Association of Oily and Nonoily Fish Consumption and Fish Oil Supplements With Incident Type 2 Diabetes: A Large Population-Based Prospective Study

Guo-Chong Chen,[1] Rhonda Arthur,[1] Li-Qiang Qin,[2] Li-Hua Chen,[2] Zhendong Mei,[3] Yan Zheng,[3] Yang Li,[1] Tao Wang,[1] Thomas E. Rohan,[1] and Qibin Qi[1,4]

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OBJECTIVE

To evaluate associations of oily and nonoily fish consumption and fish oil supplements with incident type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

We included 392,287 middle-aged and older participants (55.0% women) in the UK Biobank who were free of diabetes, major cardiovascular disease, and cancer and had information on habitual intake of major food groups and use of fish oil supplements at baseline (2006–2010). Of these, 163,706 participated in one to five rounds of 24-h dietary recalls during 2009–2012.

RESULTS

During a median 10.1 years of follow-up, 7,262 incident cases of T2D were identified. Compared with participants who reported never consumption of oily fish, the multivariable-adjusted hazard ratios of T2D were 0.84 (95% CI 0.78–0.91), 0.78 (0.72–0.85), and 0.78 (0.71–0.86) for those who reported <1 serving/week, weekly, and ≥2 servings/week of oily fish consumption, respectively (*P*-trend < 0.001). Consumption of nonoily fish was not associated with risk of T2D (*P*-trend = 0.45). Participants who reported regular fish oil use at baseline had a 9% (95% CI 4–14%) lower risk of T2D compared with nonusers. Baseline regular users of fish oil who also reported fish oil use during at least one of the 24-h dietary recalls had an 18% (8–27%) lower risk of T2D compared with constant nonusers.

CONCLUSIONS

Our findings suggest that consumption of oily fish but not nonoily fish was associated with a lower risk of T2D. Use of fish oil supplements, especially constant use over time, was also associated with a lower risk of T2D.

Fish, especially oily fish such as salmon, is the major dietary source of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) (e.g., eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]). Mounting evidence supports a beneficial role of n-3 LCPUFA intake, from either fish or fish oil supplements, in the development and progression of cardiovascular disease (CVD) (1,2). This evidence has led to recommendations in national guidelines on increasing consumption of fish, especially nonfried species high in n-3 LCPUFAs, as an important part of healthy dietary patterns (3,4).

[1]*Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY*
[2]*Department of Nutrition and Food Hygiene, School of Public Health, Jiangsu Key Laboratory of Preventive and Translational Medicine for Geriatric Diseases, Soochow University, Suzhou, China*
[3]*State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai, China*
[4]*Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA*
Corresponding author: Qibin Qi, qibin.qi@einsteinmed.org

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Despite the dietary recommendations, epidemiologic studies that have assessed the association between fish consumption and risk of type 2 diabetes (T2D) have yielded conflicting results. Meta-analyses of prospective cohort studies have suggested geographic differences in the fish-T2D association, with an inverse association when combining studies conducted in China, Japan, and Australia; no association in European studies; and a positive association among studies conducted in the U.S. (5,6). One potential explanation for such regional differences in the fish-T2D association might involve variations in the fat content of fish consumed by different study populations. In this regard, in a pooled analysis of eight European cohorts, consumption of fatty fish rather than lean fish was inversely associated with risk of T2D (7), but findings from other cohort studies on the potential influence of the fat content of fish on T2D risk have been limited and inconsistent (8–10). Thus, additional large cohort studies of fish consumption and risk of T2D, especially studies that distinguish between fatty and nonfatty fish, are still needed.

In the current study, we examined the associations between consumption of oily and nonoily fish and risk of T2D in a large prospective study of a U.K. population (the UK Biobank [11]). We also examined the relationship between habitual use of fish oil supplements and risk of T2D.

RESEARCH DESIGN AND METHODS

Study Population and Design

The UK Biobank is a large, prospective, observational study established to provide a resource for investigation of the genetic, environmental, and lifestyle factors associated with a wide range of diseases, including diabetes. The full UK Biobank study protocol is available online (https://www.ukbiobank.ac.uk/media/gnkeyh2q/study-rationale.pdf). Briefly, ~500,000 men and women of various ethnicities aged 37–73 years were recruited from across 22 centers located throughout England, Wales, and Scotland between 2006 and 2010 (11). Participants underwent various measurements and provided a wide range of information on health and diseases at recruitment. The UK Biobank received ethical approval from the research ethics committee (REC reference for UK Biobank 11/NW/0382), and participants provided written informed consent.

Dietary Assessment

Information on habitual dietary intake at baseline was collected through a touchscreen food frequency questionnaire that included 29 questions about the average intake of major foods or food groups over the past year. The questions on consumption of oily fish, nonoily fish, and meat (beef, lamb, pork, processed meat, and poultry) had six frequency categories ranging from never to once or more daily. The questions asking about habitual consumption of oily fish and nonoily fish are reported in Supplementary Fig. 1. For fruit, vegetables, cereal, and coffee, participants were asked to directly enter the integer number of pieces, heaped tablespoons, bowls, and cups, respectively, that they ate or drank per day or to select less than one if the consumption was less than daily. Participants who responded do not know or prefer not to answer for a specific dietary item were considered to have missing information on that dietary intake. Information on habitual use of fish oil supplements was collected by asking, "Do you regularly take any of the following?" Furthermore, participants were asked whether they had made any major changes to their diet in the past 5 years and if the answer was yes, the reason for the changes. More details about the questions and possible responses are available online (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100052).

