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Prenatal exposure to polybrominated diphenyl ethers (PBDEs) and cognitive ability in early childhood

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ABSTRACT

Background: Prenatal exposure to polybrominated diphenyl ethers (PBDEs) has been associated with adverse neurodevelopmental outcomes in children, but evidence remains mixed regarding sex differences in this association.
Objective: To examine the prospective association between prenatal PBDE exposure and cognitive ability in young children, as well as potential sex differences.
Methods: The study was conducted in a multi-site Canadian pregnancy cohort recruited in 2008–11. PBDEs were measured in maternal plasma samples collected early in pregnancy. Cognitive ability was assessed using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) in children at age 3 years (mean = 3.4). Multiple linear regression was used to analyze the association between maternal PBDE plasma concentrations (lipid-standardized and log10-transformed) and Verbal, Performance, and Full Scale IQ scores on the whole sample and stratified by sex, adjusting for confounders.
Results: The sample was composed of 592 children (291 boys and 301 girls). A tenfold increase in maternal blood PBDE concentration (sum of BDE-47, −99, −100, and −153) was associated with lower Full Scale scores in boys (−3.4 points; 95% CI: −7.0, 0.1), after adjusting for confounders. BDE-47 was the congener with the highest concentrations in maternal blood and a tenfold increase in exposure was associated with significantly lower Full Scale IQ scores in boys (−4.4 points; 95% CI: −7.9, −0.9), after adjusting for confounders. Verbal and Performance IQ scores were similarly associated with PBDE exposure. Maternal blood PBDE concentrations were not associated with IQ scores in girls.
Conclusions: Prenatal exposure to background levels of PBDEs, especially BDE-47, was associated with lower IQ scores in boys, but not in girls. Our results support that exposure to PBDEs during early development may be sex-dependent and detrimental to a child's neurodevelopmental trajectory.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are chemicals used as flame retardants in many household items, including textiles, furniture, appliances, and electronics. PBDEs, which are semi-volatile compounds added during the polymer manufacturing process, are not chemically-bound to substrates and can leach into the environment (Costa and Giordano, 2007; Linares et al., 2015). There are 209 different congeners

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of PBDEs based on the number of bromine atoms in the molecule (Darnerud et al., 2001; Klincic et al., 2020). Importantly, PBDEs are lipophilic persistent organic pollutants (POPs) that bioaccumulate and biomagnify in the food chain (Darnerud et al., 2001; Linares et al., 2015). PBDEs are highly resistant to degradation, with biological half-lives ranging from 2 to 12 years in humans (Geyer et al., 2004; Trudel et al., 2011).

Levels of PBDEs have decreased over the last two decades due to reductions in their use, driven by regulations limiting their utilization (Guo et al., 2016; Health Canada, 2019b; Ma et al., 2013). Still, populations continue to be exposed to PBDEs since these chemicals are persistent and PBDE-containing products are still in use. Blood concentrations of PBDEs are higher in North American than European populations by approximately one order of magnitude (Frederiksen et al., 2009a). Primary exposure routes for PBDEs include ingestion, inhalation, and dermal absorption of house dust (Frederiksen et al., 2009a; Klincic et al., 2020). Exposure is also linked to diet, with high lipid-content foods (e.g., fish, meat, dairy products) often containing higher concentrations of PBDEs than low lipid-content foods (Frederiksen et al., 2009a; Klincic et al., 2020). Furthermore, exposure can occur *in utero* because PBDEs readily cross the placenta (Doucet et al., 2009; Mazdai et al., 2003; Vizcaino et al., 2014). This finding is particularly concerning given that the prenatal stage is a vulnerable period in human life and that prenatal development can set the stage for future development (Grandjean and Landrigan, 2014; Vizcaino et al., 2014).

Findings from animal studies indicate that prenatal exposure to PBDEs adversely impacts neurodevelopment. Indeed, prenatal exposure to the deca-BDE congener BDE-209 has been related to disruptions in the response of cholinergic receptors, which are closely linked to behavioural and cognitive functioning, as well as decreased habituation, and impaired learning and memory (Buratovic et al., 2014; Viberg et al., 2007). Similar results were found for exposure to BDE-153 (Viberg et al., 2003), BDE-99 (Branchi et al., 2002), and BDE-47 (Eriksson et al., 2001; Gee and Moser, 2008). Importantly, these rodent studies identified a sensitive period characterized by a brain growth spurt during which exposure can be particularly detrimental to neurodevelopment. In rats, this period corresponds to the first four weeks of life, with a peak occurring at postnatal day 10 (Viberg et al., 2007). In humans, that period is equivalent to that extending from the beginning of the third trimester of pregnancy to the first two years of life (Viberg et al., 2007).

