

Prenatal mercury exposure, fish intake and child emotional behavioural regulation in the Norwegian Mother, Father and Child Cohort Study

Kristine Vejrurp ^{1,2}, Anne-Lise Brantsæter ³, Helle Margrete Meltzer,³ Mohammadreza Mohebbi,⁴ Helle Katrine Knutsen,³ Jan Alexander,³ Margareta Haugen,³ Felice Jacka^{5,6}

To cite: Vejrurp K, Brantsæter A-L, Meltzer HM, *et al.* Prenatal mercury exposure, fish intake and child emotional behavioural regulation in the Norwegian Mother, Father and Child Cohort Study. *BMJ Nutrition, Prevention & Health* 2022;5:e000412. doi:10.1136/bmjnp-2021-000412

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjnp-2021-000412>).

For numbered affiliations see end of article.

Correspondence to
Dr Kristine Vejrurp;
kristine.vejrurp@fhi.no

Received 12 December 2021
Accepted 26 October 2022
Published Online First
15 November 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

ABSTRACT

Objective While maternal fish consumption in pregnancy has consistently been linked to better cognitive and emotional outcomes in children, fish is also a primary source of exposure to methyl mercury (MeHg), which has been linked to poorer child cognitive outcomes. The aim of this study was to evaluate the associations between MeHg exposure, using calculated MeHg exposure from maternal diet and total mercury (Hg) concentration in maternal blood during pregnancy, and child internalising and externalising behaviours at 3 and 5 years of age.

Design and participants The study sample comprised 51 238 mother–child pairs in the Norwegian Mother, Father and Child Cohort Study. Data on maternal blood Hg concentration in gestational week 18 were available for a sub-sample of 2936 women. Maternal MeHg exposure from diet was calculated from a validated Food Frequency Questionnaire answered in mid-pregnancy. Mothers reported children's emotional behaviour at age 3 and 5 years by questionnaires including twenty items from the Child Behaviour Checklist. Longitudinal associations were examined using generalised estimating equations, adjusted for potential confounders and stratified by maternal fish intake.

Results Maternal blood Hg concentration (median=1.02 µg/L, 90th percentile=2.22, range=0–13.8) was not associated with emotional behaviour in children. Increasing dietary MeHg intake (median 0.15 µg/kg body weight/week, 90th percentiles=0.31, range=0–1.86) was significantly associated with lower internalising $\beta=-0.03$ (95% CI -0.05 to -0.00) and externalising child behaviours $\beta=-0.04$ (95% CI -0.07 to -0.02) in adjusted models. The inverse associations were also apparent when stratifying by low/high maternal fish intake (<400 and ≥400 g/week).

Conclusions The results indicated that prenatal MeHg exposure, well below the weekly tolerable intake established by European Food Safety Authority (1.3 µg/kg bw), did not adversely affect child emotional regulation. Children of mothers consuming fish regularly were less likely to show signs of emotional behavioural problems.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Maternal diet plays an important role in child development.
- ⇒ Fish consumption is recommended as part of a healthy diet and contributes key nutrients but is also a source of exposure to environmental contaminants, including mercury.

WHAT THIS STUDY ADDS

- ⇒ We explored prospective associations between prenatal exposure to mercury and maternal fish intake with child emotional regulation up to 5 years.
- ⇒ The results showed that maternal fish intake and associated prenatal mercury exposure below tolerable intakes were associated with fewer behavioural problems in children.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The study supports findings from other studies showing no adverse effects of prenatal mercury exposure on child emotional regulation when the source of mercury is fish containing relatively low concentrations of mercury.

INTRODUCTION

Diet is the main contributor to mercury (Hg) exposure in humans, and the main food source is fish and other seafood.¹ Population studies consistently show that fish intake correlates with Hg concentration measured in biological samples,^{2 3} including during pregnancy and in cord blood samples.⁴ Large predatory fish species at the top of the food chain contain the largest quantities.

Birth cohort studies have investigated the potential effects of prenatal Hg exposure, resulting from a maternal diet including fish and seafood with varying Hg levels, on subsequent child development. The findings from two pioneer Hg cohort studies conducted in populations with high, but varied, seafood

diets reported conflicting results concerning the magnitude of prenatal Hg exposure that may cause impaired childhood neurodevelopment, performance and behaviour.^{5–9}

Studies in populations with a moderate intake of fish, defined as 1–3 servings of fish per week and a lower exposure level of Hg also show variation in the association to child emotional development.^{10–14}

Previous research in large cohort studies has indicated that healthier maternal dietary patterns and diet quality assessed during pregnancy are related to better emotional and cognitive health in children over the first years of life.¹⁵ These relationships persist even when considering the potential confounding effect of familial and maternal factors, such as mothers' mental health, parent education level, income, marital status and parenting styles.¹⁶ The meta-analysis by Borge *et al*,¹⁶ which included data from a large pregnancy cohort in Norway, found relatively small effect sizes and indicated a slightly larger effect size for the cognitive than for the affective domain.

Previous studies in the Norwegian cohort have shown mixed findings for Hg exposure and health outcomes. Hg exposure in pregnant women was associated with delayed language and communication skills in children at age 3 years, OR 2.22 (95% CI 1.31 to 3.72),¹⁷ but with favourable child language outcomes at 5 years.²

The aim of this study is to follow up the previous findings in the cohort and assess if there is a relationship between higher prenatal Hg exposure and adverse child emotional health outcomes. We will investigate the associations between Hg concentration in maternal blood during pregnancy, and calculated MeHg exposure from maternal pregnancy diet, and associations with child internalising and externalising behaviours at 3 and 5 years of age from the Child Behaviour Checklist (CBCL).

MATERIAL AND METHODS

Data sources

The Norwegian Mother, Father and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health (NIPH).¹⁸ The recruitment period was from 1999 to 2008 and pregnant women and their partners from all parts of Norway were invited to the study. Mothers could participate with more than one pregnancy and the cohort includes 95 200 mothers and 114 500 children. Of the invited pregnant women, 41% consented to participation. All participants gave written informed consent at recruitment.

