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ORIGINAL CONTRIBUTION

Fish consumption and frying of fish in relation to type 2 diabetes incidence: a prospective cohort study of Swedish men

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Abstract
Purpose Epidemiological evidence on the association between fish consumption and risk of type 2 diabetes is heterogeneous across geographical regions. Differences related to fish consumption pattern could possibly help explain the discrepancy between the findings. We therefore aimed to investigate the association between fish consumption (total, fried, specific fish items) and type 2 diabetes incidence, taking exposure to contaminants present in fish (polychlorinated biphenyls and methyl mercury) into consideration.
Methods The population-based Cohort of Swedish Men, including 35,583 men aged 45–79 years, was followed from 1998 to 2012. We estimated hazard ratios (HRs) with 95 % confidence intervals (CIs) using Cox proportional hazards models.
Results During 15 years of follow-up, 3624 incident cases were identified. Total fish consumption (≥4 servings/week vs. <1 serving/week) was not associated with type 2 diabetes in multivariable-adjusted analysis (HR 1.00; 95 % CI 0.85–1.18); however, a statistically non-significant inverse association was observed after adjustment for dietary contaminant exposures (HR 0.79; 95 % CI 0.60–1.04). Fried fish (≥6 servings/month vs. ≤1 servings/month) and shellfish consumption (≥1 serving/week vs. never/seldom) were associated with HRs of 1.14 (95 % CI 1.03–1.31) and 1.21 (95 % CI 1.07–1.36), respectively.
Conclusions We observed no overall association between total fish consumption and type 2 diabetes. The results indicated that dietary contaminants in fish may influence the relationship. Fried fish and shellfish consumption were associated with higher type 2 diabetes incidence. These findings suggest that more specific advice on fish species sub-types (varying in contamination) and preparation methods may be warranted.

Keywords Fish · Fried foods · Polychlorinated biphenyls · Methyl mercury · Type 2 diabetes · Cohort study

Introduction

Type 2 diabetes is a growing public health burden, and the prevalence has reached epidemic proportions globally [1]. Fish consumption has been hypothesized to be protective for type 2 diabetes given the beneficial effects seen on cardiovascular risk factors and cardiovascular diseases (CVD) [2]. Results from epidemiological studies on fish consumption in relation to risk of developing diabetes have, however, been largely inconsistent and inconclusive [3–16]. Several meta-analyses have highlighted the heterogeneity of results and brought attention to potential geographical differences, with inverse associations observed in studies conducted in Asia, overall null associations in European populations and higher risks in US populations [17–19]. Differences in fish consumption pattern potentially

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determined by geographical location (e.g. types of fish consumed, preparation methods and degree of contamination) could possibly help explain the discrepancy between the findings, but previous studies on fish consumption in relation to type 2 diabetes risk have not fully accounted for such factors. Frying of fish could potentially be of importance because of formation of advanced glycation end products (AGEs) [20], mutagenic compounds [21], changes in fatty acid composition or increased energy–density. Further, studies on CVD where fried fish was distinguished from non-fried fish have indicated that the associations may vary by preparation method [22–26]. Contaminants present in fish may also be of importance. Fish is the main source of dietary exposure to both persistent organic pollutants such as polychlorinated biphenyls (PCBs) [27] and methyl mercury (MeHg) [28], which have been associated with type 2 diabetes [29, 30]. We therefore aimed to investigate the association of total fish consumption, fried fish and specific fish items with incidence of type 2 diabetes in a large population-based prospective study, taking exposure to contaminants present in fish into consideration.

Subjects and methods

Study population

The Cohort of Swedish Men is a prospective population-based study initiated in the autumn of 1997. All men born between 1918 and 1952 (45–79 years of age) and residing in Örebro and Västmanland counties of central Sweden received an invitation to participate in the study together with a questionnaire on diet and other lifestyle factors. A total of 48,850 men returned the questionnaire (response rate 49 %). In 2008, an extended questionnaire on health, including a question on diabetes status, was sent out (response rate 70 %). The cohort is representative of Swedish men aged 45–79 years in terms of age distribution, educational level and prevalence of overweight [31]. The study was approved by the Regional Ethical Review Board at Karolinska Institutet (Stockholm, Sweden), and return of the completed questionnaire was considered to imply informed consent.

