Association Between Type of Dietary Fish and Seafood Intake and the Risk of Incident Type 2 Diabetes

The European Prospective Investigation of Cancer (EPIC)-Norfolk cohort study

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OBJECTIVE — To investigate the association between fish and seafood intake and new-onset type 2 diabetes.

RESEARCH DESIGN AND METHODS — This was a population-based prospective cohort (European Prospective Investigation of Cancer [EPIC]-Norfolk) study of men and women aged 40–79 years at baseline (1993–1997). Habitual fish and seafood intake (white fish, oily fish, fried fish, and shellfish) was assessed using a semiquantitative food frequency questionnaire and categorized as less than one or one or more portions/week. During a median (interquartile range) follow-up of 10.2 (9.1–11.2) years, there were 725 incident diabetes cases among 21,984 eligible participants.

RESULTS — Higher total fish intake (one or more versus less than one portions/week) was associated with a significantly lower risk of diabetes (odds ratio [OR] 0.75 [95% CI 0.58–0.96]), in analyses adjusted for age, sex, family history of diabetes, education, smoking, physical activity, dietary factors (total energy intake, alcohol intake, and plasma vitamin C) and obesity (BMI and waist circumference). White fish and oily fish intakes were similarly inversely associated with diabetes risk, but the associations were not significant after adjustment for dietary factors (oily fish) or obesity (white fish). Fried fish was not significantly associated with diabetes risk. Consuming one or more portions/week of shellfish was associated with an increased risk of diabetes (OR 1.36 [1.02–1.81]) in adjusted analyses.

CONCLUSIONS — Total, white, and oily fish consumption may be beneficial for reducing risk of diabetes, reinforcing the public health message to consume fish regularly. Greater shellfish intake seems to be associated with an increased risk of diabetes, warranting further investigation into cooking methods and mechanisms.

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Potential benefits of a diet rich in fish and seafood were previously highlighted with the observation of low prevalence of chronic diseases among Greenland Inuit populations consuming a predominantly marine diet (1). Substantial evidence demonstrates an inverse association between habitual fish intake and coronary heart disease (2) and stroke (3). Such evidence has been translated into dietary recommendations to eat at least "two portions of fish per week, one of which should be oily" (4).

Evidence regarding the beneficial effects of fish intake on risk of type 2 diabetes is inconclusive. An ecological study of 41 countries found that countries with the lowest fish/seafood intake had the highest prevalence of diabetes (5). Some (6,7), but not all (8), cross-sectional evidence suggests a beneficial effect of fish intake on glycemic status. A cross-sectional analysis of the European Prospective Investigation of Cancer (EPIC)-Norfolk Study showed that different types of fish intake were differentially associated with A1C levels in age- and sex-adjusted analyses. However, upon adjustment for lifestyle factors, these associations were rendered nonsignificant (9). Prospective evidence is limited, with one study reporting a beneficial effect with lower risk of impaired glucose tolerance among Dutch elderly men and women who habitually consumed a small amount of fish (mean intake 24 g/day) compared with non–fish eaters (adjusted odds ratio [OR] 0.47 [95% CI 0.23–0.93]) (10). Conversely, the Nurses' Health Study found no significant association between total fish intake (two or more vs. less than one portions/week) and diabetes risk (11). Similarly, there is conflicting evidence from intervention trials, which have focused mainly on fish oil supplements (12,13). Thus, there is uncertainty about the association between fish intake and blood glucose levels or diabetes risk. Our aim was to investigate whether habitual intake of different types of fish and seafood was associated with future risk of developing type 2 diabetes in a prospective analysis of the EPIC-Norfolk cohort.