Participants were also invited to complete five rounds of 24-h dietary recalls conducted using the Oxford WebQ between 2009 and 2012 (12). Of 211,025 participants who completed at least one dietary recall, we included 163,706 participants (55.7% women) who did not have diabetes, major CVD, or cancer at any of the dietary assessments and who had realistic total energy intake (3,349–16,747 kJ/day [800–4,000 kcal/day] in men and 2,093–14,654 kJ/day [500–3,500 kcal/day] in women [13]). If a participant reported during a 24-h recall that he or she did not eat or drink normally the day before (e.g., because of fasting, illness, or other reasons), dietary data from that 24-h recall were omitted. Using dietary data collected from these 24-h recalls, we calculated mean intakes of meat, oily fish, and nonoily fish for each of the six frequency categories (described above) among this subsample and then assigned these means to the same intake categories in the whole study sample to generate average meat/fish intakes that may be reflective of the amounts of long-term intake (14).

Ascertainment of Diabetes

Prevalent diabetes at baseline was identified through multiple procedures that took into account type of diabetes (e.g., type 1, type 2) and sources of the diagnosis (e.g., self-report, medical record) (15) in addition to potential undiagnosed diabetes (hemoglobin A_{1c} [HbA_{1c}] $\geq$6.5% [48 mmol/mol]) (16). Diabetes that occurred during follow-up was identified using hospital inpatient records from the Hospital Episode Statistics for England, Scottish Morbidity Record data for Scotland, and Patient Episode Database for Wales. Incident T2D was defined by ICD-10 code E11 (17), and information on date of diagnosis was collected through cumulative medical records of hospital diagnoses.

Assessment of Other Covariates

Information on demographic and socioeconomic factors, lifestyle behaviors, reproductive and medical histories, and medication use was collected at baseline through a touchscreen questionnaire and nurse-led interviews. The Townsend deprivation index, a composite measure of deprivation that is based on four socioeconomic variables (unemployment, non–car ownership, non–home ownership, and household overcrowding), was generated. BMI was calculated using measured weight and height (kg/m^2). Hypertension was defined as a measured systolic/diastolic blood pressure of $\geq$140/90 mmHg, self-reported physician's diagnosis, or self-reported use of antihypertensive medications. Hyperlipidemia was defined as self-reported physician's diagnosis or self-reported lipid-lowering medication use. Baseline physical activity was assessed using the self-reported short-form international physical activity questionnaire, and the data were summarized and reported in MET-h per week. A binary variable was created to reflect whether a participant met the 2017 U.K. Physical Activity Guidelines (150 min/week of moderate activity or 75 min/week of vigorous activity). Multiple blood biomarkers, including serum major lipids and C-reactive protein and plasma HbA_{1c}, were quantified using blood samples collected at baseline (18).

Statistical Analysis

For the current analysis, we excluded participants who had self-reported or diagnosed diabetes ($n = 31,229$) or self-reported or diagnosed CVD (i.e., myocardial infarction, stroke) or cancer ($n = 65,547$) at baseline. We further excluded participants with missing data on fish intake or fish oil supplements ($n = 8,356$) or other major foods or food groups ($n = 5,014$) and participants who withdrew from the study ($n = 884$). After these overlapping exclusions, 392,287 participants (176,531 men and 215,756 women) remained for the main analyses. Because of a small number of incident cases of T2D (<80) among participants who had oily fish or nonoily fish intake of above four times a week, we created four categories (never, <1, 1, and ≥ 2 servings/week) by combining the upper categories for both intakes. Baseline participant characteristics were summarized according to the four categories of oily or nonoily fish intake.

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs of T2D for each category of oily/nonoily fish intake (the lowest intake category was used as the reference), for fish intake of 1 serving/week, or for habitual use of fish oil supplements (yes vs. no). Person-time of follow-up was calculated from the date of enrollment through the date of diagnosis of T2D, death, or end of the most recent follow-up (1 April 2019), whichever came first. Three main models were constructed to account for potential confounders. The minimal model was adjusted for age at baseline, sex, ethnic group, Townsend deprivation index, and BMI. The second model was additionally adjusted for lifestyle factors (smoking status, pack-years of smoking, alcohol consumption, and total physical activity), other major foods or food groups (coffee, cereal, fresh fruit, fresh vegetables, red meat, poultry, and processed meat consumption), and oily or nonoily fish consumption or fish oil supplement use where appropriate. The full model was further adjusted for hypertension and hyperlipidemia statuses.