From the baseline population, we excluded men with incorrect or incomplete national identification number ($n = 205$), those who returned an inadequately completed questionnaire ($n = 92$) and those who died ($n = 55$) or had a cancer diagnosis (not including non-melanoma skin cancer; $n = 2592$) before 1 January 1998. We further excluded prevalent cases of diabetes based on registry data from the Swedish National Diabetes Register (NDR) and the Swedish National Patient Register (NPR) and baseline self-reports ($n = 3404$). Moreover, we excluded those who reported a diabetes diagnosis in the 2008 questionnaire that could not be confirmed by registry data ($n = 67$) and those who were registered with non-type 2 diabetes during the follow-up period ($n = 200$). In addition, we excluded participants with a history of CVD (myocardial infarction, angina and stroke; $n = 4537$), because they may have changed their dietary habits after diagnosis and for comparability with other studies. We also excluded those with implausible values for total energy intake (± 3 SD from the log-transformed mean energy intake; $n = 398$), those who did not fill in any of the questions in the fish intake section of the questionnaire ($n = 239$) and those with missing information on frying frequency ($n = 1478$). After these exclusions, 35,583 men remained for analysis.

Assessment of diet and covariates

Dietary intake was assessed at baseline using a 96-item food frequency questionnaire (FFQ) in which participants were asked to report their average frequency of consumption of various foods over the previous year. Eight predefined frequency categories were used (never/seldom; 1–3 times/month; 1–2 times/week; 3–4 times/week; 5–6 times/week; 1 time/day; 2 times/day; $\geq$3 times per day). With regard to fish consumption, participants were asked to report consumption frequency of three different finfish types (herring/mackerel, salmon/whitefish/char, cod/saithe/fish fingers) as well as of shellfish (shrimp/crayfish, etc.). Partial non-response in the fish intake section was assumed to imply never/seldom. This was based on a study among Swedish men and women showing that 82 % of omitted answers on fish consumption corresponded to non-consumption [32]. The midpoint of the chosen frequency range on each item was converted to servings/week and summed to obtain an estimate of total fish consumption (sum of herring/mackerel, salmon/whitefish/char and cod/saithe/fish fingers). Moreover, participants were specifically asked to report monthly frequency of fried fish consumption in a separate open section of the questionnaire (without predefined frequency categories).

Calculation of total energy intake was based on age-specific ($\leq$52, 53–61, 62–69, $\geq$70 years) portion sizes that were derived from two 1-week weighted dietary records completed by a random sample of 152 men. Food composition values were obtained from the Swedish National Food Agency Database [33].

The validity of the FFQ has been assessed in a random sample of 248 men aged 40–74 years. The Spearman correlation coefficients between FFQ-based estimates and the mean of 14 repeated 24-h recall interviews during a 1-year period were 0.65 for macronutrients and 0.62 for micronutrients [34]. In a validation study of the FFQ among 129 women of the same age and from the same study area, the

correlation between the FFQ-based estimates and those from four 1-week weighted diet records ranged from 0.4 to 0.6 for fish and shellfish items (A. Wolk, unpublished data).

To account for overall diet in the analyses and reduce the number of covariates included in the models, we used a quality score instead of several single food groups. As an overall dietary quality score, we calculated a DASH (Dietary Approaches to Stop Hypertension) diet component score using the score proposed by Fung et al. [35], which ranks participants according to their intake of eight dietary components. Higher scores were given for high intake of fruits, vegetables, nuts and legumes, low-fat dairy and whole grains, and for low intake of sodium, sweetened beverages, and red and processed meats.

