Intakes of Fish and Long-Chain n-3 Polyunsaturated Fatty Acid Supplements During Pregnancy and Subsequent Risk of Type 2 Diabetes in a Large Prospective Cohort Study of Norwegian Women

Jannike Øyen,[1] Anne Lise Brantsæter,[2] Ole Jakob Nøstbakken,[1] Kåre I. Birkeland,[3] Margareta Haugen,[2] Lise Madsen,[1,4] and Grace M. Egeland[5,6]

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OBJECTIVE

To investigate associations between intakes of total fish, lean fish, fatty fish, and long-chain n-3 polyunsaturated fatty acid (LCn-3PUFA) supplements and risk of type 2 diabetes in women after pregnancy. Furthermore, we sought to compare the estimated intakes of methylmercury (MeHg) and sum of dioxins and dioxin-like polychlorinated biphenyls (dl-PCBs) with tolerable weekly intakes (TWI).

RESEARCH DESIGN AND METHODS

Women free of diabetes at baseline (n = 60,831) who participated in the population-based Norwegian Mother, Father and Child Cohort Study (MoBa) were prospectively evaluated for incident type 2 diabetes, identified on the basis of medication usage >90 days after delivery, ascertained through the Norwegian Prescription Database. Dietary intake data were obtained with a validated 255-item food-frequency questionnaire (FFQ), which assessed habitual diet during the first 4–5 months of pregnancy. Intakes of MeHg and sum of dioxins and dl-PCBs were derived with use of a contaminant database and the FFQ.

RESULTS

Median age was 31 years (interquartile range 27, 34) at time of delivery, and follow-up time was 7.5 years (6.5, 8.5). Type 2 diabetes occurred in 683 (1.1%) participants. Multivariable Cox regression analyses identified lower risk of type 2 diabetes with increasing energy-adjusted lean fish intake (25 g/1,000 kcal: hazard ratio 0.71, 95% CI 0.53–0.95, P = 0.022). However, in stratified analyses, a lower risk was found only in women with prepregnancy BMI ≥25 kg/m^2. There were no associations between intake of total fish, fatty fish, or LCn-3PUFA supplements and type 2 diabetes. MeHg intake was low, but the intake of the sum of dioxins and dl-PCBs (picograms of toxic equivalents/kilograms of body weight/week) exceeded the TWI set by the European Food Safety Authority (EFSA) for the majority of participants.

CONCLUSIONS

Intake of lean fish, but not fatty fish or LCn-3PUFA supplements, was associated with lower risk of pharmacologically treated type 2 diabetes in Norwegian women who were overweight or obese. Fatty fish, which contain dioxins and dl-PCBs, did not increase the risk of type 2 diabetes, but the exceedance of the EFSA TWI for dioxins and dl-PCBs is a health concern.

[1]Seafood and Nutrition, Institute of Marine Research, Bergen, Norway
[2]Department of Environmental Health, Norwegian Institute of Public Health, Oslo, Norway
[3]Department of Transplantation Medicine, Oslo University Hospital, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[4]Department of Biology, University of Copenhagen, Denmark
[5]Division of Health Data and Digitalisation, Department of Health Registry Research and Development, Norwegian Institute of Public Health, Bergen, Norway
[6]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

Corresponding author: Jannike Øyen, jannike.oyen@hi.no

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The global burden of type 2 diabetes has increased in recent decades, and the number of disability-adjusted life-years associated with diabetes reached 24 million in 2017 (1). Overweight, obesity, and unhealthy diets are well-established risk factors that together with physical activity may be addressed through preventive measures (2).

On the basis of data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016) and the EAT-*Lancet* Commission, increases in fish intake are recommended (2,3). While fish and shellfish are excellent sources of long-chain n-3 polyunsaturated fatty acids (LCn-3PUFA), high-quality protein, and numerous vitamins and minerals, these food items are also major sources of environmental contaminants. Lean fish is a predominant source of dietary exposure to methylmercury (MeHg), while fatty fish contain lipophilic persistent organic pollutants (POPs), such as dioxins and dioxin-like polychlorinated biphenyls (dl-PCBs). Concerns related to contaminant exposures and risk of type 2 diabetes have been raised due to observed associations between both MeHg exposure (4,5) and POP exposure (6) and type 2 diabetes. Depending on the context of fish consumption, high-frequency fish consumers may approach or exceed the tolerable weekly intake (TWI) for MeHg of 1.3 μg/kg body wt/week (7) or for the sum of dioxins and dl-PCBs, which was recently reduced from 14 to 2 pg toxic equivalents (TEQ)/kg body wt/week by the European Food Safety Authority (EFSA) (8).

More knowledge regarding potential associations between fish intake and type 2 diabetes risk is needed. Inconsistent results have been noted in longitudinal studies with evaluation of fish intake and risk of type 2 diabetes (9–13) and also within Europe where average intake varies greatly (14,15). Beneficial or detrimental associations between fish intake and type 2 diabetes may be more likely to be observed in populations with a high intake, such as in Norway. Further, type 2 diabetes is affecting an increasing number of young adults, but prospective studies evaluating young adult populations are lacking. Therefore, our main aim was to evaluate the associations between total fish, lean fish, fatty fish, and LCn-3PUFA supplements intake and risk of incident type 2 diabetes in a Norwegian cohort of women of childbearing age with a relatively high intake of fish. A second aim was to compare estimated intakes of MeHg and the sum of dioxins and dl-PCBs in the current study population to established tolerable intake values.

