Fish, shellfish, and long-chain n−3 fatty acid consumption and risk of incident type 2 diabetes in middle-aged Chinese men and women[1–3]

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ABSTRACT

Background: Long-chain polyunsaturated n–3 (omega-3) fatty acids, found mainly in fish, have been postulated to reduce type 2 diabetes (T2D) risk. However, the role of long-chain n−3 fatty acids and fish intake in the development of T2D remains unresolved.

Objective: We examined associations between fish, shellfish, and long-chain n−3 fatty acids and the risk of T2D in a middle-aged Chinese population.

Design: This was a prospective population-based cohort study in 51,963 men and 64,193 women free of T2D, cardiovascular disease, and cancer at baseline with valid dietary information. Dietary intake, physical activity, and anthropometric measurements were collected. A Cox regression model was used to evaluate the association of fish, shellfish, and long-chain n−3 fatty acid (in g/d) with risk of T2D.

Results: Fish, shellfish, and long-chain n−3 fatty acid intakes were inversely associated with T2D in women. The relative risks [RRs (95% CI)] for quintiles of fish intake were 1.00, 0.96 (0.86, 1.06), 0.84 (0.75, 0.94), 0.80 (0.71, 0.90), and 0.89 (0.78, 1.01) (*P* for trend = 0.003) and for shellfish were 1.00, 0.91 (0.82, 1.01), 0.79 (0.71, 0.89), 0.80 (0.71, 0.91), and 0.86 (0.76, 0.99) (*P* for trend = 0.006). In men, only the association between shellfish intake and T2D was significant. The RRs (95% CI) for quintiles of fish intake were 1.00, 0.92 (0.75, 1.13), 0.80 (0.65, 1.00), 0.89 (0.72, 1.11), and 0.94 (0.74, 1.17) (*P* for trend = 0.50) and for shellfish intake were 1.00, 0.93 (0.76, 1.12), 0.70 (0.56, 086), 0.66 (0.53, 0.82), and 0.82 (0.65, 1.02) (*P* for trend = 0.003).

Conclusions: An inverse association between fish and shellfish intake and T2D in women was found. No evidence of a detrimental effect of fish intake in this population was observed. *Am J Clin Nutr* 2011;94:543–51.

INTRODUCTION

One of the dietary factors postulated to influence the development of type 2 diabetes (T2D) is long-chain polyunsaturated n–3 (omega-3) fatty acids, which are found mainly in fish. This hypothesis is based on ecological studies reporting that populations with a high consumption of fish and marine animals have a lower prevalence of T2D than do other populations (1). The potential benefit of long-chain n−3 fatty acids in insulin sensitivity may be the consequence of their incorporation into cell membranes, because insulin sensitivity is directly related to the proportion of long-chain polyunsaturated fatty acids present in cell membranes (2). However, long-chain n−3 fatty acid intervention studies have found no evidence of a beneficial effect on insulin sensitivity or blood glucose concentrations in nondiabetic persons (3–5). Data from epidemiologic studies on the associations between fish intake and the risk of T2D (6–12) and between long-chain n−3 fatty acids and T2D incidence (11, 13, 14) are inconclusive.

We evaluated the association of fish and shellfish intake levels with the incidence of T2D in 2 large, population-based, prospective studies of middle-aged women and men—the Shanghai Women's Health Study (SWHS) and the Shanghai Men's Health Study (SMHS)—conducted in Shanghai, China, where consumption of fish and shellfish is high. We also evaluated the potential interactions between intake of fish, shellfish, and long-chain n−3 fatty acids with overall and central obesity.

SUBJECTS AND METHODS

Study population

The SWHS and SMHS are both population-based, prospective cohort studies based in urban Shanghai, China. The SWHS began first and recruited 74,942 women aged 40–70 y from 1996 to 2000 (15). The SMHS recruited 61,500 men aged 40–74 y from 2002 to 2006 (16). The overall response rates were 92% for women and 75% for men. The study protocols were approved by the institutional review boards of all institutes involved in the studies, and written informed consent was obtained from all participants before interview. For members of both cohorts, trained interviewers administered detailed in-person interviews at baseline using a structured questionnaire to collect information on demographic characteristics, dietary habits, physical activity, disease and surgery history, personal habits (including smoking, alcohol consumption, and tea consumption), residential history, occupational history, family cancer history, reproductive history, and hormone use (for women only). Body measurements, including height, weight, and waist and hip circumferences were also made at

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baseline. Previous publications have described information on the baseline methods in more detail for the SWHS (15) and the SMHS (16). The cohorts are followed-up by biennial in-person survey and record linkage with the Shanghai vital statistic registry. Three biennial in-person follow-ups for all living cohort members in the SWHS have been conducted by in-home visit between 2000 and 2002, 2002 and 2004, and 2004–2006 with response rates of 99.8%, 98.7%, and 94.9%, respectively. For the SMHS, the first follow-up for all living cohort members was conducted by in-home visits from 2004 to 2008, with a response rate of 97.65%.