Among the subsample of 163,706 participants with dietary data collected from the 24-h dietary recalls, a secondary analysis with additional adjustment for total energy intake was performed for the associations of oily and nonoily fish consumption (per 1 serving/week) with risk of T2D. In addition, on the basis of the status of fish oil supplement use reported at baseline and during the five rounds of 24-h dietary recalls, we categorized participants into five groups: constant nonusers who used fish oil neither at baseline nor during the 24-h recalls; occasional users who used fish oil at baseline only or during the 24-h recalls only; and constant users who used fish oil both at baseline and during one (modestly constant), two (moderately constant), or three or more (highly constant) 24-h recalls. The occasional user group and the three constant user groups were compared with the group of constant nonusers for risk of T2D after multivariable adjustment and further adjustment for total energy intake and total number of completed dietary assessments.

We performed stratified analyses for the main analyses and tested for potential interactions of oily/nonoily fish consumption or fish oil supplement use with age, sex, smoking status, alcohol consumption, BMI, physical activity, hypertension, hyperlipidemia, fish consumption (for fish oil supplements), fish oil supplements (for fish consumption), and processed meat consumption. Sensitivity analyses were performed to test the robustness of the findings by excluding participants who responded that they had made major changes to their diet in the past 5 years or incident T2D cases that were identified within the first 4 years of follow-up. Finally, we performed additional exploratory analyses in which the multivariable-adjusted associations of fish/fish oil with risk of T2D were further adjusted for individual metabolic biomarkers (i.e., triglycerides, HDL cholesterol, non-HDL cholesterol, C-reactive protein, HbA_{1c}). For these analyses, biomarker concentrations were transformed using a rank-based inverse normal transformation to approximate a normal distribution (19), and all results were further adjusted for fasting time (hours) for blood samples. Statistical analyses were performed using Stata 15.1 software (StataCorp).

RESULTS

Participant Characteristics

Compared with participants with lower intake of oily fish at baseline, those with higher intake were older, less likely to be male, White, or current smokers, and more likely to drink alcohol moderately, be physically active, and have hypertension and hyperlipidemia (Table 1). The distributions of baseline participant characteristics according to nonoily fish (Table 1) or fish oil supplement use (Supplementary Table 1) were similar to those according to oily fish intake. However, higher intake of oily fish was associated with lower BMI, higher intakes of fresh fruit and vegetables, and lower intake of processed meat, whereas higher nonoily fish intake was associated with higher BMI and higher intake of processed meat. Intakes of oily and nonoily fish were positively correlated (Pearson $r = 0.39$), and both intakes were associated with regular use of fish oil supplements.

Oily Fish and Nonoily Fish Consumption and Risk of T2D

At baseline, 17.5% ($n = 68,747$) and 16.2% ($n = 63,674$) of participants reported oily fish and nonoily fish consumption of ≥ 2 servings/week, respectively. During a median 10.1 years of follow-up, 7,262 incident cases of T2D were identified. As shown in Table 2, regardless of the degree of adjustment for potential confounders, there was a significant inverse association between oily fish consumption and risk of T2D (P-trend < 0.001). Compared with participants who reported never consumption of oily fish, those reporting ≥ 2 servings/week of oily fish consumption had a 22% (95% CI 14–29%) lower risk of T2D after full adjustment for potential confounders. Each additional increment in oily fish intake of 1 serving/week was associated with an 8% (4–11%) lower risk of T2D. Consumption of nonoily fish was significantly associated with a lower risk of T2D after adjustment for age, sex, ethnic group, Townsend deprivation index, and BMI (P-trend = 0.002) but not after the full adjustment (P-trend = 0.45). Among the subsample of 163,706 participants with dietary data collected from 24-h dietary recalls, oily fish consumption remained inversely associated with risk of T2D (per 1 serving/week: HR 0.92 [95% CI 0.86–0.98]) after multivariable adjustment in addition to adjustment for total energy intake (Table 2).

Fish Oil Supplements and Risk of T2D

At baseline, 31.4% ($n = 123,350$) of participants reported regular use of fish oil supplements. Compared with participants without regular use of fish oil, those who

Table 1—Baseline participant characteristics according to oily fish and nonoily fish intake in the UK Biobank

