Original article

Maternal seafood intake during pregnancy, prenatal mercury exposure and child body mass index trajectories up to 8 years

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Abstract

Background: Maternal seafood intake during pregnancy and prenatal mercury exposure may influence children's growth trajectories.

Methods: This study, based on the Norwegian Mother, Father and Child Cohort Study (MoBa), includes 51 952 mother-child pairs recruited in pregnancy during 2002–08 and a subsample ($n = 2277$) with maternal mercury concentrations in whole blood. Individual growth trajectories were computed by modelling based on child's reported weight and length/height from 1 month to 8 years. We used linear mixed-effects regression analysis and also conducted discordant-sibling analysis.

Results: Maternal lean fish was the main contributor to total seafood intake in pregnancy and was positively but weakly associated with child body mass index (BMI) growth trajectory. Higher prenatal mercury exposure (top decile) was associated with a reduction in child's weight growth trajectory, with the estimates ranging from -130 g [95% Confidence Intervals (CI) = -247, -12 g] at 18 months to -608 g (95% CI = -1.102, -113 g) at 8 years. Maternal fatty fish consumption was positively associated with child weight and BMI growth trajectory, but only in the higher mercury-exposed children (*P*-interaction = 0.045). Other seafood consumption during pregnancy was negatively associated with child weight growth compared with no intake, and this association was stronger for higher mercury-exposed children (*P*-interaction = 0.004). No association was observed between discordant maternal seafood intake and child growth in the sibling analysis.

Conclusions: Within a population with moderate seafood consumption and low mercury

exposure, we found that maternal seafood consumption in pregnancy was associated with child growth trajectories, and the direction of the association varied by seafood type and level of prenatal mercury exposure. Prenatal mercury exposure was negatively associated with child growth. Our findings on maternal seafood intake are likely non-causal.

Key Messages

- Seafood consumption is a healthy dietary habit and the main contributor of several nutrients, but also a source of human exposure to several environmental contaminants with toxicological properties, including mercury. The association between maternal seafood intake in pregnancy and child postnatal growth, and the role of prenatal mercury exposure, is unclear.
- We examined the prospective association between maternal self-reported total seafood, lean fish, fatty fish and other seafood intake of 51 952 pregnant women and the growth of their children from 1 month to 8 years. We also examined the association between prenatal mercury exposure, measured as whole-blood mercury concentrations in maternal samples, with child growth in 2227 mother–child pairs. We also conducted separate analyses within 10 528 pairs of siblings.
- We found that maternal total seafood and lean fish intake in pregnancy were positively but weakly associated with child growth trajectory, and other seafood intake was negatively associated with child growth. However, these results were not confirmed within siblings with discordant maternal seafood and lean fish intake.
- We also found that children prenatally exposed to high mercury levels (top decile) were more likely to follow a reduced growth trajectory. In the high mercury-exposed children, high maternal fatty fish intake in pregnancy was associated with increased growth whereas other seafood intake was associated with reduced growth, compared with no intakes.

Introduction

Fish and seafood are important sources of protein, long-chain n-3 polyunsaturated fatty acids, vitamin D, iodine and selenium.[1–3] Fish and seafood consumption is an important component of the Mediterranean and Nordic diets, and high adherence has been associated with reduced health risks.[4–9] The maternal diet and nutritional status before conception and during pregnancy has long-lasting implications for offspring health and is a key factor of 'early life programming', linking an unfavourable *in utero* environment with increased risk of diseases in adult life.[10,11] Regarding birth outcomes, maternal fish and seafood consumption itself in pregnancy, as well as adherence to dietary patterns rich in fish, are found to be protective against preterm delivery[12,13] and fetal growth restriction,[13–16] but evidence varies largely.[17]

On the other hand, fish and seafood consumption is the main source of human exposure to toxic environmental contaminants, including perfluorinated compounds, methylmercury, and organochlorine compounds, and it has been positively associated with contaminant concentrations in human biological samples globally,[18–21] including pregnant women.[22–27] During pregnancy, these environmental contaminants can pass from the mother through the placenta and reach the fetus, with varying transfer rates.[28–33] In contrast to the maternal seafood intake, high prenatal exposure to contaminants, for which several fish are the main source, has been consistently associated with restricted fetal growth.[34–41] Altered fetal growth patterns related to *in utero* exposures may increase the risk of subsequent obesity and cardiometabolic disorders, as fetal growth retardation followed by accelerated infant growth is associated with increased adiposity and cardiometabolic risk markers in later childhood.[42,43] Maternal fish consumption in pregnancy has been positively associated with child body mass index (BMI) in a meta-analysis[44] but null[45] or negatively[46] associated in other studies. Regarding prenatal exposure to fish-derived contaminants, positive, null and negative associations have been reported for organochlorine compounds and perfluorinated compounds,[47–54] and null or negative associations for prenatal mercury exposure and weight and BMI in childhood.[54–56]

The guidelines on seafood consumption in pregnancy do not differ from those of the general adult population.[57] Pregnant women are often advised to avoid large predatory fish with high methylmercury content, based on the detrimental effects of methylmercury on birth outcomes and neurodevelopment.[57] However, the toxic effects of other environmental chemicals and the beneficial effects of nutrients for which fish is the main source have received less attention, as well as the evidence for other long-term health outcomes.[57,58] The focus on adverse effects has resulted in a reduction of seafood intake in pregnant women, who are already low consumers.[57,59] Shedding light in the long-term health effects of maternal seafood consumption in pregnancy in a holistic way could assist the development of clearer dietary guidelines.

