# Fish intake and risk of chronic obstructive pulmonary disease in 2 large US cohorts[1–4]

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**ABSTRACT**

**Background:** Despite mechanistic data that linked fish and omega-3 (n–3) PUFAs with lower risk of chronic obstructive pulmonary disease (COPD), epidemiologic data remain scarce. Fish and n–3 PUFAs are an important component of the prudent dietary pattern that is thought to be protective in the onset of COPD.

**Objective:** We examined the role of fish and PUFA intakes on risk of developing COPD while taking into account the overall dietary pattern.

**Design:** We investigated the objective in 120,175 women and men from the Nurses' Health Study and Health Professionals Follow-Up Study. Over the study period (1984–2000), there were 889 cases of newly diagnosed COPD. Cumulative average intakes of fish, eicosapentaenoic acid, docosahexaenoic acid, n–3 PUFAs, n–6 PUFAs, and the n–3:n–6 ratio were calculated from repeated food-frequency questionnaires. Because fish is a food group included in the prudent pattern, we derived a new prudent pattern without the contribution from fish, and we termed this pattern the "modified prudent" pattern. We performed multivariable Cox proportional hazards models.

**Results:** Before the dietary pattern was taken into account, and with 14 factors controlled for, we showed that more-frequent fish intake (≥4 servings/wk) was inversely associated with risk of COPD [adjusted pooled HR for the highest intake compared with the lowest intake (<1 serving/wk): 0.71; 95% CI: 0.54, 0.94]. After additional adjustment for the dietary pattern (modified prudent and Western patterns), the association was NS (0.84; 95% CI: 0.63, 1.13). No significant associations were shown between PUFA intakes and risk of COPD.

**Conclusion:** Although COPD-prevention efforts should continue to focus on smoking cessation, these prospective findings support the importance of promoting a healthy diet in multi-interventional programs to prevent COPD instead of focusing on changes in an isolated food or nutrient. *Am J Clin Nutr* 2015;101:354–61.

**Keywords** diet, epidemiology, respiratory diseases, fish, dietary patterns

## INTRODUCTION

In the 2010 Global Burden of Disease report, chronic obstructive pulmonary disease (COPD)[5] was the third most-common cause of death worldwide (1). The predominant risk factor for COPD in the developed world is cigarette smoking, but up to one-third of COPD patients have never smoked, suggesting that other factors are involved. Besides smoking cessation, relatively little attention has been paid to other interventions that might decrease risk of developing COPD. For example, there is longstanding interest in the balance between potentially toxic or inflammatory oxidants and antioxidant defenses, including those derived from the diet, and their potential role in COPD pathogenesis. On the basis of this prevailing hypothesis, most of the diet-lung research to date has focused on dietary factors (especially nutrients) with antioxidant or anti-inflammatory properties (2).

All of this nutrient-oriented research has failed, in some respects, to appreciate the complexity of dietary assessment. Because we eat meals instead of isolated nutrients or even foods, we have promoted "dietary patterns" to gain a broader picture of the diet (3). Of 5 studies that looked at the association between dietary patterns with spirometry or COPD symptoms or incidence (4–8), 3 studies reported a protective association for a "prudent" dietary pattern characterized by high intakes of fruit, vegetables, fish, and wholegrain cereals (4, 7, 8), consistent with the prevailing hypothesis. Fish and PUFAs, especially n–3 PUFAs, are an important component of the prudent dietary pattern. Fish oils are thought to have anti-inflammatory effects because of the influence of the n–3 PUFAs EPA and DHA on arachidonic

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[5] Abbreviations used: aHR, adjusted HR; ALA, $\alpha$-linolenic acid; COPD, chronic obstructive pulmonary disease; FFQ, food frequency questionnaire; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

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acid metabolism (9), and n–3 PUFA supplementation has biological effects of potential relevance to COPD of decreased systemic inflammation and altered leukotriene metabolism (10). Despite these appealing mechanistic data, epidemiologic data on the relations of fish and PUFA intakes to lung function or COPD symptoms remain scarce; most studies were cross-sectional and contradictory (11–22), and the only 2 longitudinal studies reported no association (23, 24). None of these studies accounted for the potential impact of the overall dietary pattern on the association between fish intake and COPD.

We hypothesized that differences in fish intakes would have an association with newly diagnosed COPD as part of a prudent dietary pattern. Thus, the objective of our study was to investigate relations of fish and PUFA intakes with risk of COPD before and after adjustment for the prudent dietary pattern in 2 large US cohorts.

## SUBJECTS AND METHODS

### Overview

The Nurses' Health Study (NHS) began in 1976, when 121,701 female nurses 30–55 y old who were living in 11 US states, responded to a mailed health questionnaire (25). The Health Professionals Follow-Up Study (HPFS) began in 1986 when 51,529 male US health professionals aged 40–75 y answered a detailed mailed questionnaire (26). In both cohorts, follow-up questionnaires were sent every 2 y thereafter. Participants also completed a food-frequency questionnaire (FFQ) in 1984 for the NHS and at baseline for the HPFS. Similar FFQs were sent every 2–4 y thereafter. An institutional review board approved the NHS and the HPFS protocols, and written consent was obtained from all subjects. The study was conducted according to the ethical guidelines of Brigham and Women's Hospital. After the exclusion of participants with missing or unreasonable information on diet (**Supplemental Materials and Methods**) or who reported a diagnosed asthma or COPD at baseline, the final baseline population included 73,228 women and 46,947 men (combined $n$ = 120,175).

