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Periconceptional seafood intake and pregnancy complications

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Abstract

Objective: To investigate associations of maternal periconceptional shellfish, lean fish and fatty fish intake with risk of pregnancy complications.

Design: In this prospective cohort study, we collected information on intake of seafood subtypes using FFQ. We categorized seafood intake into frequencies of <0·2 servings/month, 0·2 servings/month– <0·5 servings/week, 0·5–1·0 servings/week and >1 servings/week. We ascertained gestational hypertension, pre-eclampsia, gestational diabetes and preterm birth diagnoses from medical records. Using generalized linear models with a log link, the Poisson family and robust standard errors, we estimated risk ratios and 95 % confidence intervals across seafood intake categories.

Setting: The Omega study, a study of risk factors for pregnancy complications among women recruited from prenatal clinics in Washington State, USA, 1996–2008.

Subjects: The current study included 3279 participants from the Omega study.

Results: Median (interquartile range) shellfish, lean fish and fatty fish intake was 0·3 (0–0·9), 0·5 (0–1·0) and 0·5 (0·1–1·0) servings/week, respectively. Lean fish intake of >1 servings/week (*v.* <0·2 servings/month) was associated with a 1·55-fold higher risk of preterm birth (95 % CI 1·04, 2·30) and was not associated with the other pregnancy complications. Higher intake of seafood (total or other subtypes) was not associated with pregnancy complications (separately or combined).

Conclusions: Higher intake of lean fish, but not fatty fish or shellfish, was associated with a higher risk of preterm birth; these findings may have significance for preterm birth prevention. Studies of mechanisms and potential contributing factors (including seafood preparation and nutrient/contaminant content) are warranted.

Key words
Seafood intake
Pregnancy
Lean fish
Preterm birth
Pregnancy complication

Pregnancy complications, including pre-eclampsia (PE), gestational hypertension (GH), gestational diabetes (GDM) and preterm birth (PTB), complicate over 20 % of pregnancies, co-occur and are associated with maternal and infant cardiometabolic morbidity and mortality[1–3]. Cardiometabolic benefits of seafood intake, especially from fatty/dark-meat fish, a major dietary source of EPA and DHA, have been demonstrated among men and non-pregnant women[4,5]. However, results from studies of seafood, EPA or DHA intake and risk of pregnancy complications have been inconsistent[6–16].

Results from randomized clinical trials generally support associations of higher intakes of EPA and DHA (through supplementation/enriched foods) with a lower risk of PTB[14], but not GH[14,15], PE[14,15] or GDM[15]. Findings from several, but not all[6–8], observational studies support inverse or U-shaped associations of seafood intake or maternal EPA and DHA status during pregnancy with these complications[9–12,16].

Inconsistencies in findings across studies may be partly explained by differences in the timing of seafood or EPA and DHA intake since pathogenesis of these pregnancy complications begins in early pregnancy[1,2,17]. In addition, inconsistencies may arise from differences in study population characteristics. Despite study results in men and non-pregnant women that support heterogeneous effects of seafood intake (depending on factors including

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seafood species and/or preparation method)[4,5,18] on the risk of CVD outcomes, little is known about potential variation in associations of seafood intake and risk of pregnancy complications by seafood subtype.

We investigated associations of periconceptional seafood intake and risk of PE, GH, GDM and PTB. We hypothesized that higher intake of seafood is associated with a lower risk of these pregnancy complications and that associations vary by seafood subtype.

Methods

The Omega prospective cohort study is designed to examine dietary and metabolic risk factors associated with adverse pregnancy outcomes. Participants were recruited from women attending prenatal care clinics affiliated with Swedish Medical Center and Tacoma General Hospital in Seattle and Tacoma, WA, USA, respectively[13]. Eligible women initiated prenatal care before 20 weeks' gestation, were aged >18 years, were able to speak and read English, and planned to carry the pregnancy to term and to deliver at either hospital.

During the study period (1996–2008) 5063 eligible women were approached; 4000 (79 %) consented to participate; and 3892 (97 %) completed study follow-up. We excluded 118 participants with multifetal pregnancies, seventy-two with implausible total energy intake of <2092 kJ/d (<500 kcal/d) or >14 644 kJ/d (>3500 kcal/d), 422 participants with missing seafood intake information and one participant who reported implausible seafood intake of 46 servings/week. A total of 3279 participants remained for analyses.

