.

In addition, we supplemented this ancillary study with FFQ data (collected between 1997 and 2001) and used a prospective cohort design to analyze the relation of dietary n−3 FA and fish intake with incident HF occurring during a follow-up period from 1997 to 2010. A total of 19,649 study participants had data on dietary n−3 FAs and 19,508 on fish consumption; however, because of missing covariate data, 19,097 and 18,968 were studied in the multivariate models, respectively.

### Ascertainment of incident HF

In the PHS, annual follow-up questionnaires have been used to ascertain disease endpoints. Cases of HF were identified by a self-reported diagnosis. HF diagnoses in PHS were previously validated by reviewing medical records in a subsample, and self-reported HF was confirmed in 91% of the cases evaluated (13).

### Measurement of plasma phospholipid n−3 FAs

During 2011, the plasma FA profile was determined in EDTA-treated plasma from previously frozen blood samples by using the method previously described by Cao et al (14). Briefly, lipids are extracted from plasma with a mixture of chloroform:methanol (2:1, vol:vol), and cholesterol, triglycerides, and phospholipid subclasses are separated on a silica thin-layer chromatography plate in a solvent mixture of petroleum ether, diethyl ether, and glacial acetic acid (80:20:1, vol:vol:vol). The phospholipid band is harvested and used for the formation of methyl esters by using

14% boron trifluoride in methanol and then extracted with petroleum ether. The final product is dissolved in heptane and injected onto a capillary Varian CP7420 100-m column with a Hewlett-Packard 5890 gas chromatograph equipped with an HP6890A autosampler. The gas chromatograph is configured for a single capillary column with a flame ionization detector and interfaced with HP Chemstation software. Adequate separation of FA methyl esters is obtained over an 80-min period with an initial temperature of 190°C for 25 min. The temperature is increased to 240°C at a rate of 2°C/min and held for 5 min. FA methyl esters from 12:0 through 24:1n−9 are separated, identified, and expressed as a percentage of total FAs. The following CVs were obtained on 20 blind duplicates: linoleic acid, 2.6%; ALA, 2.4%; arachidonic acid, 2.4%; EPA, 3.3%; DPA, 2.9%; DHA, 2.7%; 16:1n7c, 8.5%; and 18:1n7c, 4.6%.

### Assessment of fish intake and dietary n−3 FAs

Information on fish consumption and dietary n−3 FAs was obtained by using FFQs. Nutrients were computed by using the food-composition database from the Harvard School of Public Health and manufacturer information. The validity and reproducibility of FFQs were published elsewhere (15, 16). We used the residual method to adjust nutrients for energy intake (17). The Spearman correlation coefficient between marine n−3 FA concentrations derived from FFQs and plasma concentrations (measured at the same clinic visit) was reported to be 0.54 (18). We examined the Spearman correlation in our data from plasma and dietary measures at different time points (1982–1983 and 1997–2001, respectively) in 1122 participants.

### Other variables

Demographic information was obtained through self-report by using questionnaires. At baseline, each subject provided information on exercise (How often do you exercise vigorously enough to work up sweat?), and exercise per week was categorized into 0, 1–4, or 5–7 d/wk for analysis of plasma phospholipid n−3 FAs and 0, <1, 1–2, 3–4, or 5–7 d/wk in the larger study of dietary n−3 FAs. Smoking history (never, former, or current smoker) and alcohol intake were self-reported. Alcohol was categorized on the basis of the number of drinks per week: <1/wk, 1–4/wk, 5–7/wk, or ≥8/wk. Alcohol for the dietary analysis was used as a continuous variable. Self-reported baseline weight and height were used to compute BMI [weight (in kg)/height (in m)$^2$]. Data on comorbidity—including hypertension, atrial fibrillation, valvular heart disease, hyperlipidemia, and diabetes—were collected at baseline and through follow-up questionnaires.

### Statistical analyses

In the analysis of plasma n−3 FAs, we defined quintiles of marine n−3 FAs and ALA using the control sample and applied those cutoffs to cases. We performed conditional logistic regression using 788 matched pairs and additionally adjusted for age at the time of blood sampling, atrial fibrillation, hypertension, BMI, alcohol, smoking, and exercise. Because of missing data on smoking history, 2 pairs were excluded from the final multivariate model. Baseline characteristics of the study participants are presented according to marine n−3 FA and ALA quintiles.