### Dietary assessments

Dietary assessments are shown in the supplemental material. Dietary intake information was collected by using a semiquantitative FFQ designed to assess average food intake over the previous 12 mo. Dietary intakes were identified from each FFQ administrated in 1984, 1986, 1990, 1994, and 1998 in the NHS and in 1986, 1990, and 1994 in the HPFS. To better represent long-term dietary intake, and reduce measurement errors, cumulative averages of fish and fatty acid intakes were calculated.

With regard to fish, FFQs used in the NHS (in 1984, 1986, and 1990) and HPFS (in 1986, 1990 and 1994) included the following 4 items: *1*) dark-meat fish such as mackerel, salmon, sardines, bluefish, or swordfish (3–5 oz; 84–140 g); *2*) canned tuna (3–4 oz; 84–112 g); *3*) other fish (3–5 oz; 84–140 g); and *4*) shrimp, lobster, or scallops as a main dish. In the NHS, one fish item was added in the 1994 and 1998 FFQs [i.e., breaded fish cakes, pieces, or fish sticks (1 serving, store bought)]. We divided the cumulative average of fish into 3 categories as follows: $<$1, 1–3.9, and $\geq$4 servings/wk. The middle category is consistent with the US Dietary Guidelines recommendation of $\sim$2 fish servings/wk (27).

With regard to PUFAs (intake from foods and supplements), we calculated the long-chain n–3 fatty acids 20:5 (EPA) and 22:6 (DHA) described in detail elsewhere (28), n–3 PUFA intake (EPA, DHA, 22:5n–3 [docosapentaenoic acid], and 18:3 [$\alpha$-linolenic acid (ALA)]), n–6 PUFA intake [18:2 (linoleic acid) and 20:4 (arachidonic acid)], and the ratio n–6:n–3. Information on fish-oil supplement was specifically requested from the 1990 questionnaire onward in both cohorts. All nutrients were adjusted for total energy by using the residual method (29).

Previously, in these 2 cohorts, we reported a strong association between dietary patterns (prudent and Western) and risk of newly diagnosed COPD (7, 8). Because fish is a food group included in the prudent pattern, we redid dietary pattern analyses by not including fish as one of the variables in the model. We derived a new prudent pattern without a contribution from fish, and we termed this the "modified prudent" pattern.

### Assessment of respiratory phenotypes

Self-reported COPD was defined by the affirmative response to doctor-diagnosed chronic bronchitis or emphysema and report of a diagnostic test at diagnosis (i.e., pulmonary function testing, chest radiograph, or chest computed tomography) (supplemental material). We previously validated this epidemiologic definition by using a medical record review (30). Female nurses reported 723 cases of newly diagnosed COPD between 1984 and 2000, whereas male health professionals reported 166 cases between 1986 and 1998.

Adult-onset asthma also was self-reported and defined by a new doctor diagnosis of asthma plus the use of an asthma medication within the past 12 mo. We previously validated this epidemiologic outcome by using a medical record review (31). Female nurses reported 1742 incident cases of asthma between 1984 and 2000, whereas male health professionals reported 226 cases between 1986 and 1998.

### Statistical analysis

When possible, covariates were obtained from the baseline questionnaire, which was updated every 2 y and used as time-varying variables (supplemental material). Fish intake was analyzed by using the Cox proportional hazards model with 3 different adjustments as follows: *1*) a raw model adjusted only for age, smoking status, pack-years of smoking, and pack-years squared of smoking (model 1); *2*) a fully-adjusted model without dietary intake; i.e., model 1 further adjusted for secondhand tobacco exposure (only in the NHS), race-ethnicity, physician visits, US region, spouse's highest educational attainment (only in the NHS), menopausal status (only in the NHS), BMI, physical activity, multivitamin use, and total caloric intake (model 2); and *3*) a fully adjusted model with dietary patterns; i.e., model 2 further adjusted for modified prudent and Western patterns (model 3).

Because residual confounding by smoking remains an important possible bias in studies of diet and respiratory diseases, we further investigated the association in exsmokers and current smokers (the number of newly diagnosed COPD in never smokers was too small to conduct a meaningful analysis). In a sensitivity analysis, we excluded participants with previous comorbidities (cardiovascular diseases and cancer). To avoid the potential for preclinical COPD leading to reverse causation, we also performed lagged analyses by omitting cases from the initial 4 y of follow-up.

To evaluate whether the dietary intake of ALA, which is a n–3 PUFA present in some vegetable oils, walnuts, and some green vegetables, influences the association between fish intake and COPD, we also stratified our analysis according to the median of ALA intake. We tested this specific hypothesis to better understand how intake of PUFA from vegetables competes with that of fish (and long-chain fish oils), and therefore, models were not adjusted for the dietary pattern.

To address missing data, we added a missing category for each categorical variable and a dummy variable in the model for each continuous variable. A test for trend across categories of fish intake was calculated by treating categories as an ordinal variable in a proportional hazards model. After calculating sex-specific HRs, we combined the $\log_e$ HRs, which were weighted by the inverse of their variances, by using a random-effects model. We tested for between-study heterogeneity by using the $Q$ statistic, and we provided the $I^2$ index. Two-sided 95% CIs were calculated. All tests were 2 sided, with statistical significance set at $P < 0.05$ for comparisons. All analyses were conducted with SAS version 9.3 software (SAS Institute).