At or near enrolment (16 weeks' gestation on average), trained interviewers conducted in-person 45–60 min interviews to collect data on sociodemographic characteristics, reproductive and medical histories, height and pre-pregnancy weight, recreational physical activity, alcohol and tobacco consumption, and medication use. Participants completed self-administered, validated, semi-quantitative FFQ to assess diet during the periconceptional period (the three months before and the first three months of the index pregnancy)[13]. Participants also completed a supplementary Seafood Intake Scale FFQ[19] to assess usual intake of thirty-five types of seafood available in the Pacific Northwest during the prior three-month period. Participants provided non-fasting peripheral blood samples at this initial visit, these were analysed for erythrocyte membrane EPA and DHA, among a random subset (60 %) of initial participants (enrolled from 1996 to 2000 in the Omega study, *n* 586)[13]. After delivery, trained personnel abstracted the course and outcomes of pregnancy from maternal and infant medical records.

We calculated habitual seafood intake (ounces/month) by multiplying the Seafood Intake Scale FFQ-reported monthly frequency of intake by the reported typical serving size, in ounces, for thirty-five types of seafood. We calculated seafood intake in servings/month by dividing ounces/month by 3, since 3 oz is a typical medium serving size of seafood[20]. The lowest reportable amount of seafood on the Seafood Intake Scale FFQ was <0·2 servings/month, which represents little or no seafood intake. Seafood was categorized into shellfish, lean fish or fatty fish groups. Briefly, shellfish included crab, lobster, shrimp or prawns, clams, mussels, oysters, scallops, abalone, octopus and squid. Lean fish included regular canned tuna, catfish, cod, flounder or sole, haddock, halibut, mahi mahi, snapper or rockfish, shark, imitation crab, imitation lobster and fish sticks. Fatty fish included anchovies, herring (pickled or regular), kipper snacks, salmon (canned, fresh or smoked), sardines, albacore tuna, swordfish, rainbow trout, smelt and mackerel.

Using US Department of Agriculture data, we assigned average EPA and DHA values for each type of seafood[21–24] and multiplied these values by the Seafood Intake Scale FFQ-reported amount and frequency for each type of seafood (see online supplementary material, Table S1). We estimated overall EPA + DHA intake by summing the values across all seafood types. We defined quartiles of total EPA + DHA for individuals who consumed at least 0·2 servings seafood/month.

We used published diagnostic criteria to define GH and PE[17]. Briefly, GH was defined as sustained blood pressure of ≥140/90 mmHg with readings measured ≥6 h apart on or after 20 weeks' gestation. PE was defined as sustained blood pressure of ≥140/90 mmHg with readings measured ≥6 h apart on or after 20 weeks' gestation with proteinuria based on urine protein concentrations of ≥30 mg/dl (≥1 + reading on a urine dipstick) from two or more urine specimens collected ≥4 h apart. All Omega study participants were evaluated for GDM according to the American Diabetes Association guidelines[25] between 24 and 28 weeks' gestation using a screening 50 g glucose challenge test and a follow-up (within one to two weeks) 100 g, 3 h oral glucose tolerance test if they failed the glucose challenge. Women were diagnosed with GDM if they did not indicate a prior chronic diabetes diagnosis and they had two or more of the following abnormal plasma glucose concentrations in the oral glucose tolerance test: fasting ≥105 mg/dl; 1 h ≥190 mg/dl; 2 h ≥165 mg/dl; 3 h ≥145 mg/dl. PTB was defined as birth occurring before thirty-seven completed weeks of gestation. Gestational age was estimated using the last menstrual period and ultrasound dates from early pregnancy, if available. In addition, we constructed a composite pregnancy complication variable indicating presence of any of these complications. There were sixty-four (2 %) women missing PE status, 143 (4 %) missing GH status or had a prior chronic hypertension diagnosis, seventy-four (2 %) missing GDM status or had a prior chronic diabetes diagnosis, and 103 (3 %) missing PTB status. The composite pregnancy complication variable was missing for 156 (5 %) women.

We examined frequency distributions of maternal characteristics across categories of seafood subtypes and quartiles of EPA + DHA intake. For seafood (subtypes and total), we chose categories of <0·2 servings/month, 0·2 servings/month–<0·5 servings/week, 0·5–1·0 servings/week and

>1 servings/week, to allow for approximately equal frequencies of participants across seafood subtype categories above the reference (<0·2 servings/month). According to the American Heart Association guidelines, we considered a typical single seafood serving as approximately 85 g (3·0 oz)[20].

We fit generalized linear models with a log link, Poisson family (a 'log-Poisson' regression model) and robust standard errors to estimate risk ratios (RR) and 95 % confidence intervals for each pregnancy complication and the composite. The log-Poisson regression model with robust standard errors allows estimation of RR for prospective studies with binary outcome data[26]. In these models, each non-reference intake category of seafood or quartile of EPA + DHA was modelled as an indicator variable and compared with the reference. Indicator variables allowed us flexibility for fitting possible non-linear associations. We assessed model fit by examining regression residual diagnostics. Based on prior literature that suggests potential linear trends across higher intakes of seafood and EPA + DHA[8], we calculated Wald *P* values for grouped linear terms of either seafood (subtypes or total) or EPA + DHA. Adjusted models for seafood subtypes as the exposure included non-referent indicator variables for intake of shellfish, lean fish and fatty fish simultaneously. For example, to observe associations of shellfish with pregnancy complications, independent of fatty fish or lean fish, we included non-referent indicator variables for all three seafood subtypes.

