American Journal of Epidemiology

Vol. 179, No. 12
DOI: 10.1093/aje/kwu086
Advance Access publication:
May 8, 2014

Original Contribution

Suicide Mortality in Relation to Dietary Intake of n-3 and n-6 Polyunsaturated Fatty Acids and Fish: Equivocal Findings From 3 Large US Cohort Studies

Alexander C. Tsai*, Michel Lucas, Olivia I. Okereke, Éilis J. O'Reilly, Fariba Mirzaei, Ichiro Kawachi, Alberto Ascherio, and Walter C. Willett

* Correspondence to Dr. Alexander C. Tsai, Center for Global Health, Massachusetts General Hospital, 100 Cambridge Street, 15th floor, Boston, MA 02114 (e-mail: actsai@partners.org).

Initially submitted September 12, 2013; accepted for publication March 13, 2014.

Intake of n-3 and n-6 polyunsaturated fatty acids (PUFAs) has been implicated in the pathogenesis of depression. We sought to estimate the association between intake of fish and n-3 and n-6 PUFAs and suicide mortality over the course of long-term follow-up. In this prospective cohort study, biennial questionnaires were administered to 42,290 men enrolled in the Health Professionals Follow-up Study (1988–2008), 72,231 women enrolled in the Nurses' Health Study (1986–2008), and 90,836 women enrolled in Nurses' Health Study II (1993–2007). Dietary fish and n-3 and n-6 PUFA intakes were assessed every 4 years using a validated food-frequency questionnaire. Suicide mortality was ascertained through blind physician review of death certificates and hospital or pathology reports. Adjusted relative risks of suicide mortality were estimated with multivariable Cox proportional hazards models and pooled across cohorts using random-effects meta-analysis. The pooled multivariable relative risks for suicide among persons in the highest quartile of intake of n-3 or n-6 PUFAs, relative to the lowest quartile, ranged from 1.08 to 1.46 for n-3 PUFAs (P_{trend} = 0.11–0.52) and from 0.68 to 1.19 for n-6 PUFAs (P_{trend} = 0.09–0.54). We did not find evidence that intake of n-3 PUFAs or fish lowered the risk of completed suicide.

diet; docosahexaenoic acid; eicosapentaenoic acid; fish; linoleic acid; n-3 polyunsaturated fatty acids; suicide

Abbreviations: ALA, α-linolenic acid; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II; PUFA, polyunsaturated fatty acid; SD, standard deviation.

The marine-derived n-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA; 20:5n-3), docosahexaenoic acid (DHA; 22:6n-3), and the plant-derived α-linolenic acid (ALA; 18:3n-3) have been hypothesized to play a role in maintaining cell membrane fluidity, regulating neurotransmitters, and suppressing cytokine production (1). Syntheses of these findings implicate low n-3 PUFA levels in the pathogenesis of major depressive disorder and bipolar disorder, as well as schizophrenia (2). First, cross-sectional studies suggest an inverse association between population-level intake of fish and the prevalence of depressive disorders (3) and between intake of fish and severity of depression symptoms measured at the individual level (4). Second, moderately decreased levels of EPA and DHA have been identified in various blood fractions (e.g., plasma, serum, and/or erythrocytes) of persons diagnosed with major depressive disorder (5). Third, in some cohort studies, greater intake of n-3 PUFAs or fish has been associated with a reduced incidence of depressed mood (6–8). However, in other cohort studies, no statistically significant association has been observed (9, 10). In addition, while numerous randomized controlled trials have tested different preparations of EPA + DHA in the treatment of persons with depressed mood or depressive disorders, meta-analyses of these trials have yielded conflicting findings (11–13).

Little work has extended the above findings to the study of completed suicide, a significant, terminal outcome that has been relatively ignored in the field (14). The first randomized controlled trial of n-3 PUFA supplementation for reduction of completed suicides and suicide attempts (Defense Medical

Research and Development Program 12023001; Principal Investigator: B. Marriott) began enrolling participants last year. This area of research could have an important public health impact, given that changes in dietary n-3 PUFA intake, even if relatively small in magnitude from the perspective of specific individuals, could, as Rose (15, 16) classically argued, have substantial implications for the population burden of disease (17, 18). The Omega-3 Fatty Acids Subcommittee of the American Psychiatric Association issued a recommendation that all adults consume fish at least 2 times per week and that persons with depressive disorders achieve a minimum intake of 1 g of EPA + DHA per day (2). Such a level of EPA + DHA intake would require the consumption of, for example, 23 ounces (652 g) of Atlantic cod or 2.5 ounces (71 g) of sockeye salmon per day (19). Yet the conflicting evidence reviewed above suggests the need for more study about the effects of n-3 PUFA intake on completed suicide, arguably the most significant terminal outcome for abnormal mental health.

To address this substantive gap in our current knowledge base, we used repeated dietary assessment data from men and women enrolled in 3 large US cohort studies to estimate the association between n-3 PUFA and n-6 PUFA intake and the incidence of suicide mortality over the course of long-term follow-up. In doing so, we sought to make the following contributions to the literature. First, of the 3 previous studies (9, 20, 21), the positive study by Hirayama (20) did not adjust for any potentially confounding variables, and the 2 null studies by Hakkarainen et al. (9) and Poudel-Tandukar et al. (21) were based on smaller cohorts followed for shorter periods of time. Second, none of these studies measured n-6 PUFA intake. The n-6 PUFA linoleic acid (18:2n-6) is a precursor of arachidonic acid (20:4n-6), from which proinflammatory eicosanoids and cytokines are derived, leading some to hypothesize that imbalance between n-3 PUFA intake and n-6 PUFA intake may lead to depression (22, 23). Because the n-3 PUFAs and the n-6 PUFAs require the same metabolic enzymes and compete with each other (24, 25), a more comprehensive analysis of the putative benefits of n-3 PUFA intake should account for both n-3 and n-6 PUFAs. Third, none of these studies accounted for changes in diet between baseline and follow-up. Given that dietary patterns may change over time, studies with only a single measurement of n-3 PUFA intake may be prone to exposure misclassification.