## RESULTS

Baseline characteristics of women and men according to fish intake are shown in **Table 1**. In both groups, participants with the highest intake of fish (≥ 4 servings/wk) were more likely to be exsmokers, live in New England, be physically active, and take multivitamin supplements than were participants with lowest fish intake (<1 serving/wk). As regards fish-oil supplementation, men were twice as likely as women to use this kind of supplementation. Women and men with high fish intakes also had higher intakes of fruit and vegetables, fiber, and vitamin D than did those who rarely consumed fish. With regard to fatty acids, <0.02% of DHA and EPA intakes came from supplements. The most-common food sources of these fatty acids were tuna, dark fish, and white fish; in the NHS, 31% of these fatty acids were from tuna, 24% of these fatty acids were from dark fish, and 24% of these fatty acids were from white fish, whereas in the HPFS, 41% of these fatty acids were from dark fish, 22% of these fatty acids were from white fish, and 19% of these fatty acids were from tuna.

### Fish intake and risk of COPD

In the pooled analysis, we showed that women and men who ate ≥4 servings fish/wk had lower risk of newly diagnosed COPD compared with that of participants who ate <1 serving fish/wk (**Table 2**). After additional adjustments (model 2), the association remained of similar magnitude and statistically significant. However, after taking into account the overall dietary pattern, the magnitude of the association was attenuated and became nonsignificant [the pooled adjusted HR (aHR) for highest compared with lowest intakes of fish was 0.84 (95% CI: 0.63, 1.13)]. The modified prudent pattern remained associated with risk of COPD after adjustment for fish intake both in women (aHR for highest compared with lowest scores of the modified prudent pattern: 0.78; 95% CI: 0.57, 1.05; $P$-trend = 0.04) and men (aHR: 0.81; 95% CI: 0.48, 1.37; $P$-trend = 0.09).

To examine whether smoking status modifies the relation between fish intake and risk of COPD, we restricted analyses to ever smokers (exsmokers and current smokers) (**Table 3**). After adjustment for potential confounders and dietary pattern, we still showed no association between fish intake and COPD either in exsmokers or current smokers. We examined whether sex modified the association between fish intake and risk of COPD (Table 2); after adjustment for potential confounders and dietary patterns, there was no association between fish intake and COPD either in women or men with no heterogeneity between studies ($P = 0.72$). In a sensitivity analysis that looked at a study population without cancer or cardiovascular disease at baseline ($n$ = 105,153 participants; 770 cases of newly diagnosed COPD), we reported similar associations (aHR: 0.95; 95% CI: 0.56, 1.63). We also performed lagged analyses with the exclusion of cases that occurred in the first 4 y ($n$ = 207), and again, we observed no significant association between fish intake and risk of COPD (aHR: 0.75; 95% CI: 0.53, 1.06). Finally, we stratified our analyses according to ALA intake (**Table 4**); in participants with lower intake of ALA, fish intake was not related to risk of COPD (aHR: 0.92; 95% CI: 0.62, 1.34), whereas in participants with higher intake of ALA, fish intake was negatively associated with risk of COPD (aHR: 0.55; 95% CI: 0.36, 0.83).

### Fatty acid intake and risk of COPD

After adjustments for potential confounders and dietary patterns, we showed no significant association between intakes of DHA and EPA, n–3 PUFAs, and n–6 PUFAs and the ratio n–6:n–3 with risk of newly diagnosed COPD (**Table 5**).

### Fish, fatty acids, and risk of adult-onset asthma

After adjustments for potential confounders and dietary patterns, no significant association was reported between fish intake and adult-onset asthma (aHR for high compared with low intake: 1.05; 95% CI: 0.89, 1.24) or intakes of EPA and DHA (aHR: 1.06; 95% CI: 0.92, 1.23).

## DISCUSSION

In a prospective cohort analysis of >120,000 US women and men, we showed, in initial analyses, that higher fish intake (≥4 servings/wk) was associated with lower risk of newly diagnosed COPD, independently of smoking and other known COPD risk factors. However, this lower risk was probably attributable to the overall dietary pattern in which the person ate higher amounts of fish. Intakes of fatty acids also were unrelated to COPD risk. Nevertheless, we could not totally rule out a small or modest independent effect of fish intake on COPD risk, especially for top-end intake.

Regarding the potential role of fish intake on COPD-related outcomes, a 1990 cross-sectional study of 9074 US adults reported that, after adjustment for other dietary factors (the dietary intake ratio of sodium:potassium, serum concentrations of vitamin C, and zinc:copper ratio), dietary fish intake was no longer associated with COPD symptoms (14). Soon after, 3 cross-sectional studies reported an inverse association between fish intake and COPD-related outcomes (11–13), but none of the studies adjusted for other dietary intakes. More recently, most cross-sectional studies reported no association (15, 16, 18), except in a study of Chinese older adults (17). An ecologic study performed across 7 countries but including only men reported an inverse

**TABLE 1**
Age-standardized baseline characteristics in women from the NHS ($n$ = 73,228) and men from the HPFS ($n$ = 46,947) according to fish intake[1]

