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Prenatal and concurrent blood mercury concentrations and associations with IQ in canadian preschool children

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A R T I C L E I N F O

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A B S T R A C T

Background: Prenatal and childhood mercury (Hg) exposures have been associated with negative impacts on child neurodevelopment. It is unclear if associations persist at the low Hg exposures typical in Western countries.
Objective: To examine associations between prenatal/childhood blood Hg concentrations and child IQ in Canadian male and female children while considering the potential modifying role of prenatal fish consumption.
Methods: We analyzed data from the Maternal-Infant Research on Environmental Chemicals study. Hg was measured in first trimester (n = 527), cord (n = 430), and child (at 3–4 years of age, n = 355) blood and examined sex-stratified associations between blood Hg and children's Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), and General Language Composite (GLC) scores (assessed with WPPSI-III). Prenatal Hg analyses were further stratified by prenatal fish consumption (low: 0–2, moderate: 3–7, or high: ≥8 times/month).
Results: Higher cord blood Hg concentrations were associated with lower PIQ (ß = −3.27; 95%CI: 6.44, −0.09) in male children with the lowest prenatal fish consumption. Progressively stronger positive associations were observed with PIQ in male children for moderate (ß = 1.08; 95%CI: 0.10, 2.26) and high (ß = 3.07; 95%CI: 1.95, 4.19) prenatal fish consumption. Cord blood Hg concentrations were positively associated with female children's FSIQ (ß = 1.29; 95% CI: 0.77, 1.81) and PIQ (ß = 2.01; 95% CI: 1.19, 2.83); however, when stratified only in the highest fish consumption subgroup. Among female children, higher child blood Hg concentrations were associated with an approximately 1-point increase in FSIQ, VIQ, and GLC.
Conclusions: Prenatal exposure to low levels of Hg was associated with lower PIQ scores in male children with low prenatal fish intake. Positive associations between cord and child blood Hg concentrations and IQ were primarily observed in female children and may be due to beneficial effects of prenatal fish intake.

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1. Introduction

Mercury (Hg), an ubiquitous environmental contaminant, is a global public health concern because of its deleterious health effects, such as those on the nervous system and impairments in cognitive development (Choi and Grandjean, 2008; Goldman et al., 2001; Mergler et al., 2007; United Nations, 2019). The developing fetus is particularly susceptible to the neurotoxic effects of Hg because their nervous system is undergoing rapid development (Clifton II, 2007; Goldman et al., 2001; Ruggieri et al., 2017). Epidemiological studies have demonstrated that prenatal exposure to Hg can have harmful impacts on children's cognitive function (Crump et al., 1998; Grandjean et al., 1997; Jacobson et al., 2015; Jeong et al., 2017; Suzuki et al., 2010), such as intelligence quotient (IQ) (Jacobson et al., 2015; Jeong et al., 2017). In addition, childhood exposure to Hg has also been negatively associated with some neurodevelopmental outcomes (dos Santos-Lima et al., 2020; Myers et al., 2009), including Verbal IQ (VIQ) (dos Santos-Lima et al., 2020).

Most studies of Hg and cognitive function have been conducted in populations with higher levels of exposure than is typically experienced by pregnant women and children in the general Canadian population, such as that observed in the Canadian Health Measures Survey (CHMS) (Health Canada, 2011, 2019a). Moreover, few studies have measured Hg at multiple time points to directly compare the impacts of prenatal and childhood exposures on cognitive function (Davidson et al., 2010; Hsi et al., 2014; Plusquellec et al., 2010). Several epidemiological studies have not found associations between early life Hg exposure and cognitive function (Cao et al., 2010; Davidson et al., 1998; Golding et al., 2016, 2017, 2022; Hibbeln et al., 2018; Oken et al., 2016); these discrepant findings may be due to the protective role of fish and shellfish consumption during pregnancy.

While some fish species can be a common source of Hg, especially for the more toxic form methylmercury, fish are also an important source of omega-3 fatty acids, protein, vitamin D, and other minerals essential for optimal fetal development (Health Canada, 2007) and ultimately children's neurodevelopment (Avella-Garcia and Julvez, 2014). Several studies have found that fish consumption during pregnancy can modify the association between prenatal Hg exposure and neurodevelopmental outcomes (Golding et al., 2017; Jacobson et al., 2015; Jeong et al., 2017), showing that the beneficial effects of nutrients in fish and seafood sources may offset the adverse effects of exposure to low levels of Hg.

However, co-exposures to other contaminants (e.g., lead, polybrominated diphenyl ethers (PBDEs), or polychlorinated biphenyls (PCBs)), nutrients (e.g., selenium), as well as sociodemographic factors may confound or modify associations between prenatal and childhood Hg exposures and child neurodevelopment (Azar et al., 2021; Castriotta et al., 2020; Kim et al., 2020; Orenstein et al., 2014; Tratnik et al., 2017). Selenium may be protective against the toxic effects of Hg exposure (Cuvin-Aralar and Furness, 1991; Parizek et al., 1969; Pelletier, 1986; Ralston and Raymond, 2010) as Hg and selenium interact and can form complexes reducing the biological availability of Hg (Raymond and Ralston, 2004).

Finally, these associations between prenatal Hg and child neurodevelopment may differ according to child sex (Llop et al., 2012; Sagiv et al., 2012; Wang et al., 2019). Sex-specific associations between prenatal exposures to other environmental contaminants and child IQ have been observed in previous analyses from our Maternal-Infant Research on Environmental Contaminants (MIREC) cohort study (Azar et al., 2021; Desrochers-Couture et al., 2018; Green et al., 2019; Nkinsa et al., 2020). Generally, negative associations were more commonly seen for the male children in these studies.

Further studies are needed to examine the sex-specific associations between the low levels of Hg exposure during pregnancy and early childhood that are typical in Western countries (Basu et al., 2018; Wong and Lye, 2008) and child cognitive function, with consideration of the potential modifying role of fish consumption during pregnancy.