METHODS

Study population

For this study, we analyzed data from 3 ongoing US cohort studies: the Nurses' Health Study (NHS) (26, 27), the Health Professionals Follow-up Study (HPFS) (28), and Nurses' Health Study II (NHS2) (29). Participants in all cohort studies provided written informed consent and were followed with biennial questionnaires on lifestyle, medication use, and disease incidence. To identify an analytic sample comprised of study participants who were healthy at baseline and to reduce the possibility of unobserved confounding, we excluded participants with self-reported histories of serious cardiovascular conditions (myocardial infarction, angina, or stroke) (30, 31) or cancer (except nonmelanoma skin cancer) (32) at baseline. After these exclusions, data from 42,290 HPFS participants, 72,231 NHS participants, and 90,836 NHS2 participants were available for analysis. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health.

Assessment of n-3 and n-6 PUFA and fish intake

Dietary intakes were assessed every 4 years using semiquantitative food-frequency questionnaires (33). These questionnaires employed common units or portion sizes for each food (34), with 9 possible frequency responses ranging from "never" to "6 or more per day." We then calculated the average daily intake of nutrients by multiplying the frequency of consumption of each item by its nutrient content per serving.

Among the items included were 4 questions about seafood consumption during the past year. For calculating intake of EPA + DHA, we followed a previously published method by weighting the mean values of EPA and DHA for the most common types of fish according to 1984 landing data from the US Department of Commerce (35, 36). We assigned grams per serving as follows: 1.51 for dark-meat fish, 0.42 for canned tuna, 0.48 for other fish, and 0.32 for shrimp, lobster, or scallops. Nutrient intakes were adjusted for total energy intake by means of the residual approach (37). Baseline intake of EPA + DHA was derived primarily from fish (87% of total intake), with much lower amounts derived from chicken (7%) and liver (2%), similar to sources in the US food supply (38).

Also among the items included were additional questions about the types of fat or oil used in food preparation, consumption of specific brands or types of margarine, consumption of mayonnaise or other creamy salad dressing, and consumption of oil-and-vinegar salad dressing. These and other items enabled us to calculate intakes of ALA and linoleic acid. Nutrient values were obtained from the Harvard University Food Composition Database, derived using data from US Department of Agriculture sources (39) and supplemented with manufacturer information and direct analysis of food samples obtained from Boston, Massachusetts-area grocery stores and fast-food restaurants (40, 41). The measures of n-3 and n-6 PUFA intake used in this study have well-documented construct validity, as supported by moderate-to-strong correlations with fatty acids measured in plasma and erythrocytes (42) and adipose tissue (43) and by their ability to predict the incidence of relevant conditions such as coronary heart disease (34, 41, 44), type 2 diabetes (45), and macular degeneration (46).

Case ascertainment

The outcome of interest was suicide mortality. In most instances, study staff were informed of a participant's death by next of kin, through questionnaires returned by the US Postal Service, or through reports from participants' professional organizations. Additionally, the vital status of serial nonresponders was ascertained through the US National Death Index, a method that has been shown to have 98% sensitivity and 100% specificity for ascertainment of deaths (47, 48).

Physicians blinded to exposure status reviewed death certificates and hospital or pathology reports to classify individual causes of death. Deaths due to self-inflicted injuries were classified according to the underlying causes listed on the death certificate. For this study, we specifically examined deaths classified with codes E950–E959 according to the World Health Organization's *International Classification of Diseases, Eighth Revision* (NHS), and *International Classification of Diseases, Ninth Revision* (HPFS and NHS2).

Statistical analysis

Each participant contributed person-time from the date of return of the baseline questionnaire (1988 for HPFS, 1986 for NHS, and 1993 for NHS2) to either death or the end of follow-up (January 1, 2008, for HPFS; June 30, 2008, for NHS; and June 30, 2007, for NHS2), whichever came first. To estimate the association between n-3 and n-6 PUFA intake and suicide mortality, we fitted multivariable Cox regression models to the data (49). To adjust for potential confounding by age, calendar time, and any potential 2-way interactions between these 2 time scales, we stratified the analysis jointly by age in months at the start of follow-up and by calendar year of the questionnaire cycle. The time scale for the analysis was then measured in months since the start of the current questionnaire cycle. No departures from the proportional hazards assumption were observed.

To account for changes in dietary intake over time and to reduce random measurement error, we used the cumulative average of dietary intake from all available questionnaires. To minimize the possibility that our findings could be attributed to reverse causation, we allowed a 2- to 4-year interval between assessment of intake and the start of a follow-up cycle (50). For example, in our analysis of the NHS data, we used the cumulative average of n-3 PUFA intake based on the 1984 and 1986 questionnaires to predict suicide mortality in 1988–1990 and 1990–1992, used intakes from 1984–1990 to predict suicide mortality in 1992–1994 and 1994–1996, and so on. To test for linear trends across quintiles of intake, we modeled the median values within each category of exposure.

