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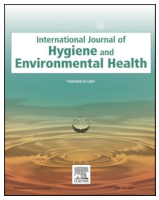

Prenatal exposure to PFAS and the association with neurobehavioral and social development during childhood

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ABSTRACT

Exposure to per- and polyfluoroalkyl substances (PFAS) is ubiquitous and may be associated with neurodevelopmental toxicity. However, epidemiological studies report mixed results on the risks of gestational PFAS exposure for children's neurobehavioral impairment. We aimed to examine the associations between prenatal PFAS exposure and children's neurobehavioral and social problems.

We measured plasma concentrations of perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulphonate (PFHxS) in first-trimester blood from 757 women from the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) study. Children were assessed at 3–4 years with the Behavior Assessment System for Children-2 (BASC-2) and the Social Responsiveness Scale-2 (SRS-2) (n = 756 and 496, respectively). We used multivariable linear regression to examine associations between individual and summed log_2-transformed PFAS and scores on these assessments. Effect modification by sex was evaluated through interaction terms and stratified analyses.

In the sample combining both sexes, a doubling of maternal PFOA was significantly associated with lower T-scores on the following SRS-2 scales: Social Motivation, DSM-Social Communication, and SRS Total score (B ranging from -1.08 to -0.78), suggesting lesser impairments with higher exposure. In sex-stratified analysis, PFOA was related to significantly lower T-scores in boys for these BASC-2 scales: Behavioral Symptoms Index, Externalizing Problems, Aggression, and Hyperactivity (B ranging from -1.32 to -1.03). In girls, however, PFAS were significantly associated more problem behaviors, but most associations were small and the CIs included the null, with the exception of PFOA being significantly associated with higher T-scores for the BASC-2Anxiety scale (B = 1.84, 95% CI: 0.36, 3.32).

In conclusion, we did not observe strong associations between prenatal exposure to the PFAS evaluated and children's neurobehavioral and social development in this population with low exposure levels. The results show mixed findings, depending on children's sex, neurodevelopmental outcome, and specific PFAS.

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1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a family of thousands of human-made organic compounds characterized by at least a perfluorinated methyl group (–CF_3) or a perfluorinated methylene group (–CF_2–) (Wang et al., 2021). PFAS have been widely used since the 1950s in many commercial and industrial products because of their strong C-F bond, their high resistance to extreme temperatures, and their oil, stain, and water-repelling properties (Buck et al., 2011; O'Hagan, 2008; Winchell et al., 2021). PFAS have been used in food packaging to prevent oil and grease leaks, in non-stick cookware as an anti-adhesive coating, in textiles to repel water, and in personal care products to increase durability and water resistance. Because of their unique physical-chemical properties, PFAS are employed in virtually all industries (e.g., aerospace, energy, mining, oil and gas, automotive, and construction) and they are used as a key ingredient in the production of some firefighting foams (Gluge et al., 2020). Due to their extensive use, PFAS have become ubiquitous in the environment, contaminating drinking water, crops, livestock, and wildlife (Peritore et al., 2023). These compounds are known for their resistance to degradation and tendency to bioaccumulate in the environment and other living organisms, including humans (Panieri et al., 2022).

Human exposure pathways to PFAS primarily include ingestion of contaminated food (e.g., fish, shellfish, eggs, and meat products), water, indoor air, and dust (Jian et al., 2017; Morales-McDevitt et al., 2021; Tittlemier et al., 2007). PFAS preferentially bind to albumin proteins in the blood and circulate throughout the body (Bischel et al., 2010; Forsthuber et al., 2020). Over 99% of the general Canadian population have detectable amounts of perfluorooctanate (PFOA), perfluorooctane sulfonate (PFOS), and perfluorohexane sulphonate (PFHxS) in the bloodstream (Health Canada, 2021).