Outcome ascertainment

Incident T2D was identified through outcome follow-up surveys. For the SWHS, 3037 participants reported having a T2D diagnosis since the baseline survey, of whom 3034 participants had valid dietary data. For the SMHS, there were 903 self reported T2D cases, valid dietary data were available for 900. We considered a case of T2D to be "confirmed" if the participants reported having a diagnosis of T2D and met at least one of the following criteria as recommended by the American Diabetes Association (15): *1*) fasting glucose concentration $\geq$7 mmol/L on $\geq$2 separate occasions, *2*) an oral-glucose-tolerance test (OGTT) performed in their doctor's office with a value $\geq$11.1 mmol/L, and/or *3*) use of hypoglycemic medication (ie, insulin or oral hypoglycemic drugs). Of the 3034 SWHS self-reported cases, a total of 2262 participants met the study outcome criteria and are referred to as "confirmed" cases of T2D. Because information on the number of abnormal fasting glucose tests and OGTT was not collected in the first follow-up survey, nearly one-third of self-reported cases did not meet our confirmation criteria. Therefore, cases identified during the first follow-up survey could not be confirmed. Of the 900 T2D cases from the SMHS, 833 were considered confirmed according to our study criteria. We performed analyses with all T2D cases and after exclusion of the probable cases and found similar trends; thus, we report results with all participants in this report. The total follow-up time was 8.9 y for the SWHS and 4.1 y for the SMHS.

Dietary intake

Usual dietary intake was assessed through an in-person interview by using a validated food-frequency questionnaire (FFQ) at the baseline recruitment survey and again at the first follow-up survey for both the SWHS (17) and SMHS (18). The specific FFQ data used in the analysis depended on when participants developed T2D. For participants who developed T2D, cardiovascular disease, or cancer between baseline and the first follow-up survey, we used data from the baseline FFQ, because the diagnosis of T2D could have resulted in changes in diet that could have been reflected on the follow-up FFQ. We used averages of data from the baseline and follow-up FFQ for all other participants. This was the case for participants of both the SWHS and SMHS.

The average daily intake of individual food items (in g/d) was combined to compute overall intake of the following food groups: combined fish and shellfish, shellfish, and 2 mutually exclusive fish groups—saltwater fish and freshwater fish. We used the Chinese Food Composition Tables to estimate intakes of energy (kcal/d), vitamin A, and specific fatty acids. We calculated the total consumption of long-chain n$-$3 fatty acids by combining intakes of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Other factors as potential confounders

Information on sociodemographic factors such as age, level of education (none, elementary school, middle/high school, or college), family income in yuan/y for women (<10,000, 10,000–19,999, 20,000–29,999, or $\geq$30,000) and individual yuan/y for men (<500, 500–900, 1000–1999, or >1999), occupation (professional, clerical, or manual labor for men and professional, clerical, manual labor, or housewife/retired for women), smoking (smoked $\geq$1 cigarette/d for >6 mo continuously), and alcohol intake (ever drank beer, wine, or spirits $\geq$3 times/wk for >6 mo), presence of hypertension at baseline, and family history of diabetes was collected by using a structured questionnaire.

All anthropometric measurements, including weight, height, and circumferences of waist and hips, were made at the baseline interview according to a standard protocol by trained interviewers who were retired medical professionals (20). From these measurements, the following variables were created: body mass index (BMI), calculated as weight (in kg) divided by the square of height (in m), and waist-to-hip ratio (WHR), calculated as waist circumference divided by hip circumference.

Detailed assessment of physical activity was collected by using validated questionnaires (21, 22). The questionnaires evaluated regular exercise and participation in sports during the 5 y preceding the interview, daily activity, and the daily commute to and from work. We calculated the metabolic equivalents (METs) for each activity using a compendium of physical activity values (23). We combined each of the exercise and lifestyle activity indexes to derive a quantitative estimate of overall nonoccupational activity (MET-h/d).

We previously identified 3 dietary patterns in both the SWHS and the SMHS: a vegetable-rich pattern, a fruit-rich pattern, and a meat-rich pattern. These dietary patterns were adjusted for in the analysis (16, 24).

Statistical analysis

There were 64,229 participants in the SWHS and 52,054 participants in the SMHS, all of whom were free of T2D and/or glycosuria, cancer, and cardiovascular disease at baseline. We excluded participants who had extreme values for total energy intake [<500 or >3500 kcal/d for women (*n* = 36) and <800 or >4200 kcal/d for men (*n* = 91)] (25), which left 64,193 women and 51,963 men for the final analysis.

Person-years of follow-up for each participant were calculated as the interval between the baseline recruitment to the diagnosis of T2D, censored at death, or completion of the second follow-up. The Cox proportional hazards model was used to assess the effect of fish and long-chain n$-$3 fatty acid intakes on the incidence of T2D. Food groups (in g/d) were categorized by quintile distribution, with the lowest quintile serving as the reference. Tests for trend were performed by entering the categorical variables as continuous variables in the models. Sociodemographic factors and other T2D risk factors were adjusted for in the analyses as potential confounders.

We conducted the stratified analysis by BMI and WHR categories. The log-likelihood ratio test was used to evaluate interactions between food groups with BMI and WHR. All analyses were performed by using SAS (version 9.1), and all tests of statistical significance were based on 2-sided probability.

