Fish consumption and risk of non–gallstone-related acute pancreatitis: a prospective cohort study

Viktor Oskarsson, Nicola Orsini, Omid Sadr-Azodi, and Alicja Wolk

ABSTRACT

Background: Epidemiologic data on the role of diet in acute pancreatitis are sparse.

Objective: We examined the association of total fish consumption, as well as of consumption of fatty fish and lean fish separately, with risk of non–gallstone-related acute pancreatitis.

Design: We used data from 2 prospective cohorts, the Cohort of Swedish Men and the Swedish Mammography Cohort, that included 39,267 men and 32,191 women who were aged 45–84 y at the start of a 13-y follow-up period (1998–2010). Fish consumption was assessed by using a food-frequency questionnaire at baseline, and cases of incident non–gallstone-related acute pancreatitis were identified by linkage to the Swedish National Patient Register. HRs were estimated by using Cox proportional hazard models.

Results: During a total follow-up of 860,176 person-years, 320 cases of incident non–gallstone-related acute pancreatitis were identified. We observed that total fish consumption ≤2.0–3.0 servings/wk was associated with a significantly decreased risk of the disease (P-nonlinearity = 0.017). Compared with 0.9 servings/wk, multivariable-adjusted HRs were 0.86 (95% CI: 0.76, 0.96), 0.77 (95% CI: 0.62, 0.96), and 0.85 (95% CI: 0.65, 1.10) for 1.4, 2.4, and 3.5 servings/wk, respectively. In the analysis of fatty fish and lean fish, we observed that the consumption of each subtype had a similarly shaped association with risk of non–gallstone-related acute pancreatitis as that observed for total fish consumption, although neither was significant. Multivariable-adjusted HRs were 0.83 for fatty fish (95% CI: 0.65, 1.04) and 0.87 for lean fish (95% CI: 0.69, 1.11) when 0.6–2.0 were compared with ≤0.5 servings/wk.

Conclusion: Our data suggest that the consumption of total fish (fatty fish and lean fish combined) may be associated with decreased risk of non–gallstone-related acute pancreatitis. The Swedish Mammography Cohort was registered at clinicaltrials.gov as NCT01127698. The Cohort of Swedish Men was registered at clinicaltrials.gov as NCT01127711. Am J Clin Nutr doi: 10.3945/ajcn.113.076174.

Keywords cohort studies, diet, pancreatitis, prospective studies, pancreas, inflammation, food, fatty acids

INTRODUCTION

The most-important risk factors for acute pancreatitis are gallstone disease and alcohol abuse (1). Although dietary factors also might be risk factors, epidemiologic data on the role of diet in acute pancreatitis are sparse (2–5).

Fish, particularly fatty fish, is rich in long-chain n–3 (LCn–3) PUFAs such as EPA, docosapentaenoic acid, and DHA. Intake of LCn–3 PUFAs in the form of fish oil has been associated with decreased concentrations of biomarkers of inflammation (6–9) and oxidative stress (10, 11) as well as reduced triglyceride concentrations (12). These effects on inflammation, oxidative stress, and triglycerides may, in turn, be relevant to the development of acute pancreatitis. However, to the best of our knowledge, the association between fish consumption and risk of acute pancreatitis has not been studied. With the use of 2 population-based prospective cohorts, the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM), our aim was to examine the association of total fish consumption, as well as of consumption of fatty fish and lean fish separately, with risk of non–gallstone-related acute pancreatitis.

SUBJECTS AND METHODS

Study population

The SMC and the COSM are 2 cohorts from central Sweden (13, 14). The SMC was initiated between 1987 and 1990 when all women (n = 90,303) aged 40–75 y and living in Uppsala and Västmanland counties received a questionnaire that sought information on diet and other factors; 66,651 women (74%) responded. An expanded questionnaire, with more-comprehensive questions on diet, lifestyle, and medical history, was sent to all surviving women in the fall of 1997 (n = 56,030; then aged 48–83 y). The COSM was started simultaneously in 1997 when all men (n = 100,303) aged 45–79 y and living in Västmanland and Örebro counties received a questionnaire that was identical to the expanded SMC questionnaire. Response rates in 1997 were...
70% in women and 49% in men. More details about the cohorts, including study questionnaires and a list of earlier publications, can be viewed at www.ki.se/en/imm/unit-of-nutritional-epidemiology.