The following potential confounding variables were identified *a priori* and were included in all adjusted models including model 1: non-Hispanic White race/ethnicity, high school/less education, unmarried marital status, nulliparity, habitual recreational physical activity during early pregnancy based on activity in the week prior to interview, alcohol intake and cigarette smoking during pregnancy were included as binary variables. We defined three non-referent indicator variables for pre-pregnancy BMI, using the current National Institutes of Health definitions of normal weight (18·5–24·9 kg/m^2), overweight (25·0–29·9 kg/m^2) and obese (≥30·0 kg/m^2), with underweight (<18·5 kg/m^2) defined as the referent[27]. Maternal age (years), total energy consumed (kcal/d) and intake of red and processed meats (servings/d) were included in adjusted models as continuous variables. In model 2, we examined whether our results were materially altered by restricting to nulliparous women, since they are at higher risk of having a pregnancy complicated by PE[17]. In model 3, we examined whether our results were altered by excluding forty-eight women who reported taking fish-oil supplements. We also explored possible non-linear relationships between seafood intake and pregnancy complications by modelling seafood and EPA + DHA intake as a continuous variable with the addition of quadratic terms to our primary adjusted model (model 1).

All *P* values were two-sided and defined to be significant at $P < 0{\cdot}05$. Analyses were carried out using statistical software package Stata version 10·1.

Results

Most study participants were non-Hispanic White (88 %), married (90 %), nulliparous (61 %) and received post high-school education (97 %). Few smoked (6 %) or consumed alcohol (26 %) during pregnancy and very few reported taking fish-oil supplements (2 %). Mean (SD) maternal age was 32·7 (4·4) years and mean (SD) pre-pregnancy BMI 23·5 (4·8) kg/m^2. Mean (SD) and median (interquartile range) total seafood intake was 2·0 (1·9) and 1·6 (0·7–2·8) servings/week, respectively. Most participants (87 %) consumed less than 4 servings seafood/week (or 12 oz (340 g)/week), consistent with current Environmental Protection Agency and Food and Drug Administration recommendations[20].

There were some differences in participants excluded due to missing seafood intake information or implausible seafood/energy intake (*n* 495) *v.* those who were included in the study. Compared with included participants, excluded participants were less likely to be non-Hispanic White (73 % *v.* 88 %), nulliparous (39 % *v.* 61 %) or married (59 % *v.* 90 %), and had higher mean (SD) pre-pregnancy BMI (25·1 (6·4) kg/m^2 *v.* 23·5 (4·8) kg/m^2) and occurrence of PTB (12 % *v.* 8 %).

Spearman rank correlation coefficients of maternal erythrocyte membrane EPA + DHA (% of total fatty acids) with total seafood intake (all subtypes combined), shellfish, lean fish and fatty fish were $r = 0{\cdot}43$ ($P < 0{\cdot}001$), $r = 0{\cdot}34$ ($P < 0{\cdot}001$), $r = 0{\cdot}20$ ($P < 0{\cdot}001$) and $r = 0{\cdot}46$ ($P < 0{\cdot}001$), respectively. Among 547 participants with both erythrocyte EPA + DHA and dietary fat information, the correlation for total dietary fat (g)-adjusted dietary EPA + DHA with erythrocyte membrane EPA + DHA (% of total fatty acids) was $r = 0{\cdot}53$ ($P < 0{\cdot}001$). We also cross-tabulated consumption of different seafood subtypes and observed that there was a lack of collinearity between consumption of different seafood subtypes, which allowed us to evaluate associations of one subtype independent of the others (results not shown).

Women with higher seafood intake, regardless of type, tended to be Hispanic and/or non-White (except for total seafood and fatty fish) and to have received post high-school education (except for lean fish; Table 1 and online supplementary material, Tables S2–S4). Women who consumed either more total seafood or more fatty fish were less likely to be overweight or obese, pre-pregnancy. Women with higher total seafood, fatty fish or shellfish intake were older on average. Higher intake of total seafood or seafood subtypes corresponded to higher dietary EPA + DHA, total energy, fat, red and processed meats, and erythrocyte EPA + DHA.