RESULTS

The median intakes for fish and shellfish were 31.6 and 7.7 g/d for women and 31.8 and 8.5 g/d for men, respectively. Characteristics of the study populations by combined fish and shellfish intake are shown in **Table 1**. A higher intake of combined fish and shellfish was associated with younger age, higher exercise participation, higher education, having a professional job, higher household income, and higher alcohol consumption in both men and women. Participants with a higher intake of fish and shellfish were less likely to smoke. In men, combined fish and shellfish intake was inversely associated with diagnosed hypertension, whereas the opposite was found in women.

Combined fish and shellfish intake was associated with a decrease in risk of T2D in women. In the analysis adjusted for age only, the relative risks (RRs) for the lowest to highest quintiles of combined fish and shellfish intake were 1.00, 0.88, 0.79, 0.80, and 0.87 (*P* for trend = 0.001). We found similar inverse associations for fish intake and shellfish intake. The RRs for quintiles of fish intake were 1.00, 0.95, 0.84, 0.81, and 0.94 (*P* for trend = 0.02) and for shellfish intake were 1.00, 0.84, 0.71, 0.69, and 0.74 (*P* for trend < 0.001). The RRs for quintiles of long-chain n$-$3 fatty acid intake were 1.00, 0.90, 0.81, 0.87, and 0.87 (*P* for trend = 0.01) (data not shown in tables).

In multivariate analyses we found similar results (**Table 2**). Compared with the lowest quintile of intake, the multivariate-adjusted RRs of T2D across quintiles of combined fish and shellfish intake were 1.00, 0.93, 0.80, 0.83, and 0.86 (*P* for trend = 0.001). The inverse association was observed across quintiles of fish intake (all fish intake combined and intakes of saltwater fish and freshwater fish separately) and shellfish intake. Intake of long-chain n$-$3 fatty acids was also associated with a lower risk of T2D. As compared with the lowest quintile of intake, the multivariate-adjusted RRs of T2D across quintiles of long-chain n$-$3 fatty acids were 1.00, 0.90, 0.84, 0.87, and 0.84 (*P* for trend = 0.005). Although the trend tests were significant, the associations of fish, shellfish, and long-chain n$-$3 fatty acid intakes with T2D did not appear to follow a linear pattern.

We repeated the analysis in participants with "confirmed" diabetes and found similar trends. As compared with the lowest quintile of intake, the multivariate-adjusted RRs of T2D across quintiles of combined fish and shellfish intake were 1.00, 0.99, 0.81, 0.87, and 0.88 (*P* for trend = 0.02). The multivariate-adjusted RRs of T2D for fish intake were 1.00, 0.97, 0.84, 0.80, and 0.88 (*P* for trend = 0.008) and for shellfish intake were 1.00, 0.95, 0.88, 0.93, and 0.98 (*P* for trend = 0.58). The RRs of T2D for quintiles of long-chain n$-$3 fatty acid intake were 1.00, 0.94, 0.89, 0.93, and 0.88 (*P* for trend = 0.11). We excluded participants in whom a diagnosis of T2D was made in the first 2 y of follow-up and found similar results. The RRs for the lowest to highest quintiles of combined fish and shellfish intake were 1.00, 0.96, 0.83, 0.86, and 0.87 (*P* for trend = 0.02). The RRs for quintiles of fish intake were 1.00, 0.98, 0.88, 0.83, and 0.90 (*P* for trend = 0.02) and for quintiles of shellfish intake were 1.00, 0.91, 0.90, 0.93, and 0.93 (*P* for trend = 0.42). The RRs for quintiles of long-chain n$-$3 fatty acid intake were 1.00, 0.95, 0.92, 0.93, and 0.90 (*P* for trend = 0.15) (data not shown in tables).

We repeated the analysis adjusting for vitamin A, and the results did not change. The RRs for quintiles of fish intake were 1.00, 0.92, 0.78, 0.82, and 0.84 (*P* for trend = 0.001); for shellfish intake were 1.00, 0.91, 0.79, 0.80, and 0.85 (*P* for trend $<$0.001); and for fish-oil intake were 1.00, 0.90, 0.85, 0.88, and 0.86 (*P* for trend 0.02) (data not shown in tables).

In men, neither combined fish and shellfish intake nor individual intakes of fish or long-chain n$-$3 fatty acids alone were associated with T2D, whereas the intake of shellfish was inversely associated with T2D (**Table 3**). In the analyses adjusted for age only, the RRs for the lowest to highest quintiles of combined fish and shellfish intake were 1.00, 0.97, 0.80, 0.92, and 0.94 (*P* for trend = 0.46). The RRs for quintiles of fish intake were 1.00, 0.96, 0.83, 0.94, and 0.98 (*P* for trend = 0.81) and for quintiles of shellfish intake were 1.00, 0.89, 0.68, 0.63, and 0.80 (*P* for trend < 0.001). The RRs for quintiles of long-chain n$-$3 fatty acid intake were 1.00, 0.98, 0.89, 0.98, and 0.93 (*P* for trend = 0.54) (data not shown in tables). We found similar results in multivariate-adjusted analysis (Table 3). We repeated the analysis in only participants with "confirmed" T2D alone and found similar trends. Compared with the lowest quintile of intake, the multivariate-adjusted RRs of T2D across quintiles of combined fish and shellfish intake were 1.00, 0.92, 0.81, 0.90, and 0.90 (*P* for trend = 0.39). The multivariate-adjusted RRs of T2D for fish intake were 1.00, 0.92, 0.83, 0.90, and 0.93 (*P* for trend = 0.52) and for shellfish intake were 1.00, 0.98, 0.71, 0.70, and 0.81 (*P* for trend = 0.003). The RRs for quintiles of T2D for long-chain n$-$3 fatty acid intake were 1.00, 0.98, 0.88, 1.01, and 0.90 (*P* for trend = 0.58). When we repeated the analysis adjusting for vitamin A, we found similar results (data not shown in tables). The RR for quintiles of fish intake were 1.00, 0.92, 0.81, 0.91, and 0.96 (*P* for trend 0.67); for shellfish intake were 1.00, 0.93, 0.71, 0.68, and 0.87 (*P* for trend = 0.01); and for fish-oil intake were 1.00, 0.97, 0.87, 0.98, and 0.91 (*P* for trend = 0.53).