Our main aim was to examine the association between maternal consumption of total seafood, lean fish, fatty fish and other seafood in pregnancy and child growth trajectories from 1 month to 8 years, in a large mother-child cohort study with detailed seafood consumption assessment. In addition, we aimed to examine the association between prenatal mercury exposure, determined in maternal whole-blood samples, with the same outcomes, as well as the interaction with seafood intake.

Methods

The establishment of the Norwegian Mother, Father and Child Cohort Study (MoBa) and initial data collection were based on a licence from the Norwegian Data Protection Agency and approval by the regional committees for medical and health research ethics. The MoBa cohort is based on regulations in the Norwegian Health Registry Act. The current study was approved by the regional committees for medical and health research ethics for South-Eastern Norway (reference number: 2016/377).

Study population

We used information from the Norwegian Mother, Father and Child Cohort Study (MoBa), a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health.[60] Participants were recruited from all over Norway during their ultrasound visit (18th gestational week) from 1999 to 2008. With 40.6% participation rate, MoBa now encompasses 114 500 children, 95 200 mothers and 75 200 fathers. Data used in this study are based on version 10 of the quality-assured data files, released for research in July 2017. All MoBa participants provided written informed consent before enrolment into the study.

The source population was 80 435 women participating in MoBa and registered in the Norwegian Medical Birth Registry, a national health registry containing information about all births in Norway, with singleton, live-born babies without malformations or chromosomal anomalies and having available seafood intakes from the MoBa food frequency questionnaire implemented in 2002 (Supplementary Figure S1, available as Supplementary data at *IJE* online). After excluding mother-child pairs with missing information on important covariates and with implausible maternal energy intake (i.e. <4.5 megajoule and >20 megajoule),[61] the eligible population was 52 308 mother-child pairs. Further, 356 mother-child pairs were excluded because no postnatal growth measurement was available, resulting in a final study population of 51 952 mother-child pairs. From our study population, whole-blood mercury concentration in maternal blood was available for 2277 women.

Maternal seafood intake and maternal whole blood mercury

Maternal seafood intake was assessed during pregnancy by a validated semi-quantitative food frequency questionnaire (FFQ), completed around the 22nd week of gestation and designed to capture dietary habits during the first 4 to 5 months of pregnancy.[62] In the validation study, the FFQ intakes were compared with 4-day weighed food diary and several blood and urinary biomarkers in 119 MoBa participants. For total seafood intake, the correlation between FFQ and food diary was 0.49 and seafood was positively associated with the blood concentrations of mercury, arsenic, selenium and erythrocyte docosahexaenoic acid.[62,63] There were 10 questions about cold cuts and spreads made of fish or other seafood and 16 questions about fish or other seafood eaten for dinner. After assigning serving sizes, daily intakes (in grams) were calculated and food items were aggregated into food groups (Supplementary Table S1, available as Supplementary data at *IJE* online). We summed the individual food variables to generate four maternal seafood intake variables: total seafood, lean fish, fatty fish and other seafood. Finally, using a serving size of 100 g, and based on the population distribution, we categorized the intake variables into three categories: for total seafood intake: 0–1 servings/week, 2–3 servings/week and ≥4 servings/week; for lean fish: 0–1 servings/week, 2 servings/week and ≥3 servings/week; for fatty fish: none, 1 serving/week, ≥2 servings/week; for other seafood: none, any.

Maternal blood was collected during the study recruitment at the routine ultrasound in gestational week 18 [mean 18.5, standard deviation (SD) 1.3], and was then

stored in single vacutainer tubes at -20 °C.[64] Blood mercury analysis was done in 2015–16 at the Department of Occupational and Environmental Medicine at Lund University, Sweden. Mercury was determined as total mercury in acid-digested samples by cold vapour atomic fluorescence spectrophotometry.[65] The detection limit was calculated as three times the standard deviation (SD) of the blank and was equal to 0.07 μg/L; 99% of the samples had values above the limit of detection. All analysed samples were prepared and measured in duplicate and the mean value was used. The method imprecision was calculated as the coefficients of variation in measurements of duplicate preparations and was equal to 12.6%. The laboratory participated in the German External Quality Assessment Scheme, with good agreement between obtained element concentrations in quality control samples used and expected values. The analytical accuracy was verified towards certified reference materials; Seronorm Trace elements whole blood L-1 [measured value (mean $\pm$SD) = 1.37 μg/L $\pm$ 0.14 vs reference value = 1.50 μg/L, range 0.90–1.20 μg/L] and L-2 [measured value (mean $\pm$SD) = 16.5 μg/L $\pm$ 1.2 vs reference value = 16.0 μg/L, range 9.6–22.4 μg/L] (SERO AS, Billingstad, Norway). We defined high prenatal mercury exposure as maternal total whole-blood mercury in the top decile (90 percentile = 2.23 μg/L).