There were eighty-nine (3 %) cases of PE, 375 (12 %) cases of GH, 160 (5 %) cases of GDM and 259 (8 %) cases of PTB, and 800 (26 %) participants had at least one pregnancy complication. We did not observe evidence for associations of higher total seafood or shellfish intake

Table 1 Selected participant characteristics according to servings of total seafood intake; Omega study, Washington State, USA, 1996–2008

	Total seafood intake (servings)							
	<0·2/month (*n* 302)		0·2/month– <0·5/week (*n* 320)		0·5–1/week (*n* 541)		>1/week (*n* 2116)	
Characteristic	*n*	%	*n*	%	*n*	%	*n*	%
Non-Hispanic White†	272	90·1	283	88·4	474	87·6	1841	87·0
High school/less education*,†	21	7·0	19	5·9	25	4·6	46	2·2
Unmarried*,†	45	14·9	31	9·7	45	8·3	217	10·3
Nulliparous†	195	64·6	179	55·9	317	58·6	1321	62·4
Pre-pregnancy BMI (kg/m^2)*,†								
<18·5	22	7·3	12	3·8	18	3·3	86	4·1
18·5– <25·0	199	65·9	219	68·4	399	73·8	1520	71·8
25·0– <30·0	55	18·2	56	17·5	76	14·0	342	16·2
≥30·0	26	8·6	32	10·0	48	8·9	163	7·7
Current smoking†	24	7·9	17	5·3	28	5·2	110	5·2
Current alcohol intake	69	22·8	70	21·9	126	23·3	590	27·9
No current recreational physical activity†	59	19·5	65	20·3	108	20·0	359	17·0
Fish-oil supplement use	1	0·3	6	1·9	7	1·3	34	1·6
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)*,†	31·4	5·0	32·1	4·6	32·5	4·2	33·0	4·2
Gestational week at delivery†	38·8	2·0	38·8	1·8	38·8	1·8	38·9	1·9
Gestational weight gain (kg)*,†	16·8	6·2	16·2	5·9	16·0	5·7	15·9	5·5
Erythrocyte EPA + DHA (% of total fatty acids)*,†	4·3	1·2	4·7	1·0	4·9	0·8	5·6	1·1
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Dietary EPA + DHA (g/week)*	0·0	0·0–0·0	0·1	0·0–0·1	0·3	0·1–0·4	0·9	0·6–1·3
Total energy (kJ/d)†	6275	4959–8199	6156	4733–7832	6492	5209–7996	7198	5808–8811
Total energy (kcal/d)†	1499·7	1185·1–1959·7	1471·3	1131·3–1872·0	1551·6	1244·9–1911·2	1720·3	1388·1–2105·9
Total fat (g/d)†	52·8	39·4–68·6	49·8	36·2–66·0	52·2	39·1–69·3	60·5	45·7–77·7
Red/processed meats (servings/d)†	0·4	0·0–0·7	0·5	0·3–0·8	0·5	0·3–0·8	0·6	0·3–0·9

IQR, interquartile range.
*$P < 0·05$ from Pearson's χ^2 test for comparisons across highest *v.* lowest seafood intake categories for categorical or binary variables, or from one-way ANOVA test for differences in means across seafood intake categories for continuous variables.
†Some participants have missing values for these characteristics.