For each cohort, we fitted a series of nested regression models to estimate the associations between n-3 and n-6 PUFA intakes and suicide mortality. We investigated separately the 4 largest contributors to n-3 and n-6 PUFA intakes (ALA, EPA + DHA, arachidonic acid, and linoleic acid), as well as total n-3 PUFA intake and total n-6 PUFA intake. First, we fitted a regression model that adjusted for age and time interval. Second, we adjusted for smoking status, body mass index (weight (kg)/height $(m)^2$), alcohol consumption, marital status, weekly physical activity, and consumption of caffeinated coffee. For women, we further adjusted for menopausal status and use of hormone replacement therapy. Finally, we further adjusted for the cumulative average intakes of other nutrients, including energy (kcal/day), *trans* fatty acids (g/day), saturated fatty acids (g/day), monounsaturated fatty acids (g/day), and the other n-3 and n-6 PUFAs (g/day).

In sensitivity analyses, we further adjusted for self-reported regular use of minor tranquilizers (i.e., benzodiazepines) and antidepressant medications (serotonin-specific reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic agents, monoamine oxidase inhibitors, or other), as well as for self-reported use of fish oil and/or cod liver oil supplements. For women in the NHS2, we further adjusted for score on the 5-item Mental Health Inventory (51). Finally, to ensure that our findings were broadly generalizable, we refitted the regression models to the data including all study participants (i.e., including persons with serious cardiovascular conditions or cancer who were excluded from the primary analysis).

We used inverse-variance-weighted random-effects meta-analysis to pool the estimates across the 3 cohorts, and these pooled estimates are reported as our primary findings. The I^2 statistic was employed to describe the proportion of total variation in study estimates due to heterogeneity. Cohort-specific estimates, as well as the estimates corresponding to the sensitivity analyses, can be found in Web Tables 1–5 (available at http://aje.oxfordjournals.org/). All analyses were carried out with SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Across all participants at baseline, the mean daily intake of EPA + DHA was 0.30 (standard deviation (SD), 0.26) g/day for men in the HPFS cohort and 0.19 (SD, 0.15) g/day and 0.20 (SD, 0.17) g/day for women in the NHS and NHS2 cohorts, respectively. Average daily intake exceeded 0.5 g/day for only 5,691 (13.6%) men in the HPFS cohort and 2,600 (3.6%) and 4,269 (4.7%) women in the NHS and NHS2 cohorts, respectively. Men and women in higher quartiles of EPA + DHA intake reported more physical activity and lower rates of smoking, but otherwise differences across quartiles of EPA + DHA intake were minimal (Web Table 1).

Over the course of 3,511,768 person-years of follow-up across the 3 cohorts, there were 287 suicide events. There were no statistically significant associations between suicide mortality and quartile of either ALA intake or EPA + DHA intake (Table 1). In the age-adjusted regression models, each 1 g/day of ALA intake was associated with a relative risk for suicide mortality of 0.88 (95% confidence interval (CI): 0.69, 1.13), while each 0.3 g/day of EPA + DHA intake was associated with a relative risk of 1.21 (95% CI: 1.05, 1.39). In fully adjusted multivariable regression models, there was a non-statistically significant higher risk of suicide mortality across increasing quartiles of total n-3 intake ($P_{trend} = 0.11$), and the relative risk for each 1 g/day of total n-3 intake was 1.43 (95% CI: 1.01, 2.02). I^2 values ranged from 0% to 14% for the pooled estimates of ALA and total n-3 PUFA intake and from 53% to 70% for the pooled estimates of EPA + DHA intake. When disaggregated by cohort, the higher risks from EPA + DHA intake were most strongly observed among women (Web Table 2).

Greater linoleic acid intake was associated with a lower risk of suicide mortality (Table 2). In fully adjusted multivariable regression models, there was a non-statistically significant lowered risk of suicide mortality across linoleic acid intake quartiles ($P_{trend} = 0.09$), and each 5 g/day of linoleic acid intake was associated with a relative risk of 0.67 (95%

Table 1. Pooled[a] Relative Risk of Suicide Mortality According to Quartile of n-3 Polyunsaturated Fatty Acid Intake for Participants in the Nurses' Health Study (1986–2008), Nurses' Health Study II (1993–2007), and the Health Professionals Follow-up Study (1986–2008)

n-3 PUFA Type and Quartile of Intake	No. of Cases	Person-Years of Follow-up	Age-Adjusted[b]		Multivariable Model 1[c]		Multivariable Model 2[d]	
			RR	95% CI	RR	95% CI	RR	95% CI
ALA								
Quartile 1	86	880,502	1	Reference	1	Reference	1	Reference
Quartile 2	50	880,371	0.59	0.41, 0.84	0.69	0.48, 0.98	0.69	0.48, 0.99
Quartile 3	78	873,483	0.91	0.66, 1.24	1.06	0.77, 1.45	1.12	0.80, 1.57
Quartile 4	73	877,412	0.83	0.60, 1.13	0.98	0.70, 1.35	1.10	0.76, 1.59
P for trend				0.77		0.54		0.21
Per increment[e]			0.88	0.69, 1.13	0.99	0.78, 1.25	1.08	0.82, 1.43
EPA + DHA								
Quartile 1	69	876,241	1	Reference	1	Reference	1	Reference
Quartile 2	54	885,584	0.76	0.53, 1.08	0.83	0.58, 1.19	0.81	0.56, 1.17
Quartile 3	84	869,215	1.21	0.88, 1.67	1.32	0.95, 1.84	1.27	0.91, 1.77
Quartile 4	80	880,728	1.10	0.79, 1.53	1.14	0.81, 1.60	1.08	0.76, 1.54
P for trend				0.33		0.31		0.52
Per increment[e]			1.21	1.05, 1.39	1.15	0.99, 1.33	1.12	0.95, 1.30
Total n-3 PUFAs[f]								
Quartile 1	70	875,589	1	Reference	1	Reference	1	Reference
Quartile 2	75	877,506	1.03	0.74, 1.43	1.22	0.87, 1.70	1.32	0.94, 1.86
Quartile 3	69	882,400	0.95	0.68, 1.34	1.14	0.81, 1.60	1.31	0.91, 1.88
Quartile 4	73	876,272	0.99	0.71, 1.38	1.15	0.82, 1.62	1.46	0.98, 2.16
P for trend				0.78		0.62		0.11
Per increment[e]			1.01	0.74, 1.39	1.11	0.83, 1.50	1.43	1.01, 2.02

Abbreviations: ALA, α-linolenic acid; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acid; RR, relative risk.