| | Cumulative average of fish intake (servings/wk) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Women ($n$ = 73,228) | | | | Men ($n$ = 46,947) | | | |
| | <1 | 1–2.4 | 2.5–3.9 | ≥4 | <1 | 1–2.4 | 2.5–3.9 | ≥4 |
| Fish, servings/d | 0.1 ± 0.1[2] | 0.2 ± 0.1 | 0.4 ± 0.2 | 0.8 ± 0.4 | 0.1 ± 0.1 | 0.3 ± 0.1 | 0.6 ± 0.2 | 0.9 ± 0.4 |
| Age, y | 50.1 ± 7.4 | 50.2 ± 7.2 | 50.5 ± 7.0 | 50.9 ± 6.8 | 53.3 ± 9.9 | 53.7 ± 9.7 | 54.6 ± 9.6 | 55.3 ± 9.6 |
| Smoking status, % | | | | | | | | |
| Never smokers | 49.1 | 45.3 | 42.3 | 39.5 | 47.3 | 44.5 | 43.9 | 43.8 |
| Exsmokers | 26.6 | 31.4 | 36.0 | 39.2 | 38.4 | 41.8 | 44.2 | 45.3 |
| Current smokers | 24.0 | 23.1 | 21.5 | 21.0 | 10.6 | 9.9 | 7.9 | 6.4 |
| Missing | 0.3 | 0.2 | 0.2 | 0.3 | 3.7 | 3.8 | 4.0 | 4.5 |
| Pack-years in ever smokers | 22.9 ± 18.5 | 21.0 ± 17.2 | 19.9 ± 16.6 | 19.9 ± 16.8 | 26.1 ± 19.7 | 25.2 ± 18.9 | 24.0 ± 18.1 | 23.4 ± 18.1 |
| Exposure to secondhand smoke at work or home, % | 56.6 | 58.4 | 59.0 | 58.8 | — | — | — | — |
| White race-ethnicity, % | 98.0 | 98.0 | 97.4 | 96.7 | 91.1 | 91.1 | 90.8 | 89.7 |
| Physician examination, % | | | | | | | | |
| No physician visits | 12.1 | 10.7 | 9.4 | 8.5 | 20.4 | 18.6 | 15.5 | 13.4 |
| Screening visits | 58.4 | 63.0 | 64.0 | 64.0 | 44.1 | 50.4 | 53.5 | 54.2 |
| Symptom-related visits | 15.2 | 15.5 | 16.0 | 15.5 | 11.0 | 11.9 | 12.9 | 13.7 |
| Missing | 14.3 | 10.8 | 10.6 | 12.0 | 24.5 | 19.1 | 18.1 | 18.7 |
| US region, % | | | | | | | | |
| New England | 9.3 | 13.8 | 18.1 | 20.6 | 19.0 | 20.7 | 23.0 | 26.2 |
| Mid-Atlantic | 40.7 | 44.0 | 44.0 | 43.3 | 22.0 | 16.9 | 12.9 | 9.8 |
| East North Central | 25.5 | 19.4 | 15.4 | 14.3 | 19.7 | 20.6 | 20.5 | 19.0 |
| South Atlantic | 5.4 | 5.8 | 6.3 | 5.8 | 35.2 | 35.7 | 36.0 | 35.7 |
| West South Central | 5.5 | 4.9 | 4.2 | 3.6 | 0.2 | 0.2 | 0.2 | 0.2 |
| Pacific | 13.6 | 12.1 | 12.0 | 12.4 | 3.9 | 5.9 | 7.4 | 9.1 |
| Spouse's educational attainment, % | | | | | | | | |
| High school | 38.2 | 35.2 | 32.0 | 29.4 | — | — | — | — |
| College | 19.2 | 22.7 | 23.7 | 24.4 | — | — | — | — |
| Graduate school | 15.5 | 18.8 | 20.6 | 21.2 | — | — | — | — |
| Missing | 27.1 | 23.3 | 23.7 | 25.0 | — | — | — | — |
| Menopausal status, % | | | | | | | | |
| Premenopause | 45.9 | 45.9 | 44.2 | 41.2 | — | — | — | — |
| Postmenopause and never HRT use | 24.3 | 24.3 | 24.9 | 25.9 | — | — | — | — |
| Postmenopause and past user for HRT | 10.5 | 10.6 | 11.2 | 12.1 | — | — | — | — |
| Postmenopause and estrogen replacement therapy | 8.8 | 8.6 | 8.8 | 9.2 | — | — | — | — |
| Postmenopause and estrogen-progesterone replacement therapy | 0.7 | 0.8 | 0.9 | 0.9 | — | — | — | — |
| Missing | 9.8 | 9.8 | 10.0 | 10.7 | — | — | — | — |
| BMI, kg/m$^2$ | 24.8 ± 4.7 | 24.8 ± 4.6 | 25.2 ± 4.7 | 25.6 ± 4.7 | 24.9 ± 5.1 | 25.0 ± 4.9 | 24.9 ± 5.0 | 24.8 ± 5.2 |
| BMI (kg/m$^2$), % | | | | | | | | |
| <20.0 | 8.6 | 7.9 | 6.0 | 5.1 | 3.9 | 3.4 | 3.5 | 3.7 |
| 20.0–24.9 | 51.2 | 51.6 | 48.8 | 46.5 | 42.9 | 43.4 | 44.8 | 46.8 |
| 25.0–29.9 | 23.6 | 24.2 | 27.1 | 28.9 | 45.1 | 45.2 | 44.1 | 42.1 |
| ≥30.0 | 11.7 | 11.4 | 13.1 | 14.3 | 8.1 | 8.0 | 7.6 | 7.4 |
| Missing | 4.9 | 4.9 | 5.0 | 5.1 | 0.0 | 0.0 | 0.0 | 0.0 |
| Physical activity, METs/wk | 11.4 ± 19.3 | 13.4 ± 19.4 | 16.6 ± 23.6 | 19.3 ± 25.1 | 18.2 ± 28.8 | 20.6 ± 28.9 | 23.3 ± 30.3 | 25.5 ± 30.8 |
| Supplement user (any type), % | 33.4 | 36.1 | 38.7 | 42.6 | 59.0 | 62.1 | 64.4 | 65.6 |
| Supplement user (fish oil),[3] % | 1.4 | 1.7 | 2.1 | 2.9 | 2.7 | 3.5 | 4.6 | 5.8 |
| Total energy, kcal/d | 1605 ± 514 | 1736 ± 515 | 1815 ± 535 | 1880 ± 548 | 1876 ± 601 | 1978 ± 607 | 2046 ± 620 | 2153 ± 647 |
| Food and nutrient consumption | | | | | | | | |
| Fruit, servings/d | 1.2 ± 1.0 | 1.3 ± 1.0 | 1.6 ± 1.1 | 1.9 ± 1.3 | 1.3 ± 1.2 | 1.5 ± 1.2 | 1.8 ± 1.4 | 2.1 ± 1.6 |
| Vegetables, servings/d | 2.5 ± 1.5 | 3.1 ± 1.6 | 3.7 ± 1.9 | 4.5 ± 2.4 | 2.4 ± 1.5 | 2.8 ± 1.6 | 3.3 ± 1.8 | 3.9 ± 2.2 |
| Cured meat, servings/d | 0.3 ± 0.4 | 0.3 ± 0.3 | 0.3 ± 0.3 | 0.2 ± 0.3 | 0.4 ± 0.5 | 0.4 ± 0.4 | 0.3 ± 0.4 | 0.3 ± 0.3 |
| DHA and EPA, g/d | 0.1 ± 0.0 | 0.2 ± 0.1 | 0.3 ± 0.1 | 0.4 ± 0.2 | 0.1 ± 0.1 | 0.3 ± 0.1 | 0.4 ± 0.2 | 0.7 ± 0.4 |
| n–3 PUFAs,[4] g/d | 1.2 ± 0.4 | 1.3 ± 0.4 | 1.4 ± 0.4 | 1.6 ± 0.4 | 1.2 ± 0.4 | 1.4 ± 0.4 | 1.5 ± 0.4 | 1.8 ± 0.5 |
| n–6 PUFAs,[5] g/d | 10.5 ± 3.3 | 10.3 ± 3.0 | 10.3 ± 3.1 | 10.1 ± 3.1 | 11.9 ± 3.8 | 11.7 ± 3.4 | 11.5 ± 3.4 | 11.2 ± 3.5 |
| Ratio of n–6:n–3 | 8.7 ± 2.1 | 7.9 ± 1.6 | 7.2 ± 1.6 | 6.3 ± 1.6 | 10.2 ± 3.1 | 8.7 ± 2.5 | 7.6 ± 2.2 | 6.4 ± 2.1 |
| $\alpha$-Linolenic acid, g/d | 1.0 ± 0.3 | 1.0 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.4 | 1.1 ± 0.4 |