	Oily fish intake, servings/week				Nonoily fish intake, servings/week			
	Never	<1	1	≥2	Never	<1	1	≥2
Participants, *n*	42,624	132,273	148,643	68,747	18,222	114,755	195,636	63,674
Age (years)	53.5 ± 8.1	54.9 ± 8.0	56.6 ± 8.0	57.7 ± 7.9	53.5 ± 8.2	55.1 ± 8.0	56.4 ± 8.0	56.1 ± 8.1
Men	46.8	47.4	43.2	43.1	42.8	46.5	44.9	43.3
White ethnicity	91.9	91.2	91.0	89.2	88.6	89.7	91.7	90.8
Townsend deprivation index >0*	35.4	26.8	24.9	28.3	37.4	28.8	25.3	27.6
Smoking status								
Never	56.3	56.4	57.4	55.2	59.2	56.0	56.7	56.2
Former	29.1	32.8	33.8	35.9	28.3	32.9	33.8	34.0
Current	14.6	10.8	8.8	8.9	12.5	11.1	9.5	9.8
Alcohol 1–4 drinks/week	43.8	49.9	52.3	50.4	39.6	48.6	52.0	50.6
Total PA (MET-h/week)	45.6 ± 48.9	41.3 ± 43.6	44.5 ± 44.0	51.2 ± 48.4	44.9 ± 47.2	41.7 ± 44.3	44.8 ± 44.6	50.1 ± 48.1
MVPA meets guideline†	51.8	50.8	56.2	62.0	53.2	51.1	55.6	60.3
BMI (kg/m^2)	27.5 ± 5.0	27.2 ± 4.6	27.0 ± 4.4	27.0 ± 4.5	26.7 ± 4.9	27.2 ± 4.6	27.1 ± 4.5	27.2 ± 4.7
Hypertension	50.3	51.1	54.2	57.0	47.1	51.1	54.4	55.0
Hyperlipidemia	9.5	10.3	12.5	15.0	8.6	10.8	12.4	13.1
Coffee (cups/day)	2.1 ± 2.4	2.1 ± 2.1	2.0 ± 1.9	1.9 ± 2.0	1.9 ± 2.4	2.1 ± 2.2	2.0 ± 2.0	2.0 ± 2.1
Cereal (bowls/day)	0.6 ± 0.4	0.6 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.4	0.6 ± 0.4	0.7 ± 0.4	0.7 ± 0.4
Fresh fruit (pieces/day)	2.0 ± 1.7	2.0 ± 1.5	2.3 ± 1.5	2.7 ± 1.7	2.2 ± 1.8	2.0 ± 1.5	2.2 ± 1.5	2.5 ± 1.7
Fresh vegetables (heaped Tbsp/day)	4.4 ± 3.6	4.4 ± 3.0	5.0 ± 3.1	5.9 ± 3.9	5.1 ± 4.1	4.4 ± 3.2	4.9 ± 3.1	5.6 ± 3.8
Red meat ≥2 servings/week	39.0	52.2	53.5	44.2	27.9	48.9	53.6	46.4
Poultry ≥2 servings/week	41.1	47.9	49.4	51.9	28.1	45.5	49.3	56.8
Processed meat ≥2 servings/week	33.6	34.3	29.5	24.6	21.8	30.2	31.8	30.6
Oily fish ≥2 servings/week	NA	NA	NA	NA	3.0	9.5	17.6	35.9
Nonoily fish ≥2 servings/week	8.0	10.0	16.3	33.2	NA	NA	NA	NA
Fish oil supplement use	21.2	27.1	34.4	39.7	18.6	28.7	33.2	34.8

Data are mean ± SD or % unless otherwise indicated. MVPA, moderate to vigorous physical activity; NA, not applicable; PA, physical activity. *A higher Townsend deprivation index indicates a greater degree of deprivation (or lower socioeconomic status). †At or >150 min/week of moderate activity or 75 min/week of vigorous activity.

reported regular fish oil supplements had a 9% (95% CI 4–14%) lower risk of T2D after full adjustment (Table 3).

During each of the five rounds of 24-h dietary recalls, ~24% of participants reported fish oil supplement use (Fig. 1). Compared with participants who were constant nonusers of fish oil both at baseline and during the 24-h dietary recalls, baseline regular fish oil users who also reported use of fish oil at one, two, and three or more of the 24-h dietary recalls had a 15%, 22%, and 23% lower risk of T2D, respectively, after multivariable adjustment, including adjustment for total energy intake and total number of completed dietary assessments (Table 3). The HR of T2D was 0.82 (95% CI 0.73–0.92) when the latter three groups of regular fish oil users were combined and compared with the group of constant nonusers.

Subgroup and Sensitivity Analyses

The inverse associations of oily fish intake and regular use of fish oil supplements (reported at baseline) with risk of T2D were observed across various subgroups of the population (Fig. 2 and Supplementary Table 2). For both oily fish intake and fish oil supplements, the inverse associations with risk of T2D were strongest among leaner participants (BMI <25 kg/m^2) and were also evident in overweight (BMI 25 to <30 kg/m^2) but not in obese (BMI ≥30 kg/m^2) participants. Furthermore, the association of oily fish intake with risk of T2D appeared to be stronger among fish oil nonusers than among users, and the relationship between fish oil supplements and risk of T2D was stronger among participants with lower intake of oily fish (<1 serving/week) than among those with higher intake. Except for a significant inverse association in overweight participants, nonoily fish intake was not associated with risk of T2D in other subgroups of the population.

Because of the high prevalence of cardiovascular risk factors (which may lead to increased oily fish intake or initiation of fish oil use) among participants with obesity, we further stratified the examined associations according to hypertension/hyperlipidemia status for the 86,204 obese participants. The results showed that use of fish oil supplements was not associated with risk of T2D among obese participants with either hypertension or hyperlipidemia but was associated with a lower risk of T2D among those with neither of the risk factors (HR 0.77 [95% CI 0.64–0.93]) (Supplementary Table 3).