[a] Results from the 3 cohort-specific regression models were combined using random-effects meta-analysis (for cohort-specific estimates, see Web Table 2).

[b] Adjusted for age (years; continuous variable) and time interval.

[c] Further adjusted for smoking status (never smoker, former smoker, current smoker of 1–14 cigarettes/day, current smoker of 15–24 cigarettes/day, or current smoker of ≥25 cigarettes/day), body mass index (weight (kg)/height (m)^2; <25, 25–29.9, or ≥30), alcohol consumption (g/day), marital status (married/partnered, widowed, or separated/divorced/single), physical activity (metabolic equivalents/week, in quintiles), and consumption of caffeinated coffee (cups/day). For women, the multivariable regression model further adjusted for menopausal status and use of hormone replacement therapy (postmenopausal with or without hormone replacement therapy, premenopausal, or never use of hormone replacement therapy).

[d] Further adjusted for cumulative average intake of energy (kcal/day), *trans* fatty acids (g/day), saturated fatty acids (g/day), and monounsaturated fatty acids (g/day) (all continuous variables). For ALA, multivariable model 2 further adjusted for EPA + DHA and total n-6 PUFAs (all continuous). For EPA + DHA, multivariable model 2 further adjusted for ALA and total n-6 PUFAs (both continuous). For total n-3 PUFAs, multivariable model 2 further adjusted for total n-6 PUFAs (continuous).

[e] The per-increment scale was 1 g/day for ALA, 0.3 g/day for EPA + DHA, and 1 g/day for total n-3 PUFAs.

[f] Total n-3 PUFAs = ALA + EPA + DHA.

CI: 0.48, 0.95). Greater arachidonic acid intake was associated with a non-statistically significant higher risk of suicide mortality, resulting in a largely null association for total n-6 PUFA intake. I^2 values ranged from 0% to 2% for the pooled estimates of linoleic acid, arachidonic acid, and total n-6 PUFA intake. When disaggregated by cohort, the lowered risks from linoleic acid intake were most strongly observed among men (Web Table 3).

Greater fish intake did not have a statistically significant association with suicide mortality (Table 3). Across categories of intake frequency, there was a non-statistically significant reduction in risk of suicide mortality ($P_{trend} = 0.80$). Compared with those eating less than 1 serving of fish per week, the relative risk of suicide mortality among persons eating 3 or more servings per week was 1.00 (95% CI: 0.69, 1.47). I^2 values ranged from 0% to 60%

Table 2. Pooled[a] Relative Risk of Suicide Mortality According to Quartile of n-6 Polyunsaturated Fatty Acid Intake for Participants in the Nurses' Health Study (1986–2008), Nurses' Health Study II (1993–2007), and the Health Professionals Follow-up Study (1986–2008)

n-6 PUFA Type and Quartile of Intake	No. of Cases	Person-Years of Follow-up	Age-Adjusted[b]		Multivariable Model 1[c]		Multivariable Model 2[d]	
			RR	95% CI	RR	95% CI	RR	95% CI
Linoleic acid								
Quartile 1	89	880,518	1	Reference	1	Reference	1	Reference
Quartile 2	76	876,438	0.87	0.64, 1.19	1.04	0.76, 1.42	1.05	0.75, 1.47
Quartile 3	69	874,580	0.79	0.57, 1.08	0.94	0.68, 1.30	0.95	0.66, 1.38
Quartile 4	53	880,231	0.58	0.41, 0.83	0.67	0.47, 0.95	0.68	0.43, 1.07
P for trend				0.001		0.02		0.09
Per increment[e]			0.63	0.49, 0.81	0.72	0.56, 0.91	0.67	0.48, 0.95
Arachidonic acid								
Quartile 1	65	862,479	1	Reference	1	Reference	1	Reference
Quartile 2	78	900,095	1.08	0.77, 1.51	1.17	0.84, 1.64	1.14	0.81, 1.61
Quartile 3	59	854,726	0.93	0.65, 1.34	1.00	0.70, 1.44	0.95	0.65, 1.37
Quartile 4	85	894,467	1.28	0.92, 1.78	1.28	0.92, 1.79	1.19	0.83, 1.71
P for trend				0.19		0.25		0.54
Per increment[e]			1.25	1.02, 1.53	1.20	0.99, 1.47	1.15	0.92, 1.44
Total n-6 PUFAs[f]								
Quartile 1	81	877,501	1	Reference	1	Reference	1	Reference
Quartile 2	82	877,289	1.03	0.75, 1.40	1.24	0.90, 1.70	1.31	0.94, 1.83
Quartile 3	66	878,261	0.82	0.59, 1.15	1.01	0.72, 1.41	1.07	0.73, 1.56
Quartile 4	58	878,716	0.70	0.50, 0.99	0.84	0.59, 1.19	0.91	0.58, 1.43
P for trend				0.02		0.17		0.49
Per increment[e]			0.70	0.56, 0.88	0.80	0.64, 1.00	0.76	0.56, 1.03

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acid; RR, relative risk.