RESEARCH DESIGN AND METHODS

Population and Design

Pregnant women were recruited to participate in the Norwegian Mother, Father and Child Cohort Study (MoBa) from 1999 to 2008 by postal invitation prior to their first scheduled ultrasound at 18 weeks' gestation. MoBa is a prospective nationwide population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health. The women consented to participation in 41% of the pregnancies. The cohort includes 114,500 children, 95,200 mothers, and 75,200 fathers. Follow-up is conducted through questionnaires and by linkage to national health registries (16). The establishment of MoBa and initial data collection were based on a license from the Norwegian Data Protection Authority and approval from the Regional Committee for Medical Research Ethics and comply with the Norwegian Health Registry Act. The current research project is an extension of a study evaluating risk factors for chronic hypertension development within 10 years following delivery (17) and was approved by all relevant agencies and the Regional Committee for Medical Research Ethics (Region West 2013/740) with amendments (14.03.2019) for including type 2 diabetes as an outcome measure. This study is based on version eight of the quality-assured data files released for research in 2014.

MoBa was linked to the Medical Birth Registry of Norway (MBRN) (18), the Norwegian Prescription Database (NorPD), and the National Population Register for information regarding pregnancy-related risk factors, diabetes medication usage, and deaths and migrations. MBRN is a compulsory registry containing information for all births (>16 weeks' gestation) in Norway, and the NorPD contains information on all dispensed prescriptions to noninstitutionalized individuals. Given that the NorPD was not established until 2004, only women who delivered between 2004 and 2009 and completed the baseline MoBa questionnaire and the dietary questionnaire were eligible for inclusion in the current study (n = 62,601 women). We excluded those with an invalid energy intake (<1,070 or >4,400 kcal/day) (n = 1,351) (19), diabetes prior to pregnancy ascertained with three data sources (MoBa, MBRN, and NorPD) (n = 439), and nonviable births (birth weight <500 g or missing birth weight at gestational age <22 weeks) (n = 15). With minor overlap in exclusions, a total of 60,831 women remained eligible for the analyses (Supplementary Fig. 1).

Dietary Intake

Information on dietary intake was obtained with a validated 255-item semiquantitative food-frequency questionnaire (FFQ) at week 22 of pregnancy (20). The MoBa FFQ was validated in 119 MoBa participants using a 4-day weighed food diary, motion sensors as a marker of energy expenditure, and biological markers measured in blood and 24-h urine samples as markers of foods and nutrients, including nutrients from dietary supplements (20,21). The results showed that the FFQ enables reasonable ranking of the participants' diet according to major food groups and nutrients as well as nutrient intakes through dietary supplements. The energy-adjusted correlation for total fish intake by the FFQ and the food diary was ρ = 0.49 (95% CI 0.34–0.62) (20). Total fish intake (and relevant subcategories) also correlated positively with erythrocyte membrane docosahexaenoic acid and with blood mercury, selenium, and arsenic concentrations (22,23).

The FFQ included 16 questions about fish or shellfish (crustaceans) eaten as dinner, 10 questions about cold cuts and spreads from fish or shellfish, and four questions about cod liver oil, cod liver oil capsules, or fish oil capsules. Fish items (g/day) were grouped as lean fish and fatty fish and included items consumed as dinner and as cold cuts and bread spreads. In mixed dishes, e.g., fish au gratin, only the fish component of the meal was considered in estimating fish intake. Lean fish species (i.e., 0.3–6.0% fat) included cod, saithe, haddock, pollock, halibut, plaice, flounder, tuna, perch, pike, and Atlantic catfish. Fatty fish species (10–24% fat) included mackerel, herring, salmon, and trout. In this study, total fish included lean and fatty fish (salt and freshwater

fish, fish-based spread), liver, roe, and shellfish.

Other nutrient variables were also obtained from the FFQ and included total energy intake (kilocalories per day), fiber, total protein, total carbohydrate, and total fat, saturated fat, monounsaturated fat, and polyunsaturated fat modeled as percentage of energy (E%) and as continuous variables (grams per day). FoodCalc and the Norwegian Food Composition Table were used for nutrient calculations (20). LCn-3PUFA intake was separately estimated from food sources and from supplements and was defined as the sum of eicosapentaenoic acid and docosahexaenoic acid and presented as grams per day.

Contaminants

We calculated exposure to dioxins and dl-PCBs (total toxic equivalents [TEQ]) by combining information on food consumption, based on the FFQ, with a database of concentrations of dioxins and dl-PCBs in Norwegian food (24). The database included 284–361 food analyses covering 37 food items during the years 2000–2006. The 37 food groups included eggs, poultry, red meat/offal, dairy products, and various species of fish and shellfish, as well as fish oil and fish liver oil supplements. Congener concentrations in other foods were estimated from their lipid content based on foods of the same origin. For instance, for all bovine meat the same standard unit for a contaminant per gram of meat was multiplied by the lipid levels for the specific food item recorded in the Norwegian Food Composition Table. With measurements and estimations, the database of the concentrations in 340 foods was established. These 340 foods included single food items as well as foods that are included in composite meals based on recipes, such as sauces and stews. For food items with contaminant analytical values lower than the limit of detection, the food concentration was set to zero (lower bound approach). For each participant, the dietary intakes of dioxins and dl-PCBs were calculated per kilogram of body weight.

The total dietary intake of Hg was calculated with use of Hg values compiled in a database previously described in detail (25). As for dioxins and dl-PCBs, food concentrations with analytical values below the level of detection were set to zero. MeHg is the organic and most toxic form of mercury. Total fish contributes 88% of the total Hg among women in MoBa (26), and we considered Hg from total fish to reflect MeHg exposure (7). These databases represent the same time period as that of the dietary data collection. Estimated intakes of dioxins and dl-PCBs and MeHg in this study were compared with the health-based guidance values, i.e., TWI, established by EFSA (7,8).