After excluding the 142,530 participants (3,511 cases) who reported major changes to their diet in the 5 years before the baseline assessment, intake of oily fish (*P*-trend < 0.001) but not nonoily fish (*P*-trend = 0.40) remained significantly and inversely associated with risk of T2D, while the association became marginally nonsignificant for fish oil (*P* = 0.053) (Supplementary Table 4). Results were similar after excluding the 2,084 incident cases of T2D that were identified within

Table 2—Consumption of oily fish and nonoily fish and risk of T2D in the UK Biobank

			HR (95% CI)		
	Cases/participants	Intake, servings/day*	Model 1	Model 2	Model 3
Oily fish intake					
Never	1,026/42,624	0.02 ± 0.13	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
<1 serving/week	2,437/132,273	0.11 ± 0.33	0.79 (0.74–0.85)	0.83 (0.77–0.90)	0.84 (0.77–0.91)
1 serving/week	2,552/148,643	0.20 ± 0.43	0.73 (0.68–0.79)	0.78 (0.72–0.85)	0.78 (0.72–0.85)
≥2 servings/week	1,247/68,747	0.36 ± 0.53	0.72 (0.66–0.79)	0.79 (0.72–0.87)	0.78 (0.71–0.86)
P-trend			<0.001	<0.001	<0.001
Per 1 serving/week	7,262/392,287		0.89 (0.86–0.92)	0.93 (0.90–0.97)	0.92 (0.89–0.96)
Per 1 serving/week (energy adjustment)†	1,798/163,706		0.89 (0.83–0.94)	0.92 (0.86–0.99)	0.92 (0.86–0.98)
Nonoily fish intake					
Never	387/18,222	0.05 ± 0.33	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
<1 serving/week	2,074/114,755	0.27 ± 0.59	0.80 (0.72–0.89)	0.89 (0.79–1.01)	0.89 (0.79–1.01)
1 serving/week	3,658/195,636	0.37 ± 0.68	0.82 (0.74–0.91)	0.97 (0.87–1.09)	0.96 (0.85–1.09)
≥2 servings/week	1,143/63,674	0.52 ± 0.79	0.76 (0.68–0.86)	0.92 (0.80–1.04)	0.90 (0.79–1.03)
P-trend			0.002	0.59	0.45
Per 1 serving/week	7,262/392,287		0.95 (0.92–0.98)	0.99 (0.96–1.03)	0.99 (0.95–1.02)
Per 1 serving/week (energy adjustment)†	1,798/163,706		0.95 (0.90–1.00)	0.98 (0.92–1.04)	0.98 (0.72–1.04)

Data are *n* or mean ± SD unless otherwise indicated. Model 1 was adjusted for age (years), sex, ethnic group (White, other), Townsend deprivation index, and BMI (kg/m^2). Model 2 was adjusted for covariates in model 1 and smoking status (never, former, current), pack-years of smoking (for current smokers), alcohol consumption (never, former, current [<1, 1–4, ≥5 drinks/day]), total physical activity (MET-h/week), consumption of coffee (cups/day), cereal (bowls/day), fresh fruit (pieces/day), fresh vegetables (Tbsp/day), red meat (servings/day), poultry (servings/day), processed meat (servings/day), and fish oil supplement use (yes, no). Oily fish and nonoily fish were mutually adjusted for each other. Model 3 was adjusted for covariates in model 2 and hypertension (yes, no) and hyperlipidemia (yes, no). *Values were estimated from 163,706 participants who had dietary data collected from both the baseline food frequency questionnaire and the 24-h dietary recalls. All participants did not have T2D, major CVD, or cancer at any of the dietary assessments and had a realistic total energy intake. If a participant reported during a 24-h recall that he or she did not eat or drink normally the day before (e.g., because of fasting, illness, or other reasons), dietary data from that 24-h recall were omitted. †The analyses were conducted among the 163,706 participants described above, and all models were additionally adjusted for total energy intake.

the first 4 years of follow-up (Supplementary Table 5). Among 338,134 participants (6,264 cases) with measures of various metabolic biomarkers, the associations of oily/nonoily fish intake or fish oil use with risk of T2D were not materially changed by further adjustment for individual metabolic biomarkers (Supplementary Table 6).

CONCLUSIONS

In a large prospective study that included 7,262 incident cases of T2D among 392,287 U.K. men and women, intake of oily fish was significantly and inversely associated with risk of T2D, while intake of nonoily fish was not associated with risk of T2D. Regular use of fish oil supplements reported at baseline was also associated with a modestly lower risk of T2D, and the lowest risk was observed

Table 3—Fish oil supplement use and risk of T2D in the UK Biobank

		HR (95% CI)		
	Cases/participants, *n*	Model 1	Model 2	Model 3
Fish oil supplements (baseline FFQ) (*n* = 392,287)				
0 (no)	5,111/268,937	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
1 (yes)	2,151/123,350	0.88 (0.83–0.92)	0.91 (0.87–0.96)	0.91 (0.86–0.96)
P		<0.001	0.001	<0.001
Fish oil supplements (baseline FFQ/24-h recalls) (*n* = 163,706)*				
Constant nonuse (0/0)†	1,178/102,683	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Occasional use (1/0 or 0/≥1)†	256/23,683	0.91 (0.80–1.04)	0.93 (0.81–1.07)	0.93 (0.81–1.07)
Modestly constant use (1/1)†	200/17,868	0.83 (0.71–0.97)	0.85 (0.73–1.00)	0.85 (0.73–0.99)
Moderately constant use (1/2)†	79/8,756	0.77 (0.61–0.97)	0.78 (0.62–0.99)	0.78 (0.62–0.99)
Highly constant use (1/≥3)†	85/10,716	0.77 (0.61–0.97)	0.77 (0.61–0.98)	0.77 (0.61–0.98)
P-trend		<0.001	<0.001	<0.001
Any constant use (1/≥1)†	364/37,340	0.80 (0.71–0.90)	0.83 (0.73–0.93)	0.82 (0.73–0.92)