In the analysis of dietary n−3 FAs, we created quintiles of marine n−3 FAs and ALA using the entire study population. Fish-consumption categories were defined as <1 serving/mo, 1–3 servings/mo, 1 serving/wk, and ≥2 servings/wk. We used Cox proportional hazards regression to estimate the HR of HF using the lowest category/quintile as the reference. The models examining quintile dummy variables were adjusted for age, atrial fibrillation, valvular heart disease, hypertension, BMI, alcohol, current and former smoking, and exercise. The model examining fish consumption included the above covariates and ALA quintiles.

To obtain $P$ values for linear and quadratic trend, we created a new variable that was assigned the median value of marine n−3 FAs and ALA in each quintile and fitted such a variable and its quadratic term in the regression. In the analysis of plasma n−3 FAs, median values were defined among controls. All analyses were performed by using SAS (version 9.1; SAS Institute), and the $\alpha$ level was set at 0.05. All $P$ values were 2-sided.

## RESULTS

The baseline characteristics of the study participants, according to quintiles of plasma and dietary marine n−3 FAs and ALA, are presented in **Table 1** and **Table 2**, respectively. The proportion of participants with high cholesterol increased with increasing marine n−3 FA concentrations, and a similar pattern was observed for increasing fish intake. A larger proportion of participants reported current smoking in the study of plasma n−3 FAs from blood samples drawn at baseline than in the dietary study from FFQ. The cohort study of dietary data included participants with an older mean age that reported a higher frequency of high cholesterol, hypertension, atrial fibrillation, and valvular heart disease in comparison with the plasma study. The Spearman correlation between plasma and dietary measures was computed in 1122 participants, and the correlation coefficient for marine n−3 FAs was 0.25 ($P <$ 0.0001), but the correlation for ALA was −0.02 ($P = 0.45$). For the individual marine n−3 FAs, the correlation coefficients between plasma and dietary levels ($P$ values) were $r = 0.27$ ($P < 0.0001$) for DHA, $r = 0.15$ ($P < 0.0001$) for EPA, and $r = 0.03$ ($P = 0.38$) for DPA.

The association with HF for both dietary- and plasma-based quintiles of marine n−3 FAs and ALA with full covariate adjustment is presented in **Table 3**. Minimally adjusted models produced results similar to those shown. For plasma measures of ALA, minimally adjusted models that controlled for matched factors only produced ORs of 0.71 (95% CI: 0.52, 0.96), 0.67 (95% CI: 0.49, 0.92), 0.62 (95% CI: 0.45, 0.85), and 0.71 (95% CI: 0.49, 1.04) for quintiles 2, 3, 4, and 5, respectively. Plasma measures of ALA were associated with a lower risk of HF in a nonlinear manner ($P$-quadratic trend = 0.01 when controlled for matching factors only and 0.02 for the fully adjusted model). The adjusted OR for plasma ALA in quintile 4 compared with the lowest quintile was 0.66 (95% CI: 0.47, 0.94). Quintiles 2–4 of dietary ALA showed trends toward an association, with an 18–21% lower risk of HF.

In analyses of the marine n−3 FAs separately, plasma phospholipid DPA was inversely related to HF in a nonlinear fashion, with the lowest ORs observed in quintile 2 (OR: 0.55; 95% CI:

0.39, 0.79) and quintile 5 (OR: 0.67; 95% CI: 0.46, 0.99). Dietary DPA was associated with a lower risk of HF in a nonlinear fashion; the smallest HR was identified in quintile 3, with an RR estimate of 0.71 (95% CI: 0.56, 0.90) and $P$-quadratic trend of 0.07. Plasma phospholipid EPA and DHA did not show an association with HF. Dietary EPA and DHA were each associated with lower odds of HF in quintile 4: EPA HR = 0.80 (95% CI: 0.64, 1.01) and DHA HR = 0.79 (95% CI: 0.63, 1.0), but neither linear nor quadratic trends were significant ($P > 0.1$).