Epidemiological human studies conducted with prospective birth cohorts around the world have also found that prenatal exposure to PBDEs is associated with adverse effects on various developmental domains. In infancy and toddlerhood, prenatal exposure to PBDEs has been linked to slower psychomotor and cognitive development (Herbstman et al., 2010) and to lower levels of social and language development (Ding et al., 2015). At preschool- and school-age, prenatal exposure to PBDEs has been related to poorer fine motor skills (Eskenazi et al., 2013; Roze et al., 2009), consistent with previously discussed results suggesting psychomotor alterations in studies of rodents and infants. At a behavioural and socioemotional level, prenatal PBDE exposure has been related to greater hyperactivity (Chen et al., 2014) and externalizing problems (Roze et al., 2009; Zhang et al., 2017), suggesting potential alterations in self-regulation and neurodevelopment. Lastly, at a cognitive level, prenatal PBDE exposure has been linked to lower intelligence quotients (IQ) (Chen et al., 2014; Eskenazi et al., 2013; Herbstman et al., 2010; Zhang et al., 2017), reading skills (Zhang et al., 2017), executive function (Vuong et al., 2016), and attentional abilities (Cowell et al., 2015; Eskenazi et al., 2013; Roze et al., 2009), which are also consistent with disruptions of neurodevelopment.

Some evidence suggests potential sex differences in the association between PBDE exposure and various developmental domains. For instance, Vuong and colleagues (2016) examined executive function in school-age children and reported a significant interaction between maternal PBDE concentrations and sex. Further sex-stratified analyses revealed that adverse associations were present in boys, but not in girls (Vuong et al., 2016). Some studies of prenatal PBDE exposure and child development either did not control for sex (Braun et al., 2017) or included sex as a covariate without examining its interaction with exposure or conducting a sex-stratified analysis (Herbstman et al., 2010; Zhang et al., 2017). Other studies included an interaction term and/or conducted a sex-stratified analysis, but did not find an effect modification by sex for outcomes like IQ, externalizing problems, attention, and hyperactivity (Chen et al., 2014; Cowell et al., 2015; Eskenazi et al., 2013; Sagiv et al., 2015). These inconsistent findings suggest that child sex should be further investigated in relation to potential PBDE-related neurodevelopmental outcomes.

The effect of prenatal exposure to PBDEs on neurodevelopment in preschool and school-age children has primarily been studied in the United States (Gibson et al., 2018), where exposure levels are higher than in Canada (Gravel et al., 2018). In addition, the birth cohorts used in these American studies conducted their sample recruitment between 1999 and 2006 (Eskenazi et al., 2013; Herbstman et al., 2010; Vuong et al., 2016). This is particularly relevant given that two of the main commercial PBDE mixtures (i.e, PentaBDE and OctaBDE) were eliminated from world-wide manufacturing in 2006 (Health Canada, 2019a). As such, the first goal of the present study is to examine whether prenatal exposure to PBDEs is associated with cognitive development in a sample of Canadian children whose mothers had lower exposure and were recruited from 2008 to 2011. A second goal of the study is to examine the association between prenatal PBDE exposure and child cognitive development separately in boys and girls in order to observe any potential sex differences.

2. Methods

2.1. Study participants

Participants were 3-year-old children (range = 3.0–4.1, mean = 3.4, standard deviation = 0.3) born to mothers who were enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort. MIREC is a prospective pregnancy cohort of 2000 women recruited during the first trimester of pregnancy from obstetric and prenatal clinics across 10 Canadian cities. Recruitment took place between 2008 and 2011. Eligibility criteria at maternal enrolment included (a) the ability to consent; (b) speaking English or French; (c) being aged 18 years or older; (d) being between 6 and 13 weeks pregnant; and (e) intending to receive prenatal care and deliver at the local study site (please see Arbuckle et al., 2013 for full information regarding recruitment, eligibility, and study follow-ups). Exclusion criteria included congenital malformations or abnormalities of the fetus as well as maternal medical complications, history of major chronic illness, history of illicit drug use, and threatened abortion.

Participants from the six largest study sites were invited to participate in a follow-up study to assess child neurodevelopment around age 3 years. These sites, which are located across the country, were prioritized due to practical reasons in order to maximize the number of participants that could be recruited. At the time of initial recruitment, there were 1537 participants (i.e., singleton, live births) across these six study sites. Of those, 610 children (39.7%) participated in the neurodevelopmental assessment follow-up visit. The cognitive testing took place during a home visit.