The goal of the present study was to examine the sex-specific associations between Hg exposure during two critical developmental windows (prenatal and early childhood) and early childhood IQ, as well as to determine whether fish consumption during pregnancy modifies these associations. Additionally, we explored the potential for an interaction between child blood Hg and child blood selenium concentrations. Finally, we adjusted for co-exposure to lead, PBDEs, or PCBs to determine if co-exposure to these chemical contaminants affect the associations observed between early life Hg exposures and child IQ.

2. Methods

2.1. Study design and population

We analyzed data from the MIREC pregnancy cohort (Arbuckle et al., 2013) and the MIREC-Child Development (CD) Plus follow-up study (Fisher et al., 2023). In the MIREC study, participants were recruited in their first trimester of pregnancy between 2008 and 2011 from obstetric and prenatal clinics from ten cities in Canada. Participants were eligible if they were able to communicate in English or French, >18 years of age, <14 weeks gestation, and planning to deliver at a local hospital. A subset of participants were followed from six of the initial 10 MIREC sites in 2013–2015 when the children were 2–5 years old (Fisher et al., 2023). In the MIREC-CD Plus follow-up study, the birthing parent completed a questionnaire to capture covariate information while children provided a blood sample and participated in neurodevelopment tests administered by trained examiners. Both studies were approved by the Research Ethics Boards of Health Canada/Public Health Agency of Canada, Sainte-Justine University Hospital, as well as the ethic boards for all MIREC-affiliated study sites. Informed consent was obtained from all participants, as well as child assent. Of the participants recruited for the MIREC study (n = 2001), this analysis was restricted to the subset of participants that were included in the MIREC-CD Plus follow-up study and had complete neurodevelopment data (n = 527) (Supplementary Fig. 1).

2.2. Hg and other analyte concentrations

Total Hg concentrations were measured in whole blood samples collected during the first trimester (6–13 weeks), from the umbilical cord at birth (Arbuckle et al., 2013, 2016), and from children collected concurrently with the IQ assessment (Fisher et al., 2023). Methylmercury can readily cross the blood-brain barrier and the placenta (Clifton II, 2007; Goldman et al., 2001); therefore, cord blood provides a more proximal marker of fetal exposure than first trimester blood (Clifton II, 2007; Goldman et al., 2001). As previously described (Arbuckle et al., 2013, 2016), blood samples were analyzed at the Centre de Toxicologie, Institut National de Santé Publique du Québec, using inductively coupled plasma mass spectrometry (ICP-MS) (PerkinElmer ELAN ICP-MS DRC II; Norwalk CT, USA). The limit of detection (LOD) for total Hg was 0.12 μg/L in first trimester blood and 0.40 μg/L for cord blood (Arbuckle et al., 2016). The LODs for total Hg concentrations in children's blood were between 0.05 and 0.06 μg/L.

As previously described, lead concentrations were also measured by ICP-MS in first trimester, umbilical cord, and children's whole blood with LODs of 0.1 μg/dL, 0.1 μg/dL, and 0.21 μg/dL respectively (Arbuckle et al., 2016; Desrochers-Couture et al., 2018). PBDE and PCB concentrations were measured in first trimester plasma samples (with LODs ranging from 0.005 to 0.3 μg/L) along with total lipid concentrations, as previously described (Fisher et al., 2016). Total selenium concentrations were also measured by ICP-MS in child whole blood samples with a LOD of 8.15 μg/L.

2.3. Child IQ

Neurodevelopment visits were conducted between 36 and 47 months of age among singleton children who were born >28 weeks gestation and without major congenital birth defects, seizures, or major neurological disorders during the perinatal period. The majority (98%) of neurodevelopment visits were conducted at the child's home by study staff. Training, monitoring, and oversight of test administration was performed by a licenced clinical psychologist. The Wechsler Preschool and Primary Scale of Intelligence–3rd Edition (WPPSI-III), short version, was used to assess cognitive function (Wechsler, 2002). Results on the five subtests (Block Design, Object Assembly, Receptive Vocabulary, Information, and Picture Naming) were used to calculate four composite scores: Full-scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ), and General Language Composite (GLC). These composite scores were age-standardized to Canadian norms (Wechsler, 2004) with a mean of 100 and a standard deviation of 15 points. The Canadian edition of the WPSSI-III was normed and standardized based on a validation sample of 700 Canadian children whose demographic characteristics corresponded to those reported in the 2001 Canadian census (Wechsler, 2004). In the validation sample of 2.5–7.3 year old children, composite scores had excellent internal consistencies (Cronbach's alpha = 0.90–0.96) and the test-retest reliability coefficients were good (intra-class correlation = 0.83–0.90) (Wechsler, 2004). In the MIREC-CD Plus study, examiners, parents, and children were not aware of the prenatal or child blood Hg concentrations at the time of the neurodevelopment visit.