RESEARCH DESIGN AND METHODS

— The EPIC-Norfolk Study recruited a total of 25,639 men and women, aged 40–79 years at baseline (1993–1997), who were resident in and around Norwich, England. This study has been described in detail previously (14). Since the baseline health-check visit, there were three follow-up assessments: a postal questionnaire at 18 months, a re-

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peat health-check visit (1998–2000), and a further postal questionnaire (2002–2004). Participants with prevalent diabetes, cardiovascular disease, or cancer (n = 3,114) were excluded from this analysis because they may have changed their dietary habits after diagnosis. We excluded participants with baseline missing food frequency questionnaire (FFQ) data (n = 541) or with >10 missing FFQ lines or if they were in the top or bottom 1% of the ratio of energy intake to basal metabolic rate (15). This left 21,984 participants (9,801 men and 12,183 women) for inclusion in the current analysis. Participants provided written informed consent, and ethics approval for the study was given by the Norwich District Ethics Committee.

Data collection

Health and lifestyle information was collected using a baseline questionnaire, which asked about participants' personal and family health, demography, lifestyle, social status (education), and diet. At the baseline visit, a standardized health check was performed by trained nurses, including measurement of height (centimeters), weight (kilograms), and waist circumference (centimeters) as described previously (14). At baseline, self-reported physical activity was derived into a four-scale index (inactive, moderately inactive, moderately active, and active) by combining levels of occupational and recreational physical activity (16). Nonfasting blood samples were collected. For plasma vitamin C measurement venous blood was drawn into citrate bottles and kept overnight in a dark container at 4–7°C. The samples were centrifuged, and plasma was stabilized using a standardized volume of metaphosphoric acid and measured using a fluorometric assay.

Dietary assessment

Participants completed a validated 130-item semiquantitative FFQ about their habitual diet and dietary supplement use in the past year (17). For all food items, respondents were asked to report the frequency of intake on a 9-point scale (ranging from "never or less than once per month" to "more than six times per day") for a "medium serving or portion."

The FFQ included six items of fish/seafood intake: "fried fish in batter, as in fish and chips"; "fish fingers/fish cakes"; "other white fish, fresh or frozen, e.g., cod, haddock, plaice, sole, halibut", "oily fish, fresh or canned, e.g., mackerel, kippers, tuna, salmon, sardines, herring"; "shellfish, e.g., crab, prawns, mussels"; and "fish roe, e.g., taramasalata." Each fish type was collapsed into a dichotomous variable, less than one or one or more portions/week. Total fish intake per week was calculated as the sum of all six fish categories and dichotomized as above.

Ascertainment of diabetes status

New cases of diabetes occurring up until 31 December 2005 were ascertained using multiple data sources including: self-report of doctor-diagnosed diabetes on three follow-up health and lifestyle questionnaires, i.e., a positive response to the question "Has a doctor ever told you that you have diabetes?" or self-reported diabetes medication or diabetes medication brought to the follow-up visit. In addition, record linkage was used to trace each participant for diabetes diagnosis including listing with general practice diabetes registers, regional hospital outpatient diabetes registers, and hospital admissions information that screened for any conditions linked to diabetes. Diabetes-related deaths were flagged by linkage to the national death registry. Criteria for qualification as a confirmed diabetes case were *1*) confirmation of self-report by another data source or *2*) diagnosis captured by an external source alone, independently of participation in study follow-up questionnaires or visit. Possible cases based solely on self-report and not confirmed by another data source (n = 74) did not qualify as a confirmed case of diabetes.

Statistical analysis

Baseline characteristics were summarized for those with incident diabetes and the rest of the cohort using means ± SD (for normally distributed continuous variables), medians (interquartile ranges [IQR]) (for nonnormally distributed continuous variables), and frequencies and percentages (for categorical variables). Differences were tested using either Student's t, Wilcoxon rank-sum, or χ^2 tests.