[a] Results from the cohort-specific regression models were combined using random-effects meta-analysis (for cohort-specific estimates, see Web Table 3).

[b] Adjusted for age (continuous) and time interval.

[c] Further adjusted for smoking status (never smoker, former smoker, current smoker of 1–14 cigarettes/day, current smoker of 15–24 cigarettes/day, or current smoker of ≥25 cigarettes/day), body mass index (weight (kg)/height $(m)^2$; <25, 25–29.9, or ≥30), alcohol consumption (g/day), marital status (married/partnered, widowed, or separated/divorced/single), physical activity (metabolic equivalents/week, in quintiles), and consumption of caffeinated coffee (cups/day). For women, the multivariable regression model further adjusted for menopausal status and use of hormone replacement therapy (postmenopausal with or without hormone replacement therapy, premenopausal, or never use of hormone replacement therapy).

[d] Further adjusted for cumulative average intake of energy (kcal/day), *trans* fatty acids (g/day), saturated fatty acids (g/day), and monounsaturated fatty acids (g/day) (all continuous variables). For linoleic acid, multivariable model 2 further adjusted for arachidonic acid and total n-3 PUFAs (both continuous). For arachidonic acid, multivariable model 2 further adjusted for linoleic acid and total n-3 PUFAs (both continuous). For total n-6 PUFAs, multivariable model 2 further adjusted for total n-3 PUFAs (continuous).

[e] The per-increment scale was 5 g/day for linoleic acid, 0.1 g/day for arachidonic acid, and 5 g/day for total n-6 PUFAs.

[f] Total n-6 PUFAs = linoleic acid + arachidonic acid.

for the pooled estimates of fish intake. When disaggregated by cohort, greater fish intake was associated with a higher risk of suicide mortality among women in the NHS cohort and lower risks of suicide mortality among women in the NHS2 cohort and among men in the HPFS cohort, but these estimates were not statistically significant (Web Table 4).

Further adjustment for severity of depression symptoms (NHS2 only) and self-reported use of minor tranquilizers, antidepressant medications, and fish oil and/or cod liver oil supplements did not yield any substantive changes in the point estimates (Web Tables 2–4), nor did inclusion of study participants with histories of serious cardiovascular disease or cancer (Web Table 5).

Table 3. Pooled[a] Relative Risk of Suicide Mortality According to Category of Fish Intake for Participants in the Nurses' Health Study (1986–2008), Nurses' Health Study II (1993–2007), and the Health Professionals Follow-up Study (1986–2008)

Fish Intake, Servings/Week	No. of Cases	Person-Years of Follow-up	Age-Adjusted[b]		Multivariable Model 1[c]	
			RR	95% CI	RR	95% CI
<1	57	827,311	1	Reference	1	Reference
1–1.9	109	1,351,974	1.06	0.76, 1.47	1.14	0.82, 1.58
2–2.9	59	730,667	0.94	0.65, 1.36	1.02	0.70, 1.49
≥3	62	601,814	0.95	0.65, 1.38	1.00	0.69, 1.47
P for trend			0.90		0.80	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Results from the cohort-specific regression models were combined using random-effects meta-analysis (for cohort-specific estimates, see Web Table 4).

[b] Adjusted for age (years; continuous variable) and time interval.

[c] Further adjusted for smoking status (never smoker, former smoker, current smoker of 1–14 cigarettes/day, current smoker of 15–24 cigarettes/day, or current smoker of ≥25 cigarettes/day), body mass index (weight (kg)/height $(m)^2$; <25, 25–29.9, or ≥30), alcohol consumption (g/day), marital status (married/partnered, widowed, or separated/divorced/single), physical activity (metabolic equivalents/week, in quintiles), and consumption of caffeinated coffee (cups/day). For women, the multivariable regression model further adjusted for menopausal status and use of hormone replacement therapy (postmenopausal with or without hormone replacement therapy, premenopausal, or never use of hormone replacement therapy).

DISCUSSION

Using data from 205,357 US men and women followed for a period of 14–22 years, we did not find evidence that intake of n-3 PUFAs or fish lowered the risk of completed suicide. Moreover, depending on the specification, EPA + DHA intake and total n-3 PUFA intake were associated with *higher*, but not statistically significant, risks of suicide mortality. We also found no evidence that intake of n-6 PUFAs raised the risk of completed suicide. These estimates were robust to both linear and nonlinear specifications of the exposure variables, as well as alternative configurations of potentially confounding variables.

Our finding that n-3 PUFA intake, specifically EPA + DHA intake, did not exert a protective influence against completed suicide is consistent with the null findings of 2 of the 3 previously published cohort studies that have examined the relationship between n-3 PUFA intake and suicide risk (9, 21). Although we cannot exclude the possibility of a small benefit of n-3 PUFA intake, the lower confidence limit of the pooled relative risk for total n-3 PUFA intake was very close to 1. Thus, we find it unlikely that n-3 PUFA and/or fish intake exerted protective effects against suicide that were large in magnitude.