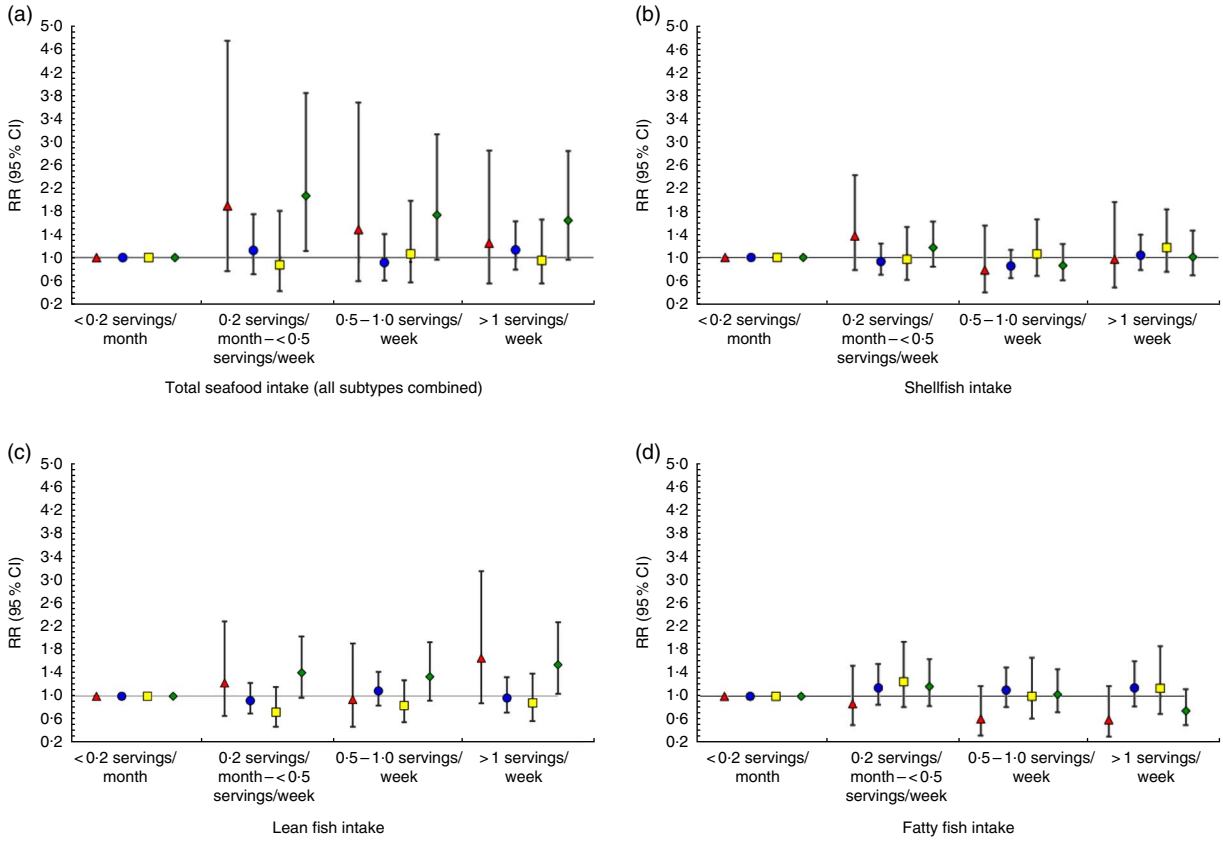

Fig. 1 Associations of servings of (a) total seafood, (b) shellfish, (c) lean fish and (d) fatty fish intake with risk of pregnancy complications (▲, PE; ●, GH; □, GDM; ◆, PTB); Omega study, Washington State, USA, 1996–2008. Relative risks (RR) and 95 % onfidence intervals (represented by vertical bars) were calculated using generalized linear models with a log link, Poisson family and robust standard errors. Models are adjusted for maternal age, non-Hispanic White race, post high-school education, unmarried marital status, pre-pregnancy BMI (indicator variables: 18·5–24·9, 25·0–29·9, ≥30·0 kg/m^2), total energy (kcal/d), current recreational physical activity, current smoking, current alcohol intake, nulliparity and intake of red/processed meats (servings/d). For shellfish, lean fish and fatty fish analyses, alternative seafood subtypes (indicator variables for non-reference categories) were also included. For PE, GH, GDH and PTB, respectively, Wald *P* values for a grouped linear term for total seafood or seafood subtypes are: 0·83, 0.44, 0·95 and 0·41 (a); 0·65, 0·97, 0·47 and 0·67 (b); 0·23, 0·83, 0·74 and 0·05 (c); and 0·09, 0·51, 0·88 and 0·10 (d). PE, pre-eclampsia; GH, gestational hypertension; GDM, gestational diabetes; PTB, preterm birth

across non-referent categories for any of the pregnancy complications, including the composite pregnancy complication (Fig. 1(a) and (b) and online supplementary material, Table S5, model 1). On the other hand, pregnant women who consumed >1 servings lean fish/week had a 1·55-fold higher risk of PTB compared with those who consumed little or no lean fish (<0·2 servings lean fish/ month; RR = 1·55; 95 % CI 1·04, 2·30; linear trend across higher intake categories, $P = 0·05$; Fig. 1(c) and Table S6, model 1). Lean fish intake was not associated with PE, GH, GDM or the composite pregnancy complication in our adjusted models (Fig. 1(c) and Table S6, model 1). Also, higher fatty fish intake (Fig. 1(d) and Table S6) and dietary EPA + DHA quartile from seafood (Table 2) were not associated with pregnancy complications in our primary adjusted models.

Except for total seafood and PTB, our main findings were not materially altered by restricting to 2012 nulliparous pregnancies (online supplementary material, Tables S5 and S6, model 2) or exclusion of forty-eight women who took fish-oil supplements (Tables S5 and S6, model 3). For total seafood intake and PTB, after excluding women who reported taking fish-oil supplements (Table S5, model 3), we found a higher risk of PTB across all categories of seafood intake, compared with the referent category. Total seafood intake of 0·2 serving/ month–<0·5 servings/week, 0·5–1·0 servings/week and >1 servings/week compared with intake of <0·2 servings/ month (referent) was associated with 2·26 (95 % CI 1·20, 4·26), 1·88 (95 % CI 1·02, 3·45) and 1·76 (95 % CI 1·00, 3·09) higher risk of PTB (linear trend across higher intake categories, $P = 0·37$).