In this prospective analysis all exposures are measured at baseline. Multiple logistic regression was used to assess the prospective association between fish intake and risk of diabetes. The following models were constructed to account for potential confounders and mediators. Model 1 was adjusted for age (continuous) and sex. Model 2 included additional adjustment for established risk factors of diabetes and socioeconomic status: family history of diabetes (yes/no), smoking habit (1 = never, 2 = former, or 3 = current), education level (1 = lowest to 4 = highest), and physical activity level (1 = inactive to 4 = active). Model 3 included additional adjustment for dietary factors: total energy intake (kilocalories per day), alcohol (grams per day), and plasma vitamin C (micromoles per liter) as an objective biomarker of fruit/vegetable intake reflecting possible healthier lifestyles (18). Model 4 included additional adjustment for BMI (weight in kilograms divided by the square of height in meters) and waist circumference (centimeters) because obesity may mediate the association between fish intake and diabetes. We also repeated model 3 with fruit/vegetable intake (grams per day) instead of plasma vitamin C. In a series of sensitivity analyses we also examined the effect of fish oil supplement use, multivitamin supplement use, lipid-lowering or antihypertensive medication use, vegetarian (non–meat eating) lifestyle, and the simultaneous adjustment for the intake of other fish types. We added each of these covariates individually to model 4 to examine their effect as potential confounders of our main association between fish intake and diabetes risk. We also examined dietary n-3 polyunsaturated fatty acid (n-3 PUFA) content (eicosapentaenoic acid plus docosahexaenoic acid ([grams per day]) by oily fish and white fish intake status. A possible interaction between fish intake and sex was tested using a likelihood ratio test. Because no interaction was found (P = 0.36), men and women were analyzed together. There was no interaction between fish intake and BMI (P = 0.70). All analyses were performed using Stata (version 10.1; StataCorp, College Station TX).

RESULTS — During a median (IQR) follow up of 10.2 (9.1–11.2) years, there were 725 incident cases of diabetes. Overall, 4.4% of the cohort reported not consuming any fish/seafood. White fish, oily fish, fried fish, shellfish, fish fingers, and fish roe were consumed by 73.8, 72.3, 56.7, 29.9, 21.1, and 6.5% of the cohort, respectively. Baseline characteristics of the cohort by diabetes case status are shown in Table 1. Those who developed diabetes were older, were more likely to be men, had a higher mean BMI, and were less likely to be physically active. Case patients also reported lower baseline intakes of alcohol and fruit/vegetables and had lower plasma vitamin C levels. Consumption of total, white, and oily fish was

Table 1—*Baseline characteristics of the study population according to incident diabetes status in 21,984 men and women: EPIC-Norfolk Study 1993–2005*

	No incident diabetes	Incident diabetes	*P*
n	21,259	725	
Demographic characteristics			
Age (years)	58.0 ± 9.3	61.3 ± 8.3	≤0.0001
Women	11,871 (55.8)	312 (43.0)	≤0.001
BMI (kg/m^2)	26.2 ± 3.8	29.7 ± 4.7	≤0.0001
Waist circumference (cm)	87.5 ± 12.1	99.4 ± 12.6	≤0.0001
Family history of diabetes	2,594 (12.2)	164 (22.6)	≤0.001
Smokers, current	2,495 (11.8)	77 (10.7)	0.37
Education level			≤0.001
1 (lowest)	8,187 (38.5)	342 (47.2)	
2	2,796 (13.2)	80 (11.0)	
3	7,452 (35.1)	231 (31.9)	
4 (highest)	2,808 (13.2)	72 (9.9)	
Physical activity			≤0.001
Inactive	6,046 (28.4)	306 (42.2)	
Moderately inactive	6,199 (29.2)	167 (23.0)	
Moderately active	4,951 (23.3)	136 (18.8)	
Active	4,062 (19.1)	116 (16.0)	
Dietary characteristics			
Total energy intake (kcal/day)	2,030.2 ± 579.1	2,054.1 ± 621.0	0.94
Fat intake (g/day)	77.1 ± 29.6	77.0 ± 29.8	0.94
n-3 PUFA intake (g/day)	1.5 (1.1–2.0)	1.5 (1.2–2.0)	0.13
Carbohydrate intake (g/day)	255.9 ± 86.8	256.4 ± 82.2	0.89
Fiber intake (g/day)	17.6 (14.0, 21.9)	16.8 (13.1, 21.6)	<0.01
Protein intake (g/day)	83.2 ± 21.4	82.8 ± 21.5	0.64
Alcohol intake (g/day)	4.7 (0.8–10.9)	2.8 (0–10.4)	≤0.001
Fruit and vegetable intake (g/day)	451.7 (246.4)	431.8 (238.1)	0.02
Plasma vitamin C (μmol/l)	54.2 ± 20.1	43.5 ± 18.0	≤0.0001
Fish oil supplements at baseline (yes)	6,530 (30.7)	208 (28.7)	0.24
Multivitamin supplement use at baseline (yes)	9,717 (45.7)	283 (39.0)	≤0.0001
Fish intake (≥1 portions/week of fish intake)			
Total fish intake	18,505 (89.2)	607 (86.7)	0.04
White fish intake	8,850 (41.8)	274 (38.0)	0.04
Oily fish intake	7,645 (36.1)	220 (30.5)	≤0.01
Fried fish intake	5,030 (23.8)	188 (26.0)	0.18
Fish fingers intake	1,290 (6.1)	42 (5.9)	0.82
Shellfish intake	1,534 (7.2)	74 (10.2)	≤0.01
Fish roe intake	214 (1.0)	5 (0.7)	0.40