2.4. Covariates

We identified covariates *a priori* from studies that have described correlates of both prenatal (Arbuckle et al., 2016) and child blood Hg (Garí et al., 2013; Hrubá et al., 2012; Vogel et al., 2021), as well as previous studies examining associations between Hg and various neurodevelopmental outcomes (Barbone et al., 2019; Crump et al., 1998; Davidson et al., 1998; Grandjean et al., 1997; Jacobson et al., 2015; Jeong et al., 2017; Suzuki et al., 2010). We developed directed acyclic graphs (DAGs) for exposure to Hg during both the prenatal and childhood time-periods (Supplementary Figs. 2 and 3). For the prenatal exposures, covariates included the birthing parent's: age (continuous), pre-pregnancy body mass index (BMI) (continuous), parity (nulliparous vs. multiparous), level of education during early pregnancy (high school diploma or less, completed/some college or trade school, university degree), cigarette smoking status during early pregnancy (never, former, current/quit during pregnancy), alcohol use during early pregnancy (yes vs. no), place of birth (Canada vs. other), study site (random effect), and fish consumption during early pregnancy (low, moderate, high). For the sensitivity analyses, covariates also included if the birthing parent had dental fillings (zero, more than one, unknown), and whether the birthing parent had any dental filling replaced in the past 12 months (yes or no). Participant socio-demographic and lifestyle characteristics were collected through questionnaires administered during each trimester, and child sex at birth was extracted from medical records. Participants also completed a food frequency questionnaire indicating daily, weekly, or monthly consumption of 25 species of fish during the month prior to their first trimester clinic visit. We calculated summary scores for the monthly frequency of consuming all fish species and categorized fish consumption in early pregnancy as low (0–2 times/month), moderate (3–7 times/month) and high (≥8 times/month). We also examined the frequency of consuming fish classified as being high in Hg (i.e., tuna, marlin, orange roughy, shark, swordfish, mackerel, escolar) (Health Canada, 2019b). Consumption of fish high in Hg was moderately correlated with the total fish consumption (consumption of the 25 species of fish) (Spearman r = 0.62). The frequency of consumption of fish high in Hg tended to increase across the categories created for total fish consumption (Supplementary Tables 1A and 1B). Given these correlations and that fish consumption is not just a source of Hg but is also a source of nutrients required for optimal neurodevelopment, we stratified fish consumption frequency according to consumption of all 25 species of fish.

For childhood Hg exposure, covariates included the birthing parent's age during pregnancy (continuous), education during pregnancy (high school diploma or less, completed/some college or trade school, university degree), parity as of early pregnancy (nulliparous vs. multiparous), birthing parent's depression at follow-up (continuous), and included the child's blood selenium concentrations (continuous), duration of breastfeeding (none, <6 months, ≥6 months), and a Home Observation for Measurement of the Environment (HOME) inventory score (continuous) measured at follow-up. The birthing parent's depression was assessed using the Center for Epidemiological Studies Depression Scale (CES-D), with scores ranging from 0 to 60 and higher scores indicating greater depressive symptoms (Radloff, 1977) and a derived depression score ranging from 0 to 10 was calculated. At follow-up, the birthing parent also completed the 55-item HOME inventory, which assessed the quality of support and stimulation that children receive at home, with a HOME total score ranging from 0 to 55 (Caldwell and Bradley, 2001).

2.5. Statistical analysis

All analyses were conducted in SAS Enterprise Guide 7.1 (SAS institute, Cary, NC). Analyte concentrations below the LOD were substituted with one-half of the analyte and matrix-specific LOD. Missing covariate data were imputed using multiple imputation with the fully conditional specification method using a logistic model for categorical variables and a linear model for continuous variables. The proportion of missingness across covariates was less than 5% for categorical and continuous variables, with the exception of pre-pregnancy BMI (missingness for pre-pregnancy BMI was 9% and 3% for male and female children respectively) (Table 1). We used 5 imputations, which provided >99% relative efficiency suggesting that additional imputations were not necessary. Iteration-specific parameter estimates were combined to provide appropriate variance estimation. Summary statistics (median (IQR) or n (%) as appropriate) are presented by child sex as well as stratified by fish consumption frequency categories. Hg concentrations were $\log_2$-transformed to normalize distributions and to allow for interpretation of parameter estimates as per a 2-fold increase in exposure. We used separate generalized linear mixed models to investigate the associations between Hg concentrations at each time point (first trimester, cord, and child blood) and FSIQ, VIQ, PIQ, and the GLC. These models were adjusted for confounders included in the DAGs as fixed effects, with study site included as a random effect. All models were stratified by child sex. We also explored associations of first trimester and cord blood Hg concentrations stratified by fish consumption during pregnancy and child sex. Furthermore, in the models examining the associations between child Hg and IQ, we explored the interaction between child blood Hg and child blood selenium concentrations.

As with any cohort study, one of the threats to internal validity is selection bias via differential loss to follow-up (Lash et al., 2020). We used inverse probability weighting (IPW) with stabilized weights (Seaman and White, 2013) to minimize the potential effect of differential loss to follow-up on the observed associations. We used logistic regression to derive the predicted probability of participation in the follow-up study (of those participants from the six eligible sites) based on a range of factors that may be associated with retention (Supplementary Table 2). The inverse of these predicted probabilities of follow-up participation was included as a weight in the analysis.

2.6. Sensitivity analysis

We conducted several sensitivity analyses to compare the change in effect size when adjusting the models for additional exposures or covariates, or when applying additional exclusion criteria. For the models examining the associations between prenatal blood Hg concentrations (first trimester and cord blood Hg concentrations) and child IQ, we separately adjusted for: 1) first trimester or cord blood lead

Table 1
Participant characteristics stratified by child sex, MIREC (2008–2011) and MIREC-CD Plus (2013–2015) studies.