For FFQ-based estimation of dietary exposure to PCBs and MeHg, we have used recipe-based databases created for the FFQ. The PCB database, described in detail elsewhere [27], was based on the PCB congener 153, the most abundant congener in Swedish food and an excellent indicator for total PCB in food, blood and adipose tissue [36, 37]. Concentrations of PCBs and MeHg in foods were obtained from the Swedish National Food Agency and the Swedish Environmental Protection Agency, and dietary exposure estimates were calculated using the consumption frequency and age-specific portion sizes of the respective foods. For each food item in the FFQ, the contaminant calculations were based on a larger number of specific food types according to the distribution of consumption in the population. The exposure estimates were adjusted to the mean energy intake in the cohort using the residual method [38]. Fish and shellfish contributed to about 2/3 of the total dietary PCB exposure in the cohort. Estimation of dietary MeHg exposure was based on fish and shellfish only as it is practically the only source of dietary MeHg, with lean fish species contributing to about 50 % in the cohort. The long-term dietary PCB exposure estimates showed reasonable validity against the sum of 6 PCB congeners measured in serum [correlation (r), 0.48; $p < 0.001$] in a sample of 201 Swedish women [27]. FFQ-estimated fish consumption has been shown to correlate well with hair mercury concentrations in a Swedish population ($r = 0.75$; $p < 0.001$) [28].

Information on height, body weight, education, alcohol consumption, smoking habits and physical activity was collected via the baseline questionnaire. Body mass index (BMI) was calculated by dividing weight (in kg) by the square of height (in m). For total physical activity, the reported daily time spent in specific activities (work/occupational activity, home/household work, walking/bicycling, watching TV/reading, exercising and sleeping) was multiplied by their typical energy expenditure requirements [expressed in metabolic equivalents (METs)] and summed to create a MET-h/day score [39].

Case ascertainment and follow-up of the cohort

Study participants were followed from 1 January 1998 to 31 December 2012. Incident cases of type 2 diabetes were identified by linkage of the study cohort with the Swedish National Diabetes Register (NDR) and the Swedish National Patient Register (NPR). The NDR was initiated in 1996 and contains clinical information from patient visits reported at least once per year, and it also includes retrospective recording of diabetes onset year. Based on expected diabetes prevalence, the coverage of NDR is estimated to be nearly complete in the study area [40]. In validation against the Swedish Prescribed Drug Register, over 90 % of individuals aged 50–80 years on diabetes medication were covered by NDR [40]. Reporting to the NPR is mandatory, and it includes information on main and secondary diagnoses for all inpatient care visits in Sweden since 1987 and also outpatient visits from both private and public caregivers since 2001. ICD-10 code E11 was used to identify cases of type 2 diabetes. The first available date in either of the two registers was considered as the diagnosis date. Dates of death were obtained from the Swedish Death Register.

Statistical analysis

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) with 95 % confidence intervals (CIs) for the associations between total fish consumption (sum of three finfish items: herring/mackerel, salmon/whitefish/char and cod/saithe/fish fingers), fried fish consumption, specific fish items and incidence of type 2 diabetes. Total fish was categorized in five groups (<1, 1–<2, 2–<3, 3–<4 and ≥4 servings/week). Of note, the recommended fish consumption in Sweden, 2–3 servings/week, is represented in the mid-category. Overall, the categorization reflects the consumption pattern in the study population. As the number of participants reporting no fish consumption was small ($n = 911$; 2.6 %), we also included low consumers in the reference category. Nevertheless, to test the robustness of our results, we performed additional analyses with only non-consumers of fish as the reference group. For the categorization of fried fish consumption, we used approximate quintiles (≤1, 2, 3–4, 5, ≥6 servings/month). Individual fish items were categorized into three groups (never/seldom, 1–3 servings/month, ≥1 serving/week) with the two lower directly corresponding to the two lowest predefined frequency categories in the FFQ and the third combining the remaining six higher response categories. Age was used as underlying timescale in all analyses. Each participant contributed person-time from 1 January 1998 until the date of type 2 diabetes diagnosis, death or end of follow-up, whichever came first.