In stratified analyses, we assessed the potential effect modification by BMI ($\leq$25 or $>$25) with intakes of combined fish and shellfish, fish, saltwater fish, freshwater fish, shellfish, and long-chain n$-$3 fatty acids with T2D for the SWHS participants (**Table 4**). The inverse association between intakes of combined fish and shellfish, saltwater fish, and long-chain n$-$3 fatty acids was more evident in participants with a low BMI, and the coefficient of interaction was significant. The associations between intakes of shellfish and freshwater fish and T2D did not appear to be modified by BMI. We found no interaction between intakes of fish, shellfish, and long-chain n$-$3 fatty acids and BMI in the SMHS (data not shown in tables).

When we looked at associations between food group and long-chain n$-$3 fatty acid intakes with T2D stratified by WHR categories in SWHS participants (Table 4), we observed results similar to results from analyses stratified by BMI categories. The *P* value for interaction was significant for analyses of intakes of combined fish and shellfish, saltwater fish, and long-chain n$-$3 fatty acids. In SMHS participants, we found no interaction between WHR and intakes of fish, shellfish, or long-chain n$-$3 fatty acids and the risk of T2D (data not shown in tables).

DISCUSSION

In our large, prospective, population-based studies of middle-aged Chinese women and men, we found that higher intakes of

TABLE 1
Characteristics of the study population by quintile (Q) of combined fish and shellfish intakes[1]

	Shanghai Women's Health Study (n = 64,193)					Shanghai Men's Health Study (n = 51,936)				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
Age (y)[2]	54 (46, 64)	49 (44, 59)	48 (43, 56)	47 (43, 54)	46 (43, 53)	54 (48, 65)	52 (47, 61)	51 (46, 59)	51 (46, 58)	49 (45, 56)
Energy intake (kcal/d)[3]	1483.6 ± 323.4	1579.8 ± 306.9	1645.0 ± 310.1	1712.1 ± 319.6	1843.9 ± 360.6	1777 ± 394.7	1859 ± 378.8	1920 ± 382.1	1997 ± 399.6	2121 ± 453.6
BMI (kg/m^2)[3]	24.3 ± 3.6	23.8 ± 3.3	23.7 ± 3.3	23.6 ± 3.2	23.6 ± 3.2	23.4 ± 3.1	23.6 ± 3.0	23.6 ± 3.1	23.7 ± 3.0	23.7 ± 2.9
WHR[3]	0.82 ± 0.05	0.80 ± 0.05	0.80 ± 0.05	0.80 ± 0.05	0.80 ± 0.05	0.89 ± 0.06	0.89 ± 0.06	0.90 ± 0.05	0.90 ± 0.05	0.90 ± 0.05
Smoking (%)	4.1	2.1	1.7	1.6	1.6	60.2	60.4	61.2	62.0	64.9
Alcohol (%)	2.2	1.8	2.3	2.4	2.8	25.0	28.2	29.9	31.5	37.4
Exercise (%)	33.8	32.5	32.2	32.9	33.1	32.6	32.6	32.3	34.1	32.8
Education (%)										
None	22.3	9.5	6.0	4.2	2.5	11.3	6.1	4.2	3.4	2.5
Elementary	16.5	11.3	8.2	6.8	4.7	38.1	35.0	34.0	32.2	28.9
High school	53.4	66.6	70.9	72.7	75.6	32.3	37.4	38.0	38.4	41.4
College	7.8	12.6	15.0	16.3	17.2	18.2	21.5	23.7	25.9	27.2
Income level (%)[4]										
I	24.0	15.6	13.3	12.0	11.7	16.4	13.3	11.8	11.8	12.2
II	41.5	39.2	37.8	36.5	35.1	46.9	43.0	42.2	39.5	36.5
III	23.0	29.1	29.7	31.2	30.6	30.2	34.9	36.6	36.9	37.3
IV	11.5	16.2	19.2	20.3	22.7	6.3	8.6	9.2	11.7	13.6
Occupation (%)										
Professional	11.2	18.6	21.4	23.7	24.5	22.6	24.0	25.9	26.8	27.3
Clerical	9.8	12.5	13.4	14.2	15.2	20.5	21.9	21.8	22.1	23.8
Manual labor	18.9	23.2	23.8	24.3	24.7	56.9	54.1	52.2	51.1	48.9
Housewife/retired	60.1	45.8	41.4	37.8	35.5	N/A	N/A	N/A	N/A	N/A
Hypertension (%)	23.0	20.0	18.4	16.7	16.2	54.6	52.4	50.9	50.0	48.5
Family history of T2D (%)	12.5	15.2	16.2	16.8	18.7	15.0	16.6	16.3	17.4	17.5

[1] WHR, waist-to-hip ratio; T2D, type 2 diabetes.