Data are means ±SD, *n* (%), or median (IQR). *P* values correspond to *t* test for continuous variables, χ^2 test for categorical variables, and Wilcoxon rank-sum test (for medians).

lower, and shellfish intakes were higher in individuals with diabetes compared with the rest of the cohort.

Characteristics of the cohort by fish intake are shown in Table 2 (for all except fried fish, fish fingers, and fish roe for which there was no significant association with diabetes risk). Those consuming one or more portions/week of total fish were less likely to have diabetes, were older, were more likely to be women, were less likely to be current smokers, and had higher total energy intake, alcohol and fruit/vegetable intakes, and higher plasma vitamin C levels than those consuming less than one portion/week. Regular consumers of white fish and oily fish (one or more vs. less than one portions/week) were more likely to be women and generally had healthier profiles. Regular shellfish consumers were more likely to be women, had higher mean BMI and waist circumference, were more likely to be smokers, and had higher intakes of total energy, alcohol, and fruit/vegetable.

Table 3 shows the ORs (95% CI) for diabetes comparing one or more portions versus less than one portion/week of total and individual fish types. Higher total fish intake was associated with a decreased risk of diabetes, OR 0.77 (95% CI 0.61–0.96, model 1) and 0.75 (0.58–0.96, model 4). The results were similar for white fish intake; however, the association was no longer significant after adjustment for obesity (OR 0.83 [95% CI 0.73–1.03]). Oily fish intake was also associated with a decreased risk of diabetes, although this association was nonsignificant after adjustment for dietary factors (model 3) and obesity (model 4). Intakes of fried fish, fish fingers, and fish roe were not associated with diabetes risk in age- and sex-adjusted analyses. Those who ate one or more portions/week of shellfish had a 36% increased risk of developing diabetes compared with those who ate less than one portion/week after adjustment for all measured confounders and mediators (1.36 [1.02–1.81]). Our sensitivity analyses showed that the effects of fish intake were similar in magnitude and direction when fruit/vegetable intake was included in model 3 instead of plasma vitamin C. There was no material change in the magnitude or direction of our original observed associations in any of the sensitivity analyses we performed (see RESEARCH DESIGN AND METHODS; results not shown). Intake of dietary n-3 PUFAs was significantly higher in those consuming one or more versus less than one portions/week of oily fish (median 0.43 [IQR 0.37–0.90] vs. 0.20 [0.11–0.26] g/day, $P = 0.0001$) and white fish (0.36 [0.23–0.46] vs. 0.22 [0.12–0.32] g/day, $P = 0.0001$).