Study population

This study is based on MoBa datafile V.9 released for research in 2015. The dataset is linked to data from the Medical Birth Registry of Norway a national health registry containing information about all births in Norway. The questionnaires used in the current study were sent out in gestational week 15 (Q1) and 22 (Q2), at 6 months after

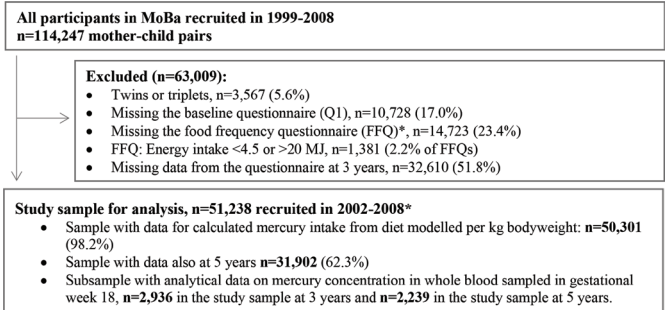


Figure 1 Flow chart of inclusion. *The MoBa food frequency questionnaire was introduced in March 2002. MoBa, Norwegian Mother, Father and Child Cohort Study.

birth (Q4), and when the child reached age 3 years (Q3y) and 5 years (Q5y). Q2 is a Food Frequency Questionnaire (FFQ), while Q1, Q4, Q3y and Q5y are general questionnaires covering maternal and child health, lifestyle and background factors. We excluded participants with multiple births and mothers reporting unlikely energy intake (<4.5 or >20 MJ). The final study population included 51 238 women with singleton live births who had answered questionnaires Q1, Q2, Q3y, of whom 31 902 also had answered the questionnaire Q5y (figure 1).

Exposure

Pregnant women in MoBa completed a comprehensive semi-quantitative FFQ designed to capture their average dietary intakes since the start of pregnancy. The FFQ included questions about intake of 255 food items with special emphasis on various seafood items. Food frequencies were converted to food amounts, and food and nutrient intakes were calculated with use of the FoodCalc program¹⁹ and the Norwegian food composition table.²⁰ A validation study in 119 MoBa participants showed that the FFQ is a reliable and useful tool for estimating the intakes of nutrients and foods, including fish and seafood.^{21 22}

Concentrations of total Hg in Norwegian fish and other food items were compiled in a database described previously.²³ Prenatal dietary Hg exposure was calculated by combining reported food intakes with this database. MeHg is the organic and most toxic form of mercury, constitutes 80%–100% of the total Hg in seafood. Seafood contributes 88% of the total Hg dietary exposure among women in MoBa, and we considered Hg from seafood to reflect MeHg exposure. Total fish intake was calculated as the sum of lean and oily fish species, reported as intakes in the form of bread spread, salad, mixed dishes and dinners (including only the fish part of processed fish items and mixed fish dishes). To perform stratified analysis, we used a cut-off at 400 g of fish intake per week. The rationale for this cut-off is the recommendation by the Norwegian Directorate of Health for a weekly fish intake of 300–450 g.²⁴

Maternal whole blood specimens were obtained around 18 weeks of gestation. The samples were stored at the MoBa biobank. Maternal whole blood samples from 3000 individuals were retrieved from the biobank in 2015 for

the Human Environmental Biobank project (MoBa Etox) at NIPH.²⁵ Maternal blood concentrations of Hg were made available for this study. In total, $n=2936$ individuals in the MoBa Etox sample had data from the questionnaire at 3 years and $n=2239$ also had data from the questionnaire at 5 years. Mercury analysis was conducted at the Department of Laboratory Medicine at Lund University (Sweden) and was determined as total mercury in acid-digested samples by cold vapour atomic fluorescence spectrophotometry. For a more detailed description of the measurement method, see our previous paper.²

Outcome

The primary outcome of this study was maternal report of child emotional behavioural regulation assessed by the CBCL included in the 3-year and 5-year questionnaire. CBCL is a widely used method of identifying internalising symptoms of anxiety and depression and externalising symptoms of aggressive behaviour and attention problems in children and is the most renowned parental report tool of behavioural problems for young children. MoBa questionnaires at 3 and 5 years include a selection of 26 items from the original CBCL. Adequate sensitivity (71%) and specificity (92%), for prediction of psychiatric disorders using CBCL was found in Norwegian study.²⁶ Latent factor analysis of the MoBa subset of CBCL questions on the two expected constructs of internalising and externalising was found to correlate 0.92 with the full original scale.²⁷ CBCL has been used to assess the effect of MeHg on emotional behaviour in previous studies.²⁸

The CBCL in MoBa consisted of 9 items of internalising behaviours (min 9, max 21) and 10 items of externalising behaviours (min 10, max 30) (for information on items see online supplemental table S1). The mother assesses statements about the child behaviour with three response options: 'true', 'somewhat or sometimes true' and 'not true'. For the purpose of this study, the scale is presented such that higher scores represent more internalising and externalising behaviours.

Covariates

Covariates considered as potential confounders were selected a priori on theoretical grounds. The following variables were obtained from the baseline questionnaire answered around pregnancy week 17: prepregnancy bodymass index was calculated from self-reported weight and height and categorised according to WHO categories, level of educational, smoking, annual income and maternal symptoms of anxiety and depression in early pregnancy assessed by the Hopkin Symptom Checklist (HCBL-5). The following variables were obtained from the medical birth registry: age at delivery and parity dichotomised as primiparous and parous.

Statistics

The same questionnaire items and exposure measurements were used at 3 and 5 years. Generalised estimation equation (GEE) regression models were used for

estimating association between mercury exposure and internalising or externalising behaviour scores after accounting for potential confounders. The GEE models assumed a Gaussian distribution for the dependant variables and employed an unstructured covariance pattern to account for within participants autocorrelation in internalising/externalising behaviour scores across age 3 and 5 years assessments. Missing data in the CBCL scores were imputed by using scores within the same dimension. There had to be at least one value per dimension, or it was coded as system missing. For the covariates, we used a complete case approach and excluded participants with missing data in the covariates.