The current study used information from 48,850 men and 39,227 women who completed the questionnaire in 1997. Ethical approval was granted by the Regional Ethical Board at Karolinska Institutet, and return of the completed questionnaire was treated as informed consent. The recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology initiative were followed whenever applicable (15).

Assessment of dietary variables

Information on food consumption was obtained in 1997 by using a 96-item food-frequency questionnaire. Participants reported how often, on average, they had consumed the foods over the previous year by using the following 8 predefined answers: never, 1–3 times/mo, 1–2, 3–4, or 5–6 times/wk, and 1, 2, or ≥3 times/d. The food-frequency questionnaire contained one question on lean fish (cod, saithe, and fish fingers) consumption and 2 questions on fatty fish (salmon, whitefish, and char, and herring and mackerel) consumption. Questions on fish consumption were validated by comparing them with four 1-wk weighted diet records; Spearman’s $r$ was 0.5 for fatty fish and 0.4 for lean fish (16). We converted the frequency response of each question to an average consumption (servings/wk) and combined them to obtain estimates of consumption of total fish, fatty fish, and lean fish.

Information on other dietary factors (including beverages) was obtained from the food-frequency questionnaire in 1997. We energy adjusted all nutrients, except alcohol, by using the residual method (to 2000 kcal/d) (17).

Assessment of other variables

The questionnaire in 1997 acquired information on education, smoking status, BMI (in kg/m$^2$), waist circumference, and use of fish-oil supplements. History of hyperlipidemia and diabetes was obtained by linkage to the Swedish National Patient Register and the Swedish National Diabetes Register, respectively, and complemented with information from the questionnaire.

Case ascertainment

Diagnoses of acute pancreatitis were identified by linkage to the Swedish National Patient Register [code 5770 in the International Classification of Diseases (ICD)-9 and code K85 in ICD-10]. Information on other exocrine pancreatic diseases (codes 5771, 5772, 5778, or 5779 in ICD-9 and codes K86 or K87 in ICD-10), cancer, and death was obtained from the Swedish National Patient Register, the Swedish National Cancer Registry, and the Swedish National Cause of Death Register, respectively.

In the current study, we classified episodes of non–gallstone-related acute pancreatitis that occurred between 1998 and 2010 as cases (5). Non–gallstone-related acute pancreatitis was defined by 1) an ICD-10 code of K850, K852, K853, K858, or K859 and 2) the absence of cholelithiasis (code K80 in ICD-10) and gallbladder surgery (code JKA20, JAK21, JKE00, JKE02, JKE12, JKE18, or JKB30 in the Nordic Medico-Statistical Committee’s Classification of Surgical Procedures) within 3 mo after the index episode.

The diagnosis of acute pancreatitis in the Swedish National Patient Register was recently validated (18). In total, 530 medical charts recorded in 1998 or 2007 were reviewed, of which 83% were classified as definitive acute pancreatitis and 15% as probable acute pancreatitis, which left only 2% as wrongly diagnosed. To be classified as definitive acute pancreatitis, the combination of 2 of the 3 following criteria was required: 1) upper abdominal pain, 2) elevated pancreatic enzymes (≥3 times the upper normal reference value), or 3) typical signs on medical imaging (e.g., computed tomography scan or MRI).

The incidence of acute pancreatitis in our cohorts between 1998 and 2003 was similar to that reported in a previous Swedish study that was based on nationwide data (19). Namely, as an example of the similarities, the incidence rate per 100,000 Swedish individuals in the age group from 60 to 69 y was 66 cases in men and 52 cases in women; corresponding values in our cohorts were 69 cases in men and 49 cases in women.