Informed consent was obtained in writing for both the prenatal biomonitoring and neurodevelopmental assessment phases of the study. The studies were approved by the Research Ethics Boards of Health Canada, Centre de Recherche du CHU de Québec-Université Laval, Centre de recherche du CHU Sainte-Justine, and each local study site. The study coordinating centre is at the Centre de recherche du CHU Sainte-Justine in Montreal.

2.2. Maternal blood concentration of PBDEs

PBDEs were measured in maternal blood samples collected during the first trimester of pregnancy. Laboratory analyses were conducted by the Centre de Toxicologie du Québec of the Institut National de Santé Publique du Québec (please see Fisher et al., 2016 for full report of PBDE exposure in the MIREC cohort). Nine PBDE congeners were measured, namely BDE-15, −17, −25, −28, −33, −47, −99, −100, and −153 using an Agilent 6890 Network or 7890A gas chromatograph (GC) coupled to an Agilent 5973 Network or 5975C mass spectrometer (Agilent Technologies; Mississauga, Ontario, Canada). The limits of detection (LOD) were 0.03 μg/L for BDE-15, −17, −25, −28, −33, −47; and 0.02 μg/L for BDE-99, −100, and −153. Blood PBDE concentrations were standardized for total lipid concentrations. Total cholesterol (TC), free cholesterol (FC), triglycerides (TG) and phospholipids (PL) levels were measured (in g/L) using enzymatic methods and colorimetry at the laboratory of Centre Hospitalier de l'Université Laval. Total lipid concentration was calculated using the following formula: 1.677 * (TC − FC) + FC + TG + PL (Patterson et al., 1991).

2.3. Child cognitive ability

Child cognitive ability was measured during the home visit, through the administration of the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III), a valid and reliable instrument providing scores of verbal, nonverbal, and global intellectual function in young children (Wechsler, 2002). Children completed five subtests, namely Receptive Vocabulary, Information, Block Design, Object Assembly, and Picture Naming. The scores obtained from these five subtests result in three composite scores with a mean of 100 and a standard deviation of 15, namely the Verbal IQ (VIQ), the Performance IQ (PIQ), and the Full Scale IQ (FSIQ).

2.4. Covariates

We carefully considered the selection of covariates for inclusion in the models to limit confusion bias. Potential confounding variables were identified based on previous studies on developmental neurotoxicity of PBDEs (reviewed in Gibson et al., 2018). The variables considered as potential confounders were: maternal age during the first trimester of pregnancy, pre-pregnancy body mass index (BMI), birth weight, gestational age, race/ethnicity, maternal birth country, maternal education, household annual income, marital status, parity, self-reported smoking during pregnancy assessed in the third trimester, self-reported alcohol consumption during pregnancy, child sex, and study site. Then, we only retained variables that could be causally-related to prenatal PBDE exposure and IQ. For instance, we ensured that the timing of variables was logical for a causal association: variables used as potential confounders had all been assessed during pregnancy or at birth. Furthermore, we did not include variables that could be on the causal pathway (i.e., gestational age). In order to build a more parsimonious model and maintain statistical power for sex-stratified analyses, we conducted ANOVAs between each of these variables and a) the sum of maternal blood PBDE concentration (BDE-47, −99, −100, and −153) and b) FSIQ. The variables that were related to both maternal PBDEs and FSIQ ($p < 0.20$) were included as covariates: maternal education, maternal birth country, maternal smoking during pregnancy, study site, and child sex.

2.5. Statistical analyses

We transformed lipid-adjusted PBDE concentrations using log10 to normalize the distribution and reduce the influence of outliers. We conducted our analyses using the four congeners with a detection rate ≥ 20%, namely BDE-47 (detection frequency 66%), BDE-99 (19%), BDE–100 (21%), and BDE-153 (42%). The other PBDE congeners, namely BDE-15, −17, −23, -25, and −33, were not included in analyses as their respective detection rates were below 2%. Values below the LOD for the four analyzed congeners were imputed with regression on order statistics (Helsel, 2005). We considered three cognitive outcome variables (i.e, FSIQ, VIQ, and PIQ scores on the WPPSI-III), and conducted multiple linear regression models to assess the association with maternal blood PBDE concentrations. Separate regression models were built for log10-transformed lipid-standardized maternal blood concentrations of a) sum of those four congeners (Σ_4PBDEs), b) BDE-47, and c) BDE-153 (only these two congeners were analyzed individually given their relatively high detection rate). We first examined the raw, unadjusted model followed by the adjusted models. Each adjusted model included the same set of covariates, as outlined in the previous section (i.e., maternal education, maternal birth country, smoking during pregnancy, study site, and child sex). An interaction term between maternal PBDEs and child sex was included to test effect modification by sex. Lastly, we conducted sex-stratified multiple regression analyses, adjusting for the same set of covariates, to examine potential differences in association between boys and girls (as decided *a priori* for the second study objective). Statistical analyses were conducted using SPSS version 25. A threshold of $p < 0.05$ was used for statistical significance.