The baseline characteristics of the participants, according to categories of fish intake, are presented in **Table 4**. The 4 categories of increasing fish intake represented 5.9%, 20.5%, 38.5%, and 35.1% of the sample, respectively. In a multivariable model, we observed ∼30% lower risk of HF for any fish consumption relative to no fish intake in this population.

## DISCUSSION

In this cohort of US male physicians, a lower risk of HF was observed with plasma phospholipid ALA above the lowest quintile in a nonlinear fashion. Quintile 3 of dietary ALA estimated by FFQ was also associated with a lower risk of HF. Whereas plasma phospholipid EPA and DHA were not associated with HF risk, plasma DPA showed a lower risk of HF in quintiles 2 and 5. Higher levels of dietary marine n−3 exhibited a trend toward lower HF risk in a nonlinear fashion, and we observed a lower incidence of HF among physicians who consumed fish one or more times per month.

### n−3 FA and incident HF

Our results for ALA based on diet and plasma measures suggest a lower risk of HF with higher concentrations, although the relation is not linear. In plasma ALA, we observed the smallest OR in quintile 4 (OR: 0.66; 95% CI: 0.47, 0.94) and ORs ranging from 0.71 to 0.84 in the other quintiles. In dietary data, the smallest HR was 0.79 (95% CI: 0.63, 1.00) in quintile 3. The nonlinear pattern was similar to that observed for dietary marine n−3 FA, in which the highest quintile of n−3 concentrations had the smallest beneficial effect. This pattern may be the result of confounding by indication related to increased dietary intake of n−3 FA by physicians with cardiovascular risk factors.

The inconsistency in results for marine n−3 FAs and ALA between dietary and plasma concentrations may reflect the difference in these sample sizes, participants' age and comorbidities, and different time points when the information was ascertained. The blood samples used for plasma measures were collected between 1982 and 1983, whereas the FFQ data were obtained between 1997 and 2001. Marine n−3 FAs showed a weak nonlinear inverse association with HF when an FFQ was used to assess n−3 but no association when an objective biomarker from an earlier time point was used, despite a strong correlation between the dietary and plasma measures. The negative correlation between dietary and plasma ALA concentrations may explain the difference in results, and the lack of a significant trend for dietary ALA was consistent with a recent report from a Swedish study of women (19). Our biomarker study of ALA suggests a nonlinear inverse association between ALA and HF.

**TABLE 1**
Characteristics of study participants by plasma marine omega-3 (n−3) FAs and ALA[1]

| Characteristics | Quintiles of plasma EPA+DHA+DPA | | | Quintiles of plasma ALA | | |
|---|---|---|---|---|---|---|
| | 1 (n = 308) | 3 (n = 332) | 5 (n = 292) | 1 (n = 361) | 3 (n = 305) | 5 (n = 313) |
| Age (y) | 58.6 ± 8.2[2] | 58.1 ± 7.7 | 59.6 ± 8.0 | 58.6 ± 8.1 | 59.0 ± 7.5 | 58.4 ± 7.9 |
| BMI (kg/m$^2$) | 25.2 ± 2.8 | 25.2 ± 3.1 | 25.0 ± 2.9 | 25.7 ± 3.1 | 25.2 ± 2.7 | 24.7 ± 2.9 |
| High cholesterol (%) | 10.64 | 14.09 | 20.00 | 15.63 | 13.60 | 16.67 |
| Current smoking (%) | 15.91 | 10.54 | 6.16 | 10.53 | 10.82 | 12.86 |
| Former smoking (%) | 39.94 | 44.58 | 46.23 | 41.27 | 46.56 | 45.02 |
| Current drinking (%) | 69.28 | 76.44 | 76.21 | 73.61 | 70.16 | 79.03 |
| Exercise >1 time/wk (%) | 72.73 | 74.09 | 70.34 | 69.75 | 75.99 | 76.28 |
| Hypertension (%) | 28.43 | 33.43 | 35.05 | 31.56 | 30.92 | 31.51 |
| Atrial fibrillation (%) | 4.22 | 3.31 | 3.42 | 4.43 | 3.28 | 3.51 |
| Valvular heart disease (%) | 0.97 | 0.90 | 1.03 | 0.83 | 0.66 | 0.64 |
| Diabetes mellitus (%) | 8.12 | 6.93 | 3.77 | 7.20 | 3.61 | 2.88 |
| Quintile median (% of total FAs)[3] | 3.204 (2.999–3.407) | 4.412 (4.285–4.588) | 6.458 (5.951–7.340) | 0.097 (0.085–0.105) | 0.143 (0.137–0.148) | 0.306 (0.221–0.379) |

[1] ALA, α-linolenic acid; DPA, docosapentaenoic acid; FAs, fatty acids.
[2] Mean ± SD (all such values).
[3] IQR in parentheses (all such values).