Statistical analysis

For the current analysis, we excluded the following participants: 540 subjects whose personal identity numbers were incorrect, 5135 subjects with a baseline history of cancer (other than nonmelanoma skin cancer) or exocrine pancreatic disease, 1042 subjects with an extreme energy intake (>3 SDs of the sex-specific log-transformed mean), and 260 subjects who developed pancreatic cancer during follow-up. We also excluded 4522 participants with missing information on lean fish consumption, 3818 participants with missing information on fatty fish consumption, and 1302 participants with a total fish consumption >7.0 servings/wk to avoid modeling where data were very sparse (95th percentile: 4.5 servings/wk). Thus, of 48,850 men and 39,227 women who completed the questionnaire in 1997, 39,267 men and 32,191 women were included in the analysis.

We tabulated means and percentages of demographic, behavioral, and health characteristics by sex and total fish consumption (<1.0, 1.0–1.9, 2.0–3.0, and >3.0 servings/wk). We used Cox proportional hazard models to estimate HRs and corresponding 95% CIs of non–gallstone-related acute pancreatitis. Participants contributed person-years from the start of follow-up on 1 January 1998 to the date of diagnosis of acute pancreatitis, date of diagnosis of other exocrine pancreatic diseases, date of death, or 31 December 2010, whichever came first. All models were stratified by age (5-y categories) and sex to avoid violations of the proportional hazards assumption. Total fish consumption was modeled as a continuous variable by using restricted cubic splines with 3 knots at fixed percentiles of the distribution in cases (10th, 50th, and 90th percentiles, which corresponded to 0.9, 1.4, and 3.5 servings/wk, respectively) (20). Varying the location (25th, 50th, and 75th percentiles) or number of knots (4 knots: 5th, 35th, 65th, and 95th percentiles) had highly similar results as well. A test for a nonlinear trend was conducted by testing the coefficient of the second spline transformation equal to zero, and a test for an overall association was conducted by testing coefficients of spline transformations jointly equal to zero. To present results in tabular form, we
calculated HRs in correspondence with median values of the aforementioned intakes [0.9 (reference), 1.4, 2.4, and 3.5 servings/wk]. Subtypes of fish (fatty and lean; Spearman’s \( r = 0.2 \)) were modeled as categorical variables with 3 intakes \( \leq 0.5 \) (reference), \( 0.6–2.0, \) and \( >2.0 \) servings/wk). A test for an overall association was conducted by testing coefficients of categorical variables jointly equal to zero. The proportional hazards assumption was tested by modeling the interaction between the follow-up time and consumption of total fish, fatty fish, and lean fish. We observed no evidence of departure from this assumption.

Our multivariable models were adjusted for education (primary school, high school, and university), smoking status (never smoker, past smoker with \( <10 \) or \( \geq 10 \) pack-years, and current smoker with \( <20 \) or \( \geq 20 \) pack-years), level of adiposity (BMI \( \leq 25, 25–29, \) and \( \geq 30 \)) or waist circumference [WHO classification (21); \( <80, 80–87, \) and \( 88 \) cm for women and \( <94, 94–101, \) and \( 102 \) cm for men] depending on the model), alcohol intake (average [g/d in sex–specific quartiles] or per occasion \( \leq 2, 2–4, \) and \( \geq 5 \) drinks [12 g alcohol]) depending on the model), use of fish-oil supplements (no or yes), vegetable consumption (servings/d in quartiles), history of diabetes (no or yes), and history of hyperlipidemia (no or yes). Additional adjustment for meat consumption (servings/d in quartiles), glycemic load intake (score/d in quartiles), total fat intake (g/d in quartiles), dietary fiber intake (g/d in quartiles), and total energy intake (kcal/d in sex–specific quartiles) did not change the results. For each covariate, we included an extra category (an indicator) for missing data in the multivariable model, if necessary.