	Male children		Female children	
	n[a]	Median (IQR) or n (%)	n[a]	Median (IQR) or n (%)
Hg concentrations				
First trimester blood Hg (μg/L)[b]	257	0.68 (0.36–1.28)	270	0.60 (0.28–1.12)
Cord blood Hg (μg/L)[b]	214	0.91 (<LOD – 1.64)	216	0.62 (<LOD – 1.15)
Child blood Hg (μg/L)[b]	181	0.18 (<LOD – 0.52)	174	0.20 (<LOD – 0.50)
WPPSI-III				
Full-scale IQ	257	105 (96–113)	270	110 (100–117)
Verbal IQ	255	108 (98–116)	269	111 (103–119)
Performance IQ	253	100 (91–112)	269	103 (94–115)
General Language Composite	254	105 (98–117)	270	108 (100–120)
Child characteristics				
Age (months)	257	40 (37–44)	270	39 (37–43)
Breastfeeding status				
Never	18	7%	24	9%
Breastfeeding <6 months	132	51%	113	42%
Breastfeeding ≥6 months	103	40%	126	47%
Missing	4	2%	7	3%
HOME Total Score	251	47 (44–50)	261	49 (46–51)
Birthing parent characteristics				
Age at delivery (years)	257	32 (29–36)	270	32 (30–36)
Parity				
0	112	44%	122	45%
1+	145	56%	148	55%
Level of education				
High school diploma or less	17	7%	10	4%
Completed/Some college/trade school	79	31%	79	29%
University degree	160	62%	180	67%
Missing	1	<1%	1	<1%
Smoking status during early pregnancy				
Never	170	66%	180	67%
Current/Quit During Pregnancy	24	9%	19	7%
Former	63	25%	71	26%
Alcohol use during early pregnancy				
Yes	117	46%	112	41%
No	140	54%	157	58%
Missing	0	0%	1	<1%
Place of birth				
Canada	216	84%	227	84%
Other	41	16%	43	16%
Monthly consumption of fish in early pregnancy				
Low (0–2 times/month)	101	39%	101	37%
Moderate (3–7 times/month)	88	34%	93	34%
High (≥8 times/month)	68	26%	76	28%
Pre-pregnancy BMI (kg/m^2)	234	24 (22–28)	250	24 (21–27)
CES-D depression score	249	6 (3–9)	259	4 (2–7)
Additional analytes				
First Trimester blood lead (μg/dL)	256	0.62 (0.44–0.87)	270	0.62 (0.46–0.83)
First trimester blood PBDEs[c] (μg/L)	255	0.08 (0.05–0.16)	264	0.08 (0.04–0.13)
First trimester blood PCBs[d] (μg/L)	257	0.10 (0.07–0.15)	267	0.10 (0.06–0.16)
First trimester plasma lipids (g/L)	257	5.9 (5.2–6.8)	267	6.0 (5.4–6.9)
Cord blood lead (μg/dL)	214	0.83 (0.58–1.04)	216	0.79 (0.60–1.06)
Child blood lead (μg/L)	181	0.68 (0.51–1.00)	174	0.67 (0.47–0.99)
Child blood selenium (μg/L)	181	150 (142–158)	174	150 (142–158)

WPPSI – Weschler Preschool and Primary Scale of Intelligence; HOME – Home Observation for Measurement of the Environment (HOME) inventory score; BMI – Body Mass Index; CES-D – Center for Epidemiological Studies Depression Scale.
[a] Sample sizes may differ for continuous variables due to missing data.
[b] For male children, 8%, 25%, and 37% of the values were < LOD for the first trimester, cord, and child blood Hg concentrations respectively. For female children, 12%, 34%, and 29% of the values were < LOD for the first trimester, cord, and child blood Hg concentrations, respectively.
[c] Sum of PBDE 47, 99, and 153.
[d] Sum of PCB 138, 153, and 180.

concentrations (separately for each time point); 2) sum of first trimester plasma PBDEs 47, 99, and 153; 3) sum of first trimester plasma PCBs 138, 153, and 180; 4) the presence of dental amalgams; and 5) having dental amalgams replaced in the past 12 months. We included plasma lipid concentration in the models containing PBDEs and PCBs. For the models examining the associations between childhood blood Hg concentrations and child IQ, we conducted separate sensitivity analyses adjusting for: 1) child blood lead concentrations; and 2) cord blood Hg concentrations. Lastly, in separate sensitivity analyses for all time-points, we ran models excluding children born preterm.

3. Results

3.1. Descriptive results

First trimester blood Hg and child blood Hg concentrations were similar when stratified by child sex, but cord blood Hg was higher in male children (Table 1). Higher first trimester and cord blood Hg concentrations were found with increasing fish consumption frequency during pregnancy in both male and female children (Supplementary Tables 3A and 3B). Compared with the lowest fish consumption strata (consuming fish 0–2 times/month), Hg concentrations were 2–3 times higher in the highest fish consumption strata (consuming fish ≥8 times/month). Sociodemographic and other covariate data, along with IQ scores, were similar across categories of fish consumption (Supplementary Tables 3A and 3B). Mercury concentrations (first trimester and cord blood) and fish consumption during early pregnancy in the analytical sample did not differ from that of the full MIREC cohort (Supplementary Table 4). On average, child IQ (FSIQ, VIQ, PIQ, and GLC) scores were slightly higher for female children compared to male children (Table 1) but were similar across categories of fish consumption during pregnancy (Supplemental Tables 3A and 3B). The IQ measures were positively intercorrelated among male children ($r = 0.39$ to 0.86), as well as among female children ($r = 0.22$ to 0.84) (Supplementary Table 5A and 5B). Hg concentrations and IQ scores stratified by relevant covariates are included in Supplementary Tables 6A, 6B, 7A, 7B, and 8.

3.2. Prospective associations between first trimester blood Hg concentrations and child IQ

First trimester blood Hg concentrations were not associated with FSIQ, PIQ, VIQ, and GLC in either male or female children (Table 2A and 2B). However, each doubling of first trimester blood Hg concentration was associated with a 2.3-point increase PIQ in both male (ß = 2.34, 95% CI = 0.52, 4.16) and female children (ß = 2.37, 95% CI = 0.32, 4.42) in the highest fish consumption frequency subgroup (≥8 times/month). Additionally, for PIQ for male children, we observed a monotonic response across prenatal fish consumption categories, such that the associations were more strongly positive with increasing fish consumption. First trimester blood Hg concentration were also positively associated with female children's FSIQ scores (ß = 0.77, 95% CI = 0.31, 1.23) in the moderate frequency fish consumption (3–7 times/month) subgroup. When stratified by sex and fish consumption, associations were less precise, which may reflect the smaller sample sizes in these stratified groups (Table 2A and 2B).

Table 2A
Prospective associations between first trimester blood Hg concentrations and child IQ for male children and stratified by prenatal fish, MIREC (2008–2011) and MIREC-CD Plus (2013–2015) studies.