We further investigated the unexpected finding that shellfish intake increased the risk of diabetes in our study. The cholesterol content of shellfish is high, and thus we compared dietary cholesterol and serum cholesterol levels in those with regular and infrequent shellfish intake. Median serum total cholesterol was different between those who reported eating one or more or less than one portions/week of shellfish (median 6.2 [IQR 5.4–6.9] vs. 6.1 [5.4–6.9] mmol/l, respectively, $P = 0.052$). Dietary cholesterol intake was significantly greater in the higher shellfish intake

Table 2—*General baseline characteristics of the cohort according to total and different types of fish intake: EPIC-Norfolk Study*

	Portions/week			
	Total fish		White fish	
	<1	≥1	<1	≥1
*n**	2,330	19,112	12,781	9,124
Incident diabetes*	93	607†	447	274
Age (years)	56.9 ± 9.2	58.2 ± 9.2‡	57.0 ± 9.2	59.7 ± 9.0
Sex (women)	1,204 (51.7)	10,649 (55.7)†	6,666 (52.2)	5,461 (59.9)§
BMI (kg/m^2)	26.1 ± 3.9	26.3 ± 3.9	26.3 ± 3.9	26.2 ± 3.8‡
Waist circumference (cm)	87.9 ± 12.4	87.8 ± 12.3	88.3 ± 12.3	87.3 ± 12.2§
Family history of diabetes	294 (12.6)	2,406 (12.6)	447 (3.5)	274 (3.0)
Smokers, current	359 (15.6)	2,146 (11.3)	1,664 (13.1)	896 (9.9)§
Education level				
1 (lowest)	933 (40.1)	7,321 (38.3)	4,915 (38.5)	3,569 (39.2)
2	279 (12.0)	2,528 (13.2)	1,682 (13.2)	1,184 (13.0)
3	814 (35.0)	6,724 (35.2)	4,556 (35.7)	3,109 (34.1)
4 (highest)	303 (13.0)	2,526 (13.2)	1,621 (12.7)	1,253 (13.8)
Physical activity				
Inactive	697 (29.9)	5,477 (28.7)	3,705 (29.0)	2,623 (28.8)‡
Moderately inactive	636 (27.3)	5,581 (29.2)	3,604 (28.2)	2,746 (30.1)
Moderately active	546 (23.4)	4,433 (23.2)	3,018 (23.6)	2,051 (22.5)
Active	451 (19.4)	3,620 (18.9)	2,453 (19.2)	1,704 (18.7)
Total energy intake (kcal/day)	1,839.5 ± 566.1	2,068.6 ± 597.42§	2,010.4 ± 598.2	2,090.8 ± 596.9§
Alcohol intake (g/day)	2.3 (0–9.4)	4.7 (0.8–11.0)§	3.6 (0.8–10.5)	4.9 (0.8–11.3)§
Fruit and vegetable intake (g/day)	340.2 (229.1–478.7)	418.2 (295.7–571.2)†	374.6 (258.3–517.1)	460.4 (335.2–623.6)§
Plasma vitamin C (μmol/l)	53 (38–66)	55 (42–66)§	53 (40–65)	56 (44–68)§
Fish oil supplements at baseline	535 (23.0)	6,023 (31.5)	3,499 (27.4)	3,222 (35.3)§

Data are means ± SD, *n* (%), or median (IQR) unless otherwise stated. *P* values correspond to *t* test for continuous variables, χ^2 test for categorical variables, and Wilcoxon rank-sum test (for medians). *Because of missing values for categories of fish intake numbers do not total 21,984, the cohort total (missing: total fish, 542; white fish, 79; oily fish, 60; and shellfish, 57). Similarly, numbers of cases do not total 725 because of missing values for fish intake (missing: total fish, 25; white fish, 4; oily fish, 3; and shellfish, 1). †$P \leq 0.05$; ‡$P \leq 0.01$; §$P \leq 0.0001$.