Child postnatal growth

Anthropometric measurements of the children were reported with exact age by the mothers at 11 time points and in six different questionnaires: around the age of 6 weeks, 3 months and 6 months (questionnaire administered at 6 months), around the age of 8 months, 1 year and 18 months (questionnaire administered at 18 months), around the age of 2 years and 3 years (questionnaire administered at 3 years), the age of 5 years (questionnaire administered at 5 years), the age of 7 years (questionnaire administered at 7 years) and 8 years (questionnaire administered at 8 years). From 6 weeks to 18 months, mothers were asked to refer to their child's health card (measurements performed by nurses), whereas for measurements from 2 to 8 years no specification was provided. From birth to 5 years, weight and height of Norwegian children are screened in scheduled voluntary appointments at the public health centres. On average, seven repeated measurements of weight and height (10th–90th percentiles of the number of measurements for weight and for height = 3–10) were included for each child, providing a total of 373 261 weight measurements and 365 578 height measurements for our study population. Of the included children, 2101 had complete reports of weight and height measurements (Supplementary Figure S2, available as Supplementary data at *IJE* online).

We obtained individual growth trajectories from 1 month to 8 years using the Jenss-Bayley growth curve model. This structural growth model implies a basic functional form of growth and is suitable for describing growth of weight or length up to 8 years, before growth starts to accelerate due to the start of puberty.[66] Using the Jenss-Bayley equation through a mixed-effects approach by adding individual random effects in each equation parameter, a set of four parameters was used to characterize each child's growth trajectory, and individual weight and length/height were calculated at several time points (at 1, 2, 3, 6, 9, 12 and 18 months, and at 2, 3, 4, 5, 6, 7, and 8 years). The models were fitted using the Stochastic Approximation of Expectation-Maximization algorithm in the 'SAEMIX' package in the R software,[67,68] BMI was calculated as weight (kg) divided by squared height (m) using the predicted growth values[69] (Supplementary Table S2, available as Supplementary data at *IJE* online). Implausible anthropometrics were identified and excluded by separately implementing two different methods: (i) by identifying measured values with a >|3 SD| difference from the predicted value as derived from the Jenss-Bayley growth curve model; and (ii) by the conditional growth percentiles method.[70] Based on these methods, 2% of weight and 2% of length/height measurements were excluded as implausible. In order to define growth trajectories independent of birth size, and to be able to further assess the association of seafood intake with early growth independent of the effect on birth size,[71] birthweight and length were not included in the growth models.

Statistical analysis

We used linear mixed-effects regression analysis, adjusted for confounders, to investigate the associations between the exposures of interest and child's postnatal growth from 1 month to 8 years, with random intercept by child and a random slope for age. The primary growth outcome of interest was BMI (kg/m^2). We also studied weight (g) and length/height (cm) as secondary outcomes. Age- and sex-standardized z-scores were used for length/height, as the crude length/height models did not converge. The low consumption category was used as the reference group. Based on previous knowledge and a directed acyclic graph approach (Supplementary Figure S3, available as Supplementary data at *IJE* online), we selected the following covariates for model adjustment: maternal educational level (low: <12 years, average : 13–16 years, high: ≥17 years), pre-pregnancy BMI (continuous, kg/m^2), parity (nulliparous, multiparous) and smoking during pregnancy (no, occasionally, daily). The same set of covariates was used in all models. We also examined maternal fibre intake in pregnancy as a confounder and

as a proxy for a healthy dietary pattern because it has been positively correlated with a health-conscious, traditional dietary pattern that includes seafood.[72] Adjusting our models for fibre intake did not change the point estimates and the confidence intervals were marginally wider (change in third digit). Hence, our final models do not include maternal fibre intake in pregnancy as a covariate.

We examined the effect estimate on the overall growth as well as effect of exposure by child age, as there were interactions between the intake variables and child age on growth. In addition, to take into account that postnatal growth can vary by birthweight and gender, two interaction terms, one with child age and birthweight and one with child age and gender, were included in the models. The inclusion of these interaction terms resulted in better model fit, as shown by the likelihood ratio test between the models without and with these terms (P-value for lr test < 0.001 for all models, df $= 4$). We fitted separate models for maternal total seafood intake and prenatal mercury exposure levels (below or above >90th percentile) and one model where lean fish, fatty fish and other seafood intakes were mutually adjusted. Further, we explored the interaction between prenatal mercury exposure and maternal intake by including a three-way interaction term between the intake variable, child age and prenatal mercury exposure levels. We also performed stratified analysis by prenatal mercury exposure levels and by gender. In addition, the frequency of child fish intake was assessed at 3 years by a food questionnaire filled by the mother, and it was positively correlated with maternal total seafood intake in pregnancy (rho $= 0.32$, $P < 0.001$). Adjustment for child fish intake did not modify our results and no effect modification was observed, hence, our final models did not include child fish intake.