	Full sample		Stratified by frequency of fish consumption					
			0-2 times/month		3-7 times/month		≥8 times/month	
	n	ß (95% CI)	n	ß (95% CI)	n	ß (95% CI)	n	ß (95% CI)
Full-scale IQ	257	−0.18 (−2.30, 1.94)	101	−0.44 (−3.38, 2.49)	88	−0.48 (−3.66, 2.70)	68	1.11 (−1.39, 3.61)
Verbal IQ	255	−0.50 (−2.73, 1.73)	100	−0.10 (−2.51, 2.32)	88	−1.01 (−4.21, 2.18)	67	0.12 (−2.01, 2.24)
Performance IQ	253	0.18 (−1.67, 2.02)	100	−0.64 (−3.75, 2.48)	87	0.11 (−2.55, 2.77)	66	2.34 (0.52, 4.16)
General Language Composite	254	0.05 (−2.13, 2.23)	101	0.43 (−2.72, 3.57)	86	0.15 (−1.93, 2.23)	67	0.25 (−2.10, 2.61)

Table 2B
Prospective associations between first trimester blood Hg concentrations and child IQ for female children and stratified by prenatal fish consumption, MIREC (2008–2011) and MIREC-CD Plus (2013–2015) studies.

	Full sample		Stratified by frequency of fish consumption					
			0-2 times/month		3-7 times/month		≥8 times/month	
	n	ß (95% CI)	n	ß (95% CI)	n	ß (95% CI)	n	ß (95% CI)
Full-scale IQ	270	0.44 (−0.84, 1.72)	101	0.29 (−1.32, 1.90)	93	0.77 (0.31, 1.23)	76	0.69 (−0.19, 1.58)
Verbal IQ	269	−0.09 (−1.18, 1.00)	100	0.51 (−1.55, 2.57)	93	−0.57 (−2.04, 0.91)	76	−0.68 (−2.81, 1.45)
Performance IQ	269	0.82 (−1.03, 2.66)	101	0.46 (−1.08, 2.00)	93	1.67 (−0.34, 3.68)	76	2.37 (0.32, 4.42)
General Language Composite	270	−0.74 (−2.08, 0.60)	101	−0.63 (−2.91, 1.65)	93	−0.62 (−2.49, 1.26)	76	−0.41 (−2.18, 1.36)

All models are adjusted for birthing parent age, birthing parent pre-pregnancy BMI, parity, smoking status in early pregnancy, alcohol consumption in early pregnancy, birthing parent country of birth, HOME total scores, birthing parent education, and site (random effect). Missing covariate data were imputed and models include IPW. The full sample model is additionally adjusted for the frequency of fish consumption in early pregnancy.
Regression coefficients represent a 1-point change in IQ score for each 2-fold increase in Hg concentration.

Associations between first trimester blood Hg concentrations and child IQ for male children (Supplementary Table 9A) and female children (Supplementary Table 9B) remained relatively unchanged in sensitivity analyses after adjusting for first trimester blood concentrations of lead, PBDEs, or PCBs, as well as for the presence or replacement of dental amalgams, or when excluding children born preterm.

3.3. Prospective associations between cord blood Hg concentrations and child IQ

Overall, cord blood Hg concentrations and FSIQ, PIQ, VIQ, and GLC, were not associated for male children (Table 3A). We observed an inverse association between cord blood Hg concentrations and PIQ among male children in the low frequency of fish consumption subgroup (ß = −3.27, 95% CI = −6.44, −0.09); however, the associations were positive among male children in the moderate (ß = 1.08, 95% CI = −0.10, 2.26) and high (ß = 3.07, 95% CI = 1.95, 4.19) fish consumption subgroup. Among participants with moderate frequency of fish consumption during pregnancy, cord blood Hg concentrations were positively associated with FSIQ (ß = 1.56, 95% CI = 0.88, 2.25), VIQ (ß = 1.27, 95% CI = −0.01, 2.56) and GLC (ß = 2.58, 95% CI = 0.98, 4.17) in male children (Table 3A) while the associations were not seen in those with low or high prenatal fish consumption.

Among the female children, each doubling of cord blood Hg concentrations was associated with higher scores on the FSIQ (ß = 1.29, 95% CI = 0.77, 1.81) and PIQ (ß = 2.01, 95% CI = 1.19, 2.83) (Table 3B). When stratified by fish consumption during pregnancy, these associations were most prominent among female children with a high prenatal fish consumption. However, the pattern of association across fish consumption categories was non-monotonic in female children. Cord blood Hg concentrations were inversely associated with VIQ (ß = −2.02, 95% CI = −3.04, −1.00) and GLC scores (ß = −2.37, 95% CI = −4.32, −0.43) among female children with moderate prenatal fish consumption (Table 3B).

Associations between cord blood Hg and child IQ among male children (Supplementary Table 10A) and female children (Supplementary Table 10B) remained relatively unchanged in sensitivity analyses after adjusting for cord blood lead concentrations, first trimester blood concentrations of PBDEs or PCBs, as well as for the presence of or replacement of dental amalgams, or when excluding children born preterm.

3.4. Concurrent associations between child blood Hg concentrations and child IQ

Child blood Hg concentrations were not associated with IQ among male children (Table 4). However, among female children, each doubling of blood Hg concentration was associated with approximately 1-point increase in FSIQ (ß = 0.97, 95% CI = 0.09, 1.84), VIQ (ß = 1.04, 95% CI = 0.41, 1.67), and GLC (ß = 1.09, 95% CI = 0.23, 1.82), but not PIQ score. We did not observe an interaction between child blood Hg and selenium concentrations in either male or female children (Supplementary Table 11).

Table 3A
Prospective associations between cord blood Hg concentrations and child IQ for male children and stratified by prenatal fish consumption, MIREC (2008–2011) and MIREC-CD Plus (2013–2015) studies.