3. Results

3.1. Sample characteristics

While 610 children participated in the neurodevelopmental follow-up, the following analyses are based on the 592 children with measures of maternal blood PBDEs and to whom all WPPSI-III subtests were administered. Table 1 presents the characteristics of the study population, including median concentrations of PBDEs in maternal blood. The sample was approximately evenly distributed in terms of child sex (50.8% female) and comprised a majority of children whose mothers were born in Canada (82.4%), university-educated (66.6%), aged under 35 years during pregnancy (65.7%), and non-smokers (87.7%). Household annual income was $80,000 CAD or more for 58% of the sample. In terms of parity, 43.9% of mothers were nulliparous and 41.6% were primiparous. Most mothers were in the normal BMI range before pregnancy (56.1%). Boys and girls were comparable in terms of maternal and family characteristics. We observed higher median blood concentrations of Σ_4PBDEs in women born in Canada, those who quit smoking during pregnancy, and in those bearing boys.

The characteristics of the mother–child pairs included in the present study were comparable to those of the initial MIREC cohort, both across all ten sites and within the six study sites involved in the neurodevelopmental follow-up study (Ntantu Nkinsa et al., 2020; Table S1). The median blood concentrations of Σ_4PBDEs was 12.9 ng/g lipid among women who participated in this follow-up study ($n = 592$; Table 2), while it was 13.1 ng/g lipid for those who did not ($n = 1335$). Thus, prenatal exposure to the Σ_4PBDEs was not significantly different between children who completed this follow-up study and those who did not ($t(1925) = 0.50$, $p = 0.614$). The mean FSIQ score for the overall sample of children was 106.9. Scores were lower for boys than for girls (104.1 and 109.9, respectively; Table 3). Similarly, VIQ and PIQ mean scores were also slightly lower among boys (106.5 and 112.1 for VIQ; 101.2 and 104.9 for PIQ, respectively for boys and girls). The mean IQ score was in the "average" range of cognitive ability (which spans scores of 85 to 115) for the FSIQ, VIQ, and PIQ, and all scores were normally distributed.

3.2. Association between maternal blood concentrations of PBDEs and IQ scores

We first examined the unadjusted association between IQ and maternal concentrations of PBDE (Table S2). There was a statistically significant decrease of 2.2 points (95% CI: −4.4, −0.1) on FSIQ per tenfold increase in maternal Σ_4PBDEs (see Table S2). The association

Table 1
Characteristics of study participants and median maternal blood PBDE concentrations for the sum of BDE-47, −99, −100, and −153 (Σ_4PBDE in ng/g lipid).

	Overall sample		Boys		Girls	
	n	Median Σ_4PBDEs	n	Median Σ_4PBDEs	n	Median Σ_4PBDEs
Overall	592	12.9	291	13.6	301	12.3
Study site[1]						
Site A	55	11.3	30	12.4	25	7.2
Site B	66	9.5	32	8.1	34	10.8
Site C	81	14.7	43	16.4	38	11.5
Site D	130	14.8	53	16.8	77	14.1
Site E	150	13.4	76	13.5	74	13.3
Site F	110	13.0	57	14.7	53	11.5
Maternal education[2]						
High school or less	30	17.1	19	17.6	11	14.8
College or trade school	166	14.3	86	15.5	80	13.9
Undergraduate diploma	234	11.9	109	12.0	125	11.6
Graduate diploma	160	12.2	76	13.0	84	10.7
Missing	2	9.8	1	9.9	1	9.8
Maternal age[2]						
18–29 years	146	14.0	78	16.9	68	11.9
30–34 years	243	13.6	114	12.5	129	13.9
35–39 years	170	12.0	82	12.4	88	11.8
40 + years	33	9.0	17	9.0	16	9.0
Household annual income[2] (Canadian dollars)						
<50 K	90	13.6	55	13.6	35	10.8
50–80 K	137	12.8	64	15.3	73	11.0
80–100 K	117	12.9	58	12.6	59	14.1
>100 K	229	12.6	107	13.2	122	12.4
Missing	19	12.5	7	16.8	12	10.8
Maternal birth country[2]						
Canada	488	13.9	239	14.9	249	13.0
Other	104	9.4	52	10.8	52	8.6
Parity[2]						
Nulliparous	260	13.5	126	14.8	134	12.2
1	246	12.5	118	12.5	128	12.0
2 or more	86	13.0	47	12.8	39	13.2
Smoking during pregnancy[3]						
Non smoker	519	12.3	255	12.5	264	12.2
Quit during pregnancy	34	24.9	20	26.7	14	24.5
Current smoker	15	12.6	5	18.8	10	11.5
Missing	24	12.5	11	15.4	13	11.1
Maternal pre-pregnancy BMI[2]						
Underweight (<18.5)	14	13.1	8	9.1	6	39.3
Normal (18.51–25)	332	12.9	150	13.5	182	12.7
Overweight (25.1–30)	115	12.5	59	16.0	56	11.1
Obese (≥30)	90	14.6	50	13.9	40	15.3
Missing	41	10.2	24	12.6	17	6.8