Discordant sibling analysis

We performed a discordant sibling analysis to further elucidate the association between the exposure and the outcome, free of familial sociocultural or genetic factors affecting maternal consumption.[73,74] Within our study population we identified 10 528 siblings. We calculated the sibship mean and the difference of each sibling from the sibship mean, and we defined discordance as a difference of: $>|0.5|$ servings/week for maternal total seafood and lean fish in pregnancy and $>|0.3|$ servings/week for maternal fatty fish in pregnancy, corresponding approximately to the interquartile range of the difference from the sibship mean. Discordant intake of maternal other seafood intake in pregnancy was defined as change from none to any intake between siblings. This resulted in $n = 4198$ discordant siblings for maternal total seafood intake, $n = 2334$ discordant siblings for maternal lean fish intake, $n = 3318$ discordant

siblings for maternal fatty fish intake and $n = 2650$ discordant siblings for maternal other seafood intake. There were only 24 sibling pairs in the sub-population with available maternal mercury concentrations, hence the sibling analysis was not conducted for mercury.

The analyses were performed using Stata 14 statistical software (Stata Corporation, College Station, TX) except for growth modelling that was conducted in R version 3.2.2.[75]

Results

Maternal seafood intake in pregnancy and prenatal mercury

The median (5th-95th percentiles) maternal weekly intakes in pregnancy were 2.4 servings of total seafood (0.5–5.2 servings/week), 1.3 servings of lean fish (0.1–3.1 servings/week) and 0.6 servings of fatty fish (0–2.6 servings/week); 66% of the women reported any intake of other seafood, with a weekly median of 0.3 servings (0.1–0.9 servings/week). Half of our study population (48%) consumed 2–3 servings of total seafood and 13% more than 3 servings weekly, during pregnancy (Table 1). Maternal total seafood intake in pregnancy was positively associated with maternal age, total energy intake and whole-blood mercury. Pregnant women with medium and high seafood intake were less likely to be nulliparous and more likely to be highly educated. In addition, the median mercury in maternal whole blood was 1.03 µg/L [interquartile range(IQR) $= 0.96$ µg/L, minimum-maximum $= 0.003$–12.68 µg/L]. Pregnant women with mercury (Hg) in the top decile (Hg ≥ 2.23 µg/L) had higher lean fish and lower energy intakes, and were more likely to consume other seafood and to be older, nulliparous and highly educated compared with women with lower mercury levels (Supplementary Table S3, available as Supplementary data at *IJE* online). A positive correlation was found between maternal whole-blood mercury and number of servings of total seafood intake (Spearman's rho $= 0.32$), lean fish (Spearman's rho $= 0.24$), fatty fish (Spearman's rho $= 0.22$) and other seafood in pregnancy (Spearman's rho $= 0.33$ for all, and Spearman's rho $= 0.17$ for other seafood after excluding $n = 701$ non-consumers).

Maternal seafood intake in pregnancy and child growth

Maternal lean fish intake during pregnancy was positively, though weakly, associated with child BMI growth trajectory, overall and by gender [overall effect estimate $= 0.02$ kg/m^2, 95% confidence interval (CI) $= 0.00$–0.04 kg/m^2] (Figure 1 and Supplementary Table S4,

Table 1. Characteristics of 51 952 Norwegian mother-child pairs, overall and by total maternal seafood intake category

	All	By maternal total seafood intake (in servings/week)		
	($n = 51\ 952$)	0-1 ($n = 20\ 065$, 39%)	2-3 ($n = 24\ 708$, 48%)	>3 ($n = 7179$, 13%)
Diet in pregnancy				
Lean fish n (%)				
0-1 servings/week	30 090 (58%)	19 071 (95%)	9819 (40%)	1200 (17%)
2 servings/week	15 588 (30%)	994 (5%)	12 169 (49%)	2425 (34%)
$\geq$3 servings/week	6274 (12%)	0	2720 (11%)	3554 (50%)
Fatty fish n (%)				
0 servings/week	22 690 (44%)	14 836 (74%)	7235 (29%)	619 (9%)
1 servings/week	21 267 (41%)	5139 (26%)	14 143 (57%)	1985 (28%)
$\geq$2 servings/week	7995 (15%)	90 (0.5%)	3330 (14%)	4575 (64%)
Other seafood, yes n (%)	34 484 (66%)	11 599 (58%)	17 666 (72%)	5219 (73%)
Energy intake kcal, median (IQR)	2214 (752)	2135 (734)	2228 (723)	2411 (836)
Maternal characteristics				
Pre-pregnancy BMI kg/m^2, mean (SD)	24.0 (4.2)	24.2 (4.3)	23.9 (4.1)	23.9 (4.2)
Age, years, mean (SD)	30.3 (4.4)	29.7 (4.3)	30.6 (4.4)	30.8 (4.7)
Nulliparous, yes n (%)	24 060 (46%)	10 348 (52%)	10 590 (43%)	3122 (44%)
Maternal education, years, n (%)				
Low ($\leq$12 years)	14 405 (28%)	6154 (31%)	6094 (25%)	2157 (30%)
Average (13-16 years)	22 993 (44%)	8800 (44%)	11 216 (45%)	2977 (42%)
High ($\geq$17 years)	14 554 (28%)	5111 (26%)	7398 (30%)	2045 (29%)
Smoking in early pregnancy, no n (%)	48 439 (93%)	18 547 (92%)	23 257 (94%)	6635 (92%)
Whole-blood Hg (μg/L, median, IQR)[a]	1.03 (0.96)	0.78 (0.83)	1.14 (0.93)	1.39 (1.22)
Whole-blood Hg in top decile, yes n (%)[a]	227 (10%)	51 (6%)	126 (11%)	50 (20%)
Offspring characteristics				
Birthweight, kg n (%)				
$\leq$2.5	1372 (3%)	589 (3%)	598 (2%)	185 (3%)
2.6-3.5	23 295 (45%)	9 260 (46%)	10 916 (44%)	3119 (43%)
3.6-4.4	24 994 (48%)	9385 (47%)	12 065 (49%)	3544 (49%)
$\geq$4.5	2291 (4%)	831 (4%)	1129 (5%)	331 (5%)
Male sex, n (%)	26 562 (51%)	10 196 (51%)	12 638 (51%)	3728 (52%)