We explored model fit using deviance residuals and Cook's distance and identified several potential outlying and influential points. Further examination of these observations did not suggest erroneous or implausible

Table 2 Risk of pregnancy complications according to dietary EPA + DHA quartile from seafood for participants with seafood intake ≥0·2 servings/month†; Omega study, Washington State, USA, 1996–2008

EPA + DHA Range (g/month) Mean, SD (g/month)	Quartile 1‡ (*n* 744) 0·02–2·06 1·02, 0·57		Quartile 2 (*n* 745) 2·06–4·31 3·12, 0·67		Quartile 3 (*n* 744) 4·32–7·56 5·84, 0·92		Quartile 4 (*n* 745) 7·56–56·93 12·64, 5·99		
	RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI	*P* for trend
PE§									
Unadjusted	1·0	–	0·52	0·29, 0·93	0·52	0·29, 0·93	0·49	0·27, 0·89	0·02
Model 1‖	1·0	–	0·74	0·41, 1·36	0·69	0·37, 1·29	0·63	0·33, 1·21	0·16
Model 2¶	1·0	–	0·72	0·36, 1·47	0·73	0·35, 1·51	0·55	0·25, 1·20	0·16
Model 3††	1·0	–	0·73	0·39, 1·35	0·72	0·38, 1·35	0·67	0·35, 1·28	0·23
GH§									
Unadjusted	1·0	–	1·19	0·89, 1·59	1·13	0·85, 1·52	1·16	0·87, 1·55	0·40
Model 1‖	1·0	–	1·20	0·90, 1·62	1·10	0·81, 1·48	1·14	0·84, 1·54	0·55
Model 2¶	1·0	–	1·17	0·82, 1·66	1·15	0·81, 1·63	1·16	0·81, 1·65	0·47
Model 3††	1·0	–	1·24	0·92, 1·67	1·11	0·82, 1·51	1·15	0·85, 1·57	0·53
GDM§									
Unadjusted	1·0	–	0·95	0·60, 1·50	1·00	0·64, 1·58	1·16	0·75, 1·79	0·49
Model 1‖	1·0	–	0·97	0·60, 1·55	1·15	0·72, 1·85	1·16	0·73, 1·83	0·42
Model 2¶	1·0	–	1·19	0·62, 2·26	1·42	0·73, 2·76	1·27	0·67, 2·41	0·40
Model 3††	1·0	–	0·96	0·60, 1·55	1·15	0·71, 1·84	1·16	0·73, 1·84	0·42
PTB§									
Unadjusted	1·0	–	0·94	0·68, 1·32	0·92	0·66, 1·29	0·90	0·64, 1·26	0·52
Model 1‖	1·0	–	0·98	0·69, 1·37	0·94	0·66, 1·33	0·88	0·60, 1·27	0·47
Model 2¶	1·0	–	0·84	0·55, 1·28	0·90	0·59, 1·37	0·82	0·53, 1·28	0·47
Model 3††	1·0	–	0·97	0·69, 1·37	0·91	0·64, 1·29	0·88	0·61, 1·27	0·44
Comp§									
Unadjusted	1·0	–	0·93	0·78, 1·11	0·91	0·76, 1·08	0·96	0·80, 1·14	0·58
Model 1‖	1·0	–	0·99	0·83, 1·18	0·96	0·80, 1·15	0·98	0·82, 1·18	0·76
Model 2¶	1·0	–	0·98	0·78, 1·21	0·99	0·79, 1·23	0·98	0·79, 1·23	0·92
Model 3††	1·0	–	1·00	0·84, 1·20	0·96	0·80, 1·15	0·99	0·82, 1·19	0·80

RR, relative risk; PE, pre-eclampsia; GH, gestational hypertension; GDM, gestational diabetes; PTB, preterm birth; Comp (composite), one or more of PE, GH, GDM or PTB.
†Relative risks were calculated using generalized linear models with a log link, Poisson family and robust standard errors.
‡Reference category.
§For dietary EPA + DHA corresponding to increasing quartile: no. of PE cases/no. at risk = 32/721, 17/735, 17/738 and 16/730; no. of GH cases/no. at risk = 75/707, 90/713, 86/716 and 88/714; no. of GDM cases/no. at risk = 35/716, 34/736, 36/736 and 41/725; no. of PTB cases/no. at risk = 64/712, 62/731, 60/727 and 58/719; no. of Comp cases/no. at risk = 189/695, 183/722, 178/722 and 184/707.
‖Model 1 is adjusted for maternal age, non-Hispanic White race, post high-school education, unmarried marital status, pre-pregnancy BMI (indicator variables: 18·5–24·9, 25–29·9, ≥30·0 kg/m^2), total energy (kcal/d), current recreational physical activity, current smoking, current alcohol intake, nulliparity and intake of red/processed meats (servings/d).
¶Model 2 is adjusted for the same variables as model 1 but was restricted to nulliparous women.
††Model 3 is adjusted for the same variables as model 1 but excluded fish-oil supplement users.