[1] As participants from each site were not representative samples from each city, the cities have not been identified.
[2] Variables assessed in the first trimester of pregnancy.
[3] Variable assessed in the third trimester of pregnancy.

was slightly larger for BDE-47, whereby a tenfold increase in maternal BDE-47 concentrations was associated with significantly lower VIQ (−2.7 points; 95% CI: −4.8, −0.5) and FSIQ (−2.8 points; 95% CI: −5.0, −0.6) scores. Maternal concentrations of Σ_4PBDEs and BDE-47 were associated with lower PIQ scores (−2.1; 95% CI: −4.5, 0.2 and −2.3; 95% CI: −4.7, 0.2, respectively), although the associations did not reach significance. The associations of BDE-153 with VIQ, PIQ, and FSIQ were all negative, but were not statistically significant.

After adjusting for covariates, the association estimates for maternal PBDE concentrations and IQ scores were smaller and no longer significant, except for the association between Σ_4PBDEs and PIQ, whereby a

Table 2
Distribution of lipid-standardized maternal blood PBDE concentrations (ng/g lipid) for the overall sample and by child sex.

	BDE-47	BDE-99	BDE-100	BDE-153	Σ_4PBDEs
Study overall sample (n = 592)					
Detection frequency	66%	19%	21%	42%	n/a
5th percentile	0.9	0.1	0.1	0.1	1.8
25th percentile	3.3	0.3	0.3	0.7	7.1
50th percentile	7.0	0.8	0.8	2.1	12.9
75th percentile	12.2	2.3	2.4	5.9	23.0
95th percentile	39.5	8.8	12.4	40.0	103.2
Maximum	727.3	169.1	327.3	527.3	1750.9
Boys (n = 291)					
Detection frequency	70%	22%	24%	45%	n/a
5th percentile	1.3	0.1	0.1	0.2	2.8
25th percentile	3.7	0.4	0.3	0.8	8.0
50th percentile	7.3	1.0	0.9	2.4	13.6
75th percentile	14.0	2.6	3.0	6.6	25.7
95th percentile	38.2	10.9	13.8	40.5	116.6
Maximum	727.3	127.3	213.6	211.4	1279.6
Girls (n = 301)					
Detection frequency	65%	20%	20%	40%	n/a
5th percentile	0.8	0.2	0.1	0.1	1.3
25th percentile	3.0	0.3	0.2	0.6	6.5
50th percentile	6.7	0.7	0.7	2.0	12.3
75th percentile	11.1	2.0	2.1	5.5	21.4
95th percentile	43.9	7.7	11.6	39.7	96.0
Maximum	727.3	169.1	327.3	527.3	1750.9

Note. n/a: non applicable.

Table 3
Distribution of IQ scores from the WPPSI-III in the overall sample and by child sex.

	Overall	Boys	Girls
FSIQ			
n	589	289	300
Minimum	51	51	77
Maximum	143	139	143
Mean	106.9	104.1	109.6
Standard deviation	13.6	14.5	12.0
VIQ			
n	586	287	299
Minimum	58	58	77
Maximum	144	141	144
Mean	109.4	106.5	112.1
Standard deviation	13.2	14.0	11.9
PIQ			
n	584	285	299
Minimum	55	55	61
Maximum	144	141	144
Mean	103.1	101.2	104.9
Standard deviation	14.9	15.5	14.1

Table 4
Differences in IQ scores (95% CIs) for a tenfold increase in maternal blood PBDE concentrations, adjusting for covariates, along with p-values for the interactions between maternal blood PBDE concentrations and child sex.