Covariates

The baseline prepregnancy covariates came from the first MoBa questionnaire administered at 15–17 weeks' gestation: daily cigarette smoking, height and weight for calculating BMI (calculated as weight in kilograms divided by the square of height in meters), educational level (primary, secondary, and any college/university), marital status (married/cohabitation with partner vs. other), and leisure-time physical activity ($<$3 vs. $\geq$3 times/week).

The MBRN provided information on maternal age at delivery, parity, health conditions, and pregnancy-related complications (gestational diabetes mellitus or type unspecified, gestational hypertension/preeclampsia) and whether pregnancy was a multiple birth pregnancy.

Gestational diabetes mellitus status was ascertained through three sources: MoBa questionnaire, MBRN, and use of medications noted in the NorPD during pregnancy.

Outcome

We identified all women initiating diabetes medication use (Anatomical Therapeutic Chemical classification code ATC A10) with a dispensed prescription of at least 90 days following delivery. This included both insulin and oral agents but excluded those only taking insulin regularly through to the end of follow-up. A total of 711 ATC A10 medication users were identified, of whom we excluded 28 with long-term and regular use of insulin and insulin only through to 2013 or at time of censoring. The majority of medication users (70%) were missing any mention of an underlying indication for treatment diagnostic code.

Statistical Analyses

Descriptive characteristics by total fish consumption categories are presented as percentages and as median and interquartile range (IQR) for categorical and continuous variables, respectively. Tests for trends in descriptive characteristics across increasing categories of total fish intake included logistic and linear regression for dichotomous and continuous descriptive variables, respectively.

We energy adjusted all dietary intakes using the nutrient density method. Cox proportional hazards analyses evaluated the association between total fish intake and development of type 2 diabetes up to 10 years following delivery (i.e., through 31 December 2014). Further, lean and fatty fish intakes were evaluated separately in another analysis. All intakes were evaluated both as continuous variables (g/1,000 kcal and 25 g/1,000 kcal) and as ranked quintile categorical variables. The Norwegian Directorate of Health recommends a weekly fish intake of 350–400 g (2–3 dinners) for all adults (27). This equals $\sim$55 g/day and corresponds to 25 g/1,000 kcal in our study population. We used this amount for total fish as well as for lean and fatty fish, although the dietary guideline does not include shellfish and highlights that at least one-half of the fish consumed should be fatty fish. In supplementary analyses, absolute intakes of total fish, lean fish, and fatty fish were evaluated as continuous variables (25 g/day) and divided into the following categories: never/rarely ($<$5 g/day), $<$1 serving/week ($>$5–20 g/day), 1–2 servings/week ($>$21–40 g/day), 2–3 servings/week ($>$40–60 g/day), and $\geq$3 servings/week ($>$60 g/day). We assumed, as in previous MoBa publications, a serving size of 140 g for dinner and of 20–25 g for bread spreads (28).

Similarly, we evaluated LCn-3PUFA supplement use as grams per day and as intake level (none, median intake $<$0.4 g/day, and median intake $\geq$0.4 g/day) in Cox proportional hazards analyses.

The Cox regression models were adjusted for potential confounders with use of three models: *1*) adjustment for energy intake and age; *2*) model 1 adjustments plus BMI, gestational diabetes mellitus, and gestational hypertension/preeclampsia; and *3*) model 2 adjustments plus maternal education, smoking, and dietary fiber. Dietary fiber was chosen, a prior, as a proxy of overall dietary quality, as it reflects the intake of vegetables, whole grain, and a

dietary pattern in line with healthy eating. Additional adjustments for other food groups (g/1,000 kcal or g/day) (e.g., vegetables, fruits, red meat, pork meat, poultry, milk/dairy, eggs, and total added sugar), civil status, and physical activity were evaluated one at a time, and then together with model 3 covariates, but as their inclusion did not alter the results (data not shown) they were not included in the final models presented. We also explored consistencies in results in analyses stratified by BMI categories ($<$25 and $\geq$25 kg/m^2).

The proportionality assumptions for the Cox models were evaluated graphically with log-minus-log plots. The hazard ratios (HRs) were stable, and the proportion ratios were validated for all models.

The relationship between lean fish intake and MeHg, fatty fish intake and polychlorinated biphenyl (PCB)-153, and fatty fish intake and dioxins and dl-PCBs were investigated using Spearman rank order correlation.

There were 1,435 (2.3%), 1,185 (1.9%), and 303 (0.5%) women with missing baseline values for prepregnancy BMI, maternal education, and civil status, respectively. Missing values were imputed with use of multiple imputation for SPSS. Two-tailed P values $<$0.05 were considered statistically significant. The analyses were performed with IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY).

RESULTS

Characteristics and Dietary Intake

Median absolute intake of total fish and lean and fatty fish was 33.3 g/day (IQR 21.4, 46.9), 18.4 g/day (10.6, 27.2), and 7.5 g/day (3.2, 13.9), respectively (Supplementary Table 1), and the median energy-adjusted total fish and lean and fatty fish intake was 14.9 g/1,000 kcal/day (9.5, 21.4), 8.1 g/1,000 kcal/day (4.6, 12.4), and 3.4 g/1,000 kcal/day (1.4, 6.4). Participant median age at time of delivery was 31 years (27, 34) years, prepregnancy weight 65 kg (59, 74), and prepregnancy BMI 23.1 kg/m^2 (21.1, 26.0) (Table 1), and 68.1% had a BMI $<$25 kg/m^2.