Prenatal dietary Hg exposure calculated from maternal diet and maternal Hg blood level measurement was used as a continuous exposure. In addition, reported fish intake was dichotomised using ≥ 400 g per week defined as a high intake to construct a nominal high and low intake exposure variable. Secondary analyses were performed using this dichotomised exposure. A nominal measurement time was included in the regression equation and the main effect of mercury exposure average across age 3 and 5 years measurements was investigated. Three models were employed to account for potential confounders. Model 1 adjusted for maternal age, maternal education and income; model 2 additionally adjusted for prepregnancy body mass index (BMI), maternal smoking, parity and model 3 made further adjustment for maternal symptoms of anxiety and depression during pregnancy.

All analyses were performed using IBM SPSS Statistics V.23 for Windows (SPSS). All p values were two sided and values below 0.05 were considered statistically significant.

RESULTS

Total blood mercury ($\mu\text{g/L}$) was available for $n=2936$ pregnant women. The median maternal blood Hg concentration was $1.02 \mu\text{g/L}$ (10th and 90th percentiles; $0.34, 2.22 \mu\text{g/L}$) (range $0-13.8 \mu\text{g/L}$).

Of the 51 238 mothers who had answered the questionnaire at child age 3 years, 31 737 (62%) had also answered the questionnaire at 5 years. Comparison of key maternal characteristics and prenatal Hg exposure by the two time points indicated no notable difference for key characteristics or for dietary MeHg exposure and blood Hg concentration for drop-outs and non-drop-outs (online supplemental tables S2-S4).

In the study sample ($n=51\ 238$), the mean age of the women at the time of delivery was 30 years and the mean prepregnant BMI was 23.8 kg/m^2 . Most women (72%) reported to have attained at least one or more year of college/university, 93% of the women did not smoke during pregnancy and nearly half (48.7%) were nulliparous.

The median dietary MeHg exposure was $0.15 \mu\text{g/kg bw/week}$ (10th and 90th percentiles; $0.06, 0.31 \mu\text{g/kg bw/week}$) (range $0-1.86 \mu\text{g/kg bw/week}$). The blood Hg concentration and calculated dietary MeHg exposure

Table 1 Distribution of mean CBCL scores at children aged 3 and 5 years and by maternal reported weekly fish intake below and above 400 g

CBCL outcome	All		<400 g fish weekly		≥400 g fish weekly	
	N*	Mean (SD)	N	Mean (SD)	N	Mean (SD)
3y Internalising	51 238	9.2 (8.3)	47 516	9.3 (8.3)	3722	8.7 (8.2)
3y Externalising	51 238	12.6 (7.2)	47 516	12.7 (7.2)	3722	12.2 (7.2)
5y Internalising	31 624	6.6 (7.8)	29 404	6.6 (7.8)	2220	6.2 (7.1)
5y Externalising	31 737	8.7 (7.0)	29 508	8.7 (7.1)	2229	8.3 (7.1)

Higher CBCL scores are indicating increased internalising and externalising behaviour problems.

*Participants that answered the 5-year questionnaire were included if they had also answered the 3-year questionnaire and the CBCL score.

The number of participants that answered the CBCL externalising score at 5 years was n=31 737, while n=31 624 answered the CBCL internalising score.

CBCL, Child Behaviour Checklist.

correlated moderately; Spearman $r_s=0.37$ (95% CI 0.34 to 0.40). Both dietary MeHg exposure and blood Hg concentration increased with increasing fish intake (online supplemental table S3).

The median maternal weekly fish intake was 181 g/week with 10th and 90th percentiles at 57 and 366 g/week (range 0–1850 g/week). The participants were divided into low or high fish consumers, based on intakes <400 g per week or ≥400 g per week. Only 7.3% (n=3722) of the women reported eating 400 g of fish or more per week.

Maternal fish intake (n=51 238) correlated strongly with MeHg calculated from the diet (Spearman $r_s=0.88$, 95% CI 0.88 to 0.88) and moderately with maternal blood Hg concentration (n=2936, $r=0.36$, 95% CI 0.33 to 0.39).

The CBCL scores for internalising and externalising child behaviour at 3 and 5 years are described separately and by maternal fish intake below and above 400 g per week (table 1). The group of mothers who reported a weekly fish intake ≥400 g reported slightly lower scores for child emotional behavioural problems at both 3 and 5 years.

In the analysis with prenatal dietary MeHg as the exposure, MeHg intake was associated with lower internalising and externalising problem scores in both crude and adjusted models. We adjusted for covariates in the models by adding more variables into the analysis in three steps. The first model included maternal age, education and income. In model 2, we included prepregnancy BMI, smoking and parity, and in the third full model we included maternal anxiety and depression (HCBL-5) during pregnancy. The effect estimates were attenuated by the adjustment but remained significant in the final model with beta=−0.03 (95% CI −0.05 to −0.00) for internalising behaviour and beta=−0.04 (95% CI −0.07 to −0.02) for externalising behaviour (table 2). When using maternal blood Hg concentration as the exposure variable, the effect estimates indicated no associations with child emotional behavioural outcomes in either crude or adjusted analyses (table 2).