Model 1 was adjusted for age (years), sex, ethnic group (White, other), Townsend deprivation index, and BMI (kg/m^2). Model 2 was adjusted for covariates in model 1 and smoking status (never, former, current), pack-years of smoking (for current smokers), alcohol consumption (never, former, current [<1, 1–4, ≥5 drinks/day]), total physical activity (MET-h/week), and consumption of coffee (cups/day), cereal (bowls/day), fresh fruit (pieces/day), fresh vegetables (Tbsp/day), red meat (servings/day), poultry (servings/day), processed meat (servings/day), oily fish (servings/day), and nonoily fish (servings/day). Model 3 was adjusted for covariates in model 2 and hypertension (yes, no) and hyperlipidemia (yes, no). FFQ, food frequency questionnaire. *The analyses included 163,706 participants described in Table 2 legend, and all models were additionally adjusted for total energy intake and total number of dietary assessments. †The first number indicates the status of habitual fish oil use at baseline (0 = no, 1 = yes), and the second number indicates the number of reported use of fish oil (yes) during the 24-h dietary recalls. For example, 0/0 indicates that the participants reported neither habitual use at baseline nor use during the 24-h dietary recalls, while 1/≥3 indicates that the participants reported habitual use at baseline and also reported use of fish oil during at least three of the 24-h dietary recalls.

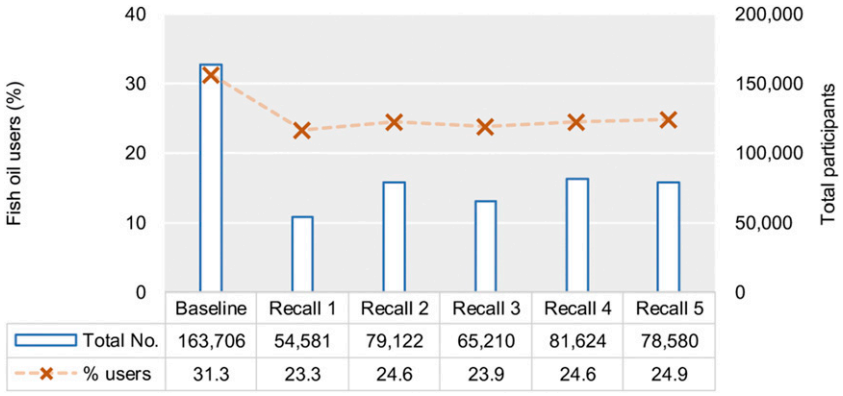

Figure 1—Percentage of fish oil users at baseline and during five rounds of 24-h dietary recalls in the UK Biobank. Data are from 163,706 participants who reported the status of fish oil use both at baseline and during the 24-h dietary recalls (see Table 2 legend).

for baseline regular users who constantly reported use of fish oil supplements on the subsequent 24-h dietary recalls.

Comparison With Findings From Other Studies

Previous epidemiologic studies examining the association of total fish consumption with risk of T2D have yielded conflicting results. Findings from several meta-analyses of prospective studies have indicated geographic differences in the association (5,6), with an inverse association for studies conducted in China, Japan, and Australia; a positive association for studies from the U.S.; and no association for European studies. Findings from two subsequent prospective studies are also inconsistent. In a cohort of 461,036 Chinese adults (20), higher total fish consumption was associated with a modestly higher risk of T2D, but the association became nonsignificant after further adjustment for BMI. In another cohort of 15,100 Chinese adults (21), low to moderate total fish consumption was associated with a higher risk of T2D.

In the current study, we observed that higher intake of oily fish, but not nonoily fish, was associated with a lower risk of T2D. Thus, it is possible that the potential regional differences in the fish-T2D association might be partially attributable to the variations in the fat content of fish consumed by different study populations. Several previous cohort studies have taken into account the fat content of fish when assessing the fish-T2D association. In a pooled analysis of cohorts from eight European countries (7), fatty fish intake was modestly and inversely associated with risk of T2D, while lean fish was not associated with risk of T2D. In a cohort of Japanese men and women (8), oily fish intake was inversely associated with risk of T2D only in men, and there was no association for lean fish in either sex. In the Rotterdam Study (9), higher lean fish intake was associated with a higher risk of T2D, while there was no association for fatty fish. Finally, in a cohort of Norwegian women (10), higher lean fish intake was associated with a lower risk of T2D, while no association was found for fatty fish.