In the Cardiovascular Health Study, plasma phospholipid EPA was associated with a lower risk of HF (7), and in the Atherosclerosis Risk in Communities Study, plasma DHA (both phospholipid and cholesterol ester) was associated with a lower risk of HF among women only (6). Our results from plasma concentrations of EPA and DHA do not replicate those findings. However, we observed a nonlinear and inverse relation of plasma DPA with HF, and dietary results for both EPA and DHA showed the lowest risk of HF in quintile 4, with an HR of 0.81 from the FFQ.

In previous studies of plasma n−3 FAs, an association between ALA and HF was not observed (6, 8). In these data, dietary ALA showed trends toward an association with HF, with 17–21% lower risks observed for each quintile compared with the lowest quintile. The association of plasma ALA provided evidence of a lower risk of HF with higher ALA concentrations with a nonlinear pattern. This may suggest that for ALA, the precision of the laboratory-assessed values and the matched design have improved power to detect an association in comparison with measures from the FFQ.

**TABLE 2**
Characteristics of study participants by dietary marine omega-3 (n−3) FAs and ALA[1]

| | Quintiles of dietary EPA+DHA+DPA | | | Quintiles of dietary ALA | | |
|---|---|---|---|---|---|---|
| | 1 (n = 3808) | 3 (n = 3813) | 5 (n = 3805) | 1 (n = 3803) | 3 (n = 3833) | 5 (n = 3814) |
| Age (y) | 67.5 ± 9.7[2] | 66.0 ± 9.1 | 65.8 ± 8.4 | 66.6 ± 9.3 | 66.3 ± 9.2 | 66.5 ± 8.9 |
| BMI (kg/m$^2$) | 25.8 ± 3.6 | 26.0 ± 3.5 | 25.9 ± 3.6 | 25.3 ± 3.2 | 25.8 ± 3.5 | 26.2 ± 3.8 |
| Fish intake (%) | | | | | | |
| <1 time/mo | 28.34 | 0.24 | 0.63 | 5.82 | 4.79 | 7.98 |
| 1–3 times/mo | 55.10 | 12.02 | 2.05 | 21.44 | 20.25 | 20.64 |
| 1 time/wk | 16.56 | 87.09 | 4.26 | 36.61 | 39.16 | 38.19 |
| ≥2 times/wk | 0 | 0.66 | 93.05 | 36.13 | 35.80 | 33.19 |
| High cholesterol (%) | 38.44 | 41.27 | 47.42 | 42.99 | 40.89 | 40.49 |
| Current smoking (%) | 5.12 | 3.36 | 2.08 | 3.10 | 3.08 | 4.06 |
| Former smoking (%) | 41.23 | 40.94 | 44.10 | 41.99 | 41.51 | 43.65 |
| Current drinking (%) | 74.61 | 82.11 | 85.10 | 82.86 | 84.01 | 77.56 |
| Exercise >1 time/wk (%) | 61.40 | 64.44 | 68.07 | 67.92 | 66.27 | 62.61 |
| Hypertension (%) | 44.30 | 43.46 | 42.21 | 42.12 | 43.05 | 44.28 |
| Atrial fibrillation (%) | 8.67 | 7.24 | 8.80 | 8.15 | 7.36 | 8.36 |
| Valvular heart disease (%) | 1.63 | 1.55 | 1.66 | 1.71 | 1.70 | 1.42 |
| Diabetes mellitus (%) | 7.64 | 7.42 | 7.04 | 5.50 | 6.08 | 9.96 |
| Quintile median (g/d)[3] | 0.079 (0.048–0.092) | 0.152 (0.142–0.166) | 0.397 (0.356–0.474) | 0.576 (0.524–0.61) | 0.765 (0.746–0.784) | 1.0 (0.947–1.1) |

[1] ALA, α-linolenic acid; DPA, docosapentaenoic acid; FAs, fatty acids.
[2] Mean ± SD (all such values).
[3] IQR in parentheses (all such values).