How can these null findings on completed suicide be reconciled with previous studies linking n-3 PUFA and/or fish intake to depression? Two explanations are possible. First, n-3 PUFA intake may not, contrary to popular belief, reduce levels of depressive symptoms. In addition to the mixed evidence from observational studies reviewed in the Introduction, Bloch and Hannestad (13) summarized the findings of 13 randomized, double-blind, placebo-controlled trials and concluded that n-3 PUFA supplementation had neither a statistically significant nor a clinically significant impact on depression symptom severity. Small changes in the criteria for inclusion of studies suggested that the impact of n-3 PUFA supplementation on depression symptom severity was, at best, statistically significant but small in magnitude (52). A second possible explanation for the divergence in findings between our study and some of the other studies in the literature is that, even if low n-3 PUFA intake is linked to depression, this may not be sufficient to increase the risk of suicide. Major depressive disorder is predictive of suicidal ideation but, conditional on suicidal ideation, is not predictive of suicide attempts (53). Other important determinative factors include hopelessness (54–56), social integration (57–59), the acquired capability for suicide (60, 61), and impulsivity (62).

A significant limitation of this study is that we had a limited ability to adjust for unobserved depressive disorders or subthreshold differences in mood. However, adjustment for self-reported use of minor tranquilizers and antidepressant medications reduced the statistical significance of the tests for trend in 8 out of 12 regression models for n-3 PUFA and fish intake (Web Tables 2 and 4) and increased the statistical significance in 6 of 9 regression models for n-6 PUFA intake (Web Table 3). These patterns are the opposite of what would have been expected if unobserved differences in depression were driving the null results. Use of antidepressant medication is known to be an imperfect proxy for depressive disorders given the twin problems of underuse (i.e., persons diagnosed with depressive disorders failing to receive recommended care (63, 64)) and overuse (i.e., persons treated with antidepressant medications lacking diagnoses of depressive disorders or alternative indications for use (65, 66)) of antidepressant medications, as well as the increasing use of minimally effective antipsychotic medications in the treatment of depressive disorders (67–69). A direct measure of depression symptom severity (the 5-item Mental Health Inventory) was available from study inception onward only in NHS2, but inclusion of this variable in the regression models did

not yield strong evidence that failure to adjust for depression symptom severity in the HPFS and NHS could explain the null findings. These largely reassuring analytic results may be attributed to the relative homogeneity of the cohorts, since all 3 data sets consisted of generally healthy men and women. Moreover, participants in the NHS, NHS2, and HPFS cohort studies were not enrolled until after completing the extended, rigorous, and frequently stressful training required for entry into their respective professions, at ages exceeding the typical age of onset for severe mood disorders (70) that would have likely interfered with completion of training.

A second important limitation is that our study excluded persons younger than 29 years of age. Substantial developmental transformations are observed during adolescence and early young adulthood (71, 72). Given the hypothesized effects of n-3 PUFA intake on neuronal function and plasticity, it is possible that a sizeable protective effect of n-3 PUFA and/or fish intake could have been observed in a study focused on younger persons.

A third limitation is that the levels of long-chain n-3 PUFA intake observed in our sample were not comparable to the dosages employed in randomized controlled trials of n-3 PUFA supplementation to treat depressed mood. Across the 3 cohorts we studied, median EPA + DHA consumption among participants in the uppermost quartile of intake ranged from 0.34 g/day to 0.51 g/day, and the 95th percentile of daily intake ranged from 0.46 g/day to 0.82 g/day. In contrast, most randomized trials have employed preparations with EPA + DHA dosages exceeding 1 g/day (11–13, 52, 73–76). Yet even in the cohort study by Sanchez-Villegas et al. (6), there was no statistically significant reduction in the incidence of self-reported mental disorder among participants in the uppermost quintile of long-chain n-3 PUFA intake—despite the median intake being 1.89 g/day (a level achievable with a daily intake of 43 ounces (1,219 g) of Atlantic cod or 4.7 ounces (133 g) of sockeye salmon). We attempted to fit regression models exploring the relative risk of completed suicide at greater levels of EPA + DHA intake (e.g., ≥0.5 g/day), but small cell sizes undermined our confidence in the robustness of those estimates. Importantly, further adjustment for self-reported use of fish oil and/or cod liver oil supplements did not substantively change our findings.

In summary, our analysis of long-term follow-up data from more than 200,000 men and women enrolled in 3 large cohort studies does not provide evidence to support the hypothesis that greater intake of n-3 PUFAs or fish is associated with a lowered risk of completed suicide. Neither does our study provide evidence to support the hypothesis that greater intake of n-6 PUFAs is associated with a higher risk of completed suicide. Potential associations beyond the range of usual dietary intakes could not be excluded.

ACKNOWLEDGMENTS

Author affiliations: Chester M. Pierce, MD Division of Global Psychiatry, Massachusetts General Hospital, Boston, Massachusetts (Alexander C. Tsai); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (Alexander C. Tsai, Olivia I. Okereke); Center for Global Health, Massachusetts General Hospital, Boston, Massachusetts (Alexander C. Tsai); Mbarara University of Science and Technology, Mbarara, Uganda (Alexander C. Tsai); Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts (Michel Lucas, Éilis J. O'Reilly, Fariba Mirzaei, Alberto Ascherio, Walter C. Willett); Department of Social and Preventive Medicine, Laval University, Québec, Canada (Michel Lucas); Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Olivia I. Okereke, Éilis J. O'Reilly, Ichiro Kawachi, Alberto Ascherio, Walter C. Willett); Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts (Olivia I. Okereke, Alberto Ascherio, Walter C. Willett); Department of Psychiatry, Brigham and Women's Hospital, Boston, Massachusetts (Olivia I. Okereke); and Department of Social and Behavioral Sciences, Harvard School of Public Health, Boston, Massachusetts (Ichiro Kawachi).

A.C.T. and M.L. contributed equally to this work.