In sensitivity analyses, we performed a complete case analysis and a multiple imputation analysis by using chained-equations (HRs of 10 imputed data sets were pooled together by using Rubin’s rule to obtain valid statistical inference) (22) to compare results from different methods of handling missing data. To examine whether a preclinical or chronic illness might have affected fish consumption at baseline, the first 2 y of follow-up were excluded in another sensitivity analysis. Also, to account for a potential misclassification of our outcome because of an underdetection of gallstones (23), we performed a sensitivity analysis in which we applied a stricter definition of non–gallstone-related acute pancreatitis (i.e., no history of cholecystitis or gallbladder surgery within 3 y after the index episode). In a final sensitivity analysis, we performed a competing-risk regression analysis, with death and exocrine pancreatic diseases (other than non–gallstone-related acute pancreatitis) as competing risks. This analysis allowed us to examine the presence of bias that was due to competing risks.

Because alcohol intake is a known risk factor for acute pancreatitis (1), we used the Wald’s test to examine whether the association between total fish consumption and risk of non–gallstone-related acute pancreatitis varied by alcohol intake. To improve the power of the test, alcohol intake was modeled as a binary variable [low and high, with high defined as \( \geq 1 \) drink/d (12 g alcohol) for women and \( \geq 2 \) drinks/d for men].

Statistical significance was set at a 2-sided \( P < 0.05 \). Analyses were performed with Stata version 12.0 software (StataCorp).

RESULTS

There were 71,458 participants (39,267 men and 32,191 women) included in the analysis. Follow-up was conducted for 13 y (1998–2010; 860,176 person-years), and during this time we identified 320 cases (209 cases in men and 111 cases in women) of incident non–gallstone-related acute pancreatitis.

A median of 1.5 weekly servings of fish (mean \( \pm SD: 1.9 \pm 1.1 \) servings) were consumed at baseline including a median of 0.9 servings of fatty fish (mean \( \pm SD: 1.0 \pm 0.8 \) serving) and a median of 0.5 servings of lean fish (mean \( \pm SD: 0.9 \pm 0.6 \) servings). Baseline characteristics by sex and total fish consumption are shown in Table 1. Compared with participants with the lowest fish consumption, those with the highest fish consumption were more likely to be older and well-educated, to have ever used fish-oil supplements, and to consume more vegetables. These participants were also less likely to be current smokers, but they tended to consume more alcohol and to have a higher prevalence of diabetes and hyperlipidemia.

After adjustment for the potential confounding factors that could be identified, we observed that total fish consumption \( \leq 2.0–3.0 \) servings/wk was associated with a significantly decreased risk of non–gallstone-related acute pancreatitis (Figure 1); higher intakes yielded no additional benefit and did not reach a significant association (\( P \)-nonlinearity = 0.017). Results from the continuous exposure model are tabulated in Table 2. The lowest risk was observed for 2.4 servings/wk, for which the multivariable-adjusted HR was 0.77 (95% CI: 0.62, 0.96) compared with 0.9 servings/wk. Adjustment for waist circumference and amount of alcohol consumed per occasion, instead of BMI and average alcohol intake, did not change the results (HR: 0.77; 95% CI: 0.62, 0.96). Results were also unchanged after additional adjustment for such dietary factors as meat consumption, glycemic load score, total fat intake, dietary fiber intake, and total energy intake (HR: 0.78; 95% CI: 0.62, 0.98). In a subgroup analysis by sex, we observed that the association with total fish consumption was of similar shape and magnitude in both sexes (\( P \)-interaction = 0.76) (Table 3). Multivariable-adjusted HRs were 0.74 (95% CI: 0.57, 0.97) and 0.81 (95% CI: 0.55, 1.20) in men and women, respectively, for 2.4 compared with 0.9 servings/wk.

No appreciable change in the association between total fish consumption and risk of non–gallstone-related acute pancreatitis was observed when we performed a complete case analysis (n = 66,979 including 288 cases) and a multiple imputation analysis; multivariable-adjusted HRs for 2.4 compared with 0.9 servings/wk were 0.76 (95% CI: 0.60, 0.95) and 0.77 (95% CI: 0.61, 0.95), respectively. Results were not changed when the first 2 y of follow-up were excluded (293 cases identified during 11 y of follow-up; HR: 0.74; 95% CI: 0.59, 0.93) or when the stricter definition of non–gallstone-related acute pancreatitis was applied (39 of the original cases reclassified; HR: 0.78; 95% CI: 0.62, 0.99). When we performed a competing-risk regression analysis, we also observed no appreciable change of results (HR: 0.76; 95% CI: 0.62, 0.94).