Energy-adjusted total fish intake quintiles were positively associated with age, maternal physical activity, and educational level at prepregnancy and inversely associated with daily prepregnancy smoking and preeclampsia. Further, total fish intake was positively associated with intake of mutton and poultry, bread/cereals/pasta, eggs, vegetables/fruits/nuts, fiber, polyunsaturated fat, and LCn-3PUFA from food and supplements. In contrast, total fish intake was inversely associated with meat in general, carbohydrates, added sugar, saturated fat, and monounsaturated fat (Table 1) ($P_{trend} < 0.001$). Similar findings were observed when total fish intake was evaluated as absolute intake (g/day) (Supplementary Table 1).

LCn-3PUFA supplement intake levels were positively associated with intake of total energy, all energy-adjusted fish categories (except shellfish), milk/dairy, bread/cereals/pasta, eggs, vegetables/fruits/nuts, fiber, and protein but were inversely associated with meat in general (except mutton and poultry), added sugar, and total fat (Supplementary Table 2) ($P_{trend} < 0.001$). Similar results were identified when dietary intake was evaluated as absolute intake (grams per day) (Supplementary Table 3).

Fish and LCn-3PUFA Intakes and Risk of Type 2 Diabetes

Among the 591 participants with gestational diabetes mellitus (identified with three data sources), 191 (32%) developed type 2 diabetes during the follow-up. During the maximum 10-year and median follow-up time of 7.5 years (IQR 6.5, 8.5), 683 participants developed pharmacologically treated type 2 diabetes. In Cox regression analyses, all models identified a lower risk of type 2 diabetes with increased energy-adjusted lean fish intake (25 g/1,000 kcal; model 3: HR 0.71, 95% CI 0.53–0.95, P = 0.022) (Table 2). In contrast, no significant associations were observed for intake of total fish, fatty fish, or LCn-3PUFA from supplements (Table 2). Similar associations were observed in Cox models when fish intake was evaluated as absolute intake (25 g/day) (Supplementary Table 4).

In Cox regression analyses of quintiles of energy-adjusted fish intake, a lower risk of type 2 diabetes was seen for lean fish intake quintiles two, three, and five compared with quintile one, with the strongest association for quintile three (model 3: HR 0.69, 95% CI 0.55–0.88) (Fig. 1). Similar findings were observed for models 1 and 2 or with consideration of additional covariates, i.e., other food groups, civil status, and physical activity (data not shown). For total fish, fatty fish, and LCn-3PUFA from supplements, no significant associations were observed (Fig. 1). Results from the analyses of categories of absolute fish intake were similar to those depicted in Fig. 1 (Supplementary Fig. 2).

Sensitivity Analyses

In analyses stratified by prepregnancy BMI categories ($<$25 and $\geq$25 kg/m^2), a lower risk of type 2 diabetes was observed with increased energy-adjusted lean fish intake (25 g/1,000 kcal) only in the BMI group $\geq$25 kg/m^2 (model 3: HR 0.61, 95% CI 0.43–0.86, P = 0.005) (Table 3). No significant associations were observed for intake of total fish, fatty fish, or LCn-3PUFA from supplements (Table 3). Similar findings were observed in evaluation of fish as absolute intake (25 g/day) (Supplementary Table 5). Also, in evaluation of quintile categories of energy-adjusted fish intake and supplement LCn-3PUFA intake, only lean fish intake was associated with a significantly lower risk of type 2 diabetes (Supplementary Fig. 3). Similar findings were observed with consideration of additional covariates, i.e., other food groups, civil status, and physical activity (data not shown).

Intake of Contaminants

The estimated intakes of contaminants are shown in Table 1. The median intake of MeHg, PCB-153, and the sum of dioxins and dl-PCBs (total TEQ), was 0.13 μg/kg body wt/week (IQR 0.08, 0.21), 0.74 ng/kg body wt/day (0.49, 1.2), and 3.9 pg TEQ-05/kg body wt/week (2.8, 5.4), respectively. As expected, intake of lean fish correlated with MeHg (ρ = 0.67) and intake of fatty fish correlated with PCB-153 (ρ = 0.70) and the sum of dioxins and dl-PCBs (ρ = 0.70). Total sum of dioxins and dl-PCBs exposure, but not MeHg, exceeded the TWI established by EFSA for all quintiles (Supplementary Fig. 4).

CONCLUSIONS

In this large prospective population-based cohort study of 60,831 women of childbearing age, we found that intake of lean fish, but not total fish, fatty fish, or LCn-3PUFA supplements, was associated with lower risk of pharmacologically treated type 2 diabetes. In analyses stratified by prepregnancy BMI, a lower risk of type 2 diabetes was seen with increasing lean

Table 1—Baseline characteristics for all participants and by quintiles of energy-adjusted total fish* intake