[1]HPFS, Health Professionals Follow-Up Study; HRT, hormone replacement therapy; MET, metabolic equivalent task; NHS, Nurses' Health Study.
[2]Age-adjusted mean ± SD (all such values except for age).
[3]Use of fish-oil supplementation in 1990 (first questionnaire with this information).
[4]n–3 PUFAs include EPA, DHA, 22:5n–3 (docosapentaenoic acid), and 18:3 ($\alpha$-linolenic acid).
[5]n–6 PUFAs include 18:2 (linoleic acid) and 20:4 (arachidonic acid).

**TABLE 2**
Prospective association between the cumulative average of fish intake and risk of newly diagnosed chronic obstructive pulmonary disease[1]

| | Women | | | Men | | | Total | |
|---|---|---|---|---|---|---|---|---|
| Fish intake | *n* | Person-years | aHR (95% CI) | *n* | Person-years | aHR (95% CI) | *n* | aHR (95% CI) |
| Model 1 (servings/wk) | | | | | | | | |
| <1 | 177 | 255,555 | 1.00 (referent) | 50 | 150,705 | 1.00 (referent) | 227 | 1.00 (referent) |
| 1–2.4 | 357 | 522,397 | 1.05 (0.88, 1.26) | 77 | 211,576 | 1.15 (0.80, 1.64 | 434 | 1.07 (0.91, 1.26) |
| 2.5–3.9 | 136 | 227,678 | 1.00 (0.80, 1.25) | 24 | 88,522 | 0.93 (0.57, 1.51) | 160 | 0.98 (0.80, 1.21) |
| ≥4 | 53 | 131,469 | 0.65 (0.48, 0.88) | 15 | 70,029 | 0.84 (0.47, 1.51) | 68 | 0.69 (0.52, 0.90) |
| *P* | — | — | — | — | — | — | — | 0.44 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |
| Model 2 (servings/wk) | | | | | | | | |
| <1 | 177 | 255,555 | 1.00 (referent) | 50 | 150,705 | 1.00 (referent) | 227 | 1.00 (referent) |
| 1–2.4 | 357 | 522,397 | 1.06 (0.88, 1.27) | 77 | 211,576 | 1.02 (0.71,1.47) | 434 | 1.05 (0.89, 1.24) |
| 2.5–3.9 | 136 | 227,678 | 1.02 (0.81, 1.29) | 24 | 88,522 | 0.82 (0.50,1.35) | 160 | 0.98 (0.80, 1.21) |
| ≥4 | 53 | 131,469 | 0.71 (0.52, 0.98) | 15 | 70,029 | 0.71 (0.39,1.30) | 68 | 0.71 (0.54, 0.94) |
| *P* | — | — | — | — | — | — | — | 0.99 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |
| Model 3 (servings/wk) | | | | | | | | |
| <1 | 177 | 255,555 | 1.00 (referent) | 50 | 150,705 | 1.00 (referent) | 227 | 1.00 (referent) |
| 1–2.4 | 357 | 522,397 | 1.10 (0.91, 1.32) | 77 | 211,576 | 1.07 (0.74, 1.54) | 434 | 1.09 (0.92, 1.29) |
| 2.5–3.9 | 136 | 227,678 | 1.12 (0.88, 1.42) | 24 | 88,522 | 0.95 (0.57, 1.58) | 160 | 1.09 (0.87, 1.35) |
| ≥4 | 53 | 131,469 | 0.82 (0.59, 1.14) | 15 | 70,029 | 0.93 (0.50, 1.72) | 68 | 0.84 (0.63, 1.13) |
| *P* | — | — | — | — | — | — | — | 0.72 |
| $I^2$ | — | — | — | — | — | — | — | 0 |