[2] Values are medians; interquartile ranges in parentheses.

[3] Values are means ± SDs.

[4] For the Shanghai Men's Health Study, individual income levels are in yuan/y: level I, <500; level II, 500–900; level III, 1000–1999; level IV, >1999. For the Shanghai Women's Health Study, family income is in yuan/y: level I, <10,000; level II, 10,000–19,999; level III, 20,000–29,999; level IV, ≥30,000.

fish and shellfish and long-chain fatty acids were associated with a lower risk of T2D in women, whereas sonly shellfish intake was associated with a lower risk of T2D in men.

Data from previous studies of the relation of fish intake to T2D is inconclusive. Fish intake was associated with a lower risk of impaired glucose tolerance in the Dutch and Finnish cohorts after 20 y of follow-up (8) and in an elderly population (7). In Alaskan natives, salmon consumption was associated with a lower risk of glucose intolerance (6). In a UK population, a higher fish intake was associated with a lower risk of T2D (odds ratio: 0.75; 95% CI: 0.58, 0.96) (12). However, in an early report from the Nurses' Health Study (NHS) II, fish intake was not associated with the incidence of T2D (9) and in a recent report combining data from the NHS I and II and the Health Professionals Follow-Up Study (HPFS), a direct association between fish intake and T2D was observed. Women who consumed ≥5 servings of fish/wk had a higher risk (RR: 1.22; 95% CI: 1.08, 1.39) compared with women who consumed fish <1 time/mo (11). A direct association between fish intake and T2D has also been reported in a Dutch population. The RR was 1.32 (95% CI: 1.02, 1.70) in the group consuming the most fish (≥28 g/d) compared with non-fish-eaters (*P* trend = 0.04) (10).

Inconsistencies in the observed effect of fish consumption and T2D in different populations may reflect different preparation methods. Frying fish, especially deep frying, might produce *trans* fatty acids, which might modify the beneficial effect of fish. Fried fish was not significantly associated with T2D risk in the UK study cited above (12). In an earlier report from the same study, oily fish intake was associated with lower glycated hemoglobin, whereas fried fish was associated with higher glycated hemoglobin (26).

We analyzed saltwater fish and freshwater fish separately to account for possible contamination of river water in Shanghai. Some environmental contaminants found in fish have been

TABLE 2

Associations between quintile (Q) of fish and long-chain n−3 fatty acid intakes and the relative risk (RR) of type 2 diabetes: Shanghai Women's Health Study (*n* = 64,193)

Food groups	No. of subjects	Median	RR[1]	95% CI	*P* for trend	RR[2]	95% CI	*P* for trend
Combined fish and shellfish								
Q1	12,838	13.6	1.00		<0.001	1.00		0.004
Q2	12,834	27.7	0.92	0.83, 1.02		0.93	0.83, 1.03	
Q3	12,847	41.5	0.78	0.70, 0.88		0.80	0.71, 0.89	
Q4	12,833	60.0	0.81	0.72, 0.91		0.83	0.74, 0.94	
Q5	12,841	99.1	0.83	0.73, 0.94		0.86	0.76, 0.98	
Fish								
Q1	12,806	9.5	1.00		<0.001	1.00		0.003
Q2	12,873	20.6	0.95	0.85, 1.06		0.96	0.86, 1.06	
Q3	12,833	31.6	0.83	0.74, 0.93		0.84	0.75, 0.94	
Q4	12,843	47.1	0.79	0.70, 0.88		0.80	0.71, 0.90	
Q5	12,838	80.2	0.86	0.77, 0.98		0.89	0.78, 1.01	
Saltwater fish								
Q1	13,470	1.7	1.00		0.002	1.00		0.01
Q2	12,931	7.2	1.00	0.90, 1.11		1.00	0.90, 1.12	
Q3	11,835	13.9	0.88	0.9, 0.98		0. 89	0.79, 1.00	
Q4	13,135	24.1	0.93	0.83, 1.04		0.95	0.85, 1.06	
Q5	12,822	49.8	0.82	0.73, 0.92		0.84	0.74, 0.95	
Freshwater fish								
Q1	12,847	2.7	1.00		0.004	1.00		0.01
Q2	12,831	8.4	0.96	0.6, 1.07		0.96	0.86, 1.07	
Q3	12,842	14.5	0.81	0.3, 0.91		0.82	0.73, 0.92	
Q4	12,846	22.6	0.89	0.79, 0.99		0.89	0.80, 1.00	
Q5	12,827	42.1	0.86	0.76, 0.96		0.87	0.77, 0.98	
Shellfish								
Q1	12,354	1.4	1.00		<0.001	1.00		0.006
Q2	13,322	4.3	0.90	0.81, 1.00		0.91	0.82, 1.01	
Q3	12,840	7.7	0.77	0.69, 0.87		0.79	0.71, 0.89	
Q4	12,831	12.6	0.78	0.69, 0.88		0.80	0.71, 0.91	
Q5	12,846	23.5	0.82	0.73, 0.93		0.86	0.76, 0.99	
Long-chain n−3 fatty acids								
Q1	12,835	0.02	1.00		<0.001	1.00		0.005
Q2	12,841	0.04	0.91	0.82, 1.02		0.90	0.80, 1.00	
Q3	12,837	0.07	0.77	0.69, 0.87		0.84	0.75, 0.94	
Q4	12,838	0.11	0.81	0.72, 0.92		0.87	0.77, 0.98	
Q5	12,842	0.20	0.82	0.73, 0.93		0.84	0.74, 0.95	