	FSIQ	VIQ	PIQ
Σ_4PBDEs	−0.9 (−3.0, 1.3)	0.0 (−2.1, 2.2)	−1.5 (−3.8, 0.9)
p-value for Σ_4PBDEs × sex	0.112	0.116	0.323
BDE-47	−1.9 (−4.1, 0.3)	−1.0 (−3.1, 1.1)	−2.4 (−4.8, −0.1)
p-value for BDE-47 × sex	0.106	0.070	0.362
BDE-153	0.3 (−1.2, 1.8)	0.6 (−0.8, 2.0)	−0.1 (−1.7, 1.5)
p-value for BDE-153 × sex	0.373	0.376	0.684

Note. Models adjusted for maternal birth country, maternal smoking at the third trimester of pregnancy, maternal education, study site, and child sex.

tenfold increase in Σ_4PBDEs was associated with significantly lower PIQ scores (−2.4 points; 95% CI: −4.8, −0.1) (Table 4). Several interaction terms between sex and maternal PBDE concentrations were suggestive of a differential association between boys and girls, especially for Σ_4PBDEs and BDE-47 for which p-values hovered around 0.1.

3.3. Sex-stratified analysis

Once again, we first examined the unadjusted sex-stratified association between IQ and maternal PBDE concentrations (Table S3). There was a statistically significant decrease of 3.7 points (95% CI: –7.2, −0.3) on FSIQ per tenfold increase in Σ_4PBDEs for boys, whereas there was no association for girls. The associations for both cognitive domains approached significance for boys, with decreases of 3.3 VIQ points (95% CI: −6.6, 0.1) and 3.2 PIQ points (95% CI: −6.9, 0.5) per tenfold increase in Σ_4PBDEs; there were no statistically significant associations for girls. The association estimate was slightly larger for BDE-47 concentrations, with a statistically significant decrease of 4.4 VIQ points (95% CI: −7.7, −1.0) and 4.0 FSIQ points (95% CI: −7.5, −0.6) per tenfold increase in BDE-47 for boys; there were no statistically significant associations for girls. Meanwhile, the association estimates between BDE-153 and IQ scores were small and not statistically significant for either sex.

The pattern of results was similar for the models adjusted for confounders, with maternal PBDE concentrations being associated with lower IQ scores in boys but not in girls (Table 5). Specifically, there was a marginally significant decrease of 3.4 (95% CI: −7.0, 0.1) FSIQ points per tenfold increase in maternal Σ_4PBDEs for boys. The associations for BDE-47 were significant, whereby a tenfold increase in BDE-47 concentrations was associated with lower VIQ (−3.7 points; 95% CI: −7.1, −0.3), PIQ (−4.0 points; −7.8, −0.3), and FSIQ (−4.4 points; 95% CI: −7.9, −0.9) scores in boys. BDE-153 was not associated with IQ scores in either sex.

4. Discussion and Conclusions

The objective of this study was to examine the association between prenatal exposure to PBDEs and cognitive ability at the age of 3 years in the MIREC cohort. A secondary objective of the study was to explore the potential differential association between prenatal exposure to PBDEs and cognitive ability for boys and girls, given mixed evidence of sex differences in the literature. We observed that maternal concentrations of PBDEs were not associated with IQ scores in the overall group of children, but different results emerged when analyzing boys and girls separately. Among boys, higher maternal concentrations for the sum of BDE-47, −99, −100, and –153 were associated with lower IQ scores, although the association did not reach statistical significance. The congener BDE-47 had the highest concentration in mothers' blood, and increases in its concentration were significantly associated with poorer cognitive ability in boys, even after controlling for confounders. Specifically, a tenfold increase in maternal blood concentrations of BDE-47 was associated with a decrease of 4.4 FSIQ points in boys. The verbal and non-verbal cognitive domains (i.e., verbal and performance IQs, respectively) were similarly associated with prenatal PBDEs exposure. Thus, there was no evidence suggesting that the association is domain-specific. Among girls, there was no evidence of an association between maternal concentrations of PBDE and IQ scores. These results support the hypothesis that prenatal exposure to PBDEs may be detrimental to neurodevelopment among boys.

Table 5
Sex-stratified analyses for the differences in IQ scores (95% CIs) for a tenfold increase in maternal blood concentrations of PBDEs, adjusting for covariates.

	FSIQ	VIQ	PIQ
Σ_4PBDEs			
Boys	−3.4 (−7.0, 0.1)	−2.6 (−6.0, 0.9)	−3.2 (−7.0, 0.7)
Girls	0.9 (−1.7, 3.4)	1.8 (−0.7, 4.3)	−0.6 (−3.6, 2.4)
BDE-47			
Boys	−4.4 (−7.9, −0.9)	−3.7 (−7.1, −0.3)	−4.0 (−7.8, −0.3)
Girls	0.0 (−2.7, 2.7)	1.3 (−1.4, 3.9)	−1.5 (−4.6, 1.6)
BDE-153			
Boys	−0.7 (−3.1, 1.7)	−0.4 (−2.7, 2.0)	−0.6 (−3.2, 2.0)
Girls	1.0 (−0.8, 2.8)	1.5 (−0.3, 3.2)	0.1 (−2.0, 2.2)

Note. Models adjusted for maternal birth country, maternal smoking at the third trimester of pregnancy, maternal education, and study site.