We performed stratified analyses by maternal weekly fish intake below and above 400 g and found the same direction of associations within both groups. Within the

Table 2 General estimating equation models and association between maternal dietary Hg intake during pregnancy and maternal Hg blood concentration as continuous variables and maternal report on child internalising and externalising behaviour problems adjusting for maternal covariates in additive models

Models	Dietary MeHg exposure			Maternal Hg blood levels		
	n	Internalising β (95% CI)	Externalising B (95% CI)	n	Internalising β (95% CI)	Externalising B (95% CI)
Crude	50 301	−0.08 (−0.10 to 0.06)**	−0.10 (−0.12 to 0.08)**	2936	−0.15 (−0.40 to 0.09)	−0.03 (−0.25 to 0.20)
Model 1	47 965	−0.04 (−0.06 to 0.02)**	−0.06 (−0.08 to 0.04)**	2873	0.01 (−0.24 to 0.26)	0.09 (−0.14 to 0.33)
Model 2	47 517	−0.03 (−0.06 to 0.01)**	−0.05 (−0.07 to 0.03)**	2807	−0.06 (−0.32 to 0.20)	0.11 (−0.12 to 0.35)
Model 3	46 283	−0.03 (−0.05 to 0.00)*	−0.04 (−0.07 to 0.02)**	2744	−0.04 (−0.30 to 0.23)	0.13 (−0.11 to 0.37)

Model 1 maternal age, maternal education, income.

Model 2 maternal age, maternal education, income, prepregnancy BMI, maternal smoking, parity.

Model 3 maternal age, maternal education, income, prepregnancy BMI, maternal smoking, parity and maternal anxiety and depression during pregnancy.

df were 1 for all analysis.

*p<0.05, **p<0.01.

BMI, body mass index.

Table 3 General estimating equation models and association between maternal dietary Hg intake during pregnancy and maternal Hg blood concentration as continuous variables and maternal report on child internalising and externalising behaviour problems

Models	Fish intake	Internalising	Externalising
		β (95% CI)	β (95% CI)
Crude	<400 g	-0.08 (-0.10 to 0.05)**	-0.10 (-0.12 to 0.07)**
	≥400 g	-0.08 (-0.30 to 0.13)	-0.16 (-0.35 to 0.03)
Model 1	<400 g	-0.03 (-0.06 to 0.01)*	-0.05 (-0.08 to 0.03)**
	≥400 g	-0.06 (-0.03 to 0.02)	-0.10 (-0.29 to 0.10)
Model 2	<400 g	-0.02 (-0.05 to 0.00)	-0.03 (-0.06 to 0.01)*
	≥400 g	-0.05 (-0.06 to 0.02)	-0.04 (-0.27 to 0.19)
Model 3	<400 g	-0.02 (-0.04 to 0.01)	-0.03 (-0.06 to 0.01)*
	≥400 g	-0.08 (-0.34 to 0.18)	-0.03 (-0.25 to 0.19)

Model 1 maternal age, maternal education, income.

Model 2 maternal age, maternal education, income, prepregnancy BMI, maternal smoking, parity.

Model 3 maternal age, maternal education, income, prepregnancy BMI, maternal smoking, parity, maternal anxiety and depression during pregnancy.

df was one for all analysis.

Adjusting for maternal covariates in additive models and stratified by maternal Weekly fish intake below and above 400 g.

* $p < 0.05$, ** $p < 0.01$.

BMI, body mass index.

low fish intake group, we found that higher dietary MeHg exposure was associated with lower scores for internalising and externalising problems in both unadjusted and fully adjusted models. In the much smaller high fish intake group, the associations indicated similar a direction and effect size but the confidence intervals were wide (table 3).

DISCUSSION

In this study, we found that MeHg exposure calculated from maternal diet (median 0.15 $\mu\text{g/kg bw/week}$) was associated with fewer emotional behavioural problems in children at age 3 and 5 years. This inverse association was evident across both lower and higher intakes of seafood consumption. Prenatal maternal blood Hg concentration (median 1.02 $\mu\text{g/L}$) was not associated with increased child emotional behaviour problems in the subsample with available blood Hg values.

The dietary MeHg exposure level in MoBa was generally below the current tolerable weekly intake of 1.3 $\mu\text{g/kg bw}$ established by the European Food Safety Authority (EFSA), which is derived from hair mercury concentrations at the no-observed-adverse-effect level in populations in the Faroe Islands and Seychelles (11.5 mg/kg maternal hair).²⁹ Using a hair:blood ratio of 250 and an uncertainty factor of 2 to account for variability in this ratio, the maternal blood concentration corresponding to this hair level is 23 $\mu\text{g/L}$. The majority of women in MoBa had low exposure levels, with only a few individuals with calculated dietary MeHg values exceeding the tolerable weekly intake and none with exceeding Hg concentrations in blood. The median

maternal blood Hg concentration was 1.02 $\mu\text{g/L}$ (10th and 90th percentiles; 0.34, 2.22 $\mu\text{g/L}$) (range 0–13.8 $\mu\text{g/L}$).

There is a considerable variation in Hg exposure levels worldwide due to variability in the diet and/or due to specific local contamination. In populations with a traditionally high fish intake, we find higher levels of Hg in blood than in populations with a moderate fish intake. The geometric mean blood Hg concentration in the Republic of Korea was 3.2 $\mu\text{g/L}$,³⁰ while in US women the mean blood Hg concentration was approximately 1.0 $\mu\text{g/L}$.¹

In earlier studies in MoBa, we have shown that both the calculated dietary MeHg exposure and maternal blood Hg concentration increases with increasing fish intake.² Investigating possible effects of prenatal Hg exposure on child development, we found that prenatal dietary exposure above the 90th percentile ($>0.29 \mu\text{g/kg bw/day}$) was associated with impaired language development in children aged 3 years, indicating that for the subgroup with the highest Hg exposure, adverse effects of Hg exposure could outweigh the beneficial nutritional effect of maternal seafood consumption.¹⁷ However, in a subsequent study that focused on the MoBa children at 5 years of age, the observed associations between prenatal dietary MeHg exposure and child language and communication skills were favourable, suggesting that the benefits of fish consumption outweighed the potential negative effect of the low MeHg exposure.² Another explanation could be that the parental reported assessment of language and communication skills in children is more accurate and reliable at 5 years than at 3 years.