[1] Adjusted for age, energy intake (kcal/d), waist-to-hip ratio, BMI, smoking, alcohol consumption, physical activity, income level, educational level, occupation, family history of diabetes, and hypertension.

[2] Adjusted for age, energy intake (kcal/d), waist-to-hip ratio, BMI, smoking, alcohol consumption, physical activity, income level, educational level, occupation, family history of diabetes, hypertension, and dietary pattern.

associated with higher T2D risk (27, 28). Mouse models have shown that elevated mercury concentrations decrease plasma insulin and increase glucose concentrations (29). We found no evidence of a detrimental effect of freshwater fish consumption on the risk of T2D.

Data on associations between shellfish and T2D are limited. Consumption of one or more portions of shellfish weekly was associated with an increased risk of diabetes (odds ratio: 1.36; 95% CI: 1.02, 1.81) in adjusted analyses from the UK study cited above (12), whereas an inverse association between shellfish intake and T2D was found in our study in both women and men.

There are fewer studies on the association between long-chain n−3 fatty acids and T2D, because few databases have information on long-chain n−3 fatty acids. Consumption of seal oil was associated with a lower risk of glucose intolerance in Alaska natives (6). No association was observed between long-chain n−3 fatty acids and incidence of T2D in the HPFS (14) or in the Dutch cohort mentioned above (10). In the Iowa study, a direct association between long-chain n−3 fatty acids and incidence of T2D was found (13). The pooled multivariate analyses of the NHS I, NHS II, and HPFS RRs across quintiles of long-chain fatty acid intake were 1, 1.00, 1.05, 1.17, and 1.24 (*P* for trend < 0.001) (11).

In this study we found an inverse association between fish intake in women but not in men. A possible reason for this is that there were fewer incident diabetes cases in men than in women; thus, we might not have had enough power to detect an association in men. We tested for a possible interaction between sex and fish and shellfish, fish, shellfish and n−3 fatty acids intake by using the likelihood-ratio test. The *P* value for interaction was not significant.

A potential mechanism for the protective effect of fish and shellfish consumption on T2D may be related to long-chain n−3 fatty acids. Insulin sensitivity is related to the percentage of

TABLE 3

Associations between quintile (Q) of fish and long-chain n−3 fatty acid intakes and the relative risk (RR) of type 2 diabetes: Shanghai Men's Health Study (*n* = 51,936)

	No. of subjects	Median	RR[1]	95% CI	*P* for trend	RR[2]	95% CI	*P* for trend
Combined fish and shellfish								
Q1	10,388	14.4	1.00		0.28	1.00		0.36
Q2	10,393	28.8	0.93	0.75, 1.14		0.93	0.76, 1.14	
Q3	10,399	42.5	0.79	0.64, 0.98		0.80	0.64, 0.99	
Q4	10,379	60.4	0.87	0.70, 1.08		0.88	0.70, 1.09	
Q5	10,404	99.3	0.91	0.73, 1.12		0.92	0.73, 1.16	
Fish								
Q1	10,390	9.7	1.00		0.39	1.00		0.50
Q2	10,401	21.1	0.92	0.75, 1.13		0.92	0.75, 1.13	
Q3	10,385	31.8	0.80	0.64, 0.99		0.80	0.65, 1.00	
Q4	10,393	47.3	0.89	0.72, 1.09		0.89	0.72, 1.11	
Q5	10,394	79.0	0.92	0.74, 1.14		0.94	0.74, 1.17	
Saltwater fish								
Q1	10,399	1.8	1.00		0.46	1.00		0.56
Q2	9299	8.2	0.72	0.57, 0.90		0.72	0.58, 0.91	
Q3	10,145	15.2	1.12	0.92, 1.37		1.13	0.92, 1.37	
Q4	12,210	26.2	0.87	0.71, 1.06		0.87	0.71, 1.07	
Q5	9910	52.4	0.85	0.69, 1.06		0.87	0.69, 1.09	
Freshwater fish								
Q1	9867	1.5	1.00		0.41	1.00		0.49
Q2	10,759	7.5	0.87	0.70, 1.07		0.86	0.70, 1.07	
Q3	10,552	13.5	0.81	0.65, 1.00		0.81	0.65, 1.00	
Q4	10,430	21.4	0.95	0.77, 1.17		0.95	0.77, 1.17	
Q5	10,354	42.0	0.86	0.70, 1.07		0.88	0.70, 1.09	
Shellfish								
Q1	10,386	1.6	1.00		0.004	1.00		0.003
Q2	10,430	4.8	0.93	0.77, 1.13		0.93	0.76, 1.12	
Q3	10,386	8.6	0.70	0.57, 0.87		0.70	0.56, 0.86	
Q4	10,373	13.3	0.67	0.54, 0.83		0.66	0.53, 0.82	
Q5	10,388	24.3	0.83	0.68, 1.03		0.82	0.65, 1.02	
Long-chain n−3 fatty acids								
Q1	10,154	0.02	1.00		0.32	1.00		0.40
Q2	10,005	0.04	0.95	0.77, 1.17		0.95	0.77, 1.17	
Q3	10,105	0.07	0.85	0.69, 1.06		0.86	0.69, 1.07	
Q4	10,762	0.11	0.96	0.77, 1.18		0.96	0.77, 1.19	
Q5	10,937	0.20	0.88	0.70, 1.09		0.89	0.70, 1.12	