characteristics for these participants and our main findings were robust to the exclusion of these observations. We did not observe evidence for non-linear relationships after adding quadratic terms of seafood (total or subtypes) and EPA + DHA intake to the models (results not shown). Further examination of our results related to lean fish intake and PTB revealed evidence of a possible threshold effect. There was no indication of a (linear) trend in risk across the lean fish consumption categories above the reference category of little or no lean fish intake (<0·2 servings/month), RR = 1·05 (95 % CI 0·88, 1·25, comparing adjacent, non-reference categories. On the other hand, the comparison of the grouped non-reference categories with the reference category was statistically significant, RR = 1·42 (95 % CI 1·02, 1·96). We also found some evidence that the association of higher lean fish intake and higher risk of PTB may not be specific to PTB; when we excluded 603 women with PE, GH or GDM our results were no longer statistically significant, RR = 1·29 (95 % CI 0·80, 2·06).

Discussion

Our study suggests that associations of seafood intake and pregnancy complications may vary by seafood subtype. This evidence was strongest for PTB where we observed an association of higher lean fish intake with higher risk of PTB.

Except for PTB, we are unaware of prior studies of seafood subtypes and pregnancy complications. In a meta-analysis of nineteen European birth cohorts (of 151 880 participants), Leventakou *et al.* reported an association of total fish intake ≥3 times/week (*v.* ≤1 times/week) with 11 % lower risk of PTB (95 % CI 0·84, 0·96)[16]. However, when examined separately, fatty fish, lean fish and other seafood were not associated with PTB. Importantly, participants in the meta-analysis had a higher overall amount of seafood intake compared with our study, which could account for the differences in study findings. Compared with the meta-analysis participants, 10 % fewer of our study participants (or 23 %) consumed seafood ≥3 times/week. Intakes of specific seafood types were also higher

among the European birth cohorts, median lean and fatty fish intakes ranged from 0·3 to 3·5 times/week and from 0 to 1·0 times/week, respectively. In our study, the median intake for each of lean fish and fatty fish was 0·5 servings/week. Also, the studies in the meta-analysis considered portion sizes that ranged from 3·5 to 5 oz (99 to 142 g), whereas one serving in our study was defined as 3 oz (85 g). Another possible difference between prior studies and ours could be the timing of seafood intake. For instance, the largest study contributing to the meta-analysis, the Norwegian Mother and Child Cohort Study (*n* 58 926), examined seafood intake during the first five months of pregnancy[28]. We, on the other hand, examined intake during the periconceptional period, the three months before and the first three months of the index pregnancy. One other study of seafood subtypes, by Guldner *et al.*, reported that intake of total seafood was not associated with PTB[29]. However, each additional monthly meal of saltwater fish (lean and fatty fish) was associated with a 0·02-week longer mean gestational length (95 % CI 0·002, 0·035 week). In secondary analyses, we observed longer (although not statistically significant) mean gestational length among women who had higher shellfish and fatty fish intake (online supplemental material, Table S7).

Effects of seafood intake may vary by how the seafood is prepared[4,5,18] and content of EPA + DHA and contaminants[30]. Mozaffarian *et al.* reported that intake of tuna or other broiled/baked fish (typically made with fatty fish such as salmon, with higher EPA + DHA content) was associated with a lower risk of death from IHD[4]. On the other hand, intake of fried fish/fish sandwich (typically made with lean fish such as cod, with lower EPA + DHA content) was associated with a higher risk of IHD death. Besides introducing *trans*-fats or other less healthy fats, frying can oxidize fatty acids and lead to lower EPA + DHA content[18]. Thus, our observed association of higher lean fish intake and higher risk of PTB may be related to how the fish was prepared (e.g. frying). Xue *et al.* reported an association of higher maternal methylmercury with a higher risk of birth at <35 weeks' gestation[30]. The Environmental Protection Agency and the Food and Drug Administration caution pregnant women against consuming predatory or longer-lived seafood including shark, mackerel and swordfish due to their higher methylmercury content[20]. Our results were not materially altered when we excluded the few (4 %) participants who reported intake of predatory fish or adjusted our analyses for intake of predatory fish (results not shown). Since we did not have more detailed information on possible contaminant exposure through seafood intake or on methods of seafood preparation, it is unclear whether these factors are related to our observed association of higher lean fish intake with higher risk of PTB. Further studies are needed to clarify the role of these factors.