		Quintiles of total fish consumption (g/1,000 kcal)				
	All	Q1 (<8.3)	Q2 (8.4–12.7)	Q3 (12.8–17.1)	Q4 (17.2–23.3)	Q5 (>23.3)
N	60,831	12,166	12,166	12,167	12,166	12,166
Follow-up, years	7.5 (6.5, 8.5)	7.5 (6.5, 8.5)	7.5 (6.5, 8.5)	7.5 (5.5, 8.5)	7.5 (6.5, 8.5)	7.5 (5.6, 8.5)
Age at delivery, years	31 (27, 34)	29 (26, 33)	30 (27, 33)	31 (28, 34)	31 (28, 34)	31 (28, 34)
Height, cm	168 (164, 172)	168 (164, 172)	168 (164, 172)	168 (164, 172)	168 (164, 172)	168 (164, 172)
Prepregnancy variables						
Weight, kg	65 (59, 74)	66 (59, 75)	66 (60, 75)	65 (59, 74)	65 (60, 74)	65 (59, 74)
BMI, kg/m^2	23.1 (21.1, 26.0)	23.2 (21.1, 26.3)	23.1 (21.1, 26.1)	23.0 (21.0, 25.8)	23.1 (21.1, 26.0)	23.1 (21.1, 26.0)
Married/partner	96.9	96.2	97.4	97.5	97.0	96.7
Daily smoking	15.9	20.9	16.3	14.6	14.0	13.9
Physical activity ≥3 times/week	47.9	43.1	45.6	48.4	50.2	52.4
Education ≥17 years	28.1	22.3	27.6	29.5	31.1	30.0
Pregnancy variables						
Gestational diabetes mellitus	1.0	1.0	1.0	0.8	1.0	1.0
Gestational hypertension	2.1	2.2	2.2	2.0	2.1	2.0
Preeclampsia	3.7	4.3	3.9	3.3	3.5	3.4
Daily dietary intake						
Energy, kcal	2,216 (1,870, 2,634)	2,381 (1,975, 2,858)	2,346 (1,988, 2,779)	2,265 (1,943, 2,644)	2,160 (1,856, 2,515)	1,972 (1,668, 2,327)
Total fish, g/1,000 kcal	14.9 (9.5, 21.4)	5.4 (2.9, 7.0)	10.6 (9.5, 11.7)	14.9 (13.8, 16.0)	19.8 (18.4, 21.4)	29.1 (25.7, 34.8)
Lean fish, g/1,000 kcal	8.1 (4.6, 12.4)	2.7 (0.7, 4.3)	6.2 (4.6, 7.9)	8.7 (6.6, 10.8)	11.6 (8.8, 14.3)	16.2 (11.4, 21.1)
Fatty fish, g/1,000 kcal	3.4 (1.4, 6.4)	0.89 (0.00, 1.9)	2.5 (1.3, 3.7)	3.7 (2.2, 5.5)	5.2 (3.0, 7.7)	9.1 (5.1, 14.8)
Shellfish, g/1,000 kcal	1.0 (0.00, 2.3)	0.00 (0.00, 1.1)	0.93 (0.00, 1.9)	1.2 (0.00, 2.4)	1.4 (0.00, 2.8)	1.7 (0.00, 3.6)
Fish spread, g/1,000 kcal	1.0 (0.00, 2.6)	0.00 (0.00, 0.74)	0.60 (0.00, 1.5)	1.1 (0.00, 2.3)	1.6 (0.30, 3.7)	3.4 (0.94, 10.4)
Fish liver/roe as dinner/spreads, g/1,000 kcal	0.00 (0.00, 0.58)	0.06 (0.06, 0.16)	0.00 (0.00, 0.43)	0.08 (0.00, 0.58)	0.20 (0.00, 0.83)	0.31 (0.00, 1.59)
Total meat, g/1,000 kcal	68.1 (54.3, 84.3)	73.7 (58.4, 92.0)	69.8 (55.8, 86.0)	67.4 (54.6, 82.3)	66.0 (53.1, 81.0)	64.3 (50.7, 79.9)
Red meat, g/1,000 kcal	55.4 (42.6, 70.5)	61.2 (46.5, 78.5)	57.2 (44.4, 72.2)	55.0 (42.8, 69.2)	53.1 (41.4, 67.0)	51.1 (38.8, 65.3)
Beef, g/1,000 kcal	5.2 (2.8, 8.2)	5.2 (2.6, 8.6)	5.3 (3.0, 8.2)	5.3 (3.0, 8.1)	5.1 (2.9, 8.0)	4.9 (2.3, 8.0)
Pork, g/1,000 kcal	8.4 (5.0, 12.7)	8.8 (5.0, 13.8)	8.9 (5.4, 12.9)	8.5 (5.3, 12.7)	8.3 (5.1, 12.3)	7.5 (4.3, 11.6)
Mutton, g/1,000 kcal	5.3 (2.4, 9.5)	4.4 (1.6, 8.9)	5.2 (2.4, 9.4)	5.6 (2.6, 9.5)	5.7 (2.8, 9.8)	5.7 (2.5, 9.8)
Poultry, g/1,000 kcal	9.3 (5.4, 15.5)	8.6 (4.6, 15.5)	9.2 (5.6, 15.3)	9.1 (5.8, 14.9)	9.6 (5.9, 15.5)	9.7 (5.3, 16.3)
Game, g/1,000 kcal	0.00 (0.00, 1.7)	0.00 (0.00, 1.37)	0.00 (0.00, 1.6)	0.00 (0.00, 1.8)	0.00 (0.00, 1.9)	0.00 (0.00, 1.9)
Processed red meat, g/1,000 kcal	32.4 (23.4, 44.2)	37.9 (26.8, 51.5)	33.9 (24.8, 45.5)	31.8 (23.3, 42.9)	30.8 (22.3, 41.0)	29.1 (20.6, 39.7)
Milk/dairy, g/1,000 kcal	204 (120, 291)	194 (109, 290)	205 (124, 295)	210 (127, 294)	208 (124, 289)	199 (115, 289)
Bread/cereals/pasta, g/1,000 kcal	133 (111, 155)	131 (107, 155)	132 (111, 154)	133 (112, 154)	134 (114, 156)	135 (112, 157)
Eggs, g/1,000 kcal	9.0 (5.9, 14.3)	7.8 (4.9, 13.2)	8.9 (5.7, 14.2)	9.3 (6.2, 14.5)	9.5 (6.4, 14.6)	9.5 (6.4, 15.1)
Vegetables/fruits/nuts, g/1,000 kcal	336 (247, 445)	302 (213, 415)	326 (239, 431)	340 (253, 445)	351 (263, 456)	359 (268, 473)
Fiber, E%	5.4 (4.6, 6.2)	5.1 (4.3, 5.9)	5.3 (4.6, 6.0)	5.4 (4.7, 6.2)	5.5 (4.8, 6.3)	5.7 (4.9, 6.6)
Added sugar, E%	9.5 (7.1, 12.5)	10.9 (7.9, 14.6)	10.2 (7.6, 13.2)	9.6 (7.3, 12.5)	9.1 (6.8, 11.7)	8.1 (6.0, 10.6)
Protein, E%	15.5 (14.2, 16.9)	14.7 (13.3, 16.1)	15.1 (13.8, 16.4)	15.4 (14.2, 16.7)	15.7 (14.6, 17.0)	16.4 (15.2, 17.8)
Carbohydrate, E%	53.5 (50.5, 56.5)	54.3 (51.1, 57.6)	53.9 (50.9, 56.8)	53.6 (50.7, 56.4)	53.3 (50.5, 56.2)	52.5 (49.6, 55.5)
Total fat, E%	30.6 (27.8, 33.6)	30.6 (27.5, 33.7)	30.7 (27.8, 33.6)	30.7 (27.9, 33.6)	30.6 (27.7, 33.4)	30.6 (27.8, 33.6)
Saturated fat, E%	11.7 (10.5, 13.1)	12.0 (10.7, 13.5)	11.9 (10.7, 13.3)	11.8 (10.5, 13.1)	11.6 (10.4, 12.9)	11.3 (10.1, 12.6)