[1] Adjusted for age, energy intake (kcal/d), waist-to-hip ratio, BMI, smoking, alcohol consumption, physical activity, income level, educational level, occupation, family history of diabetes, and hypertension.

[2] Adjusted for age, energy intake (kcal/d), waist-to-hip ratio, BMI, smoking, alcohol consumption, physical activity, income level, educational level, occupation, family history of diabetes, hypertension, and dietary pattern.

long-chain polyunsaturated fatty acids present in membranes (2, 6). However, because intakes of fish and long-chain n−3 fatty acids are highly correlated, it is difficult to disentangle the effect of fatty acids from the effect of fish per se. Vessby (30) reviewed several short-term randomized controlled studies, conducted in the 1990s on dietary fat and insulin sensitivity. Overall, the results from these studies showed no significant effect of fatty acids on insulin sensitivity. Results from the KANWU Study, an intervention study in healthy subjects conducted to investigate the effect of changes in dietary fat quality on insulin action in humans, showed that addition of n−3 fatty acids influenced neither insulin sensitivity nor insulin secretion (33). Overall, n−3 fatty acids have not shown a benefit in subjects with T2D, as shown in controlled studies (30, 34). A recent report indicated that high doses of n−3 fatty acids may even impair insulin action in subjects with T2D (35).

A potential mechanism for the protective effect of fish could be the vitamin D content of oily fish. Prospective studies have reported that fish consumption reduces T2D risk in elderly Dutch men, as has its vitamin D content (36, 37). Vitamin D status has been shown to be inversely associated with glycemia in elderly men (37). In British Bangladeshi adults, lower levels of glycemia

TABLE 4

Associations between quintile (Q) of fish and long-chain n−3 fatty acids and the relative risk of type 2 diabetes stratified by BMI (in kg/m^2) and waist-to-hip ratio (WHR): Shanghai Women's Health Study[1]