**TABLE 3**
HRs (and 95% CIs) for heart failure according to quintile of dietary and plasma marine omega-3 (n−3) FAs and ALA[1]

| | Marine (EPA+DHA+DPA) | | | | ALA | | | |
| | Dietary[2] | | Plasma[3] | | Dietary[2] | | Plasma[3] | |
| Quintile | No. of cases/person-years | HR (95% CI) | No. of cases/controls | OR (95% CI) | No. of cases/person-years | HR (95% CI) | No. of cases/controls | OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| 1 | 172/31,310 | 1.0 | 151/157 | 1.0 | 157/31,772 | 1.0 | 205/156 | 1.0 |
| 2 | 151/32,151 | 0.92 (0.74, 1.14) | 182/156 | 1.26 (0.90, 1.75) | 137/32,074 | 0.82 (0.65, 1.03) | 158/163 | 0.76 (0.55, 1.05) |
| 3 | 124/32,171 | 0.84 (0.66, 1.06) | 174/157 | 1.18 (0.85, 1.64) | 131/32,302 | 0.79 (0.63, 1.00) | 145/160 | 0.71 (0.50, 1.00) |
| 4 | 123/32,550 | 0.81 (0.64, 1.02) | 145/159 | 0.97 (0.69, 1.38) | 138/32,186 | 0.82 (0.65, 1.03) | 125/151 | 0.66 (0.47, 0.94) |
| 5 | 133/32,113 | 0.94 (0.75, 1.18) | 134/157 | 0.92 (0.64, 1.33) | 140/31,961 | 0.83 (0.66, 1.05) | 153/156 | 0.84 (0.56, 1.26) |
| P-trend, linear | | 0.12 | | 0.17 | | 0.32 | | 0.03 |
| P, quadratic | | 0.09 | | 0.15 | | 0.12 | | 0.02 |

[1] All analyses were adjusted for age, atrial fibrillation, hypertension, BMI, alcohol, current smoking, former smoking, and exercise. The dietary analyses were additionally adjusted for valvular heart disease. ALA, $\alpha$-linolenic acid; DPA, docosapentaenoic acid; FAs, fatty acids.
[2] The dietary results from the cohort study were analyzed with Cox proportional hazards regression.
[3] Plasma results from the nested case-control study were analyzed with conditional logistic regression.

A recent review of n−3 FAs and cardiovascular disease reports that the most consistent beneficial effects were observed for coronary heart disease mortality and sudden cardiac death and the relation with HF and other cardiovascular outcomes is less well established (20). Biomarker studies will likely improve our understanding of these relations. Plasma phospholipid n−3 FAs were recently linked to atrial fibrillation, a risk factor for HF, with total n−3 PUFA and DHA concentrations associated with a lower risk of atrial fibrillation (21). The Lyon Diet Heart Study found plasma ALA to be associated with an improved prognosis for recurrent myocardial infarction but did not find a similar association with long-chain n−3 FAs (22). In addition,

n−3 FA supplementation was shown to be beneficial at reducing cardiovascular hospitalization and mortality after HF in the Italian Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trial (23). In contrast, supplementation was not shown to be significantly beneficial at reducing the rate of cardiovascular events among patients after myocardial infarction in the Alpha Omega Trial (24).