Our findings are in line with those from the large population cohort in the UK, ALSPAC, which found that maternal blood Hg (median 1.86 µg/L) was positively associated with child development, behaviour and scholastic performance when the mother ate fish, whereas the associations were null or negative when the mothers did not eat fish.³¹ Similar results were also found in the INMA study in Spain among populations with high fish consumption. Here they found that both increasing cord blood Hg concentration (geometric mean 8.8 µg/L),³² and maternal fish consumption above the recommended limit of 340 g/week, were associated with higher scores on neuropsychological tests.³³ A study from the New Bedford cohort in the US found that maternal hair Hg (median 0.45 µg/g) was associated with elevated risk of attention-deficit/hyperactivity disorder (ADHD)-related behaviour. However, maternal fish consumption during pregnancy (> 2 servings per week) was inversely associated with ADHD-related behaviour.¹⁴ These studies support the hypothesis that nutritional benefits are larger than the potential harm from exposure to Hg from seafood intake within the recommended levels.

The main strengths of this study include the large cohort of mothers and children from all parts of Norway, the detailed data on maternal diet and lifestyle, and the prospective design, which limits the problem associated with recall bias and reverse causality. We assessed Hg exposure using both Hg concentration in blood and calculated dietary MeHg, and both markers of Hg exposure increased with increasing seafood intake. Child behaviour was assessed using a well-established and widely used tool and longitudinal modelling minimises the impact of measurement error. This is a more robust method than studying associations between Hg exposure and outcomes for each time point separately.³⁴ An important limitation of this study is that dietary intake, covariates and child outcomes were assessed by maternal report. Self-reported data on health-related and lifestyle-related information pose many challenges.³⁵ Use of FFQ to assess dietary intake is a rather crude method and prone to misreporting. Although the FFQ has been extensively validated, misreporting and imprecision is likely to have attenuated the effect estimates.³⁶ The low response rate in MoBa is also of concern. Participants in MoBa were slightly older, leaner, better educated and included fewer smokers than the general population of pregnant women in Norway at the time, but examination of several exposure–outcome associations in MoBa found comparable effect estimates in MoBa and a nationally representative study sample.³⁷ It is possible that the beneficial association between fish intake and emotional behavioural scores could be confounded by other dietary components. However, we did not adjust for other aspects of overall diet because nearly all women in MoBa reported fish consumption.³⁸ Moreover, fish intake is not strongly associated with diet quality in women participating in MoBa.³⁹

Although we adjusted for numerous variables determined a priori, the study is observational and the

possibility of residual or unmeasured confounding cannot be excluded. The loss to follow-up is another concern and in this study nearly 40% of mother–child pairs were lost to follow-up age 3–5 years. Although participants who remain cohort members differ from those who drop out, studies in MoBa have shown that this does not severely bias the results.^{40 41}

The potential biological mechanisms for the beneficial effects of seafood have been attributed primarily to the marine long chain fatty acids.⁸ However, fish also contributes to the intake of high-quality protein and has essential elements such as iodine and selenium. It is not clear, however, whether the developmental benefits ascribed to eating fish are explained only by nutrients or could also be due to healthier lifestyles that often correlate with regular fish consumption. Overall, results from experimental and prospective observational studies conclude that moderate intake of fish species low in mercury is associated with lower risk of morbidity and mortality, including mental health, and more favourable pregnancy outcomes including child neurocognitive development.⁴² The results of the current study support the need to promote fish consumption in women of childbearing age in accordance with country-specific warnings to restrict consumption of fish species known to contain high MeHg and other contaminants.⁴²

Exposure to Hg in women of childbearing age continues to be an important public health concern, and even though the exposure to Hg from fish and seafood in pregnant women in Norway is generally low, some fish and fish products from other areas of Europe contain Hg levels exceeding those recommended for consumption by pregnant women.⁴³ The fish species most commonly consumed in Norway are cod and farmed salmon, which contain low levels of Hg. Our results indicate no association between Hg exposure and child behaviour of clinical significance in the MoBa cohort. However, it has been argued that cognitive disorders are increasing worldwide⁴⁴ and low-level environmental toxicants may contribute to subclinical decrement in brain function that can have severe consequences for individual life quality and on population level.⁴⁵

CONCLUSION

In summary, this study supports findings from other studies showing no adverse effects of prenatal Hg exposure on child emotional regulation when the source of Hg is fish containing relatively low concentrations of Hg resulting in an intake well below the tolerable intake set by EFSA. Children of mothers who consumed fish regularly had lower scores for emotional regulation problems than those of mothers reporting low fish intake (< 400 g/week). These findings corroborate existing dietary guidelines encouraging women of childbearing age to include fish regularly as part of a balanced diet, while restricting consumption of fish species with high concentration of mercury or other contaminants.

Author affiliations

- ¹Center for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway
²Institute of Military Epidemiology, Norwegian Armed Forces Joint Medical Services, Ullensaker, Norway
³Division of Climate and Environmental Health, Department of Food Safety, Norwegian Institute of Public Health, Oslo, Norway
⁴Biostatistics Unit, Deakin University Faculty of Health, Burwood, Victoria, Australia
⁵Institute for Mental and Physical Health and Clinical Translation, Food & Mood Centre, School of Medicine, Barwon Health, Deakin University, Burwood, Victoria, Australia
⁶Murdoch Children's Research Institute, Centre for Adolescent Health, Parkville, Victoria, Australia

Acknowledgements We are grateful to all the participating families in Norway who take part in this on-going cohort study.

Contributors FJ initiated the study and obtained funding for data acquisition. All authors contributed to planning the study. MH, KV and A-LB contributed with acquisition of the data, calculation of mercury exposure and project administration. FJ, MM and KV conducted the statistical analyses. KV wrote the first draft of the manuscript. All authors contributed to interpretation of the results and critically reviewed the manuscript. All authors read and approved the final manuscript. FJ and KV are responsible for the overall content as guarantors.