We observed no evidence of a significant interaction between total fish consumption and alcohol intake in relation to risk of non–gallstone-related acute pancreatitis (\( P \)-interaction = 0.16). In a subgroup analysis, multivariable-adjusted HRs for 2.4 compared with 0.9 servings/wk were 0.82 (95% CI: 0.64, 1.05) in participants with a low alcohol intake (n = 60,035 including 254 cases) and 0.52 (95% CI: 0.32, 0.86) in those with a high alcohol intake (n = 10,060 including 55 cases). Crude incidence rates of non–gallstone-related acute pancreatitis in participants...
with low and high alcohol intakes were 35 and 45 cases/100,000 person-years, respectively.

In the analysis of fatty fish and lean fish (Table 4), we observed that the consumption of each subtype had a similarly shaped association with risk of non–gallstone-related acute pancreatitis as that observed for total fish consumption, although neither was significant. Multivariable-adjusted HRs were 0.83 (95% CI: 0.65, 1.04) for fatty fish and 0.87 (95% CI: 0.69, 1.11) for lean fish when 0.6–2.0 servings/wk were compared with ≤0.5 servings/wk. Higher intakes were not associated with lower HRs. Results did not appreciably change when we combined the 2 intakes/wk. Higher intakes were not associated with lower HRs. Multivariable-adjusted HRs were 0.83 (95% CI: 0.66, 1.05) for fatty fish; HR: 0.88 (95% CI: 0.70, 1.12) for lean fish. The modeling of fatty fish and lean fish as continuous variables by using restricted cubic splines did not change the significance of the associations (P-overall association = 0.34).

**DISCUSSION**

In this prospective cohort study, we observed a significant inverse association between total fish consumption ≥2.0–3.0 servings/wk and risk of non–gallstone-related acute pancreatitis. Fish consumption of 2.0–3.0 servings/wk is recommended in dietary guidelines of many countries. Our study supports the recommendation as it showed an inverse association between this intake and risk of non–gallstone-related acute pancreatitis. Although not previously studied to our knowledge, the observed association is biologically plausible because of the content of LCn−3 PUFAs in fish. Fish-oil supplementation has been associated with decreased concentrations of proinflammatory cytokines (e.g., IL-1β, TNF-α, and IL-6) and intercellular cell adhesion molecule-1 (6–9) as well as decreased concentrations of F2-isoprostanes (a biomarker of oxidative stress) (10, 11). Prospective cohort studies have also suggested that intake of dietary LCn−3 PUFAs may be inversely associated with risk of some inflammation-related diseases, such as ulcerative colitis (24) and rheumatoid arthritis (25). Because increasing evidence indicates that numerous cytokines and free radicals may be important in the pathogenesis of acute pancreatitis (26–28), the anti-inflammatory and antioxidative properties of LCn−3 PUFAs might explain our findings. Furthermore, fish-oil supplementation may reduce triglycerides (12), which, at high

**TABLE 1**

Baseline characteristics by sex and total fish consumption in the study population (n = 71,458)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men (n = 39,267)</th>
<th>Women (n = 32,191)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1.0 (0.9)</td>
<td>1.0–1.9 (1.4)</td>
</tr>
<tr>
<td></td>
<td>2.0–3.0 (2.4)</td>
<td>&gt;3.0 (3.5)</td>
</tr>
<tr>
<td>Participants, n</td>
<td>11,087</td>
<td>14,969</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.8 ± 9.6</td>
<td>59.3 ± 9.4</td>
</tr>
<tr>
<td>University education, %</td>
<td>14.2</td>
<td>17.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.8 ± 3.3</td>
<td>25.7 ± 3.3</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>27.0</td>
<td>21.9</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>14.7</td>
<td>16.2</td>
</tr>
<tr>
<td>History of hyperlipidemia, %</td>
<td>15.5</td>
<td>16.1</td>
</tr>
<tr>
<td>Use of fish-oil supplements, %</td>
<td>4.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Food consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty fish, servings/wk</td>
<td>0.4 ± 0.2</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>Lean fish, servings/wk</td>
<td>0.4 ± 0.2</td>
<td>0.8 ± 0.5</td>
</tr>
<tr>
<td>Vegetables, servings/d</td>
<td>1.9 ± 1.4</td>
<td>2.3 ± 1.4</td>
</tr>
</tbody>
</table>