Our estimates are smaller in magnitude compared to those found in cohorts in the United States. The HOME and CHAMACOS cohorts reported statistically significant decreases of approximately 4 to 5 FSIQ points per tenfold increase in maternal prenatal concentrations (either Σ_4PBDEs or BDE-47) (Chen et al., 2014; Eskenazi et al., 2013; Zhang et al., 2017), whereas we observed a corresponding decrease of only 1 to 2 points (analysis not stratified for sex). It should be noted that the children in these American studies were aged between 5 and 8 years old, whereas the children in the present investigation were 3 years old. This is a particularly relevant difference given that adverse effects of *in utero* PBDE exposure might become more evident in older children. Indeed, it has been argued that an initial, early life insult on the brain might lead to a cascade of events, both biological and behavioural, detrimental to long-term optimal developmental trajectories (Bellinger et al., 2016). In addition, the smaller association estimates observed here may be explained by the fact that exposure levels in the HOME and CHAMACOS studies were subtantially higher than in the present study. For instance, the median concentration of the sum of four congeners (BDE-47, −99, −100, and –153) was 34.6 ng/g in the HOME cohort (Chen et al., 2014) and 24.9 ng/g in the CHAMACOS cohort (Eskenazi et al., 2013). In the present study, exposure levels were substantially lower, with a median concentration of 12.9 ng/g for the sum of these same four congeners. These findings indicating lower PBDE exposure in Canada compared with the United States are consistent with previous reports on PBDE blood concentrations from biomonitoring surveys (Gravel et al., 2018) and studies of PBDEs in dust (Harrad et al., 2008). A review investigating external sources of exposure and blood levels in different countries concluded that fire safety regulations was the most important driver of exposure differences between countries (Frederiksen et al., 2009b).

Associations between prenatal exposure to PBDEs and adverse developmental outcomes have been reported in many studies, but there is still much to investigate regarding underlying mechanisms. One hypothesized mechanism that is well-supported in the literature is a disruption in the functioning of thyroid hormones (Costa and Giordano, 2007; Gibson et al., 2018). Thyroid hormones play an important role in fetal brain development, such that maternal hypothyroidism has been related to various neuroanatomical and behavioural alterations in offspring (Costa and Giordano, 2007; Schreiber et al., 2010). PBDEs have a similar chemical structure to that of thyroxine (T_4) and have been found to bind to the thyroid hormone transport protein transthyretin and to thyroid hormone receptors. PBDEs have thus been related to a decrease in circulating T_4 levels in rodents (Costa and Giordano, 2007; Dingemans et al., 2011; Gibson et al., 2018) and a decrease in triiodothyronine (T_3) in rats (Dingemans et al., 2011). In the CHAMACOS study, it was found that PBDEs were not significantly associated with T_4 in maternal serum but rather that PBDEs were significantly inversely related to thyroid stimulating hormone (Chevrier et al., 2010). However, disruption of thyroid hormones did not fully explain the PBDE-related neurodevelopmental alterations, suggesting that other mechanisms may be involved (Eskenazi et al., 2013). For instance, animal studies suggest that PBDEs are related to neuronal oxidative stress and apoptosis in various brain regions, reduced neural cell differentiation and migration, and alteration in inter- and intracellular calcium homeostasis and signaling (Dingemans et al., 2011). Furthermore, animal studies suggest that exposure to PBDEs can alter the functioning of the central nervous system. Researchers have found adverse effects of PBDE exposure on neural circuitry of the frontal cortex and the hippocampus in rodents,

which have important roles in cognition and memory (Costa et al., 2014). In addition, many neurotransmitter systems critical for behavioural and cognitive functioning, such as acetylcholine, dopamine, GABA, and glutamate, have also been found to be disrupted following PBDE exposure (Costa et al., 2014). However, these findings have not yet been confirmed in humans.

The sex differences observed in the present study and reported in the literature (Vuong et al., 2016) may be explained by a disruption in thyroid hormone function, as well as other mechanisms. Indeed, there is some evidence suggesting that alterations in thyroid hormone function following PBDE exposure may vary based on infant sex (Leonetti et al., 2016). There is also evidence that PBDEs and other brominated flame retardants may accumulate differently in the placenta based on infant sex (Leonetti et al., 2016). Alternatively, there is evidence that estrogen, which is higher in females, may serve as a protective factor against oxidative stress (Behl et al., 1997). Further studies are necessary to fully elucidate the mechanisms underlying sex differences in PBDE-induced neurodevelopmental alterations.