Funding The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. FJ is supported by an NHMRC Investigator Grant (#1194982). She has received: (1) competitive Grant/Research support from the Brain and Behaviour Research Institute, the National Health and Medical Research Council (NHMRC), Australian Rotary Health, the Geelong Medical Research Foundation, the Ian Potter Foundation, The University of Melbourne; (2) industry support for research from Meat and Livestock Australia, Woolworths Limited, Bega Cheese, the A2 Milk Company, Be Fit Foods; (3) philanthropic support from the Fernwood Foundation, Wilson Foundation, the JTM Foundation, the Serp Hills Foundation, the Roberts Family Foundation, the Waterloo Foundation and (4) travel support and speakers honoraria from Sanofi-Synthelabo, Janssen Cilag, Servier, Pfizer, Network Nutrition, Angelini Farmaceutica, Eli Lilly, Metagenics, and The Beauty Chef. FJ has written two books for commercial publication.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (REK South-East A 2015/1346).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should apply through helsedata. Access to data sets requires approval from the Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Kristine Vejrurp <http://orcid.org/0000-0002-7448-9529>
 Anne-Lise Brantsæter <http://orcid.org/0000-0001-6315-7134>

REFERENCES

- Mahaffey KR, Clickner RP, Bodurow CC. Blood organic mercury and dietary mercury intake: National health and nutrition examination survey, 1999 and 2000. *Environ Health Perspect* 2004;112:562–70.
- Vejrup K, Brandlistuen RE, Brantsæter AL, et al. Prenatal mercury exposure, maternal seafood consumption and associations with child language at five years. *Environ Int* 2018;110:71–9.
- Ramon R, Murcia M, Aguinalde X, et al. Prenatal mercury exposure in a multicenter cohort study in Spain. *Environ Int* 2011;37:597–604.
- Papadopoulou E, Haug LS, Sakhi AK, et al. Diet as a source of exposure to environmental contaminants for pregnant women and children from six European countries. *Environ Health Perspect* 2019;127:107005.
- Grandjean P, Weihe P, Jørgensen PJ, et al. Impact of maternal seafood diet on fetal exposure to mercury, selenium, and lead. *Arch Environ Health* 1992;47:185–95.
- Julvez J, Debes F, Weihe P, et al. Sensitivity of continuous performance test (CPT) at age 14 years to developmental methylmercury exposure. *Neurotoxicol Teratol* 2010;32:627–32.
- Strain JJ, Yeates AJ, van Wijngaarden E, et al. Prenatal exposure to methyl mercury from fish consumption and polyunsaturated fatty acids: associations with child development at 20 Mo of age in an observational study in the Republic of Seychelles. *Am J Clin Nutr* 2015;101:530–7.
- Strain JJ, Love TM, Yeates AJ, et al. Associations of prenatal methylmercury exposure and maternal polyunsaturated fatty acid status with neurodevelopmental outcomes at 7 years of age: results from the Seychelles child development study nutrition cohort 2. *Am J Clin Nutr* 2021;113:304–13.
- Myers GJ, Thurston SW, Pearson AT, et al. Postnatal exposure to methyl mercury from fish consumption: a review and new data from the Seychelles child development study. *Neurotoxicology* 2009;30:338–49.
- Boucher O, Jacobson SW, Plusquellec P, et al. Prenatal methylmercury, postnatal lead exposure, and evidence of attention deficit/hyperactivity disorder among Inuit children in Arctic Québec. *Environ Health Perspect* 2012;120:1456–61.
- Lam HS, Kwok KM, Chan PHY, et al. Long term neurocognitive impact of low dose prenatal methylmercury exposure in Hong Kong. *Environ Int* 2013;54:59–64.
- Patel NB, Xu Y, McCandless LC, et al. Very low-level prenatal mercury exposure and behaviors in children: the home study. *Environ Health* 2019;18:4.
- Oken E, Radesky JS, Wright RO, et al. Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. *Am J Epidemiol* 2008;167:1171–81.
- Sagiv SK, Thurston SW, Bellinger DC, et al. Prenatal exposure to mercury and fish consumption during pregnancy and attention-deficit/hyperactivity disorder-related behavior in children. *Arch Pediatr Adolesc Med* 2012;166:1123–31.
- Pina-Camacho L, Jensen SK, Gaysina D, et al. Maternal depression symptoms, unhealthy diet and child emotional-behavioural dysregulation. *Psychol Med* 2015;45:1851–60.
- Borge TC, Aase H, Brantsæter AL, et al. The importance of maternal diet quality during pregnancy on cognitive and behavioural outcomes in children: a systematic review and meta-analysis. *BMJ Open* 2017;7:e016777.
- Vejrup K, Schjøberg S, Knutsen HK, et al. Prenatal methylmercury exposure and language delay at three years of age in the Norwegian mother and child cohort study. *Environ Int* 2016;92:93:63–9.
- Magnus P, Birke C, Vejrurp K, et al. Cohort profile update: the Norwegian mother and child cohort study (MoBa). *Int J Epidemiol* 2016;45:382–8.
- Foodcalc v.1.3. 2001 [Internet], 2019. Available: <https://github.com/jesperldk/FoodCalc> [Accessed 01 Aug 2021].
- Rimestad AH, Vesterhus KN, Sygnetveit K, et al. Den Store Matvaretabellen/The Norwegian Food Composition Table. In: *Statens råd for ernæring OG fysisk aktivitet Sn*. Oslo, Norway: Institutt for ernæringsforskning, 2005.
- Brantsæter AL, Haugen M, Alexander J, et al. Validity of a new food frequency questionnaire for pregnant women in the Norwegian mother and child cohort study (MoBa). *Matern Child Nutr* 2008;4:28–43.
- Brantsæter AL, Haugen M, Thomassen Y, et al. Exploration of biomarkers for total fish intake in pregnant Norwegian women. *Public Health Nutr* 2010;13:54–62.