*Data were missing on education for 216 participants, smoking status for 961 participants, BMI for 2194 participants, alcohol intake for 1363 participants, and vegetable consumption for 53 participants.

1Mean ± SD (all such values).
2One alcoholic drink equaled 12 g alcohol.
3Fatty fish included and char, and herring and mackerel.
4Lean fish included cod, saithe, and fish fingers.

**FIGURE 1** HRs (95% CIs) of non–gallstone-related acute pancreatitis by total fish consumption in the study population (n = 71,458), 1998–2010. The solid line represents HRs, and dashed lines represent 95% CIs. Tick marks represent the location of cases (n = 320). The histogram represents the percentage distribution of fish consumption. All estimates were derived from a Cox proportional hazard model in which total fish consumption was modeled as a continuous variable by using restricted cubic splines with knots at 10th, 50th, and 90th percentiles of the distribution in cases. Data were stratified by age (5-y categories) and sex and adjusted for education (primary school, high school, and university), smoking status (never smoker, past smoker with <10 or ≥10 pack-years, and current smoker with <20 or ≥20 pack-years), BMI (in kg/m²; <25, 25–29, and ≥30), alcohol intake (g/d in sex-specific quartiles), use of fish-oil supplements (no or yes), vegetable consumption (servings/d in quartiles), history of diabetes (no or yes), and history of hyperlipidemia (no or yes). The value of 0.9 servings/wk (the median value in subjects who consumed <1.0 serving/wk) served as the reference.
concentrations, are strongly associated with acute pancreatitis (1). Of note, one prospective cohort study showed that even moderately elevated triglyceride concentrations were associated with increased risk of acute pancreatitis, including that of non–gallstone-related acute pancreatitis (29). However, if our findings were solely due to LCn−3 PUFAs, a stronger association should have been seen for fatty fish. Thus, the similar association observed for the consumption of fatty fish and lean fish indicate a potential role of other nutrients, e.g., the mineral selenium that may act as an antioxidant (30).

The inverse association between total fish consumption and risk of non–gallstone-related acute pancreatitis was observed to be nonlinear in our study, with an apparent plateau at ~2.0–3.0 servings/wk. This finding, as well as the lack of significance for intakes above the plateau, may have been due to chance because the number of cases who consumed >3.0 servings/wk were limited. Alternatively, if participants in poor health consumed more fish, fish consumption may have reflected the presence of potential risk factors. In this population, participants with the highest fish consumption were more likely to have a history of diabetes and hyperlipidemia. Although we adjusted for these factors in multivariable analyses, the possibility of residual confounding could not be excluded. This possibility may have been of particular concern for hyperlipidemia because we had no specific data on hypertriglyceridemia, i.e., the lipid disorder associated with acute pancreatitis (1, 29).