Another possibility is that the association between higher lean fish intake and higher risk of PTB could be the result of residual confounding. This possibility is supported by our sensitivity analyses, which suggest a threshold effect of any lean fish of ≥0·2 servings/month and less evidence of a dose response over 0·2 servings/month, corresponding to little or no lean fish intake. While we attempted to control for many known confounding variables, it may be that any lean fish intake ≥0·2 servings/month relates to other unmeasured factors that reflect a less favourable overall dietary pattern or other unmeasured socio-economic/lifestyle factors, which are also related to higher risk of PTB. To assess this, we examined additional potential socio-economic and dietary confounding variables (online supplementary material, Tables S8 and S9). Also, we examined differences between women who consumed <0·2 servings lean fish/month and ≥0·2 servings lean fish/month (Table S9). Except for wholegrain foods, vegetables and Ca (related to higher lean fish intake), none of the additional variables suggested residual confounding due to socio-economic or dietary variables we have measured. Results comparing women who consumed <0·2 servings lean fish/month and ≥0·2 servings lean fish/month were similar. Finally, when we added these additional potential confounding variables to our sensitivity analysis of any lean fish intake above the reference category (<0·2 servings/week) our results for risk of PTB were not materially altered, RR = 1·62 (95 % CI 1·04, 2·52). However, there may still be potential confounding by other, unmeasured variables.

Contrary to our findings, most previous observational studies have reported inverse[9,16] or U-shaped[10] associations of total seafood intake or EPA + DHA and PTB. Our sensitivity analyses suggested associations of higher total seafood intake and higher risk of PTB when we excluded women who consumed fish-oil supplements. This association, observed among fish-oil non-consumers, may have been driven by the association of higher lean fish intake with higher risk of PTB observed among consumers and non-consumers of fish-oil supplements. Based on previous reports and our findings of seafood subtype-specific associations, assessment of total seafood intake, without consideration of subtypes, may not be an ideal approach in these investigations. Findings from observational studies of seafood intake or EPA + DHA status and risk of PE, GH and GDM have been less consistent. Some authors have reported inverse[12] or U-shaped[11] associations, while others have reported no associations[6,7]. Our study does not provide strong and/or consistent evidence for associations of seafood (total or subtypes), or EPA + DHA intake, and risk of PE, GH or GDM.

Our findings should be interpreted in view of several potential limitations. First, we cannot rule out potential measurement error of seafood and EPA + DHA intake. Second, our results should be interpreted with caution since we evaluated associations between multiple exposures and outcomes, which increased the likelihood of type I error and we did not adjust for multiple

comparisons. Third, our study's statistical power may be limited, particularly for analyses of seafood subtypes and rare pregnancy complications. For example, there was an association, although not statistically significant, of higher fatty fish intake with lower risk of PE. In *post hoc* analyses, statistical power to detect an RR of 0·60 (two-sided $\alpha = 0{\cdot}05$ and assuming a baseline risk of 3 %) for PE comparing fatty fish intake of >1 servings/week with <0·2 servings/month was approximately 40 %[31]. There may be selection bias since excluded participants, who were missing seafood intake information, differed from included participants on factors that were related to the exposure (e.g. race, marital status, parity) and the outcome (i.e. PTB). Finally, most participants were non-Hispanic White, highly educated, with normal pre-pregnancy BMI. Therefore, our results may not generalize to women of different race/ethnicity, socio-economic status or pre-pregnancy BMI.

Strengths of our study include examination of seafood intake during the periconceptional period, a critical period, missed in most prior studies of seafood intake, when the pathogenesis of pregnancy complications begins. Our study included much more detailed information on seafood intake compared with traditional FFQ, which we used to investigate the potential varied effects of seafood subtypes, a major research gap. Access to blood samples in a subset of participants permitted assessment of correlations of erythrocyte EPA + DHA with self-reported seafood and EPA + DHA intake. Correlations were as high as or higher than those cited previously[10]. Our well-characterized cohort had high rates of participation and follow-up, which allowed us to control for many previously reported confounding variables.

To our knowledge, the present study is the first of maternal periconceptional intake of total seafood, shellfish, lean fish and fatty fish and risk of PE, GH and GDM, in addition to PTB. Our findings support associations of higher lean fish intake with higher risk of PTB. Future studies may consider potential factors, such as seafood preparation and nutrient/contaminant content. If our results are replicated, they may have significance in preventing PTB, a common pregnancy complication.

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Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S136898001500316X

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