group versus lower intake group (286.6 [221.3–367.8] vs. 258.2 [192.7–336.1] mg/day, respectively, $P = 0.0001$). The positive association between shellfish intake and diabetes risk persisted with additional adjustment for total dietary cholesterol (OR 1.36 [95% CI 1.02–1.81]), whereas adjustment for total serum cholesterol attenuated the association to borderline significance (1.33 [0.99–1.77]). Finally, we found a stronger inverse association of "total" fish excluding shellfish with diabetes risk in model 4 (0.73 [0.58–0.93]).

CONCLUSIONS — This is the first population-based prospective study to examine the effect of different types of fish/seafood intake on the development of type 2 diabetes. Higher total fish intake was associated with a 25% decreased risk of diabetes, independent of known risk factors and potential confounders. Consumption of both white and oily fish was also inversely related to diabetes risk, although adjustment for dietary factors and obesity attenuated these associations. Surprisingly, higher shellfish intake was associated with a 36% increased risk of diabetes. Our novel findings are potentially important as they suggest that the type of fish consumed may differentially influence the risk of diabetes.

Unlike previous studies (6,7,11), we were able to investigate the prospective association between fish intake and risk of diabetes in a large sample of men and women, within a wide age range and in a single study. The type and amount of fish consumed may provide an explanation for the inconsistent findings between this study and previous investigations. For instance, the Nurses' Health Study (11) found no association between total fish intake (two or more vs. less than one portions/week) and diabetes risk but did not report on intake on individual types of fish. Conversely, a cross-sectional study (7) reported an inverse association between total fish intake (grams per week) and fasting plasma glucose levels (β −0.16, $P = 0.008$) in Mediterranean elderly individuals, but this study did not examine the association with risk of diabetes. Population differences in types of fish/seafood intake might account for some of the observed inconsistencies thus far. For instance, a comparison of regional EPIC study cohorts suggested that the U.K. population is one of the lowest consumers of oily fish (mean 10 g/day in women and 14 g/day in men) compared with populations of other European countries, e.g., Spain (22.3 g/day in women and 42.6 g/day in men) (19).

The associations between total fish and shellfish intake and risk of diabetes observed in our study were independent of a comprehensive range of potential confounders. These included an attempt to adjust for possible clustering of healthier lifestyles and factors that may accompany greater fish intake (physical activity, alcohol intake, smoking, plasma vitamin C levels or fruit/vegetable intake, and education level). The associations between white fish and oily fish intake and diabetes risk were not significant after adjustment for general and central obesity (BMI and waist circumference), indicating that, although the association was independent