The primary multivariable analyses were adjusted for BMI (kg/m^2; <20, 20–24.9, 25–29.9, ≥30), physical activity (MET-h/day; quartiles), education (primary school, high school, university), cigarette smoking (never, former, current ≤10 cigarettes/day or >10 cigarettes/day), total energy intake (kcal/day; quintiles), intake of alcohol (g/day; quartiles) and DASH diet component score (based on intake of fruits, vegetables, nuts and legumes, low-fat dairy, whole grains, sodium, sweetened beverages, and red and processed meats; quartiles). Analyses of specific fish items were mutually adjusted for the other three types. Multivariable model 2 was further adjusted for dietary exposure to PCBs (ng/day, quintiles) and MeHg (μg/day, quintiles). Missing values for any covariates were treated as a separate category in the model. The Schoenfeld residual test indicated no violation of the proportional hazard assumption. Tests for linear trend were performed by assigning each participant the median value in their respective exposure category and modelling this as a continuous variable. We further examined the dose–response relationship between fried fish consumption and HR of type 2 diabetes using restricted cubic splines with knots at 10, 50 and 90 % of the distribution. A p value for nonlinearity was obtained by testing the null hypothesis that the coefficient of the second spline is equal to 0.

In a sensitivity analysis, we excluded men who reported any use of fish oil supplements (n = 1649; 4.6 % of the study population).

Statistical analyses were carried out using Stata (version 13.0), and p values ≤0.05 were considered statistically significant.

Results

During 15 years of follow-up (467,961 person-years), 3624 incident cases of type 2 diabetes were identified. The mean (±SD) number of servings consumed per week was 0.6 (±0.8) of herring/mackerel, 0.4 (±0.9) of salmon/whitefish/char, 0.9 (±1.0) of cod/saithe/fish fingers and 0.4 (±0.6) of shellfish. The mean frequency of consuming fried fish was 3.2 (±2.9) times/month. The mean energy-adjusted dietary exposure to PCBs was 274 (±191) ng/day and to MeHg 1.5 (±1.3) μg/day.

Age-standardized baseline characteristics by total fish consumption are presented in Table 1. On average, men

Table 1 Age-standardized baseline characteristics of 35,583 participants of the Cohort of Swedish Men, by total fish consumption

	Categories of total fish consumption, servings/week (median)				
	<1 (0.9)	1–<2 (1.4)	2–<3 (2.4)	3–<4 (3.5)	≥4 (5.0)
No. of participants	10,867	13,458	6292	3367	1599
Age (mean ± SD, years)	58.8 ± 9.4	59.1 ± 9.2	58.7 ± 9.2	62.2 ± 9.6	62.7 ± 9.7
BMI (mean, kg/m^2)	26	26	25	26	26
Total physical activity (mean, MET-h/day)	42	42	41	42	42
University education (%)	14	18	23	21	22
Current smokers (%)	27	24	20	25	27
Alcohol (mean, g/day)	15	15	16	17	21
Energy intake (mean, kcal/day)	2529	2689	2861	2922	3263
Fried fish (mean, servings/month)	2.5	3.2	3.6	4.3	4.8
Dietary components (mean, g/1000 kcal)					
Fruits	63	68	76	75	80
Vegetables	45	53	60	61	68
Nuts and legumes	16	17	19	21	26
Whole grains	78	81	82	85	79
Low-fat dairy	116	114	113	108	101
Sodium	1.4	1.4	1.5	1.5	1.6
Red and processed meats	38	40	40	40	45
Sweetened beverages	77	72	62	65	62
Dietary PCB exposure (mean, ng/day)[a]	162	241	314	442	776
Dietary MeHg exposure (mean, μg/day)[a]	0.7	1.4	1.9	2.4	4.1

Total fish is the sum of three finfish items: herring/mackerel, salmon/whitefish/char and cod/saithe/fish fingers; all variables except age are standardized to the age distribution of the study cohort

BMI body mass index, *MET-h/day* metabolic equivalent hours per day

[a] Adjusted to the mean energy intake in the cohort

Table 2 Hazard ratios of type 2 diabetes by consumption of total fish, the Cohort of Swedish Men 1998–2012