IQR, interquartile range; BMI, body mass index; SD, standard deviation; Hg, mercury.

[a]$n = 2277$ women with available whole-blood Hg concentrations.

available as Supplementary data at *IJE* online). The strongest associations observed were for girls whose mothers consumed >2 servings of lean fish per week during pregnancy. These girls had 0.05–0.07 kg/m^2 (95% CI range = 0.01–0.14 kg/m^2) higher BMI than their low-exposed peers (0–1 servings of lean fish), from 3 years onwards. Similar small positive effect estimates were obtained overall and in boys. We did not observe associations between maternal lean fish intake and child weight and length/height z-score growth trajectories (Supplementary Tables S4-6, available as Supplementary data at *IJE* online).

No associations were found between maternal pregnancy fatty fish intake and child BMI and weight trajectories, whereas a positive association was found between fatty fish intake $\geq$1 servings and girl's height z-score from 3 years onwards (Supplementary Tables S4-6).

As for lean fish, maternal total seafood intake in pregnancy was positively, though weakly, associated with child BMI trajectory, overall and in girls and no association was found for weight and length/height z-score trajectory (Figure 1 and Supplementary Table S4, S5, and S6). In boys, high total seafood intake in pregnancy (>3 servings/week) was associated with lower weight in early life (Supplementary Table S5).

In addition, any maternal intake of other seafood in pregnancy was associated with a small reduction in child BMI trajectory, compared with no intake, overall and in boys (Supplementary Table S4). The negative association between maternal intake of other seafood was stronger for
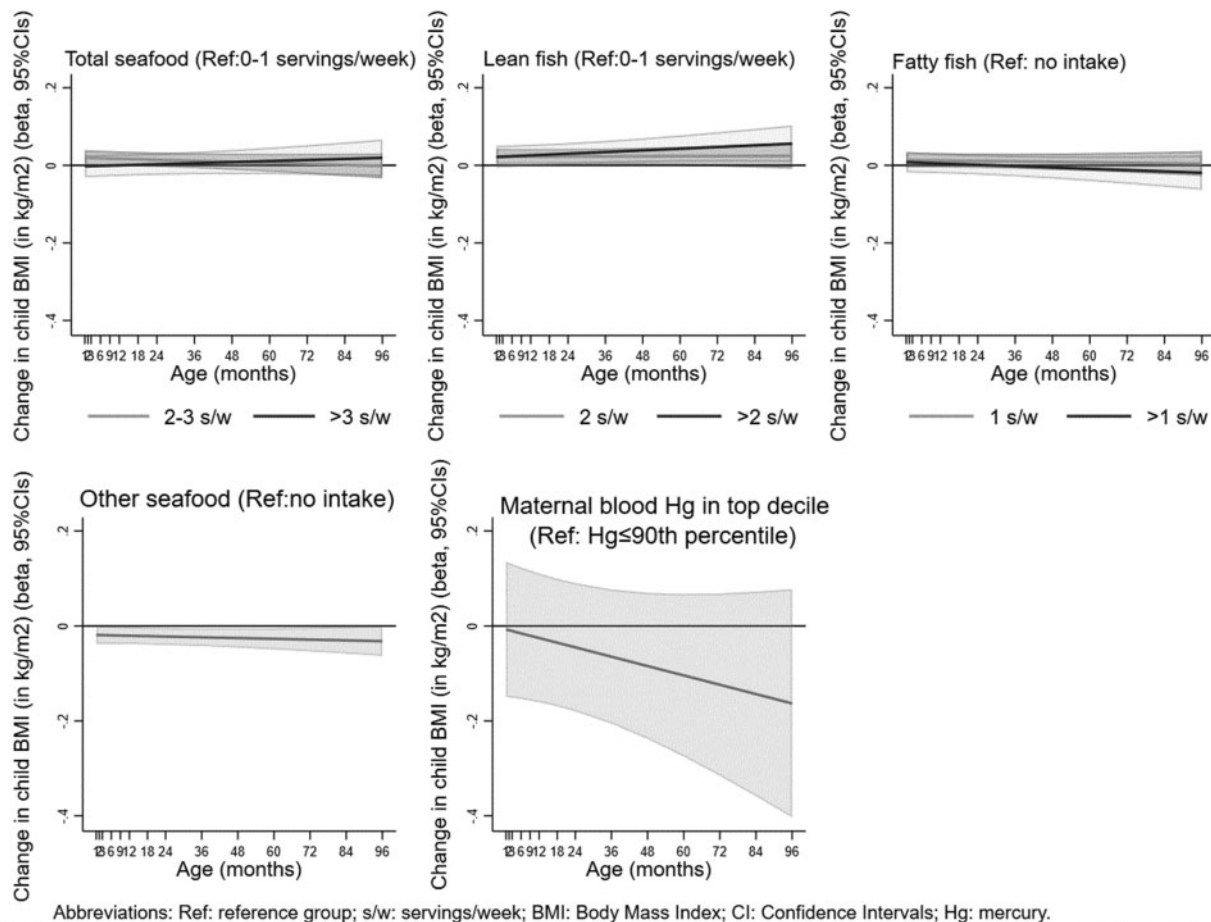
Figure 1. Adjusted changes in children's BMI (in kg/m^2) from 1st month to 8 years, associated with maternal total seafood, lean fish, fatty fish and any other seafood intake ($n = 51\,952$ mother-child pairs) and maternal Hg >90th percentile ($n = 2\,277$ mother-child pairs). Models are adjusted for: maternal educational level (low: <12 years, average: 13–16 years, high: ≥17 years), pre-pregnancy BMI (continuous, in kg/m^2), parity (nulliparous, multiparous) and smoking during pregnancy (no, occasionally, daily).