- 23 Jenssen MTS, Brantsæter AL, Haugen M, *et al.* Dietary mercury exposure in a population with a wide range of fish consumption — Self-capture of fish and regional differences are important determinants of mercury in blood. *Sci Total Environ* 2012;439:220–9.
- 24 The Norwegian Directorate of Health. *The Norwegian dietary guidelines (in Norwegian)*, 2016.
- 25 Caspersen IH, Thomsen C, Haug LS, *et al.* Patterns and dietary determinants of essential and toxic elements in blood measured in mid-pregnancy: the Norwegian environmental Biobank. *Sci Total Environ* 2019;671:299–308.
- 26 Nøvik TS. Validity of the child behaviour checklist in a Norwegian sample. *Eur Child Adolesc Psychiatry* 1999;8:247–54.
- 27 Zachrisson HD, Dearing E, Lekhal R, *et al.* Little evidence that time in child care causes externalizing problems during early childhood in Norway. *Child Dev* 2013;84:1152–70.
- 28 Myers GJ, Davidson PW. Does methylmercury have a role in causing developmental disabilities in children? *Environ Health Perspect* 2000;108 Suppl 3:413–20.
- 29 EFSA. EFSA panel on contaminants in the food chain. scientific opinion on the risk for public health related to the presence of mercury and methylmercury in food. *EFSA Journal* 2012;10:2985.
- 30 Lee JW, Lee CK, Moon CS, *et al.* Korea national survey for environmental pollutants in the human body 2008: heavy metals in the blood or urine of the Korean population. *Int J Hyg Environ Health* 2012;215:449–57.
- 31 Hibbeln J, Gregory S, Iles-Caven Y, *et al.* Total mercury exposure in early pregnancy has no adverse association with scholastic ability of the offspring particularly if the mother eats fish. *Environ Int* 2018;116:108–15.
- 32 Murata K, Dakeishi M, Shimada M, *et al.* Assessment of intrauterine methylmercury exposure affecting child development: messages from the newborn. *Tohoku J Exp Med* 2007;213:187–202.
- 33 Julvez J, Méndez M, Fernandez-Barres S, *et al.* Maternal consumption of seafood in pregnancy and child neuropsychological development: a longitudinal study based on a population with high consumption levels. *Am J Epidemiol* 2016;183:169–82.
- 34 Isaacs E, Oates J, ILSI Europe a.i.s.b.l. Nutrition and cognition: assessing cognitive abilities in children and young people. *Eur J Nutr* 2008;47 Suppl 3:4–24.
- 35 Sharma AJ, Bulkley JE, Stoneburner AB, *et al.* Bias in self-reported prepregnancy weight across maternal and clinical characteristics. *Matern Child Health J* 2021;25:1242–53.
- 36 Kipnis V, Midthune D, Freedman L, *et al.* Bias in dietary-report instruments and its implications for nutritional epidemiology. *Public Health Nutr* 2002;5:915–23.
- 37 Nilsen RM, Vollset SE, Gjessing HK, *et al.* Self-Selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol* 2009;23:597–608.
- 38 Brantsæter AL, Englund-Ögge L, Haugen M, *et al.* Maternal intake of seafood and supplementary long chain n-3 poly-unsaturated fatty acids and preterm delivery. *BMC Pregnancy Childbirth* 2017;17:41.
- 39 Jacka FN, Ystrøm E, Brantsæter AL, *et al.* Maternal and early postnatal nutrition and mental health of offspring by age 5 years: a prospective cohort study. *J Am Acad Child Adolesc Psychiatry* 2013;52:1038–47.
- 40 Vejrup K, Magnus P, Magnus M. Lost to follow-up in the Norwegian mother, father and child cohort study. *Paediatr Perinat Epidemiol* 2022;36:300–9.
- 41 Kvalvik LG, Klungsoyr K, Igland J, *et al.* Association of sweetened carbonated beverage consumption during pregnancy and ADHD symptoms in the offspring: a study from the Norwegian mother, father and child cohort study (Moba). *Eur J Nutr* 2022;61:2153–66.
- 42 EFSA Scientific Committee. Statement on the benefits of fish/seafood consumption compared to the risks of methylmercury in fish/seafood. *Efsa J* 2015;13:3982.
- 43 Kimáková T, Kuzmová L, Nevolná Z, *et al.* Fish and fish products as risk factors of mercury exposure. *Ann Agric Environ Med* 2018;25:488–93.
- 44 Landrigan PJ, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. *Environ Health Perspect* 2012;120:a258–60.
- 45 Lee D-H, Jacobs DR. Inconsistent epidemiological findings on fish consumption may be indirect evidence of harmful contaminants in fish. *J Epidemiol Community Health* 2010;64:190–2.

Supplementary Tables

Supplementary table S1. Child Behaviour Checklist (CBCL) – items used from the MoBa questionnaires at 3 year and 5 year. Sorted by internalizing and externalizing items.

The following list contains statements describing children's behavior and manner from the age of 2-3.

Items on the internalizing scale

- Clings to adults or too dependent
- Constipated, doesn't move bowels
- Disturbed by any change in routine
- Doesn't eat well
- Gets too upset when separated from parents
- Stomach aches or cramps (without medical cause)
- Sudden changes in moods or feelings
- Too fearful or anxious
- Vomiting, throwing up (without medical cause)

Items on the externalizing scale

- Can't concentrate, can't pay attention for long
- Can't sit still, restless or overactive
- Can't stand waiting, wants everything now
- Defiant
- Demands must be met immediately
- Gets in many fights
- Hits others
- Poorly coordinated or clumsy
- Punishment doesn't change his/her behavior
- Quickly shifts from one activity to another

The following list contains statements describing children's behavior from the age of 5.