### Fish intake and incident HF

In comparison with the results from the Women's Health Initiative, which showed a lower risk of HF only with ≥5 servings fish/wk (1), we showed a 30% lower risk associated

**TABLE 4**
Results for the association of fish consumption and heart failure with characteristics of the study participants[1]

| | Fish consumption | | | |
| Characteristics | <1 time/mo (n = 1119) | 1–3 times/mo (n = 3881) | 1 time/wk (n = 7313) | ≥2 times/wk (n = 6655) |
|---|---|---|---|---|
| Age (y) | 67.4 ± 9.9[2] | 66.5 ± 9.6 | 66.5 ± 9.1 | 66.2 ± 8.6 |
| BMI (kg/m$^2$) | 25.8 ± 3.8 | 25.9 ± 3.6 | 25.9 ± 3.5 | 25.7 ± 3.5 |
| High cholesterol (%) | 36.92 | 39.38 | 40.55 | 44.67 |
| Current smoking (%) | 5.09 | 4.07 | 3.69 | 2.16 |
| Former smoking (%) | 38.78 | 41.84 | 42.49 | 43.29 |
| Current drinking (%) | 60.95 | 76.73 | 83.04 | 86.78 |
| Exercise >1 time/wk (%) | 58.62 | 61.61 | 64.91 | 69.45 |
| Hypertension (%) | 45.67 | 43.03 | 43.83 | 42.40 |
| Atrial fibrillation (%) | 8.85 | 7.65 | 8.46 | 8.50 |
| Valvular heart disease (%) | 1.43 | 1.31 | 1.55 | 1.58 |
| Diabetes mellitus (%) | 9.47 | 7.40 | 6.82 | 6.48 |
| Median dietary EPA+DHA+DPA (g/d)[3] | 0.024 (0.01–0.049) | 0.10 (0.083–0.12) | 0.138 (0.118–0.163) | 0.333 (0.286–0.398) |
| Median dietary ALA (g/d)[3] | 0.791 (0.669–0.924) | 0.763 (0.657–0.876) | 0.768 (0.670–0.879) | 0.761 (0.659–0.868) |
| Heart failure | | | | |
| No. of cases/person-years | 61/9028 | 139/32,365 | 270/61,492 | 225/56,413 |
| HR (95% CI)[4] | 1.0 | 0.70 (0.52, 0.94) | 0.73 (0.55, 0.97) | 0.72 (0.54, 0.96) |

[1] ALA, $\alpha$-linolenic acid; DPA, docosapentaenoic acid.
[2] Mean ± SD (all such values).
[3] IQR in parentheses.
[4] HR from cohort study analyzed with Cox proportional hazards regression adjusted for age, atrial fibrillation, valvular heart disease, hypertension, BMI, alcohol, current smoking, former smoking, exercise, and quintiles of ALA.

with a fish intake of only ≥1 times/mo in US male physicians. This amount of fish consumption is more attainable by the general population. These results are consistent with those of the Cardiovascular Health Study, which had previously shown a 20% lower risk of HF associated with 1–2 servings fish/wk (5). Previously, a modest intake of fatty fish was shown to reduce mortality after myocardial infarction in the Diet and Re-infarction Trial among men (25). Our findings for fish consumption from the FFQ were stronger than those from marine n−3 FAs.

Major risk factors of HF include coronary heart disease, hypertension, and diabetes (26). However, data on the effects of n−3 FAs on hypertension (27, 28) and diabetes (29, 30) have been inconsistent. Some investigations suggest beneficial effects of n−3 FAs on hemodynamics (31), left ventricular indexes (32), and inflammation (33). For example, fish oil has been shown to inhibit natriuretic peptide production (34) and to alter the diacylglycerol composition in the heart and prevents activation of protein kinase C (35, 36); chronic activation of protein kinase C has been related to left ventricular hypertrophy and HF (37). Canola oil, a major dietary source of ALA, was shown to reduce the incidence of ventricular fibrillation in rats (38). The beneficial effect of n−3 FAs and fish consumption on HF may arise from one or more of these mechanisms.

## Strengths and limitations

The strengths of the study include the large sample size, the prospective design, standardized follow-up questionnaires to ascertain endpoints, a high positive predictive value of self-reported HF in male physicians, and the opportunity to compare dietary- and plasma-assessed concentrations of n−3 FAs. Because this was a study of all physicians, socioeconomic factors influencing the consumption of fish are not likely to have confounded the results. A limitation of the study was that the FFQ was administered only once; therefore, changes in dietary habits may not be reflected. Because the study participants were male physicians, it is unclear whether the results are generalizable to women and the general population. Our data are consistent with an inverse and nonlinear relation of plasma phospholipid ALA and DPA, but not EPA and DHA, with HF risk. Fish consumption greater than once per month was associated with a lower risk of HF.

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