### TABLE 3

<table>
<thead>
<tr>
<th>Total fish consumption, servings/wk (median)</th>
<th>&lt;1.0 (0.9)</th>
<th>1.0–1.9 (1.4)</th>
<th>2.0–3.0 (2.4)</th>
<th>&gt;3.0 (3.5)</th>
<th>P-overall association²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n = 39,267)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants, n</td>
<td>11,087</td>
<td>14,969</td>
<td>9000</td>
<td>4211</td>
<td>—</td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td>71/132,082</td>
<td>80/179,607</td>
<td>37/106,588</td>
<td>21/48,248</td>
<td>—</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.84 (0.73, 0.97)</td>
<td>0.72 (0.56, 0.94)</td>
<td>0.76 (0.55, 1.05)</td>
<td>0.045</td>
</tr>
<tr>
<td>Multivariable-adjusted³</td>
<td>1.00</td>
<td>0.85 (0.74, 0.99)</td>
<td>0.74 (0.57, 0.97)</td>
<td>0.78 (0.56, 1.10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Women (n = 32,191)</td>
<td>7461</td>
<td>11,930</td>
<td>8223</td>
<td>4577</td>
<td>—</td>
</tr>
<tr>
<td>Participants, n</td>
<td>31/90,786</td>
<td>39/146,653</td>
<td>25/101,014</td>
<td>16/55,198</td>
<td>—</td>
</tr>
<tr>
<td>No. of cases/person-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.82 (0.67, 1.01)</td>
<td>0.72 (0.49, 1.04)</td>
<td>0.81 (0.54, 1.22)</td>
<td>0.17</td>
</tr>
<tr>
<td>Multivariable-adjusted³</td>
<td>1.00</td>
<td>0.87 (0.70, 1.07)</td>
<td>0.81 (0.55, 1.20)</td>
<td>0.96 (0.62, 1.47)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

¹Derived from a Cox proportional hazard model in which total fish consumption was modeled as a continuous variable by using restricted cubic splines with knots at 10th, 50th, and 90th percentiles of the distribution in cases. All estimates were calculated in correspondence with median values [0.9 (reference), 1.4, 2.4, and 3.5 servings/wk]. P-overall association was conducted by testing coefficients of spline transformations jointly equal to zero.

²Test (P value) for overall association was conducted by testing coefficients of spline transformations jointly equal to zero.

³Stratified by age (5-y categories) and sex and adjusted for education (primary school, high school, and university), smoking status (never smoker, past smoker with <10 or ≥10 pack-years, and current smoker with <20 or ≥20 pack-years), BMI (in kg/m²; <25, 25–29, and ≥30), alcohol intake (g/d in sex-specific quartiles), use of fish-oil supplements (no or yes), vegetable consumption (servings/d in quartiles), history of diabetes (no or yes), and history of hyperlipidemia (no or yes).
hyperlipidemia (no or yes).

We observed that the association between total fish consumption and risk of non–gallstone-related acute pancreatitis was of similar shape and magnitude in men and women without evidence of an interaction by sex. However, the number of cases in sex-specific analyses were fairly small, and the inverse association with \( \leq 2.0–3.0 \) servings/wk did not reach significance in women.

Note that our participants were, in general, low consumers of alcoholic beverages (median alcohol intakes of 10 g/d in men and 3 g/d in women). Thus, it is questionable whether our finding of an inverse association between total fish consumption and risk of non–gallstone-related acute pancreatitis is generalizable to populations in whom the alcohol intake is higher or the pattern of drinking is different. However, although there was no strong evidence of an interaction by alcohol intake, the association seemed to be more pronounced in subjects with a high alcohol intake (median alcohol intakes of 33 g/d in men and 17 g/d in women). Participants with a high alcohol intake and who had an attack of the disease during follow-up should also have had the highest likelihood of being clinically classified as having alcohol-related pancreatitis, because such a classification is highly dependent on patients’ self-reported alcohol intakes. However, similar to the subgroup analysis by sex, we have to acknowledge the small number of cases when we assessed the interaction and performed a subgroup analysis by alcohol intake.

For subtypes of fish, we observed that the consumption of both fatty fish and lean fish had a similarly shaped association with risk of non–gallstone-related acute pancreatitis as that observed for total fish consumption (i.e., lowest risks were observed for intermediate intakes) although neither was significant. However, the variability of consumption of fatty fish (SD: 0.8 servings/wk) and lean fish (SD: 0.6 servings/wk) was rather small, especially compared with that of total fish consumption (SD: 1.1 servings/wk). Because the variability of an exposure is inversely related to its SEs and \( P \) values, the small variability most likely explains why associations were NS for fatty fish and lean fish.