Continued on p. 2342

Table 1—Continued

	All	Quintiles of total fish consumption (g/1,000 kcal)				
		Q1 (<8.3)	Q2 (8.4–12.7)	Q3 (12.8–17.1)	Q4 (17.2–23.3)	Q5 (>23.3)
Monounsaturated fat, E%	9.8 (8.7, 11.0)	9.8 (8.7, 11.0)	9.8 (8.8, 11.0)	9.9 (8.8, 11.0)	9.8 (8.7, 10.9)	9.7 (8.6, 10.9)
Polyunsaturated fat, E%	5.5 (4.7, 6.6)	5.3 (4.4, 6.4)	5.4 (4.5, 6.5)	5.5 (4.7, 6.5)	5.5 (4.7, 6.6)	5.8 (5.0, 6.8)
LCn-3PUFA from food, g	0.32 (0.20, 0.51)	0.16 (0.09, 0.23)	0.27 (0.19, 0.36)	0.34 (0.25, 0.48)	0.42 (0.30, 0.61)	0.62 (0.40, 1.0)
LCn-3PUFA from supplements, g	0.20 (0.00, 0.60)	0.14 (0.00, 0.40)	0.20 (0.00, 0.57)	0.20 (0.00, 0.60)	0.20 (0.00, 0.60)	0.20 (0.00, 0.71)
Contaminant exposures						
PCB-153, ng/kg body wt/day	0.74 (0.49, 1.2)	0.48 (0.34, 0.69)	0.64 (0.46, 0.92)	0.77 (0.53, 1.1)	0.88 (0.60, 1.3)	1.19 (0.74, 1.9)
Total TEQ,† pg/kg body wt/week	3.9 (2.8, 5.4)	2.9 (2.2, 3.9)	3.5 (2.7, 4.7)	3.9 (3.0, 5.2)	4.3 (3.2, 5.7)	5.2 (3.7, 7.3)
MeHg, µg/kg body wt/week	0.13 (0.08, 0.21)	0.04 (0.02, 0.07)	0.10 (0.07, 0.14)	0.14 (0.10, 0.19)	0.18 (0.13, 0.23)	0.24 (0.18, 0.32)

Data are median (IQR) or % unless otherwise indicated. *Total fish includes lean and fatty fish (salt and freshwater fish, fish-based spread), liver, roe, and shellfish. †Total TEQ includes dioxins and dl-PCBs.

fish intake only in women with overweight or obesity. Although dietary exposure to dioxins and dl-PCBs exceed the TWI set by EFSA for nearly all participants, and fatty fish were the main source of these exposures, no associations between fatty fish intake and type 2 diabetes were identified in the current study.

Comparison With Findings From Other Studies

Our finding that lean fish intake was associated with lower risk of type 2 diabetes is in accordance with findings of an earlier Norwegian cohort study of 33,740 women (mean age of 48 years) that a high intake of lean fish (75–100 g/day) was associated with lower type 2 diabetes risk (relative risk 0.67, 95% CI 0.46–0.98) (10). However, other studies have reported no (9,11,15) or positive associations between lean fish intake and type 2 diabetes (12). Discrepancies between our findings and those of other studies may relate to the high degree of variation in fish intake (14,15). For example, an intake of 23 g/day lean fish was considered high in a Dutch population (12) but was lower than the average intake in the Norwegian cohort described by Rylander et al. (10). Other explanations for the discrepancies in the results may for example be related to differences in definitions of lean and fatty fish, and variations in lean fish preparation (13,29). Despite the relatively high intake levels of lean fish in the current cohort, the EFSA TWI for MeHg was not exceeded.

Using stratified analyses, we assessed the potential effect modification by BMI, and our results indicated that women with BMI $\geq$25 kg/m^2 had lower risk for type 2 diabetes with increased lean fish intake, whereas no significant associations were found for those with BMI <25 kg/m^2. Overweight and obesity are well-known risk factors for type 2 diabetes, and in an ecological study of 41 countries in five continents with different sociodemographic characteristics investigators found that in countries with low fish consumption, the prevalence of type 2 diabetes increased significantly with obesity, whereas high fish consumption was associated with reduced type 2 diabetes risk in countries with high prevalence of obesity (30).