[1]In model 1, multivariate HRs were adjusted for age, smoking status, pack-years of smoking, and pack-years squared of smoking. In model 2, multivariate HRs were adjusted as for model 1 and for secondhand tobacco exposure (only in the NHS), race-ethnicity, physician visit, US region, spouse's highest educational attainment (only in the NHS), menopausal status (only in the NHS), BMI, physical activity, multivitamin use, and energy intake. In model 3, multivariate HRs were adjusted as for model 2 and for modified prudent and Western dietary patterns. *P* values are a test for between-study heterogeneity (≥4 servings/wk compared with <1 serving/wk). $I^2$ is the degree of heterogeneity between studies expressed as a percentage of total variance (≥4 servings/wk compared with <1 serving/wk). aHR, adjusted HR; NHS, Nurses' Health Study.

association between 25-y COPD mortality and fish consumption at baseline (32). To our knowledge, only 2 longitudinal studies have been reported, and they showed no association of fish consumption with the 25-y incidence of COPD (24) and 20-y COPD mortality (23), which are findings consistent with our results.

Although the epidemiologic data on fish are underwhelming, n–3 PUFAs have known effects on several mechanistic pathways that may be relevant to COPD pathogenesis by stimulating the production of anti-inflammatory and proresolving mediators and diminishing oxidative stress (10). Despite this biologically plausible hypothesis, there has been a lack of consistency across observational studies. Of cross-sectional studies, some studies reported that n–3 PUFA dietary intakes were protective regarding COPD-related outcomes (11, 19, 20), whereas another study did not (21). Regarding n–6 PUFA dietary intakes, both positive (21) and negative (20) associations were reported. Besides these PUFA dietary intakes derived from a FFQ, 2 cross-sectional studies investigated blood PUFA concentrations and reported an inverse association between the DHA content of plasma lipid-component and COPD but showed no association with EPA (22) and a positive association between DHA in serum phospholipids and lung function (19). Finally, the only longitudinal study was conducted in 793 middle-aged Dutch men and showed no association between n–3 PUFAs and the 25-y incidence of COPD but a positive association with intake of linoleic acid (24). To our knowledge, only one randomized controlled trial has been published, and it showed a beneficial effect of PUFA supplementation on the response to exercise training in patients with COPD but no change in lung function (33). Three more randomized controlled trials are currently underway (34–36).

Dietary patterns might be seen as offering a more agnostic approach, whereas nutrients and foods could be seen as more of a hypothesis-driven, pathway-based approach. In our study, the association between fish intake and risk of newly diagnosed COPD was markedly attenuated after taking into account the modified prudent pattern, suggesting that the potential benefit of fish was linked to the benefit of the prudent dietary pattern. We also note that the modified prudent pattern remained strongly associated with risk of COPD after adjustment for fish intake. We also evaluated whether ALA intake influenced relations between fish intake and COPD risk. Our findings suggested that fish intake may reduce risk of COPD in women and men when intake of plant sources of n–3 PUFAs is high. This relation is consistent with our main result whereby a healthy diet (more fish but also more vegetables) is beneficial for COPD rather than isolated changes in any specific food or nutrient.

In the current study, we also showed that fish or PUFA intakes were completely unrelated to incident asthma. Over the past decade, it has been hypothesized that variations in asthma prevalence across populations and the increase in asthma burden seen in Westernized countries might be related to a combination of progressively higher intake of n–6 PUFA and lower intake of n–3 PUFA (37). The hypothesis that n–3 PUFA intake could improve prevalent asthma by reducing inflammation seems biologically plausible (38).

**TABLE 3**
Prospective association between the cumulative average of fish intake and risk of newly diagnosed chronic pulmonary disease in exsmokers and current smokers[1]

| | Women | | | Men | | | Total | |
|---|---|---|---|---|---|---|---|---|
| Fish intake (servings/wk) | *n* | Person-years | aHR (95% CI) | *n* | Person-years | aHR (95% CI) | *n* | aHR (95% CI) |
| Exsmokers | | | | | | | | |
| <1 | 39 | 82,091 | 1.00 (referent) | 24 | 53,373 | 1.00 (referent) | 63 | 1.00 (referent) |
| 1–2.4 | 82 | 198,738 | 0.89 (0.60, 1.32) | 31 | 86,546 | 0.78 (0.45, 1.35) | 103 | 0.85 (0.62, 1.17) |
| 2.5–3.9 | 43 | 98,273 | 1.03 (0.64, 1.64) | 10 | 38,510 | 0.62 (0.29, 1.35) | 53 | 0.88 (0.56, 1.39) |
| ≥4 | 18 | 60,936 | 0.71 (0.38, 1.30) | 8 | 31,305 | 0.74 (0.31, 1.79) | 26 | 0.72 (0.44, 1.19) |
| *P* | — | — | — | — | — | — | — | 0.93 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |
| Current smokers | | | | | | | | |
| <1 | 111 | 46,187 | 1.00 (referent) | 18 | 37,824 | 1.00 (referent) | 129 | 1.00 (referent) |
| 1–2.4 | 243 | 84,963 | 1.27 (1.01, 1.60) | 41 | 39,461 | 1.95 (1.10, 3.47) | 284 | 1.45 (0.98, 2.13) |
| 2.5–3.9 | 75 | 32,224 | 1.16 (0.85, 1.59) | 13 | 13,758 | 2.20 (1.03, 4.70) | 88 | 1.45 (0.80, 2.62) |
| ≥4 | 28 | 17,767 | 0.87 (0.55, 1.35) | 5 | 9724 | 1.37 (0.48, 3.94) | 33 | 0.93 (0.62, 1.40) |
| *P* | — | — | — | — | — | — | — | 0.43 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |

[1]Multivariate HRs were adjusted for age, pack-years of smoking, pack-years squared of smoking, secondhand tobacco exposure (only in the NHS), race-ethnicity, physician visit, US region, spouse's highest educational attainment (only in the NHS), menopausal status (only in the NHS), BMI, physical activity, multivitamin use, energy intake, and modified prudent and Western dietary patterns. *P* values are a test for between-study heterogeneity (≥4 servings/wk compared with <1 serving/wk). $I^2$ is the degree of heterogeneity between studies expressed as a percentage of total variance (≥4 servings/wk compared with <1 serving/wk). aHR, adjusted HR; NHS, Nurses' Health Study.

However, there has been a lack of consistency across studies in adults, and a recent meta-analysis on fish and fish-oil intakes and asthma also showed no association in adults (39).

Our study had a few potential limitations. First, newly diagnosed COPD was defined by a self-reported doctor diagnosis of COPD, and lung-function measures were not available for these large cohorts. Nevertheless, the questionnaire-based definition of COPD was validated in a subset of our unique cohorts (30). The impact of fish intake on COPD subphenotypes merits additional study, especially on emphysema because of biological differences between emphysema and airway diseases (40). The main source of disease misclassification probably was a misdiagnosis with asthma. It remains possible that women who ate a lot of fish and developed COPD were preferentially diagnosed as having adult-onset asthma, which was a potential bias that would have created the appearance of a fish-COPD benefit. However, the

**TABLE 4**
Prospective association between the cumulative average of fish intake and risk of newly diagnosed chronic pulmonary disease according to ALA intake[1]

| | Women | | | Men | | | Total | |
|---|---|---|---|---|---|---|---|---|
| Fish intake (servings/wk) | *n* | Person-years | aHR (95% CI) | *n* | Person-years | aHR (95% CI) | *n* | aHR (95% CI) |
| ALA intake less than the median | | | | | | | | |
| <1 | 90 | 135,987 | 1.00 (referent) | 29 | 76,506 | 1.00 (referent) | 119 | 1.00 (referent) |
| 1–2.4 | 171 | 266,056 | 1.09 (0.84, 1.42) | 43 | 104,943 | 1.03 (0.63, 1.66) | 214 | 1.08 (0.85, 1.35) |
| 2.5–3.9 | 56 | 108,624 | 1.03 (0.73, 1.46) | 11 | 44,137 | 0.72 (0.35, 1.47) | 67 | 0.96 (0.71, 1.32) |
| ≥4 | 27 | 58,166 | 0.94 (0.60, 1.47) | 10 | 35,068 | 0.84 (0.39, 1.79) | 37 | 0.92 (0.62, 1.34) |
| *P* | — | — | — | — | — | — | — | 0.79 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |
| ALA intake greater than or equal to the median | | | | | | | | |
| <1 | 87 | 119,568 | 1.00 (referent) | 21 | 74,199 | 1.00 (referent) | 108 | 1.00 (referent) |
| 1–2.4 | 186 | 256,341 | 1.02 (0.79, 1.33) | 34 | 106,634 | 1.03 (0.59, 1.81) | 220 | 1.02 (0.81, 1.30) |
| 2.5–3.9 | 80 | 119,054 | 1.00 (0.73, 1.37) | 13 | 44,385 | 0.99 (0.48, 2.03) | 93 | 1.00 (0.75, 1.33) |
| ≥4 | 26 | 73,303 | 0.55 (0.35, 0.86) | 5 | 34,961 | 0.54 (0.20, 1.47) | 31 | 0.55 (0.36, 0.83) |
| *P* | — | — | — | — | — | — | — | 0.97 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |

[1]Multivariate HRs were adjusted for age, smoking, pack-years of smoking, pack-years squared of smoking, secondhand tobacco exposure (only in the NHS), race-ethnicity, physician visit, US region, spouse's highest educational attainment (only in the NHS), menopausal status (only in the NHS), BMI, physical activity, multivitamin use, and energy intake. The median value for ALA intake was 1.02 g/d in women and 1.01 g/d in men. *P* values are a test for between-study heterogeneity (≥4 servings/wk compared with <1 serving/wk). $I^2$ is the degree of heterogeneity between studies expressed as a percentage of total variance (≥4 servings/wk compared with <1 serving/wk). The interaction between ALA and fish intakes was borderline significant in women ($P = 0.08$) and NS in men ($P = 0.33$). aHR, adjusted HR; ALA, α-linolenic acid; NHS, Nurses' Health Study.

**TABLE 5**
Association between the cumulative average of fatty acids (from foods and supplements) and newly diagnosed chronic obstructive pulmonary disease[1]