A recent systematic review and meta-analysis (22) pooled data from 17 randomized controlled trials and concluded that n-3 LCPUFA supplements had limited or no effects on likelihood of diagnosis of T2D. Nevertheless, there were only six trials with a total of 229 cases (201 cases were from two trials) that had a low risk of bias, and thus, more data from large, high-quality trials are still needed. Moreover, these post hoc analyses of cardiovascular trials may be prone to competing risk when using T2D as the outcome of interest. In the largest trial (23), which contributed to 45.5% (503 of 1,105) of the T2D cases in the meta-analysis, n-3 LCPUFA supplements resulted in a 20% decrease in the risk of death compared with the control group. As such, participants in the active arm are expected to have a longer life span and, thus, more time to develop T2D than those in the control arm, which may attenuate or reverse a modest inverse association between n-3 LCPUFA supplements and risk of T2D. In addition, there is evidence that EPA and DHA in blood may be saturable at moderate n-3 LCPUFA intake (e.g., ~0.4 g/day) (24). Both in our study and in the pooled analysis of eight European cohorts (7), the reduction in risk of T2D tended to level off at modest or greater intake of oily fish (e.g., ≥1 serving/week). We also found that the inverse fish oil-T2D association was stronger among participants with oily fish intake of <1 serving/week than among those with higher intake. Because trial participants are usually health-conscious volunteers (13,25) who may have a healthy eating pattern during the intervention, their n-3 LCPUFA intake from usual diet might have been sufficient to provide benefits.

Potential Mechanisms

Adipose tissue has been postulated to be a central target for n-3 LCPUFAs in the prevention and treatment of metabolic diseases (26–28). Multiple mechanisms of action that may underlie the favorable metabolic effects of n-3 LCPUFAs have been proposed, including prevention of adipose tissue hyperplasia and hypertrophy, induction of mitochondrial biogenesis, secretion of healthy adipokines (e.g., adiponectin), and amelioration of inflammation (26–28). In animal studies, n-3 LCPUFAs attenuated diet-induced obesity and insulin resistance (29,30). Recently, the G-protein–coupled receptor 120 (or free fatty acid receptor 4), which is highly expressed in adipose tissue and is closely related to regulation of body weight and insulin sensitivity (31), has been suggested to be a functional receptor that mediates the potential insulin-sensitizing and antidiabetic effects of n-3 LCPUFAs (32–34). In obese mice fed a high-fat diet, treatment with n-3 LCPUFAs inhibited inflammation and enhanced insulin sensitivity in wild-type mice but not in G-protein–coupled receptor 120 knockout littermates (32).

Despite the plausible mechanisms, meta-analyses (22,35) of human intervention trials have reported no significant effects of n-3 LCPUFA supplements on control of plasma glucose, fasting insulin, HOMA of insulin resistance, or HbA_{1c} (although there was a reduction of HbA_{1c} when n-3 LCPUFAs were compared with n-6 LCPUFAs [22]). However, more recent findings from other trials have suggested beneficial effects of n-3 LCPUFAs on regulation of these metabolic markers (36–39), especially when n-3 LCPUFAs was supplemented with vitamin D (38,39) or a specific eating pattern (37). It is unclear to what extent these findings