	Full Sample		Stratified by frequency of fish consumption					
			0-2 times/month		3-7 times/month		≥8 times/month	
	n	ß (95% CI)	n	ß (95% CI)	n	ß (95% CI)	N	ß (95% CI)
Full-scale IQ	214	−0.58 (−2.10, 0.93)	83	−2.81 (−5.66, 0.04)	75	1.56 (0.88, 2.25)	56	0.74 (−2.49, 3.97)
Verbal IQ	212	−0.31 (−1.23, 0.60)	82	−1.53 (−3.43, 0.38)	75	1.27 (−0.01, 2.56)	55	−0.04 (−3.94, 3.86)
Performance IQ	210	−0.79 (−2.73, 1.15)	82	−3.27 (−6.44, −0.09)	74	1.08 (−0.10, 2.26)	54	3.07 (1.95, 4.19)
General Language Composite	211	−0.89 (−1.95, 0.16)	83	−2.05 (−4.23, 0.13)	73	2.58 (0.98, 4.17)	55	−0.58 (−4.38, 3.21)

Table 3B
Prospective associations between cord blood Hg concentrations and child IQ for female children and stratified by prenatal fish consumption, MIREC (2008–2011) and MIREC-CD Plus (2013–2015) studies.

	Full Sample		Stratified by frequency of fish consumption					
			0-2 times/month		3-7 times/month		≥8 times/month	
	n	ß (95% CI)	n	ß (95% CI)	n	ß (95% CI)	n	ß (95% CI)
Full-scale IQ	216	1.29 (0.77, 1.81)	87	0.66 (−0.64, 1.97)	71	−0.32 (−1.44, 0.80)	58	1.60 (0.05, 3.15)
Verbal IQ	215	−0.01 (−0.98, 0.96)	86	0.36 (−0.74, 1.46)	71	−2.02 (−3.04, −1.00)	58	−1.24 (−3.50, 1.02)
Performance IQ	215	2.01 (1.19, 2.83)	87	1.79 (−1.29, 4.88)	70	1.22 (−0.88, 3.34)	58	2.97 (1.82, 4.12)
General Language Composite	216	0.11 (−0.99, 1.22)	87	0.87 (−0.82, 2.55)	71	−2.37 (−4.31, −0.43)	58	0.15 (−3.18, 3.48)

All models are adjusted for birthing parent age, birthing parent pre-pregnancy BMI, parity, smoking status in early pregnancy, alcohol consumption in early pregnancy, birthing parent country of birth, HOME total scores, birthing parent education, and site (random effect). Missing covariate data were imputed and models include IPW. The full sample model is additionally adjusted for the frequency of fish consumption in early pregnancy.
Regression coefficients represent a 1-point change in IQ score for each 2-fold increase in Hg concentration.

Table 4
Concurrent associations between child blood Hg concentrations and IQ, MIREC (2008–2011) and MIREC-CD Plus (2013–2015) Studies.

	Male children		Female children	
	n	ß (95% CI)	n	ß (95% CI)
Full-scale IQ	181	−0.14 (−1.57, 1.29)	174	0.97 (0.09, 1.84)
Verbal IQ	181	−0.21 (−1.90, 1.47)	173	1.04 (0.41, 1.67)
Performance IQ	179	−0.03 (−1.25, 1.20)	173	0.69 (−0.73, 2.11)
General Language Composite	179	0.43 (−0.98, 1.84)	174	1.03 (0.23, 1.82)

Regression coefficients represent a 1-point change in IQ score for each 2-fold increase in Hg concentration.
Models are adjusted for parity, HOME total development scores, birthing parent education, breastfeeding status, birthing parent depression, child blood selenium concentrations, and site (random effect). Missing covariate data were imputed and models include IPW.

All sensitivity analyses had little impact on the results for male children (Supplementary Table 12A). Similarly, among female children (Supplementary Table 12B), adjusting for child blood lead concentrations had little impact on the results, while excluding children born preterm slightly attenuated the associations with FSIQ, VIQ, and GLC scores towards the null. Adjusting for cord blood Hg concentrations attenuated the association between child blood Hg and FSIQ towards the null, but slightly strengthened the positive associations with VIQ and GLC.

4. Discussion

We examined sex-specific associations between prenatal, and child blood Hg concentrations and IQ in Canadian children. We also examined the potential for effect modification by fish consumption during pregnancy in analyses of prenatal blood Hg concentrations and child IQ as well as potential interactions between child blood Hg and selenium concentrations.

4.1. Associations between prenatal Hg concentrations and child IQ

In male children, first trimester blood Hg concentrations and cord blood Hg concentrations were not associated with IQ but we found a monotonic positive association between both first trimester and cord blood Hg concentrations and PIQ with increasing frequency of prenatal fish consumption. At the lowest category of prenatal fish consumption, we found an inverse association between cord blood Hg concentrations and PIQ in male children, but in the highest prenatal fish consumption category the association was positive. For cord blood Hg concentrations, this represented a 6-point difference in PIQ score between the low and high frequency consumption groups.

In female children, cord blood Hg concentrations were positively associated with FSIQ and PIQ scores, but when stratified by prenatal fish consumption, positive associations were only observed for female children with the highest prenatal fish consumption. This association among the highest fish consumption group was also observed with first trimester blood Hg. For female children with moderate prenatal fish consumption, there were negative associations with VIQ and the GLC.

Across the models, associations between Hg exposures and PIQ and FSIQ seemed to follow a similar trend, while associations between Hg exposures and VIQ and GLC seemed to also follow a similar trend. Although all IQ measures were correlated with each other, the correlations between PIQ and FSIQ (male children = 0.86 and for female children = 0.80) and between VIQ and GLC (male children = 0.87 and for female children = 0.84) were the strongest. These correlations between FSIQ and the subscales (PIQ, VIQ, and GLC) likely explain some of the trends in results for FSIQ/PIQ and VIQ/GLC. VIQ is a measure of acquired knowledge, verbal reasoning, verbal comprehension, and attention to verbal stimuli, and the GLC is a measure of how quickly new receptive and expressive vocabulary skills are acquired. Whereas PIQ is a measure of fluid reasoning, spatial processing, attention to detail, and visual-motor integration, and FSIQ is a measure of global cognitive functioning.