| | Women | | | Men | | | Total | |
|---|---|---|---|---|---|---|---|---|
| Fatty acid intake | *n* | Person-years | aHR (95% CI) | *n* | Person-years | aHR (95% CI) | *n* | aHR (95% CI) |
| EPA and DHA (g/d) | | | | | | | | |
| <0.15 | 324 | 465,145 | 1.00 (referent) | 46 | 132,871 | 1.00 (referent) | 370 | 1.00 (referent) |
| 0.15–0.24 | 221 | 329,056 | 1.15 (0.96, 1.37) | 44 | 107,442 | 1.17 (0.77, 1.78) | 265 | 1.15 (0.98, 1.36) |
| 0.25–0.34 | 103 | 188,252 | 1.01 (0.80, 1.27) | 37 | 106,552 | 1.14 (0.73, 1.78) | 140 | 1.04 (0.84, 1.28) |
| ≥0.35 | 75 | 154,646 | 0.96 (0.73, 1.26) | 39 | 173,968 | 0.99 (0.62, 1.58) | 114 | 0.97 (0.77, 1.23) |
| *P* | — | — | — | — | — | — | — | 0.91 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |
| n–3 PUFAs (g/d) | | | | | | | | |
| <1.25 | 408 | 594,493 | 1.00 (referent) | 70 | 189,984 | 1.00 (referent) | 478 | 1.00 (referent) |
| 1.25–1.44 | 161 | 257,809 | 1.09 (0.90, 1.31) | 40 | 113,604 | 1.09 (0.73, 1.62) | 201 | 1.09 (0.92, 1.29) |
| 1.45–1.64 | 78 | 150,830 | 0.88 (0.68, 1.12) | 22 | 89,179 | 0.78 (0.48, 1.27) | 100 | 0.86 (0.69, 1.07) |
| ≥1.65 | 76 | 133,968 | 0.88 (0.68, 1.13) | 34 | 128,066 | 0.93 (0.61, 1.42) | 110 | 0.89 (0.72, 1.11) |
| *P* | — | — | — | — | — | — | — | 0.83 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |
| n–6 PUFAs (g/d) | | | | | | | | |
| <10.0 | 429 | 668,038 | 1.00 (referent) | 57 | 168,355 | 1.00 (referent) | 486 | 1.00 (referent) |
| 10.0–11.4 | 156 | 234,236 | 1.15 (0.95, 1.38) | 38 | 110,578 | 0.97 (0.64, 1.48) | 194 | 1.12 (0.94, 1.32) |
| 11.5–12.9 | 68 | 129,606 | 0.82 (0.63, 1.06) | 23 | 95,776 | 0.64 (0.39, 1.05) | 91 | 0.77 (0.61, 0.97) |
| ≥13.0 | 70 | 105,219 | 0.99 (0.76, 1.29) | 48 | 146,123 | 0.83 (0.56, 1.22) | 118 | 0.94 (0.75, 1.16) |
| *P* | — | — | — | — | — | — | — | 0.45 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |
| Ratio of n–6:n–3 | | | | | | | | |
| <7.5 | 297 | 470,674 | 1.00 (referent) | 43 | 175,994 | 1.00 (referent) | 340 | 1.00 (referent) |
| 7.5–8.4 | 206 | 314,733 | 0.97 (0.81, 1.17) | 37 | 105,753 | 1.07 (0.68, 1.68) | 243 | 0.98 (0.83, 1.17) |
| 8.5–9.4 | 118 | 190,740 | 0.94 (0.75, 1.18) | 31 | 88,527 | 1.03 (0.63, 1.66) | 149 | 0.96 (0.78, 1.17) |
| ≥9.5 | 102 | 160,653 | 0.83 (0.66, 1.06) | 55 | 150,558 | 0.93 (0.61, 1.43) | 157 | 0.86 (0.69, 1.05) |
| *P* | — | — | — | — | — | — | — | 0.66 |
| $I^2$ | — | — | — | — | — | — | — | 0.0 |

[1]Multivariate HRs were adjusted for age, smoking, pack-years of smoking, pack-years squared of smoking, secondhand tobacco exposure (only in the NHS), race-ethnicity, physician visit, US region, spouse's highest educational attainment (only in the NHS), menopausal status (only in the NHS), BMI, physical activity, multivitamin use, energy intake, and modified prudent and Western dietary patterns. *P* values are a test for between-study heterogeneity (highest compared with lowest fatty acid intakes). $I^2$ is the degree of heterogeneity between studies expressed as a percentage of total variance (highest compared with lowest fatty acid intakes). aHR, adjusted HR; NHS, Nurses' Health Study.

fish-asthma association was completely null, which suggested that a misdiagnosis with asthma was an unlikely explanation. We also acknowledge that there was likely a misclassification in the FFQ-assessed intakes of fish and PUFA; however, it was previously reported that correlations for EPA and n–6 fatty acids as assessed by our FFQs compared with the proportion in adipose tissue were 0.47 and 0.50, respectively (41). Although, we acknowledge the potential for some misclassification, these data allowed us to investigate the relations between diet and COPD in a very large sample, with repeated assessments both of diet and newly diagnosed COPD. We also acknowledge the possible residual confounding by cigarette smoking, which is a powerful risk factor for COPD. To minimize this possibility, multivariate models were adjusted with multiple time-varying measures of tobacco exposure (smoking habits, pack-years, pack-years squared, and secondhand tobacco exposure), which were assessed biennially since 1976, and analyses were stratified by smoking status. As regards statistics and our models, we acknowledge a possible effect size of the sample, and even if we controlled for several potential and known cofounders, our results might still be explained by some leftover confounding as well as by other healthy lifestyles. Finally, even if our cohorts consisted of female and male health professionals (i.e., a relatively homogenous group regarding educational level), it is possible that residual differences in socioeconomic status might have contributed to the observed results. We also recognize that our results obtained in health professionals are not necessarily generalizable to the whole population because differences in health awareness, socioeconomic status, and smoking behavior might differ significantly from the general population to our study population.

In conclusion, after adjustment for overall dietary pattern, fish intake was not related to risk of newly diagnosed COPD. Although COPD-prevention efforts should continue to focus on smoking cessation, these prospective findings support the importance of promoting a healthy diet in multi-interventional programs to prevent COPD instead of focusing on changes in an isolated food or nutrient.

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and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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