weight than for BMI, where other seafood intake was associated with a reduction between 13 to 60 g (95% CI range: 0.5 to 80 g) in child's weight from 1 year onwards, compared with no intake (Supplementary Table S5). No association was found for length/height z-score trajectory (Supplementary Table S6).

Prenatal mercury exposure and child growth

Regarding mercury levels, high prenatal exposure (top decile) was associated with a reduction in child's BMI trajectory from 1 month to 8 years (Supplementary Table S4). The strongest association was observed for girls, who had -0.21 to -0.45 kg/m^2 (95% CI range = -0.82 to 0.00 kg/m^2) lower BMI than their low exposed peers, from 3 years onwards. Regarding the components of BMI, high prenatal mercury exposure was associated with lower weight from 18 months onwards (Supplementary Table S5) and lower height z-score from 5 years onwards (Supplementary Table

S6). For weight, in all children the range of the association was -130 g (95% CI = -247, -12 g) at 18 months to -608 g (95% CI = -1.102, -113 g) at 8 years, and in girls -163 g (95% CI = -303, -23 g) at 12 months to -1.265 g (95% CI = -2.015, -516 g) at 8 years. For height z-score, in all children the range of the association was -0.14 (95% CI = -0.26, -0.01) at 5 years to -0.18 (95% CI = -0.34, -0.02) at 8 years, and in girls -0.18 (95% CI = -0.35, -0.01) at 3 years to -0.33 (95% CI = -0.56, -0.09) at 8 years.