Potential Mechanisms

The mechanisms by which lean fish may protect against development of type 2 diabetes are not yet elucidated, but certain nutrients present in lean fish (31), such as taurine, have been reported to attenuate development of metabolic syndrome and type 2 diabetes in humans (32). Our results are in line with the finding that intake of cod protein resulted in improvements in insulin sensitivity compared with other protein sources in a 4-week crossover feeding trial of 19 insulin-resistant study subjects (33). While we lack measures of insulin resistance in the current study, the women who were overweight or obese at baseline would have had a greater likelihood of insulin resistance. In a crossover trial, lean fish intake reduced postprandial concentrations of C-peptide, lactate, and the triglyceride–to–HDL cholesterol ratio in healthy normoglycemic adults with mean ± SEM BMI 25.6 ± 0.7 kg/m^2, indicating lower risk of insulin resistance and type 2 diabetes (34,35). Subsequent metabolomics analyses revealed that reduced C-peptide levels were accompanied with reduced acylcarnitines and 2PY levels in urine, and improved mitochondrial function was suggested as a mechanism by which intake of lean fish may preserve insulin sensitivity (36).

Fatty fish is the major source of fat-soluble POPs, such as dioxins and dl-PCBs, that have been associated with increased risk of type 2 diabetes (37). Their presence in fatty fish has been postulated to counteract the potentially beneficial effects of marine nutrients (38). Among First Nations populations in Canada with a high prevalence of type 2 diabetes (24.4%), dietary PCBs intake was positively associated with type 2 diabetes (odds ratio 1.07, 95% CI 1.004–1.27), whereas LCn-3PUFA intake, adjusted for PCBs intake, showed an inverse relation, against type 2 diabetes, among older individuals (38). Importantly, obesity is a key risk factor for type 2 diabetes and lipophilic POPs, such as dioxins and dl-PCBs, which are stored in adipose tissue. Increased body burden of PCBs may result from increasing adipose tissue mass (39), and a recent human prospective study demonstrated that BMI and possibly body fat prior to study recruitment affected the baseline levels of POPs and may thus confound associations even in a prospectively designed study (40). In our cohort, the risk for type 2 diabetes was not associated with intake of total

Table 2—HRs (95% CIs) for incident type 2 diabetes by energy-adjusted fish intake and LCn-3PUFA from supplements for 60,831 women with 683 type 2 diabetes events

	Model 1*	Model 2†	Model 3‡
Total fish§ (25 g/1,000 kcal)	0.86 (0.71–1.05); $P = 0.134$	0.92 (0.76–1.11); $P = 0.373$	0.91 (0.75–1.10); $P = 0.325$
Lean fish (25 g/1,000 kcal)	0.67 (0.50–0.92); $P = 0.012$	0.73 (0.54–0.98); $P = 0.035$	0.71 (0.53–0.95); $P = 0.022$
Fatty fish (25 g/1,000 kcal)	0.83 (0.58–1.18); $P = 0.291$	0.93 (0.66–1.30); $P = 0.653$	0.94 (0.67–1.32); $P = 0.704$
LCn-3PUFA supplements (g/day)	0.95 (0.83–1.09); $P = 0.439$	1.08 (0.95–1.23); $P = 0.263$	1.08 (0.95–1.23); $P = 0.250$

*Adjustment for energy intake and age. †Adjustment for energy intake, age, prepregnancy BMI, gestational diabetes mellitus, and gestational hypertension including preeclampsia. ‡Adjustment for energy intake, age, prepregnancy BMI, gestational diabetes mellitus, gestational hypertension including preeclampsia, maternal prepregnancy education and smoking, and dietary fiber. §Total fish includes lean and fatty fish (salt and freshwater fish, fish-based spread), liver, roe, and shellfish.

fish, fatty fish, or LCn-3PUFA supplements, and any potential detrimental effect of POPs may have been outweighed by beneficial effects of nutrients present in lean fish. The beneficial effects of fish are often related to the LCn-3PUFA, mainly found in fatty fish species. However, guidelines for fish intake include both lean and fatty species, and this study adds supporting evidence that also lean fish (with relatively lower LCn-3PUFA content) confer health effects, although the mechanism is not fully understood.

Strengths and Limitations

Strengths of this study include the large population-based cohort design, ascertainment of relevant prepregnancy risk factors and pregnancy-related complications, and the complete ascertainment of diabetes medication usage in a mandatory nationwide register during an average 7.5-year follow-up. Further, the MoBa cohort included women with wide ranges of fish consumption and socioeconomic status. The FFQ was detailed enough to separately evaluate types of fish and the FFQ used has been validated.

This study has some limitations. As the study is based on observational data, we cannot rule out the possibility of unmeasured confounders and causality cannot be inferred. Also, the study provided no information on diagnostic laboratory measurements, and given the large percentage of missing information on underlying indication for medication treatment, there is a possibility of misclassification in the outcome type 2 diabetes. However, it is unlikely that type 1 diabetes was included in the outcome given our exclusion criteria. Also, we could not identify nonpharmacologically treated type 2 diabetes, which likely accounts for 25% of total type 2 diabetes among women based on a recent assessment in Norway (41). Thus, our findings cannot be generalized to milder forms of type 2 diabetes handled by diet and exercise alone. Finally, we cannot entirely rule out the possibility of gestational diabetes mellitus in a subsequent pregnancy. However, given that gestational diabetes mellitus and type 2 diabetes share common risk factors and underlying aetiologies, the combination of type 2 diabetes with gestational diabetes mellitus cases in our outcome variable is not problematic for the purposes of the current study. Another limitation is that FFQs are not suitable for precise dietary intake estimates. Still, FFQs are recognized for their suitability for rank ordering of study participants by dietary intakes for epidemiological investigations.