	Categories of total fish consumption, servings/week (median)					*p* for trend
	<1 (0.9)	1–<2 (1.4)	2–<3 (2.4)	3–<4 (3.5)	≥4 (5)	
No. of cases	1104	1363	609	378	170	
Person-years	142,599	178,573	84,243	42,606	19,940	
Age-adjusted model	1.00 (ref)	0.97 (0.90–1.05)	0.93 (0.84–1.03)	1.06 (0.94–1.19)	1.01 (0.86–1.19)	0.67
Multivariable model[a]	1.00 (ref)	1.02 (0.95–1.11)	1.01 (0.91–1.12)	1.10 (0.98–1.24)	1.00 (0.85–1.18)	0.48
Multivariable model 2 (+*contaminants*)[b]	1.00 (ref)	0.95 (0.84–1.07)	0.86 (0.72–1.03)	0.89 (0.71–1.12)	0.79 (0.60–1.04)	0.13

Total fish is the sum of three finfish items: herring/mackerel, salmon/whitefish/char and cod/saithe/fish fingers

Adjusted for attained age, body mass index (kg/m^2; <20, 20–24.9, 25–29.9, ≥30), physical activity (metabolic equivalent hours per day; quartiles), education (primary school, high school, university), cigarette smoking (never, former, current ≤10 cigarettes/day or >10 cigarettes/day), total energy intake (kcal/day; quintiles), intake of alcohol (g/day; quartiles) and DASH diet component score (based on intake of fruits, vegetables, nuts and legumes, low-fat dairy, whole grains, sodium, sweetened beverages, and red and processed meats; quartiles)

[a] Additionally adjusted for dietary exposure to polychlorinated biphenyls (ng/day, quintiles) and methyl mercury (μg/day, quintiles)

who consumed more fish had a higher energy intake and a higher consumption per 1000 kcal of red and processed meats, fruit, vegetables, and nuts and legumes and a lower consumption of low-fat dairy; they were also slightly older and more likely to have a university education.

Table 2 shows HRs with 95 % CIs for type 2 diabetes by categories of total fish consumption. No association was observed in age-adjusted analyses or after multivariable adjustment for BMI, physical activity, education, cigarette smoking, alcohol and dietary factors. After further adjustment for contaminants, there was a statistically non-significant inverse association comparing those who consumed ≥4 servings/week with those who consumed <1 serving/week (HR 0.79; 95 % CI 0.60–1.04). Similar results were observed when never/seldom consumers ($n = 911$) were used as the reference, both in the primary model (HR 0.94; 95 % CI 0.73–1.21) and in the contaminant-adjusted model (HR 0.75; 95 % CI 0.52–1.07). While dietary PCB and MeHg exposure had similar impact on the association between fish consumption and diabetes incidence, neither of them were significantly associated with type 2 diabetes incidence: HRs, 1.07 (95 % CI 0.90–1.26; $p_{\text{trend}} = 0.41$) and 1.14 (95 % CI 0.95–1.36; $p_{\text{trend}} = 0.06$) for PCB and MeHg, respectively, comparing extreme quintiles.

Exclusion of the first 2 years of follow-up from the main analysis (305 cases diagnosed in 1998–1999) had little impact on the observed associations (≥4 servings/week vs. <1 serving/week of total fish, model 1: HR 1.01; 95 % CI 0.85–1.20; model 2: HR 0.79; 95 % CI 0.59–1.05).

The Spearman correlation between total fish consumption and quintiles of dietary contaminant exposure was 0.77 for PCB and 0.70 for MeHg. To explore potential impact of the statistical adjustment of collinear variables, we examined the association between total fish consumption (categorized into <1 serving/week, 1–2 servings/week and >2 servings/week) and incidence of type 2 diabetes across strata of dietary PCB and MeHg exposures (median splits). Comparing men with a high fish consumption (>2 servings per week) with those who consumed less than 1 weekly serving, the results were similar for men with dietary PCB exposure below the median (multivariable HR 0.91; 95 % CI 0.69–1.22) and above the median (multivariable HR 0.87; 95 % CI 0.70–1.09). The corresponding HRs for men below and above the median dietary MeHg exposure were 1.02 (95 % CI 0.83–1.25) and 0.91 (95 % CI 0.75–1.10).