Maternal seafood intakes and prenatal mercury exposure interactions

Regarding the associations with BMI trajectory from 1 month to 8 years, we observed an interaction between prenatal mercury levels and maternal fatty fish (P-interaction: for 1 serving/week = 0.009 and for >1servings/week = 0.045) and other seafood intakes in pregnancy (Pinteraction = 0.004) (Figure 2). Regarding the
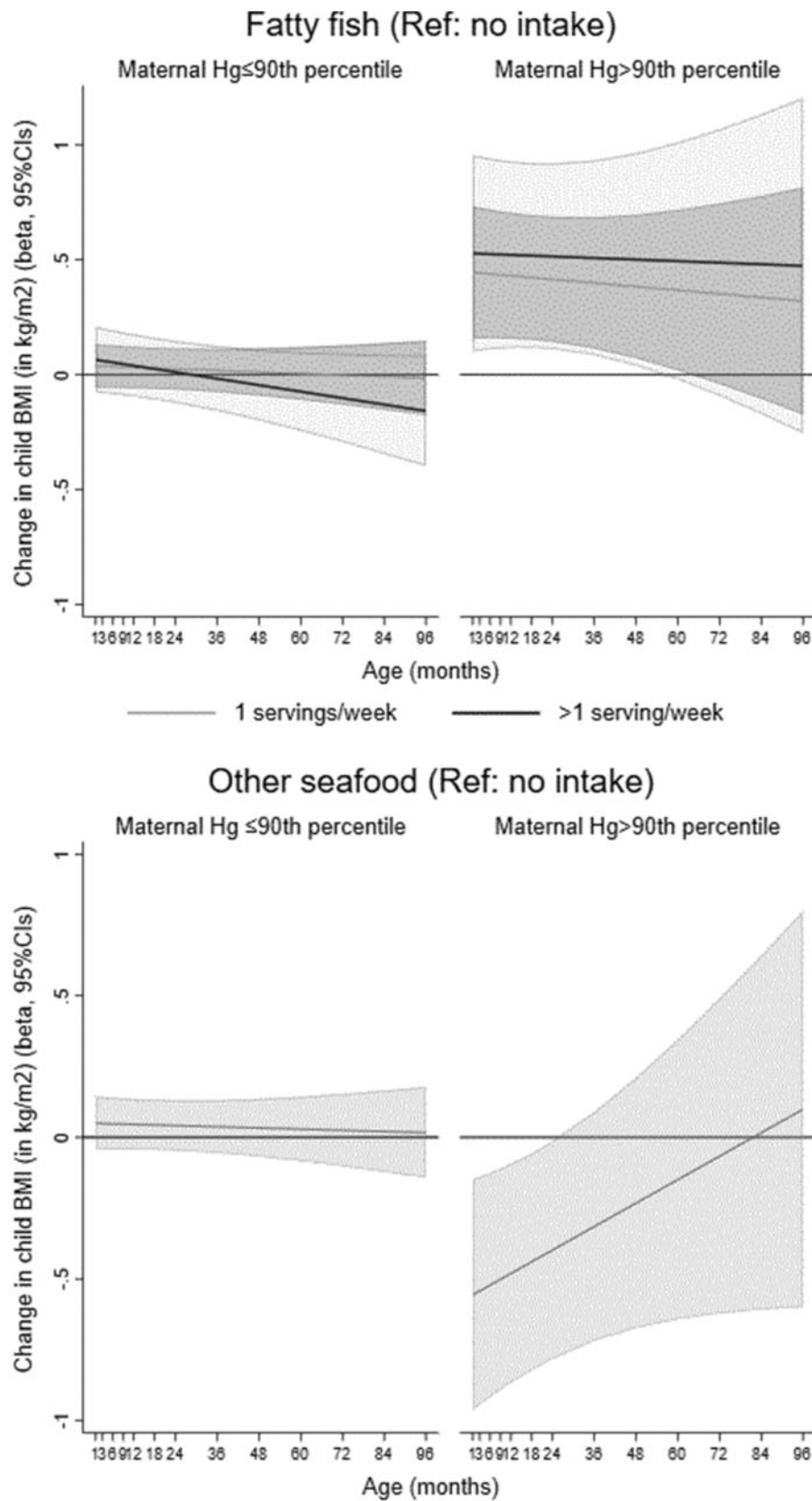
Figure 2. Adjusted changes in children's BMI (in kg/m^2) from 1st month to 8 years, associated with maternal fatty fish and other seafood intake by levels of maternal Hg ($n = 2277$ mother-child pairs). Models are adjusted for: maternal educational level (low: <12 years, average:13–16 years, high: ≥17 years), pre-pregnancy BMI (continuous, in kg/m^2), parity (nulliparous, multiparous) and smoking during pregnancy (no, occasionally, daily).

associations with weight growth trajectory from 1 month to 8 years, we observed a significant interaction between maternal other seafood intake in pregnancy with prenatal mercury (*P*-interaction = 0.006), whereas there was no evidence of interactions with fatty fish (*P*interaction: for 1 serving/week = 0.181 and for >1servings/week = 0.112). Children prenatally exposed to high mercury levels and whose mothers were consuming fatty fish in pregnancy had higher BMI and weight growth trajectories, compared with children born to mothers who did not consume fatty fish in pregnancy (Figure 2; Supplementary Tables S7 and S8, available as Supplementary data at *IJE* online). On the other hand, children prenatally exposed to high mercury levels and whose mothers were consuming other seafood in pregnancy had lower BMI and weight growth trajectories, compared with those whose mothers did not consume other seafood (Figure 2; Supplementary Tables S7 and S8). We found a marginally significant three-way interaction between maternal other seafood intake in pregnancy, prenatal mercury levels and child's age (*P*-interaction = 0.068), meaning that the direction of the interaction between other seafood and mercury levels was changing by age (Figure 2).

Siblings with discordant maternal seafood intake in pregnancy

Further, we explored the association between discordant maternal total seafood, lean fish, fatty fish and other seafood intakes on siblings' growth trajectories, in all siblings and separately for brothers and sisters. All the estimated confidence intervals included 0 (Supplementary Tables S10-12, available as Supplementary data at *IJE* online), meaning that the growth trajectory of the siblings with the increased maternal intake in pregnancy did not differ from the siblings with the decreased maternal intake.

Discussion

In this prospective study with a follow-up of the child's growth from 1 month to 8 years, we found that maternal total seafood and lean fish intakes in pregnancy were positively but weakly associated with child BMI growth trajectory, and other seafood intake was negatively associated with BMI and weight trajectories. On the other hand, children prenatally exposed to high mercury levels (top decile) were more likely to follow a reduced growth trajectory from 1 month to 8 years, especially if the mother was also consuming other seafood during pregnancy. Additionally, in high mercury-exposed children, maternal fatty fish intake in pregnancy once a week was associated with higher weight and BMI trajectories compared with no fatty fish consumption. Maternal mercury concentrations were similar to those of other European pregnant women with moderate seafood consumption.[76] None of the women had mercury concentrations exceeding 23 µg/L, a cut-off established by the European Food Safety Authority.[77]

There is accumulating evidence from birth cohorts with relatively low background exposure levels, that prenatal mercury exposure is associated with restricted fetal growth.[39,78–80] Studies examining postnatal growth up to 2 years have reported a continuation of the restricted growth trajectory.[55,56] Our findings add to the evidence of the detrimental effects of mercury on postnatal child growth by showing a persistently reduced growth pattern in high-exposed children till the age of 8 years. The disruption of maternal thyroid hormone function and regulation, due to high mercury exposure, might provide a biological mechanism through which maternal mercury levels can induce such a slow growth trajectory in the offspring, since high mercury levels in pregnant women have been negatively associated with thyroid hormones,[81,82] and thyroid status in pregnancy has been associated with intrauterine growth restriction and lower childhood BMI.[83,84] The long-term metabolic implications of the observed slower growth trajectory during an extended period needs to be further explored, as childhood is also a period of rapid physiological changes and development of dietary and activity patterns that can extend through the life course.