Follow-up of the cohorts whose data were included in this study was supported by the National Cancer Institute (National Institutes of Health (NIH) grants P01CA087969, U19CA055075, and R01CA050385). Several authors received salary support from the National Institute of Mental Health (NIH grants K23MH096620 to A.C.T. and R01MH091448 to O.I.O.) and the National Institute of Neurological Disorders and Stroke (NIH grant R01NS061858 to A.A.).

We thank our colleagues in the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (Boston, Massachusetts), for their assistance with the data from the 3 cohort studies and for reviewing the analysis protocol, findings, statistical code, and manuscript.

The views expressed in this paper are those of the authors and not necessarily those of any funding body or other persons whose support is acknowledged. The funders played no role in the study design, data collection and analysis, the decision to publish, or preparation of the manuscript. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: none declared.

REFERENCES

1. Hegarty BD, Parker GB. Marine omega-3 fatty acids and mood disorders—linking the sea and the soul. 'Food for Thought' I. *Acta Psychiatr Scand*. 2011;124(1):42–51.
2. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*. 2006;67(12):1954–1967.
3. Hibbeln JR. Re: "Fish consumption and major depression" [letter]. *Lancet*. 1998;351(9110):1213.
4. Tanskanen A, Hibbeln JR, Hintikka J, et al. Re: "Fish consumption, depression, and suicidality in a general population" [letter]. *Arch Gen Psychiatry*. 2001;58(5):512–513.

5. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol Psychiatry*. 2010;68(2):140–147.
6. Sanchez-Villegas A, Henríquez P, Figueiras A, et al. Long chain omega-3 fatty acids intake, fish consumption and mental disorders in the SUN cohort study. *Eur J Nutr*. 2007;46(6): 337–346.
7. Colangelo LA, He K, Whooley MA, et al. Higher dietary intake of long-chain omega-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women. *Nutrition*. 2009;25(10):1011–1019.
8. Li Y, Dai Q, Ekperi LI, et al. Fish consumption and severely depressed mood, findings from the first national nutrition follow-up study. *Psychiatry Res*. 2011;190(1):103–109.
9. Hakkarainen R, Partonen T, Haukka J, et al. Is low dietary intake of omega-3 fatty acids associated with depression? *Am J Psychiatry*. 2004;161(3):567–569.
10. Lucas M, Mirzaei F, O'Reilly EJ, et al. Dietary intake of n-3 and n-6 fatty acids and the risk of clinical depression in women: a 10-y prospective follow-up study. *Am J Clin Nutr*. 2011;93(6): 1337–1343.
11. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J Am Coll Nutr*. 2009;28(5): 525–542.
12. Appleton KM, Rogers PJ, Ness AR. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *Am J Clin Nutr*. 2010;91(3):757–770.
13. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol Psychiatry*. 2012;17(12):1272–1282.
14. Perlis RH. Hard outcomes: clinical trials to reduce suicide [editorial]. *Am J Psychiatry*. 2011;168(10):1009–1011.
15. Rose G. Strategy of prevention: lessons from cardiovascular disease. *Br Med J (Clin Res Ed)*. 1981;282(6279):1847–1851.
16. Rose G. Sick individuals and sick populations. *Int J Epidemiol*. 1985;14(1):32–38.
17. Heron M. Deaths: leading causes for 2008. *Natl Vital Stat Rep*. 2012;60(6):1–94.
18. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095–2128.
19. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Arterioscler Thromb Vasc Biol*. 2003;23(2):e20–e30.
20. Hirayama T. *Lifestyle and Mortality: A Large-Scale Census-Based Cohort Study in Japan.* (Contributions to Epidemiology and Biostatistics, vol. 6). New York, NY: S. Karger AG; 1990.
21. Poudel-Tandukar K, Nanri A, Iwasaki M, et al. Long chain n-3 fatty acids intake, fish consumption and suicide in a cohort of Japanese men and women—the Japan Public Health Center-based (JPHC) prospective study. *J Affect Disord*. 2011; 129(1–3):282–288.
22. Simopoulos AP. The importance of the ratio of omega-6/ omega-3 essential fatty acids. *Biomed Pharmacother*. 2002; 56(8):365–379.
23. Farooqui AA, Horrocks LA, Farooqui T. Modulation of inflammation in brain: a matter of fat. *J Neurochem*. 2007; 101(3):577–599.
24. Sprecher H. An update on the pathways of polyunsaturated fatty acid metabolism. *Curr Opin Clin Nutr Metab Care*. 1999;2(2): 135–138.
25. Calder PC. n-3 Polyunsaturated fatty acids, inflammation, and inflammatory diseases. *Am J Clin Nutr*. 2006;83(6 suppl): 1505S–1519S.
26. Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med*. 1985;313(17):1044–1049.
27. Hennekens CH, Speizer FE, Rosner B, et al. Use of permanent hair dyes and cancer among registered nurses. *Lancet*. 1979; 313(8131):1390–1393.
28. Grobbee DE, Rimm EB, Giovannucci E, et al. Coffee, caffeine, and cardiovascular disease in men. *N Engl J Med*. 1990; 323(15):1026–1032.
29. Grodstein F, Colditz GA, Hunter DJ, et al. A prospective study of symptomatic gallstones in women: relation with oral contraceptives and other risk factors. *Obstet Gynecol*. 1994; 84(2):207–214.
30. Larsen KK, Agerbo E, Christensen B, et al. Myocardial infarction and risk of suicide: a population-based case-control study. *Circulation*. 2010;122(23):2388–2393.
31. Stenager EN, Madsen C, Stenager E, et al. Suicide in patients with stroke: epidemiological study. *BMJ*. 1998;316(7139): 1206–1210.
32. Fang F, Fall K, Mittleman MA, et al. Suicide and cardiovascular death after a cancer diagnosis. *N Engl J Med*. 2012;366(14): 1310–1318.
33. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122(1):51–65.
34. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med*. 1997;337(21):1491–1499.
35. Feskanich D, Rimm EB, Giovannucci EL, et al. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. *J Am Diet Assoc*. 1993;93(7):790–796.
36. Iso H, Rexrode KM, Stampfer MJ, et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. *JAMA*. 2001; 285(3):304–312.
37. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124(1):17–27.
38. Raper NR, Cronin FJ, Exler J. Omega-3 fatty acid content of the US food supply. *J Am Coll Nutr*. 1992;11(3):304–308.
39. Consumer and Food Economics Institute. *Composition of Foods: Raw, Processed, and Prepared*. (US Department of Agriculture handbook no. 8). Washington, DC: US GPO; 1989.
40. Garland M, Sacks FM, Colditz GA, et al. The relation between dietary intake and adipose tissue composition of selected fatty acids in US women. *Am J Clin Nutr*. 1998;67(1):25–30.
41. Hu FB, Stampfer MJ, Manson JE, et al. Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. *Am J Clin Nutr*. 1999;69(5):890–897.
42. Sun Q, Ma J, Campos H, et al. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. *Am J Clin Nutr*. 2007;86(1):74–81.
43. Hunter DJ, Rimm EB, Sacks FM, et al. Comparison of measures of fatty acid intake by subcutaneous fat aspirate, food frequency questionnaire, and diet records in a free-living population of US men. *Am J Epidemiol*. 1992;135(4): 418–427.
44. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA*. 2002;287(14):1815–1821.
45. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001; 345(11):790–797.