Table 2—*Continued*

	Oily fish		Shellfish	
	<1	≥1	<1	≥1
*n**	14,059	7,865	20,319	1,608
Incident diabetes*	502	220‡	650	74‡
Age (years)	58.3 ± 9.3	58.0 ± 9.1‡	58.2 ± 9.2	57.4 ± 9.1†
Sex (women)	7,388 (52.6)	4,760 (60.5)§	11,203 (55.1)	943 (58.6)§
BMI (kg/m^2)	26.3 ± 3.9	26.2 ± 3.9‡	26.2 ± 3.8	26.7 ± 4.1†
Waist circumference (cm)	88.5 ± 12.3	86.8 ± 12.1§	87.8 ± 12.2	88.6 ± 12.9
Family history of diabetes	1,714 (12.2)	1,036 (13.2)	2,546 (12.5)	209 (13.0)‡
Smokers, current	1,833 (13.2)	735 (9.4)§	2,345 (11.6)	223 (14.0)‡
Education level				
1 (lowest)	5,624 (40.0)	2,876 (36.6)	7,924 (39.0)	581 (36.2)
2	1,744 (12.4)	1,123 (14.3)	2,644 (13.0)	221 (13.8)
3	4,978 (35.4)	2,690 (34.2)	7,089 (34.9)	580 (36.1)
4 (highest)	1,702 (12.1)	1,171 (14.9)§	2,650 (13.1)	223 (13.9)
Physical activity				
Inactive	4,351 (31.0)	1,984 (25.2)	5,868 (28.9)	464 (28.9)†
Moderately inactive	3,946 (28.1)	2,403 (30.6)	5,884 (29.0)	465 (28.9)
Moderately active	3,169 (22.5)	1,903 (24.2)	4,744 (23.4)	333 (20.7)
Active	2,592 (18.4)	1,575 (20.0)§	3,822 (18.8)	346 (21.5)
Total energy intake (kcal/day)	1,999.0 ± 596.0	2,124.0 ± 597.2§	2,035.5 ± 594.7	2,145.5 ± 645.5§
Alcohol intake (g/day)	3.6 (0.8–10.5)	5.1 (1.0–11.4)§	4.1 (0.8–10.6)	7.4 (1.6–16.1)§
Fruit and vegetable intake (g/day)	375.4 (261.6–519.0)	471.8 (347.0–635.3)§	404.9 (283.0–556.2)	478.4 (344.4–663.0)§
Plasma vitamin C (μmol/l)	53 (39–65)	57 (45–68)§	54 (41–66)	54 (42–67)
Fish oil supplements at baseline	3,888 (27.7)	2,828 (36.0)§	6,205 (30.5)	516 (32.1)

of other dietary exposures, obesity could act as a mediator between white or oily fish intake and diabetes risk. In support of this theory, it has been shown that individuals consuming white or oily fish, as part of a calorie-restricted diet for 8 weeks, on average lost 1 kg of body weight more than control subjects (20).

The finding that greater shellfish intake may increase the risk of diabetes is surprising and novel. Possible mechanisms that may explain this finding could be related to cooking method (frying and the type and amount of cooking fat used) and the accompanying condiments with which shellfish is often served (such as mayonnaise or garlic butter). In addition, shellfish is known to be a rich source of dietary cholesterol, and it has been shown that dietary cholesterol may increase blood cholesterol. For instance, in a prospective analysis of >50,000 participants, Djoussé et al. (21) reported that high daily consumption of eggs, a rich source of dietary cholesterol, is associated with increased diabetes risk. In the present analyses, the adjustment for total dietary cholesterol levels did not affect the association between shellfish intake and risk of diabetes. However, adjustment for total serum cholesterol attenuated the association, raising the possibility that higher cholesterol levels might potentially contribute to the raised diabetes risk associated with shellfish intake. A possible mechanism is that elevated cholesterol may impair pancreatic β-cell function and insulin secretion (22), although our study was not designed to test such hypotheses. Our finding of a positive association between shellfish intake and diabetes risk merits further investigation in other studies.

Table 3—*Adjusted ORs (95% CI) of developing diabetes comparing one or more with less than one portions/week of total and each type of fish intake, obtained from logistic regression analysis: EPIC-Norfolk Study*

Fish intake (≥1 vs. <1 portions/week)	OR (95% CI)			
	Model 1	Model 2	Model 3	Model 4
Total fish	0.77 (0.61–0.96)	0.76 (0.61–0.96)	0.77 (0.61–0.98)	0.75 (0.58–0.96)
White fish	0.80 (0.69–0.94)	0.81 (0.70–0.95)	0.83 (0.71–0.97)	0.87 (0.73–1.03)
Oily fish	0.83 (0.70–0.97)	0.84 (0.71–0.98)	0.92 (0.77–1.10)	0.94 (0.78–1.13)
Shellfish	1.53 (1.20–1.96)	1.50 (1.16–1.92)	1.58 (1.20–2.08)	1.36 (1.02–1.81)
Fried fish	1.04 (0.88–1.24)	0.94 (0.79–1.13)	0.95 (0.79–1.15)	0.91 (0.75–1.10)
Fish fingers	0.94 (0.69–1.30)	0.87 (0.63–1.21)	0.89 (0.64–1.24)	0.91 (0.65–1.27)
Fish roe	0.70 (0.29–1.72)	0.77 (0.32–1.89)	1.03 (0.42–2.54)	0.94 (0.38–2.35)

n = 21,984. Model 1 adjusted for age and sex; model 2 adjusted for model 1 + family history of diabetes, smoking, education level, and physical activity; model 3 adjusted for model 2 + total energy intake, alcohol intake, and plasma vitamin C; model 4 adjusted for model 3 + BMI, and waist circumference.