Items on the internalizing scale

- Clings to adults or too dependent
- Disturbed by any change in routine
- Doesn't eat well

- Gets too upset when separated from parents
- Stomach aches or cramps (without medical cause)
- Too fearful or anxious
- Unhappy, sad or depressed
- Vomiting, throwing up (without medical cause)
- Feelings are easily hurt

Items on the externalizing scale

- Can't concentrate, can't pay attention for long
- Can't sit still, restless or overactive
- Can't stand waiting, wants everything now
- Defiant
- Demands must be met immediately
- Doesn't seem to feel guilty after misbehaving
- Gets in many fights
- Hits other
- Poorly coordinated or clumsy
- Punishment doesn't change his/her behavior

To what extent are the following statements true of your child's behavior during the last two months? Options:

1-Not true

2-Somewhat or sometimes true

3-Very true or often true

Supplementary Table S2. Description of prenatal dietary mercury exposure and demographic variables in the study sample for participants with information about child behavior at child age 3 and 5 years.

	Answered 3-year questionnaire			Answered 5-year questionnaires*		
	N	mean (SD)	median	N	mean (SD)	median
Mercury µg per day	51,238	1.63 (0.99)	1.47	31,737	1.63 (0.97)	1.50
Mercury µg/ kg bw/ week**	50,301	0.17 (0.11)	0.15	31,262	0.18 (0.11)	0.16
Maternal age at delivery		%			%	
<25 years	4542	8.9		2354	7.4	
25-29 years	16,996	33.2		10,232	32.2	
30-34 years	23,175	45.2		14,795	46.6	
≥35 years	6225	12.7		4356	13.7	
Parity						
nulliparous	24,971	48.7		15,798	49.8	
multiparous	26,267	51.3		15,939	50.2	
Maternal education						
≤12 years	13,418	26.2		7007	22.1	
13-16 years	22,535	44.0		14,215	44.8	
≥17 years	14,317	27.9		9950	31.4	
missing	968	1.9		565	1.8	
Maternal income						
< 300,000 NOK per year	29,617	57.8		16,768	52.8	
≥ 300,000 NOK per year	20,140	39.3		14,188	44.7	
missing	1481	2.9		781	2.5	
Smoking during pregnancy						
no smoking	47,755	93.2		30,106	94.9	
occasional smoking	1121	2.2		554	1.7	
daily smoking	2028	4.0		885	2.8	
missing	334	0.7		192	0.6	
Pre-pregnancy BMI, kg/m ²						
<18.5	33,446	65.3		21,054	66.3	
18.5-24.9	1422	2.8		888	2.8	
25-29.9	10,816	21.1		6649	21.0	
≥30	4451	8.7		2581	8.1	
missing	1103	2.2		565	1.8	
Weekly fish servings						
0	1498	2.9		851	2.7	
1	22,109	43.1		13,740	43.3	
2	21,102	41.2		13,188	41.6	
3	3139	6.1		1926	6.1	
≥4	3390	6.6		2032	6.4	

* Participants that answered the five-year questionnaire were included if they had also answered the three-year questionnaire and the CBCL score. The number of participants that answered the CBCL externalizing score were n= 31,737, while n=31,624 participants answered the CBCL internalizing score. In this overview we present demographics based on participants that answered the CBCL externalizing score.

**Missing due to missing reports of maternal body weight.

Abbreviations: NOK; Norwegian Kroner

Supplementary Table S3. Description of maternal blood mercury ($\mu\text{g/L}$) concentration and demographic variables for participants with information about child behavior at age 3 and 5 years.

	Answered 3-year questionnaire		Answered 5-year questionnaires*	
	N	Mean (SD) median	N	Mean (SD) median
Blood mercury levels ($\mu\text{g/L}$)	2936	1.21 (0.93) 1.02	2226	1.21(0.93) 1.03
Maternal age at delivery		%		%
<25 years	236	8.0	161	7.3
25-29 years	1033	35.2	755	34.1
30-34 years	1341	45.7	1043	47.1
≥ 35 years	326	11.1	256	11.6
Parity				
nulliparous	1513	51.5	1104	49.8
multiparous	1423	48.5	1111	50.2
Maternal education				
≤ 12 years	755	25.7	511	23.1
13-16 years	1380	47.0	1066	48.1
≥ 17 years	738	25.1	590	26.6
missing	63	2.1	48	2.2
Maternal income				
< 300,000 NOK per year	1803	61.4	1329	60.0
$\geq 300,000$ NOK per year	1058	36.0	834	37.7
missing	75	2.6	52	2.3
Smoking during pregnancy				
no smoking	2749	93.6	2100	94.8
occasional smoking	66	2.2	44	2.0
daily smoking	106	3.6	60	2.7
missing	15	0.5	11	0.5
Pre-pregnancy BMI, kg/m^2				
<18.5	1889	64.3	1436	64.8
18.5-24.9	89	3.0	64	2.9
25-29.9	677	23.1	516	23.3
≥ 30	226	7.7	160	7.2
missing	55	1.9	39	1.8
Weekly fish servings				
0	91	3.1	58	2.6
1	1312	44.7	981	44.3
2	1213	41.3	934	42.2
3	169	5.8	126	5.7
≥ 4	151	5.1	116	5.2

* Participants that answered the five-year questionnaire were included if they had also answered the three-year questionnaire and the CBCL score. The number of participants that answered the CBCL externalizing score were $n = 2226$ while only $n = 2215$ participants had answered the CBCL internalizing score. In this overview we are presenting demographics based on participants that answered the CBCL externalizing score.

Supplementary Table S4. Calculated dietary methylmercury (MeHg) intake and maternal blood mercury (Hg) concentration by quintiles of maternal fish intake.

Fish intake quintile range (g/week)	MeHg ($\mu\text{g/kg}$ bw/week) mean (IQR)	Blood Hg ($\mu\text{g/L}$) mean (IQR)
<95	0.06 (0.03, 0.09)	0.87 (0.38, 1.15)
96-153	0.12 (0.09, 0.15)	1.10 (0.53, 1.44)
154-210	0.17 (0.13, 0.20)	1.26 (0.67, 1.59)
211-291	0.21 (0.16, 0.25)	1.37 (0.71, 1.73)
292-1850	0.30 (0.22, 0.36)	1.51 (0.85, 1.92)