Our finding that prenatal Hg concentrations were associated with PIQ, but not other IQ measures, is consistent with previous studies examining prenatal exposures to other contaminants, including cadmium (Jeong et al., 2015) and lead (Desrochers-Couture et al., 2018). Additionally, a study of British children showed that prenatal blood Hg concentrations were associated with PIQ and FSIQ in models that included children with prenatal fish consumption, while prenatal blood Hg concentrations were not consistently associated with VIQ (Golding et al., 2017).

The differences in associations between prenatal Hg concentrations and child IQ when stratified by child sex were not unexpected as previous analyses from the MIREC cohort (Azar et al., 2021; Desrochers-Couture et al., 2018; Green et al., 2019; Nkinsa et al., 2020) and other cohorts (Llop et al., 2017; Sagiv et al., 2012; Wang et al., 2019) have shown sex-specific associations between prenatal exposures to a variety of environmental contaminants and child IQ. For example, in a study of 8 year-olds, Sagiv et al. (2012) primarily found adverse associations between Hg and neurobehavioral outcomes in male children while protective associations were observed in female children. However, differences in the associations between blood Hg concentrations and child cognitive development by child sex have not been seen consistently in other studies (Orenstein et al., 2014; Rothenberg et al., 2021; Wang et al., 2019), including studies assessing developmental outcomes in infants/toddlers as measured using the Bayley Scales of Infant and Toddler Development (Rothenberg et al., 2021; Wang et al., 2019).

Other studies with similar or even higher prenatal blood Hg concentrations than in the MIREC cohort have also found no associations

(Davidson et al., 1998), inconsistent associations (Barbone et al., 2019; Golding et al., 2017), or positive associations (Golding et al., 2016), between prenatal blood Hg concentrations and child IQ or other cognitive outcomes. The positive associations seen in this study could be due to the nutritional benefits of fish consumption (Myers et al., 2009). Fish consumption is known to have many health benefits (Chen et al., 2022) and includes important nutrients such as omega-3 fatty acids and selenium (Health Canada, 2007). However, total fish consumption is a crude indicator of the intake of nutrients and contaminants from fish, as concentrations of nutrients and contaminants in fish tissue can vary widely based on the fish species consumed, preparation/cooking method, and the part of the fish species consumed (Du et al., 2012; Marques et al., 2019; Seves et al., 2016; Sobral et al., 2018).

Our results support the hypothesis that fish consumption during pregnancy may be an effect modifier of the associations between prenatal blood Hg concentrations and child IQ, in agreement with other studies (Jacobson et al., 2008, 2015; Golding et al., 2017; Jeong et al., 2017; Llop et al., 2017). However, the direction of modification is not always consistent. For example, Golding et al. (2017) found positive associations between prenatal blood Hg concentrations and child IQ but these positive associations were only observed for children whose mothers consumed fish (as opposed to those whose mothers did not consume fish). While Jeong et al. (2017) found negative associations between prenatal blood Hg concentrations and child IQ (VIQ and FSIQ) and when stratified by fish intake, these negative associations were only observed at the highest category of fish intake. However, prenatal fish consumption was much higher on average in the Jeong et al. (2017) study from South Korea, than in the British cohort (Golding et al., 2017) and the MIREC cohort study.

Exposure to other contaminants from fish and seafood consumption, such as PCBs, may also confound the relationship between prenatal blood Hg concentrations and child IQ (Avella-Garcia and Julvez, 2014; Counter and Buchanan, 2004; Tratnik et al., 2017). We conducted sensitivity analyses by additionally adjusting for other environmental contaminants including lead, PBDEs, and PCBs. Ultimately, this did not impact the direction, magnitude, or precision of the associations in the main models. This is consistent with previous analyses examining the potential confounding role of PCBs (Jacobson et al., 2015) and lead (Jeong et al., 2017) for the association between prenatal blood Hg concentrations and child IQ.

Additionally, the findings of null or positive associations in this study may be explained by the low levels of Hg observed in the MIREC cohort. Median first trimester blood Hg concentrations (0.68 and 0.60 μg/L for those pregnant with male and female children, respectively) were similar to blood Hg concentrations reported for women of childbearing age in the Canadian general population sampled around the same time as the MIREC cohort (Dix-Cooper and Kosatsky, 2018; Health Canada, 2011). These levels are lower than those measured in other studies of prenatal Hg exposure and child neurodevelopment where prenatal blood Hg (Golding et al., 2017; Jeong et al., 2017; Lederman et al., 2008) and/or cord blood Hg concentrations were measured (Grandjean et al., 1997; Jacobson et al., 2015; Lederman et al., 2008; Llop et al., 2012, 2017; Tratnik et al., 2017).

4.2. Associations between child blood mercury concentrations and IQ

Child blood Hg concentrations in this study were generally low and similar to blood Hg concentrations reported for those aged 3–5 years of age in the Canadian general population (Health Canada, 2011). In male children, blood Hg concentrations were not associated with IQ scores. In female children, each doubling of blood Hg concentration was associated with approximately 1-point increase in FSIQ, VIQ, and GLC scores, but not PIQ score. This is consistent with our findings for prenatal Hg exposure, where we found that cord blood Hg was positively associated with FSIQ and PIQ for female children. Studies of childhood Hg exposure have found inconsistent (Myers et al., 2009), negative (dos Santos-Lima et al., 2020), or null associations (Davidson et al., 2010; Pan et al., 2018) with child IQ. Similar to prenatal Hg exposures, it is possible that the positive associations that we observed between child blood Hg concentrations and IQ may be explained by the benefits of fish consumption. However, we did not collect data on childhood fish consumption in this cohort and are unable to examine this possibility. Future studies should explore the role of child fish consumption as a modifier of the concurrent association between blood Hg concentrations and IQ in childhood. However, childhood blood selenium concentrations were included in the model as fish can be an important dietary source of selenium, and prenatal selenium levels have previously been associated with neurodevelopmental outcomes, including child IQ (Amorós et al., 2018; Castriotta et al., 2020; Kippler et al., 2016; Liu et al., 2021; Močenić et al., 2019; Polanska et al., 2016; Tratnik et al., 2017; Yang et al., 2013). However, consistent with the study by Jacobson et al. (2015), we found no interaction between child blood Hg and selenium concentrations (Supplementary Table 11) in our models.