The n-3 PUFAs, eicosapentaenoic acid and docosahexaenoic acid, are suggested to be the beneficial components within fish that may affect health (2). High concentrations of n-3 PUFAs in hu-

man skeletal muscle cells have been associated with improved insulin sensitivity (12). The n-3 PUFA content of oily and white fish may explain their inverse associations with diabetes risk. However, if this was the primary mechanism by which fish reduced diabetes risk, one would expect oily fish to show a stronger protective effect than white fish, given the higher n-3 PUFA content of oily fish. Another potential mechanism relates to the amino acid composition of fish protein, which may increase glucose uptake by skeletal muscle via improved insulin sensitivity (23). Thus, fish protein may offer a possible explanation as to why total fish intake, largely composed of nonoily fish (i.e., high in fish protein), showed an inverse association with risk of diabetes in our study.

Limitations of this investigation also merit consideration. For pragmatic reasons in this large cohort study, we included only individuals with clinically ascertained cases of diabetes and thus diabetes status was not determined biochemically, which could lead to presence of undiagnosed diabetes in the cohort. However, this would have had the effect of attenuating the observed association and hence our estimates are conservative. Notably, our diabetes case ascertainment was rigorous, using multiple data sources that did not depend on a participant returning a follow-up questionnaire or attending a follow-up health check and was independent of continued active participation in the study. Another limitation relates to dietary assessment by FFQ in which respondents have to estimate typical intake frequencies of food items and their portion sizes, which can introduce measurement error and bias. However, we have previously found no significant difference in fish intake reported by four dietary assessment methods (FFQ, 7-day diary, first-day recall of 7-day diary, and health and lifestyle questionnaire) (24). Furthermore, FFQ-derived fish intake in our study is comparable to the amount of fish intake reported by food diary in the National Diet and Nutrition Survey, U.K. (25). It is possible that our findings might be due to residual confounding from measured and unmeasured factors. However, we were able to account for a comprehensive range of confounders and mediators, including demographic, lifestyle, social and dietary factors as well as general and central obesity. To account for potential clustering of healthier lifestyles that might accompany greater fish intake, we adjusted for the effects of fruit/vegetable intake and for plasma vitamin C level as an objective biomarker of fruit/vegetable intake, thus minimizing the possibility of residual confounding from measurement error in the assessment of this potentially important confounding factor. Our findings were robust to a range of sensitivity analyses that accounted for other potential factors that may be associated with higher fish intake. Finally, we could speculate that weight change might account for our findings, but we did not adjust for weight change for the following reasons: *1*) diabetes may have occurred in some individuals before the time that follow-up weight was reported, and hence weight change might have been influenced by the outcome and *2*) weight data were available for a shorter follow-up (2002–2004 by postal questionnaire and hence in a smaller number, $n = 13,179$) than diabetes ascertainment (until 31 December 2005, in $n = 21,984$ through record linkage). Future researchers should examine the effect of fish intake on weight change as well as diabetes risk.

In summary, we report that specific types of fish intake are differentially associated with the risk of diabetes. Total intake of both white fish and oily fish was associated with a lower risk of diabetes, reinforcing the public health message to consume fish regularly. Shellfish intake was associated with an increased risk of diabetes, which highlights the potential importance of seafood preparation and cooking methods. The increased risk of diabetes with shellfish intake requires further study.

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