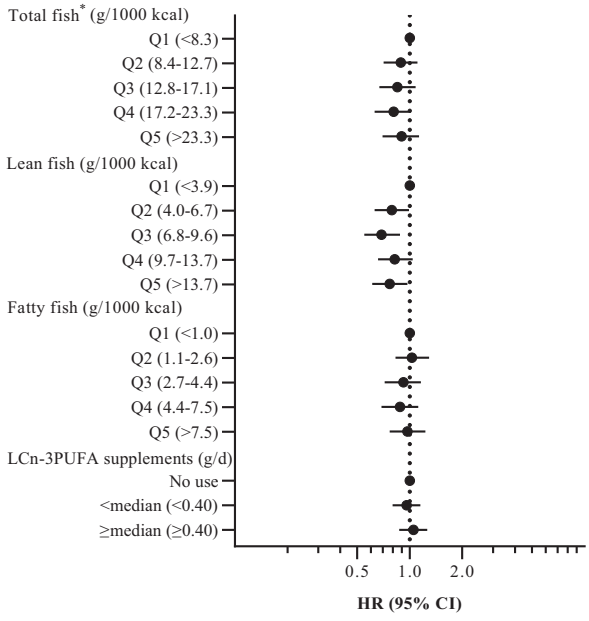

Figure 1—Forest plot showing the associations (HR and 95% CI) between quintiles of energy-adjusted fish intake (g/1,000 kcal) and categories of LCn-3PUFA from supplements (g/day) and incident type 2 diabetes in 60,831 women with 683 type 2 diabetes events. Adjusted for energy intake, age, prepregnancy BMI, gestational diabetes mellitus, gestational hypertension including preeclampsia, maternal prepregnancy education and smoking, and dietary fiber. *Total fish includes lean and fatty fish (salt and freshwater fish, fish-based spread), liver, roe, and shellfish. d, day.

Public Health Significance

In conclusion, in this large prospective population-based cohort study including women of childbearing age, we observed an association between intake of lean fish, but not of total fish, fatty fish, or LCn-3PUFA supplements, and lower type 2 diabetes risk. In stratified analyses, a lower risk of type 2 diabetes was seen only among those with a prepregnancy BMI $\geq$25 kg/m^2. Fatty fish, which contain dioxins and dl-PCBs, did not increase the risk of type 2 diabetes, but the finding that the majority of participants exceeded the TWI for the sum of dioxins and dl-PCBs is a health concern. Our results

Table 3—HRs (95% CIs) for incident type 2 diabetes by energy-adjusted fish/supplement intake stratified by prepregnancy BMI for 60,831 women with 683 type 2 diabetes events

	Model 1*		Model 2†		Model 3‡	
	BMI <25 kg/m^2	BMI ≥25 kg/m^2	BMI <25 kg/m^2	BMI ≥25 kg/m^2	BMI <25 kg/m^2	BMI ≥25 kg/m^2
N	41,417	19,414	41,417	19,414	41,417	19,414
n with type 2 diabetes	157	526	157	526	157	526
Total fish§ (25 g/1,000 kcal)	1.21 (0.82–1.79); *P* = 0.336	0.84 (0.67–1.06); *P* = 0.139	1.23 (0.83–1.83); *P* = 0.303	0.83 (0.66–1.04); *P* = 0.098	1.20 (0.80–1.78); *P* = 0.375	0.83 (0.66–1.04); *P* = 0.100
Lean fish (25 g/1,000 kcal)	1.13 (0.61–2.10); *P* = 0.695	0.64 (0.45–0.90); *P* = 0.011	1.20 (0.65–2.21); *P* = 0.569	0.62 (0.44–0.87); *P* = 0.006	1.11 (0.60–2.06); *P* = 0.731	0.61 (0.43–0.86); *P* = 0.005
Fatty fish (25 g/1,000 kcal)	0.89 (0.43–1.84); *P* = 0.747	0.91 (0.62–1.36); *P* = 0.658	0.93 (0.44–1.96); *P* = 0.847	0.92 (0.62–1.36); *P* = 0.670	0.93 (0.44–1.97); *P* = 0.855	0.94 (0.64–1.39); *P* = 0.768
LCn-3PUFA supplements (g/day)	1.09 (0.85–1.41); *P* = 0.487	1.08 (0.92–1.25); *P* = 0.356	1.11 (0.87–1.43); *P* = 0.406	1.11 (0.95–1.29); *P* = 0.184	1.09 (0.85–1.40); *P* = 0.485	1.11 (0.96–1.30); *P* = 0.165

Data are HR (95% CI) unless otherwise indicated. *Adjustment for energy intake and age. †Adjustment for energy intake, age, gestational diabetes mellitus, and gestational hypertension including preeclampsia. ‡Adjustment for energy intake, age, gestational diabetes mellitus, gestational hypertension including preeclampsia, maternal prepregnancy education and smoking, and dietary fiber. §Total fish includes lean and fatty fish (salt and freshwater fish, fish-based spread), liver, roe, and shellfish.

support the current dietary general advice for regular fish consumption, especially among those who are overweight or obese and at high risk for type 2 diabetes. Further research evaluating lean fish intake in diverse study groups and populations and studies elucidating mechanisms by which lean fish may be protective are warranted. In addition, research of relative tradeoffs between lean and fatty fish and between lean fish and other dietary constituents is needed.

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