4.3. Strengths and limitations

Strengths of the MIREC study include the longitudinal and geographically diverse study design, the availability of Hg biomarker data at multiple time points across the prenatal and childhood periods, the use of a well recognized, reliable, and validated instrument (WPPSI-III) to assess cognitive function in childhood, and the availability of data for many potential confounders, and co-exposures. An additional strength of our analysis is the use of IPW to account for potential differential loss to follow-up.

This study has some limitations. First, while the low levels of Hg exposure are a strength in terms of generalizing our findings to the Canadian population, our findings may not be generalizable to populations with higher blood Hg concentrations or more frequent fish consumption. These low levels of Hg exposure also meant that when the analyses were stratified by fish consumption during pregnancy, 51% of the cord blood mercury concentrations were below the limit of detection among participants in the strata with the lowest fish consumption. This is a limitation for the regression model in this group; however, the majority of first trimester blood Hg concentrations were above the detection limit for all three fish consumption strata, and the majority of cord blood Hg concentrations were above the detection limit for the moderate and high prenatal fish consumption strata. The higher detection frequency of mercury in the first trimester blood samples is likely due to lower LOD for first trimester samples (0.12 μg/L) vs. cord blood samples (0.40 μg/L). Both first trimester and cord blood mercury concentrations followed the same pattern across the fish consumption strata and, as expected, blood mercury concentrations increased with increased fish consumption frequency. Second, the sample size was relatively small for the models that were stratified by both child sex and fish consumption in early pregnancy. Replication with a larger sample size may be desirable. Third, data were not available for prenatal blood selenium concentrations and other nutrients known to be present in some fish (such as omega-3 fatty acids), or for childhood fish consumption, which precluded examining effect modification/interaction for these factors at these time points. Additionally, the prenatal fish consumption variable could be impacted by recall bias and may not reflect consumption patterns throughout pregnancy. Fourth, IQ was measured at a relatively young age in this study, and data from other caregivers were not available. Fifth, we analyzed blood total Hg and the speciation of Hg was not determined. However, in populations without high exposures to industrial or environmental sources of Hg, fish consumption is considered the major route of exposure to methylmercury (Hong et al., 2012; Health Canada, 2007; Schober et al., 2003) and total blood Hg concentrations should mainly reflect methylmercury exposure (Hong et al., 2012). Therefore, the use of total Hg concentrations in this study was considered suitable for the models stratified by fish consumption during pregnancy; however, there is some uncertainty regarding the main sources of Hg exposure among participants reporting no or low fish consumption during pregnancy. Dental amalgams can be a source of inorganic Hg exposure and we conducted sensitivity analyses adjusting for the total number of dental amalgams and whether any had been replaced in the past year. The results of these additional sensitivity analyses were similar to those of the base models. Future studies could examine the speciation of Hg in blood and implications of Hg speciation for the associations between prenatal and childhood blood Hg concentrations and child IQ.

Finally, the potential for confounding is a concern of any observational epidemiological study, including the current one. To address this concern, we adjusted our analyses for a number of potential confounders based on the existing literature. We also showed that the means or proportions of covariates included in the multivariable analyses were similar across strata of fish consumption, suggesting that results from stratified analyses were not driven by differences in covariate distributions between strata. Additionally, we conducted sensitivity analyses to investigate potential confounding due to: 1) co-exposure to other environmental contaminants shown to be associated with cognitive functioning, 2) the presence of dental amalgams, and 3) prematurity. One possible unmeasured confounder is parental IQ which is plausibly associated with child IQ and possibly with fish consumption (and thereby Hg exposure). Potential confounding due to this variable is likely minimal because we adjusted our models for correlates of parental IQ including education, HOME score, smoking/alcohol use in pregnancy, and breastfeeding status. Finally, the MIREC study consists mainly of participants that are white and of higher socioeconomic status than the general Canadian population; although this sociodemographic profile limits the generalizability of our findings, it also minimizes the potential for unmeasured confounding due to socioeconomic status. Nonetheless, these factors do not eliminate the potential for unmeasured confounding and we encourage replication of these findings to evaluate the stability of these associations in different settings (i.e., across populations, geography, exposure levels, and age).

5. Conclusions

In this sample of Canadian children with low levels of Hg exposure, we observed primarily null associations between both prenatal and concurrent blood Hg concentrations and IQ in early childhood. Observed associations were inconsistent across time. We found that cord blood Hg concentrations were adversely associated with child PIQ in male children with low/no prenatal fish consumption. Several positive associations were observed including between prenatal Hg concentrations and child PIQ in male and female children with the highest prenatal fish consumption. In female children, cord blood Hg concentrations were also positively associated with FSIQ in both the full sample and in those with the highest prenatal consumption of fish. The beneficial effects of fish consumption during pregnancy is a possible explanation for these findings. Concurrent blood Hg concentrations were positively associated with child IQ in female children. Although fish consumption is a source of exposure for Hg, it is also a source of important nutrients. Overall, these results reinforce the benefits of fish consumption (from low Hg containing fish species) during pregnancy, despite exposure to low levels of Hg.

Credit author statement

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Human ethics approvals

The MIREC and MIREC CD-Plus studies received ethics approval from Health Canada's Research Ethics Board and the ethics committes of the hospitals and research centers that were involved. All participants provided written informed consent.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.116463.

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