Fried fish consumption (≥6 servings/month vs. ≤1 serving/month) was associated with higher incidence of type 2 diabetes (HR 1.14; 95 % CI 1.03–1.31) in the multivariable model (Table 3). Further adjustment for the contaminants did not markedly alter these results (HR 1.13; 95 % CI 1.00–1.28). In the restricted cubic spline model, we found no evidence of a nonlinear association between fried fish consumption and incidence of type 2 diabetes ($p_{\text{nonlinearity}} = 0.21$). Each one serving/week increment in fried fish consumption was associated with an HR of 1.07 (95 % CI 1.02–1.11).

No associations were observed for the three types of finfish separately (Supplementary table), whereas consumption of shellfish (≥1 serving/week vs. never/seldom) was associated with higher type 2 diabetes incidence (HR 1.21; 95 % CI 1.07–1.36) in the multivariable model (Table 4). Additional adjustment for dietary PCB and MeHg exposure resulted in slightly lower point estimates for all finfish types, but the associations remained non-significant. The association with shellfish was not markedly influenced (HR 1.19; 95 % CI 1.04–1.35).

Exclusion of fish oil supplement users ($n = 1649$; 178 cases) had little impact on the multivariable-adjusted estimates comparing the highest vs. lowest categories of consumption (total fish: HR 1.03; 95 % CI 0.87–1.22, fried fish: HR 1.11; 95 % CI 0.98–1.25, shellfish: HR 1.18; 95 % CI 1.05–1.34).

Table 3 Hazard ratios of type 2 diabetes by consumption of fried fish, the Cohort of Swedish Men 1998–2012

	Categories of fried fish consumption, servings/month (median)					*p* for trend
	≤1 (0)	2 (2)	3–4 (4)	5 (5)	≥6 (8)	
No. of cases	779	624	1359	435	427	
Person-years	118,221	85,359	165,762	50,258	48,361	
Age-adjusted model	1.00 (ref)	1.10 (0.99–1.23)	1.20 (1.10–1.31)	1.29 (1.15–1.45)	1.25 (1.11–1.41)	<0.001
Multivariable model[a]	1.00 (ref)	1.08 (0.97–1.20)	1.15 (1.05–1.26)	1.16 (1.03–1.31)	1.14 (1.03–1.31)	0.004
Multivariable model 2 (+ *contaminants*)[b]	1.00 (ref)	1.08 (0.97–1.21)	1.15 (1.05–1.26)	1.16 (1.03–1.30)	1.13 (1.00–1.28)	0.01

[a] Adjusted for attained age, body mass index (kg/m^2; <20, 20–24.9, 25–29.9, ≥30), physical activity (metabolic equivalent hours per day; quartiles), education (primary school, high school, university), cigarette smoking (never, former, current ≤10 cigarettes/day or >10 cigarettes/day), total energy intake (kcal/day; quintiles), intake of alcohol (g/day; quartiles) and DASH diet component score (based on intake of fruits, vegetables, nuts and legumes, low-fat dairy, whole grains, sodium, sweetened beverages, and red and processed meats; quartiles)

[b] Additionally adjusted for dietary exposure to polychlorinated biphenyls (ng/day, quintiles) and methyl mercury (μg/day, quintiles)

Table 4 Hazard ratios of type 2 diabetes by consumption of shellfish, the Cohort of Swedish Men 1998–2012

	Categories of shellfish consumption (median)			*p* for trend
	Never/seldom	1–3 servings/month	≥1 serving/week (1.5)	
No. of cases	1006	2161	457	
Person-years	128,943	286,299	52,719	
Age-adjusted model	1.00 (ref)	1.05 (0.97–1.13)	1.21 (1.08–1.35)	0.001
Multivariable model[a]	1.00 (ref)	1.12 (1.03–1.22)	1.21 (1.07–1.36)	0.003
Multivariable model 2 (+*contaminants*)[b]	1.00 (ref)	1.12 (1.03–1.22)	1.19 (1.04–1.35)	0.01