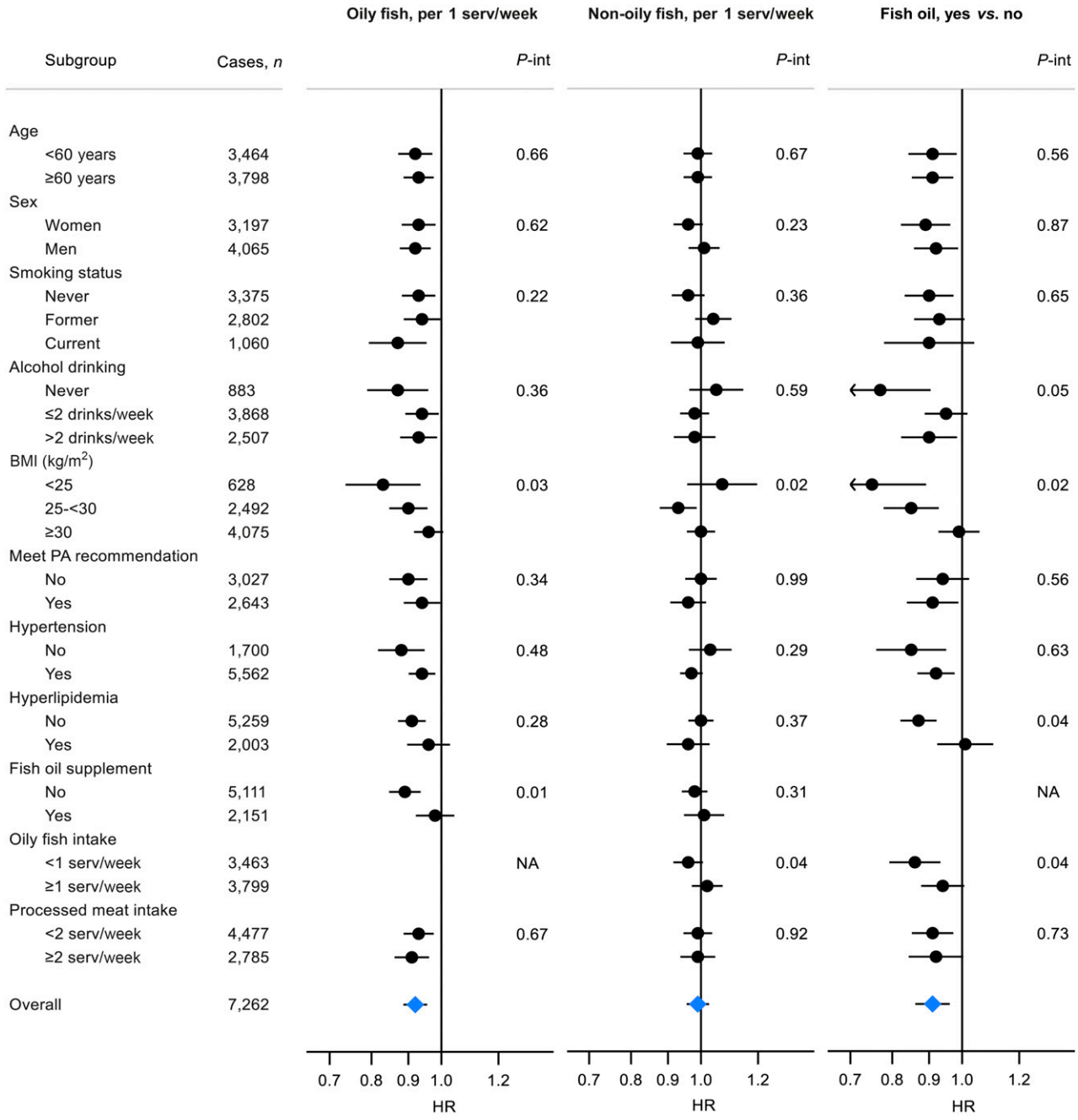

Figure 2—Subgroup analyses for the associations of oily fish and nonoily fish consumption and fish oil supplement use with risk of T2D in the UK Biobank. Results were adjusted for covariates listed for model 3 of Table 2 (for fish) or Table 3 (for fish oil). PA, physical activity; *P*-int, *P* value for interaction; serv, serving.

for the glycemic effect of n-3 LCPUFA intake may be influenced by participants' background diet (discussed above) or whether n-3 LCPUFA intake as part of a matrix of other food components is essential for its benefits with respect to glucose metabolism. Moreover, findings from two trials (40,41) have shown that administration of EPA alone moderately reduced risk of major CVD, while most other trials (42), including two published recently (43,44), have failed to find any effects of a combination of EPA and DHA on risk of major CVD. Thus, it is unclear whether fatty acid composition (e.g., EPA vs. DHA or a mixture of the two fatty acids) may also influence the association between n-3 LCPUFAs and risk of diabetes or glycemic control.

Strengths and Limitations

Strengths of our study include the prospective design, the large sample size, and the repeated assessments of dietary intake and fish oil supplement use. As well, the comprehensive collection of information on participants' characteristics allowed for statistical adjustment for a wide range of potential confounders.

Several potential limitations should be acknowledged when interpreting the findings from the current study. First, despite the adjustment for various traditional risk factors for T2D, we cannot completely exclude the possibility that the observed inverse associations of oily fish intake/regular fish oil use with risk of T2D were driven by residual or

unmeasured confounding. Second, while we examined oily and nonoily fish separately, there was no information available to allow further examination of the influence of more-specific types of fish or fish preparation methods on the examined fish-T2D association. Third, most fish consumers in our study had low to moderate levels of fish intake, and only 17.5% and 16.2% of participants had oily fish or nonoily fish intake of $\geq$2 servings/week. Furthermore, the participants were predominantly of European descent and healthier than the U.K. general population (45); thus, caution is needed when generalizing our findings to other populations. Finally, given that oily fish and fish oil are widely recommended for CVD prevention, some at-risk participants in our study may have increased fish intake and/or initiated fish oil supplements, which may partially account for the higher rates of hypertension and hyperlipidemia among those with higher fish intake or regular fish oil use (Table 1 and Supplementary Table 1). As such, the observed association of fish intake or fish oil supplements with risk of T2D may have been underestimated, especially for obese individuals among whom cardiovascular risk factors are highly prevalent.

Public Health Significance

In conclusion, in a large prospective study of a U.K. population, our findings suggest that consumption of oily fish, but not nonoily fish, is associated with a lower risk of T2D. Despite a positive association between total fish consumption and risk of T2D observed in a few previous studies conducted in Western populations (5,6), our findings support retention of the current dietary recommendation on increasing consumption of oily fish. Use of fish oil supplements was also associated with a lower risk of T2D, and the lowest risk was observed among individuals who used fish oil constantly over time. At present, it is prudent to recommend fresh oily fish as a part of a healthy dietary pattern instead of fish oil supplements for diabetes prevention. Additional prospective studies conducted in other populations with different sociodemographic and lifestyle backgrounds are warranted to confirm our findings.

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Author Contributions. G.-C.C. and Q.Q. conceived and designed the study. G.-C.C. performed the statistical analysis and drafted the manuscript. All authors contributed to the interpretation of data and critically reviewed and revised the manuscript. Q.Q. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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