In addition, we observed stronger associations in girls than in boys. The gender-related susceptibility to the toxic effects of mercury has not been extensively studied and available results are inconclusive, even for better studied endpoints suchas neurotoxicity[85,86] and fetal growth retardation.[87] Differences in the metabolism, excretion, distribution and retention of mercury between males and females that have been demonstrated in different species might explain our results.[81]

Contrary to our results, in a recent study of 1442 US mother-child pairs, prenatal mercury exposure at the 4th quartile vs 1st quartile was associated with higher overweight risk in the child from 2 to 15 years, even after conditioning on maternal fish intake.[88] In this study, 64% and 23% of medium (1–2 servings/week) and high (≥3 servings/week) seafood consumers were in the top quartile of mercury, whereas in our study the respective contributions were 40% and 58%. This difference in the seafood intake levels might explain the discrepancy in the direction of the association with child BMI

Our findings on maternal seafood intake in pregnancy are in line with a recent meta-analysis of 19 birth cohorts, with comparable maternal seafood consumption frequencies, in which maternal seafood intake of >3 servings/week was associated with higher BMI (9–15% reported seafood intakes > 3 servings/week vs 13% in our study), but no

association was found by different fish types.[44] The comparison with studies exploring total maternal seafood intake is not straightforward, especially due to the lack of prenatal mercury exposure and seafood types. To add to this complicated topic, there is compelling evidence that prenatal exposure to organochlorine compounds, for which thedietary source of exposure is mainly fatty fish, are associated with higher childhood adiposity.[47,89,90] In a Spanish cohort, prenatal exposure to organochlorine compounds was positively associated with the risk of obesity at 7 years, independently of the exposure to other chemicals, including mercury, whereas mercury was not associated with obesity.[54] By ranking the studies by levels of exposure, researchers reported that prenatal exposure to polychlorinated biphenyls (PCB), that is organochlorine compounds, was negatively associated with postnatal growth only in studies with relatively high PCB exposure levels, which suggests a non-monotonic dose–response relationship between PCB exposure and obesity.[49] In addition, researchers have previously described an antagonism between PCB and mercury in cord blood against fetal growth, where the detrimental effects of mercury exposure on fetal growth were seen when PCB status was low.[87] Hence, in light of limited evidence on the association between prenatal mercury exposure and postnatal growth, the antagonistic effects of chemicals, whose main source of exposure is seafood consumption, might explain the discrepant associations on growth trajectories for maternal fatty fish consumption (positive associations) and other seafood consumption (negative associations), in high-mercury exposed children.

Strengths and limitations

The present study has several limitations, including the lack of measured levels of co-existing seafood-related contaminants. In addition, this is a birth cohort study with long-term follow-up, and possible selection bias should be considered (Supplementary Table S3 and Figure S2). Nevertheless, by using mixed-effect growth models we were able to include all eligible mother-child pairs participating in the MoBa study. However, we still acknowledge the potential for outcome misclassification bias, as only 26% of the study population had anthropometric data at 8 years. The use of a food frequency questionnaire might induce misclassification in the exposure due to misreporting bias. Even though the misclassification bias is likely differential,[91] in an effort to account for misreporting we have excluded women with implausible energy intakes. Additionally, 84.4% of our included study population have reported adequate energy intakes (EI) for their calculated energy expenditure (EE), according to the Goldberg EI/EE cut-offs ($0.9 < EI/EE < 2.1$).[92] Nevertheless, the use of a validated dietary assessment method in a large population is a methodological advantage compared with previous meta-analyses, were variations in assessment tools, dietary patterns and seafood origin could result in biased estimates.[17,44] In addition, we conducted a discordant sibling analysis in which an exposed child is matched to their unexposed sibling. Compared with the main analyses in unrelated individuals, the siblings analysis can offer partial control of unmeasured genetic, social and lifestyle confounders that are shared within families.[73]

Overall, our findings do not provide evidence of detrimental effects of seafood consumption on child growth from birth to childhood, and support the current dietary guidelines aiming to promote weekly seafood consumption and reduce mercury exposure in women of reproductive age by choosing seafood species with low pollutant concentration, as well as the weekly consumption of a variation of seafood types.

We acknowledge that the effect estimates in the longitudinal growth analysis are of small magnitude, pointing to the need for cautious interpretation of our findings. The consent given by the participants does not allow for storage of data on an individual level in repositories or journals. Researchers who want access to datasets for replication should submit an application to [datatilgang@fhi.no]. Access to datasets requires approval from the Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

Supplementary data

Supplementary data are available at *IJE* online.

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Conflict of interest

None declared.

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