[a] Adjusted for attained age, body mass index (kg/m^2; <20, 20–24.9, 25–29.9, ≥30), physical activity (metabolic equivalent hours per day; quartiles), education (primary school, high school, university), cigarette smoking (never, former, current ≤10 cigarettes/day or >10 cigarettes/day), total energy intake (kcal/day; quintiles), intake of alcohol (g/day; quartiles), DASH diet component score (based on intake of fruits, vegetables, nuts and legumes, low-fat dairy, whole grains, sodium, sweetened beverages, and red and processed meats; quartiles) and consumption of the three finfish types (herring/mackerel, salmon/whitefish/char and cod/saithe/fish fingers; never/seldom, 1–3 servings/month, ≥1 serving/week)

[b] Additionally adjusted for dietary exposure to polychlorinated biphenyls (ng/day, quintiles) and methyl mercury (μg/day, quintiles)

Discussion

In this large population-based cohort of men, there was no overall association between total fish consumption and incidence of type 2 diabetes. However, there was a statistically non-significant inverse association after taking dietary exposure to contaminants present in fish (PCBs and MeHg) into account. Fried fish consumption and shellfish consumption were associated with higher incidence of type 2 diabetes, and these associations were not markedly influenced by additional adjustment for contaminants.

Previous cohort studies investigating total fish consumption in relation to risk of type 2 diabetes have provided conflicting results. Inverse associations were observed in three studies [6, 12, 13], no association in eight [3, 4, 9, 10, 14–16, 41] and direct associations in three studies [5, 7, 11]. Shellfish consumption has been specifically addressed in six studies, also providing heterogeneous results suggesting inverse [13], direct [6] or no association [5, 7, 12, 41] with type 2 diabetes risk. Five cohort studies distinguished between lean and fatty fish: one showed a weak inverse association with fatty fish but not with lean fish [41], one observed higher risk associated with lean fish but not with fatty fish [7], one observed an inverse association with lean fish but not with fatty fish [14], and two did not observe statistically significant associations [6, 12].

Few previous studies have taken preparation methods into account. Only one study investigated fried fish consumption, showing no association comparing ≥1 vs. <1 serving/week, whereas an inverse association with type 2 diabetes risk was observed for total fish [6]. In one other study, a direct association observed for total fish consumption was attenuated after further adjusting for intake of fried fish [7]. It is possible that different fish consumption habits and patterns in different populations, such as frequency of frying, have a part in explaining the heterogeneity among reports on the relationship between fish and diabetes. In our study population, 40 % of the total fish consumed was fried. High consumption of fried foods in general has previously been reported to be associated with type 2 diabetes

[42], as well as general and central obesity [43, 44], high blood pressure [44] and development of the metabolic syndrome [45]. In studies observing inverse associations between non-fried fish consumption and risk of heart failure [23, 26], ischaemic heart disease [22], stroke [24] and atrial fibrillation [25], high consumption of fried fish has been associated with higher risk or no association. Absorption of fat during frying results in more energy-dense foods and may contribute to a higher overall fat intake. The fatty acid composition of the food also changes, and frying fish may lead to a loss of long-chain omega-3 fatty acids and an increase in other fatty acids depending on the type of fat used for frying [46]. Moreover, high-temperature cooking, such as frying, induces formation of AGEs, which may contribute to insulin resistance [20]. Frying may further contribute to the formation of mutagenic compounds, such as heterocyclic amines [21]. We cannot, however, exclude that frying is a marker for other "unhealthy" behaviours that are unmeasured.