The present study had a larger sample size than previous studies (Gibson et al., 2018). The sample size of the present study, approaching 600 mother–child pairs, allowed for sufficiently powered sex-stratified analyses. Two published studies based on data from the MIREC cohort have examined sex differences by using sex-stratified analyses. First, prenatal PBDE exposure was not significantly related to visual acuity in 6-month-old infants in either sex (Polevoy et al., 2020). Second, the association between prenatal PBDE exposure and physical reactivity to frustration at the age of 7 months varied based on child sex (Oulhote et al., 2018). More specifically, greater prenatal PBDE exposure was related to a greater predisposition to negative vocalizations in both boys and girls. However, when evaluating frustration using physical reactivity, greater prenatal PBDE exposure was associated with greater odds of an extreme response (either no physical reactivity or high physical reactivity) in girls, but lower odds of an extreme response in boys (Oulhote et al., 2018).

4.1. Limitations

The main limitation of this study is the relatively low detection rate for PBDEs in maternal blood. The congener with the highest concentration, BDE-47, was detected in 66% of samples. Other congeners were detected even less frequently (i.e., 19% for BDE-99, 21% for BDE-100, and 42% for BDE-153). The higher analytical limit of detection in the present study compared with previous cohort studies negatively impacted our ability to detect low blood PBDE concentrations. For example, the LOD for BDE-47, the most detected congener across studies, was 0.3 to 2.6 ng/g lipid in the CHAMACOS study (Eskenazi et al., 2013), 0.3 to 8.2 ng/g lipid in the HOME study (Vuong et al., 2016), and 5.0 ng/g lipid in the present study. These differences are due to the use of a conventional gas chromatograph coupled with mass spectrometry in the MIREC study as opposed to gas chromatography coupled with isotope dilution high-resolution mass spectrometry in the HOME and CHAMACOS studies. This choice of method was made in the MIREC study because of its availability, its lower cost of operation, and the ability to analyse a wide variety of compounds, given that one of the original goals of the MIREC study was to measure exposure to a large number of chemicals during pregnancy.

Furthermore, our study sample was primarily of high socioeconomic status and was not ethnically diverse. Mothers who participated in the MIREC study were more likely to be White, born in Canada, older, and more educated than the average of pregnant women in the same time period. As such, our results may not be generalizable to more disadvantaged or diverse populations. Research on other neurodevelopmental toxicants showed that children living in higher socioeconomic environments might be less susceptible to the detrimental effects of exposure, through increased presence of mitigating factors such as cognitive stimulation or less frequent risk factors such as exposure to cigarette smoke or other environmental contaminants (Bellinger, 2008). Nonetheless, the PBDE exposure levels in the present sample were comparable to those of the full MIREC cohort (Fisher et al., 2016) and of an independent sample of Canadian women of reproductive age (20–39 years) from the Canadian Health Measures Survey (Health Canada, 2010; Oulhote et al., 2016).

Lastly, our results do not account for pre- or postnatal exposure to other neurotoxic contaminants or the potential influence of postnatal exposure to PBDEs. Notable sources of postnatal exposure to PBDEs include house dust and human milk (Frederiksen et al., 2009a). However, it is important to note that prenatal and postnatal exposure levels to these persistent contaminants are correlated (Eskenazi et al., 2013; Sagiv et al., 2015) and that it may be difficult to disentagle their specific effect on neurodevelopment.

4.2. Conclusions

Our results suggest that prenatal PBDE exposure is associated with a decrease in cognitive ability in preschool-age boys, but not in girls, at the levels of exposure experienced in Canada. This provides evidence of sex differences in the potential impact of PBDEs on cognitive development. These findings are important despite the fact that regulations were implemented to ban or reduce the use of some PBDEs. Indeed, exposure is expected to continue for decades to come given that they are common contaminants found in existing consumer goods, are highly persistent in the environment, and bioaccumulate up the food chain.

CRediT authorship contribution statement

Naomi Azar: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Linda Booij:** Conceptualization, Writing - review & editing, Supervision, Project administration. **Gina Muckle:** Investigation, Writing - review & editing, Project administration, Funding acquisition. **Tye E. Arbuckle:** Investigation, Writing - review & editing, Project administration, Funding acquisition. **Jean R. Séguin:** Writing - review & editing. **Elizabeth Asztalos:** Writing - review & editing. **William D. Fraser:** Investigation, Writing - review & editing, Project administration, Funding acquisition. **Bruce P. Lanphear:** Investigation, Writing - review & editing, Project administration. **Maryse F. Bouchard:** Conceptualization, Formal analysis, Writing - review & editing, Visualization, Supervision, Project administration.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.

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