Some additional limitations should be mentioned. First, there was a moderate correlation between food-frequency questionnaires and diet records with respect to fish consumption (Spearman’s \( r = 0.4–0.5 \)), which may have led to some exposure misclassification. However, the misclassification should have been nondifferential between cases and noncases in this prospective setting. Second, although the accuracy of the diagnosis of acute pancreatitis has been reported to be high in the Swedish National Patient Register (18), a misclassification between acute pancreatitis and other exocrine pancreatic diseases may have occurred. However, this potential bias should have been limited by our use of other exocrine pancreatic diseases as censoring events. Also, the classification of non–gallstone-related acute pancreatitis may have been subject to error because early diagnostics of acute pancreatitis may not always detect gallstones (mainly because of microlithiasis) (23). However, results were virtually unchanged in the sensitivity analysis in which cases had no history of cholelithiasis or gallbladder surgery within 3 y after the index episode. Third, we had no access to medical charts and could not determine the specific clinical classification (cause) of each case. Because gallstones (because of the case definition) and alcohol (because of the low reported intake) were not likely to be major causative factors in this population, the comparison with more-typical case populations of acute pancreatitis may be limited. Fourth, the past decades have seen additional studies are needed to confirm or refute our findings, including the potential nonlinear shape of the association. Finally, because of the observational nature of our study, we could not rule out the possibility of unmeasured or residual confounding.

Strengths of the current study were its prospective design and practically complete follow-up, which minimized the probability of a recall bias and differential loss to follow-up, respectively. Furthermore, the incidence of acute pancreatitis in our cohorts was similar to that reported in Sweden as a whole.

In conclusion, in this prospective cohort study, we observed a significant inverse association between the consumption of total

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### Table 4

| Consumption, servings/wk (median) | Fatty fish | | Lean fish | |
|----------------------------------|-----------|----------------|------------|
| \( \leq 0.5 \) (0.5) | 0.6–2.0 (0.9) | \( > 2.0 \) (3.0) | \( P \)-overall association | \( \leq 0.5 \) (0.5) | 0.6–2.0 (1.5) | \( > 2.0 \) (3.5) | \( P \)-overall association |
| Participants, \( n \) | 25,470 | 42,534 | 3454 | — | 42,643 | 28,063 | 752 | — |
| No. of cases | 130 | 174 | 16 | — | 209 | 107 | 4 | — |
| Person-years | 306,585 | 513,377 | 40,214 | — | 513,660 | 337,785 | 8730 | — |
| HR (95% CI) | Age- and sex-adjusted | 1.00 | 0.80 (0.64, 1.01) | 0.90 (0.53, 1.52) | 0.17 | Multivariable-adjusted | 1.00 | 0.83 (0.65, 1.04) | 0.93 (0.55, 1.59) | 0.27 |

1Derived from a Cox proportional hazard model in which fatty fish and lean fish were modeled as categorical variables. The lowest category of consumption was used as the reference. Fatty fish and lean fish were included simultaneously in the model.

2Test (\( P \) value) for overall association was conducted by testing coefficients of categorical variables jointly equal to zero.

3Stratified by age (5-y categories) and sex and adjusted for education (primary school, high school, and university), smoking status (never smoker, past smoker with <10 or \( \geq 10 \) pack-years, and current smoker with <20 or \( \geq 20 \) pack-years), BMI (in kg/m\(^2\); <25, 25–29, and \( \geq 30 \)), alcohol intake (g/d in sex-specific quartiles), use of fish-oil supplements (no or yes), vegetable consumption (servings/d in quartiles), history of diabetes (no or yes), and history of hyperlipidemia (no or yes).
fish (fatty fish and lean fish combined) and risk of non–gallstone-related acute pancreatitis.

The authors’ responsibilities were as follows—AW: collected the data; VO: performed statistical analyses and drafted the manuscript; NO, OS-A, and AW: reviewed and revised the manuscript; and all authors: contributed to the interpretation of results, participated in the study design and writing of the manuscript, and approved the final manuscript. Funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript. None of the authors had a personal or financial conflict of interest.

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