Food groups	BMI ≤25	BMI >25	*P* for interaction factor	WHR ≤0.85	WHR >0.85	*P* for interaction factor
Combined fish and shellfish			0.02			
Q1	1.00	1.00		1.00	1.00	0.02
Q2	0.79 (0.66, 0.95)	0.97 (0.85, 1.10)		0.91 (0.79, 1.05)	0.92 (0.78, 1.08)	
Q3	0.81 (0.67, 0.98)	0.77 (0.67, 0.90)		0.74 (0.64,0.87)	0.84 (0.71, 1.00)	
Q4	0.69 (0.56, 0.85)	0.89 (0.77, 1.03)		0.79 (0.67, 0.92)	0.90 (0.75, 1.08)	
Q5	0.83 (0.67, 1.03)	0.84 (0.71, 1.00)		0.81 (0.68, 0.97)	0.91 (0.74, 1.12)	
P for trend	0.03	0.02		<0.01	0.16	
Fish						
Q1	1.00	1.00	0.30	1.00	1.00	0.25
Q2	0.92 (0.77, 1.10)	0.98 (0.86, 1.11)		0.95 (0.83, 1.10)	0.95 (0.81, 1.11)	
Q3	0.81 (0.67, 0.98)	0.85 (0.73, 0.97)		0.80 (0.69, 0.93)	0.87 (0.73, 1.04)	
Q4	0.71 (0.58, 0.87)	0.85 (0.73, 0.98)		0.74 (0.63, 0.87)	0.89 (0.74, 1.06)	
Q5	0.89 (0.72, 1.10)	0.86 (0.74, 1.01)		0.86 (0.73, 1.01)	0.92 (0.76, 1.12)	
P for trend	0.02	0.02		<0.01	0.13	
Saltwater fish						
Q1	1.00	1.00	0.01	1.00	1.00	<0.01
Q2	0.90 (0.76, 1.08)	1.05 (0.92, 1.20)		0.87 (0.75, 0.99)	1.17 (1.00, 1.36)	
Q3	0.77 (0.63, 0.93)	0.96 (0.83, 1.11)		0.79 (0.68, 0.91)	1.02 (0.86, 1.21)	
Q4	0.81 (0.67, 0.98)	1.05 (0.91, 1.22)		0.84 (0.72, 0.97)	1.10 (0.90, 1.28)	
Q5	0.72 (0.59, 0.88)	0.92 (0.79, 1.07)		0.76 (0.65, 0.89)	0.93 (0.77, 1.13)	
P for trend	<0.001	0.63		<0.01	0.48	
Freshwater fish						
Q1	1.00	1.00	0.46	1.00	1.00	0.97
Q2	0.89 (0.74, 1.07)	1.01 (0.88, 1.15)		0.92 (0.80, 1.06)	0.97 (0.82, 1.13)	
Q3	0.82 (0.67, 0.99)	0.82 (0.71, 0.94)		0.81 (0.70, 0.95)	0.80 (0.68, 0.95)	
Q4	0.94 (0.78, 1.14)	0.86 (0.74, 0.99)		0.90 (0.77, 1.05)	0.89 (0.75, 1.06)	
Q5	0.86 (0.71, 1.06)	0.87 (0.75, 1.01)		0.84 (0.72, 1.13)	0.88 (0.73, 1.05)	
P for trend	0.23	0.01		0.08	0.04	
Shellfish						
Q1	1.00	1.00	0.93	1.00	1.00	0.28
Q2	0.95 (0.79, 1.15)	0.86 (0.76, 0.98)		0.97 (0.77, 1.02)	0.89 (0.77, 1.04)	
Q3	0.83 (0.68, 1.01)	0.74 (0.64, 0.85)		0.79 (0.67, 0.92)	0.76 (0.64, 0.91)	
Q4	0.83 (0.67, 1.01)	0.75 (0.64, 0.87)		0.790 (0.67, 0.92)	0.79 (0.66, 0.96)	
Q5	0.90 (0.72, 1.12)	0.81 (0.69, 0.96)		0.84 (0.70, 0.99)	0.91 (0.74, 1.11)	
P for trend	0.26	0.001		0.02	0.14	
Long-chain n−3 fatty acids						
Q1	1.00	1.00	<0.01	1.00	1.00	<0.01
Q2	0.90 (0.80, 1.00)	0.93 (0.81, 1.07)		0.79 (0.64, 0.92)	1.02 (0.86, 1.20)	
Q3	0.84 (0.75, 0.94)	0.86 (0.74, 0.99)		0.75 (0.64, 0.88)	0.98 (0.83, 1.17)	
Q4	0.87 (0.77, 0.98)	1.01 (0.87, 1.17)		0.79 (0.68, 0.93)	1.01 (0.84, 1.21)	
Q5	0.84 (0.74, 0.95)	0.91 (0.77, 1.07)		0.78 (0.66, 0.93)	0.97 (0.79, 1.18)	
P for trend	<0.01	0.51		0.01	0.75	

[1] All values are relative risks; 95% CIs in parentheses. Relative risks were adjusted for age, energy intake (kcal/d), smoking, alcohol consumption, physical activity, income level, educational level, occupation, family history of diabetes, hypertension, and dietary patterns. In addition, the analysis stratified by BMI was adjusted for WHR, and the analysis stratified by WHR was adjusted for BMI.

were predicted by increases in intake of fish rich in vitamin D, whereas increases in overall fish consumption predicted glycemia (38). Unfortunately, we could not adjust our analysis for vitamin D consumption, because no information on the vitamin D content of food was included in the Chinese Food Composition Tables. Fish contain additional potential protective agents, such as retinol, selenium, and fish protein, and some data from animal models suggest that cod protein might be an insulin sensitizer (31, 32). We repeated the analysis with adjustment for vitamin A, and the results did not change.

Our study had several strengths. The studies were population-based, the participation rates and follow-up rates were high, we adjusted for a wide range of potential confounders, we repeated the dietary measurements, and our population has a high consumption of fish.

Our study also had limitations. A major concern was the reliance on self-reports of T2D. The follow-up time for the SMHS was only 4.1 y; thus, it is possible that many cases of T2D could have been present at baseline. Higher fish intake was associated with higher socioeconomic status; therefore, the participants in our study with higher exposure would also have been more likely to have regular health check-ups. Given the high proportion of undiagnosed T2D in China, there is a possibility that the exposure was associated with the likelihood of testing for T2D, which may result in detection bias. Fish consumption was associated with younger age, higher socioeconomic status, and a more favorable lifestyle. There is always the possibility of residual confounding, even in fully adjusted analyses.

Misclassification of T2D can potentially either exaggerate or underestimate the association between fish intake and the risk of T2D. Three of 4 T2D cases go undiagnosed in China (31), and 2 of 5 T2D cases go undiagnosed in urban Shanghai (32). We measured fasting glucose concentration in 3978 participants of the SMHS who had no self-reported T2D history. The prevalence of undiagnosed T2D was 6% in these 3978 participants. We conducted sensitivity analyses to evaluate the effect of this bias on our risk estimates. We applied the underdiagnosis rate of 6% and observed an incidence of 6.8% to drive the RR with correction for outcome misclassification (30). The RRs with correction for outcome misclassification did not differ from those without correction, although the CIs for relevant RRs widened. The general patterns of association and our conclusions remained unchanged.

The findings of this study add to the limited data on associations between intakes of fish, shellfish, and long-chain n−3 fatty acids and the risk of T2D. Overall, we found no detrimental effect of fish intake on the risk of T2D in women or men. Although we observed an inverse association between fish and shellfish intake in women, no dose-response association was found.

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