The present study is to our knowledge the first to report results for fish consumption taking dietary exposure to PCB and MeHg into account. Fish consumption and dietary contaminant exposure were highly correlated, which may inflate confidence intervals and bias the results [47]. However, adjustment for the contaminants did not markedly inflate confidence intervals. In addition, the large sample size of the study and fairly similar results across strata of dietary PCB and MeHg exposure further support that the adjustment did not produce spurious results in multivariable-adjusted model 2. In a recent meta-analysis of prospective studies on plasma or serum PCBs in relation to incident diabetes, higher concentration of total PCBs was associated with higher risk [29]. Results from prospective studies on toenail or hair mercury have suggested higher risk [30] or no association with diabetes [15, 48]. Given the regional variation of contaminant concentrations in seafood [49, 50], it is possible that adverse effects by PCBs, MeHg or other contaminants in part may explain the inconsistent findings reported on the relationship between fish consumption and risk of diabetes. Studies of PCB concentrations in serum or plasma have shown several-fold lower concentrations in populations from parts of Asia and Africa than in populations from parts of Europe and the USA [51]. The direct association observed for shellfish consumption was on the contrary not affected by adjustment for dietary PCB and MeHg exposure. A potential explanation for the association with shellfish could be related to how shellfish is consumed, i.e., in Sweden often with mayonnaise or other fatty condiments.

Potential benefits of fish consumption in relation to insulin resistance and type 2 diabetes have been suggested to be mediated through the content of long-chain n-3 fatty acids, based on their inhibitory effects on inflammatory pathways and activation of peroxisome proliferator-activated receptors [52]. Most randomized controlled trials examining the effects of long-chain n-3 fatty acid supplementation on insulin sensitivity have, however, found no effects [53], and as for fish consumption, observational findings on dietary intake of long-chain n-3 fatty acids have been mixed [17]. Fish is an important source of other nutrients that may modify the risk of type 2 diabetes, such as vitamin D and selenium. Observational evidence suggests that low vitamin D status is associated with higher risk of type 2 diabetes [54]. However, results from a large mendelian randomization analysis indicate that the association might not be causal [55] and evidence from randomized controlled trials does not support prevention of diabetes-related outcomes through vitamin D supplementation [56]. Higher toenail selenium was associated with lower risk in a recent large prospective study [57], whereas long-term selenium supplementation (high doses) has been associated with higher diabetes risk [58]. Further, intake of fish protein has been suggested to have beneficial effects on glucose tolerance and insulin sensitivity [59, 60].

Strengths of this study include its prospective population-based design, which precludes recall bias, as well as detailed dietary information and data on other lifestyle factors. Further strengths are the size of the study and the relatively large number of incident cases of type 2 diabetes. By linkage of our cohort to national registers using the individual personal registration number provided to all Swedish citizens, we were able to objectively ascertain type 2 diabetes cases and ensure comprehensive follow-up (not relying on response rates). However, because of the progressive nature of the disease with no clear onset, and the fact that type 2 diabetes rarely leads to hospitalization in the initial stages, it is likely that some early cases remain unregistered and thus were missed.

A limitation of our study is its observational design, leading to the possibility that the results may have been influenced by other habits and behaviours linked to both fish consumption and type 2 diabetes. Although we adjusted for a range of potential confounders, unmeasured or residual confounding cannot be entirely ruled out. Further, the dietary intake estimates were based on a self-reported FFQ, administered at a single time point with three single questions of fish, which inevitably leads to some degree of measurement error of the intake. Due to a larger within-food variation for contaminants as compared to intrinsic components in food, the precision of the dietary contaminant exposure estimates is further limited. Because exposure information was collected before the occurrence of the outcome, any misclassification would, however, be non-differential and most likely attenuate the association. Finally, the questionnaire design did not allow us to separately assess consumption of non-fried fish.

In conclusion, these findings suggest that preparation methods may be important when considering the relationship between fish consumption and type 2 diabetes risk. We observed no overall association between total fish consumption and type 2 diabetes, whereas fried fish and shellfish consumption was associated with higher incidence. Our results further indicated that dietary exposure to environmental contaminants such as PCBs and MeHg may influence the net benefit of fish consumption. Current public health recommendations are not challenged on the basis of our results. However, general advice on regular fish consumption may be too imprecise, and advice on preparation methods as well as on specific fish species sub-types (varying in contamination) may be needed in order to benefit from increased consumption,

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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