46. Cho E, Hung S, Willett WC, et al. Prospective study of dietary fat and the risk of age-related macular degeneration. *Am J Clin Nutr*. 2001;73(2):209–218.
47. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol*. 1984;119(5):837–839.
48. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol*. 1994;140(11):1016–1019.
49. Cox DR, Oakes D. *Analysis of Survival Data*. London, United Kingdom: Chapman & Hall Ltd.; 1984.
50. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. *Am J Epidemiol*. 1999;149(6):531–540.
51. Stewart AL, Hays RD, Ware JE Jr. The MOS Short-Form general health survey. Reliability and validity in a patient population. *Med Care*. 1988;26(7):724–735.
52. Bloch MH, Hannestad J. Response to critiques on 'Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis' [letter]. *Mol Psychiatry*. 2012;17(12):1163–1167.
53. Nock MK, Hwang I, Sampson NA, et al. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;15(8):868–876.
54. Minkoff K, Bergman E, Beck AT, et al. Hopelessness, depression, and attempted suicide. *Am J Psychiatry*. 1973;130(4):455–459.
55. Beck AT, Steer RA, Kovacs M, et al. Hopelessness and eventual suicide: a 10-year prospective study of patients hospitalized with suicidal ideation. *Am J Psychiatry*. 1985;142(5):559–563.
56. Beck AT, Brown G, Berchick RJ, et al. Relationship between hopelessness and ultimate suicide: a replication with psychiatric outpatients. *Am J Psychiatry*. 1990;147(2):190–195.
57. Durkheim E. *Le Suicide: Etude de Sociologie*. 2nd ed. (1st ed., 1897). Paris, France: Presses Universitaires de France; 1967.
58. Naroll R. Cultural determinants and the concept of the sick society. In: Plog SC, Edgerton RB, eds. *Changing Perspectives in Mental Illness*. New York, NY: Holt, Rinehart & Winston Publishing; 1969:128–155.
59. Bearman PS. The social structure of suicide. *Sociol Forum*. 1991;6(3):501–524.
60. Joiner T. *Why People Die by Suicide*. Cambridge, MA: Harvard University Press; 2005.
61. Van Orden KA, Witte TK, Cukrowicz KC, et al. The interpersonal theory of suicide. *Psychol Rev*. 2010;117(2):575–600.
62. Mann JJ. The neurobiology of suicide. *Nat Med*. 1998;4(1):25–30.
63. Wells KB, Schoenbaum M, Unützer J, et al. Quality of care for primary care patients with depression in managed care. *Arch Fam Med*. 1999;8(6):529–536.
64. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348(26):2635–2645.
65. Larson MJ, Miller K, Fleming KJ. Treatment with antidepressant medications in private health plans. *Adm Policy Ment Health*. 2007;34(2):116–126.
66. Pagura J, Katz LY, Mojtabai R, et al. Antidepressant use in the absence of common mental disorders in the general population. *J Clin Psychiatry*. 2011;72(4):494–501.
67. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry*. 2009;66(8):848–856.
68. Olfson M, Blanco C, Liu SM, et al. National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Arch Gen Psychiatry*. 2012;69(12):1247–1256.
69. Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med*. 2013;10(3):e1001403.
70. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593–602.
71. Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 1999;2(10):861–863.
72. Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*. 2000;24(4):417–463.
73. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry*. 2007;68(7):1056–1061.
74. Sublette ME, Ellis SP, Geant AL, et al. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. *J Clin Psychiatry*. 2011;72(12):1577–1584.
75. Martins JG, Bentsen H, Puri BK. Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: a critique of Bloch and Hannestad and updated meta-analysis. *Mol Psychiatry*. 2012;17(12):1144–1149.
76. Lin PY, Mischoulon D, Freeman MP, et al. Re: "Are omega-3 fatty acids antidepressants or just mood-improving agents? The effect depends upon diagnosis, supplement preparation, and severity of depression" [letter]. *Mol Psychiatry*. 2012;17(12):1161–1163.