The nervous system is one of the most sensitive targets for environmental contaminants, especially when exposure occurs during the prenatal and infancy periods (Grandjean and Landrigan, 2014; Rodier, 1995). Human studies suggest that the developing brain is particularly vulnerable to PFAS exposure, as the compounds can cross the placental barrier between the mother and the fetus during gestation (Gutzkow et al., 2012; Manzano-Salgado et al., 2015). PFAS have been detected in the brain of human fetuses (Björvang et al., 2021; Mamsen et al., 2019). In vitro and in vivo studies in multiple species have shown that neurotoxicity associated with PFAS exposure could be due to several mechanisms, such as disruptions in calcium homeostasis in neurons, alterations in dopamine neurotransmission, and adverse changes in neuroendocrine systems implicating stress, sex and thyroid hormones (Brown-Leung and Cannon, 2022; Cao and Ng, 2021; Piekarski et al., 2020; Starnes et al., 2022). Furthermore, PFAS could disrupt the blood-brain barrier, increasing its permeability to other exogenous substances that could also exert neurotoxic effects (Wang et al., 2011).

Although several studies found prenatal PFAS to be associated with increased neurobehavioral problems in children (Harris et al., 2021; Hoyer et al., 2015, 2018; Niu et al., 2019; Vuong et al., 2021; Xie et al., 2023), some found no association (Dalsager et al., 2021; Fei and Olsen, 2011; Oulhote et al., 2016) or even inverse associations (Braun et al., 2014; Itoh et al., 2019; Jedynak et al., 2021). Furthermore, the association may differ between boys and girls, as reported by several epidemiological studies (Goodman et al., 2023; Goudarzi et al., 2016; Niu et al., 2019; Quaak et al., 2016).

To date, most studies investigating the relation between prenatal PFAS exposure and children's neurobehavioral development have been conducted in regions associated with historical or current PFAS production sites, and where substantial contamination resulted in high exposures, such as in Scandinavia (Liew et al., 2015; Long et al., 2019; Ode et al., 2014; Oulhote et al., 2016; Skogheim et al., 2021), Asia (Itoh et al., 2019; Niu et al., 2019), the United States (Ames et al., 2023; Braun et al., 2014; Harris et al., 2021; Lyall et al., 2018; Vuong et al., 2021), or the Netherlands (Fei and Olsen, 2011; Quaak et al., 2016). No studies have been conducted in the Canadian population, where PFAS have never been manufactured and where exposure levels are relatively lower (Jian et al., 2018; Longpré et al., 2020).

In this study, we aimed to examine the associations between first-trimester maternal blood PFAS concentrations and neurobehavioral problems in preschool children. Furthermore, we also examined whether sex modified these associations.

2. Material and methods

2.1. Study population

We used data from the Maternal-Infant Research on Environmental Chemicals (MIREC) study. This nationwide Canadian pregnancy study enrolled 2001 women in the first trimester of pregnancy between 2008 and 2011 across 10 cities (Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston, Toronto, Hamilton, Montreal, and Halifax). The MIREC Study was established to examine the potential role of prenatal exposure to environmental chemicals on the health of pregnant women and their children. Eligibility criteria included the ability to consent and communicate in English or French, being 18 years old or older, being less than 14 weeks pregnant, and intending to receive prenatal care and deliver at the local hospital. Exclusion criteria included congenital malformations, fetal abnormalities, maternal medical complications, history of major chronic illness, history of illicit drug use, and threatened spontaneous abortion. Questionnaires were administered during the first trimester to collect lifestyle and sociodemographic information. A detailed description of the cohort is available elsewhere (Arbuckle et al., 2013).

To assess children's neurobehavioral outcomes, we used data from MIREC-Child Development (CD-PLUS), a follow-up study that recruited 896 mother-child pairs from the original cohort in 2013–2015 when the children were aged 3–4 years old (Fisher et al., 2023). Eligibility criteria were singleton children born at a gestational age of 28 weeks or over, without major congenital anomalies, a history of convulsions or a major neurological disorder. Parents from all 10 cities of MIREC were sent the Behavior Assessment System for Children-2 (BASC-2) in an online or paper format. Owing to limited resources, at-home assessments of children were conducted in 6 cities (Vancouver, Toronto, Hamilton, Kingston, Montreal, and Halifax) among 610 participants. During the in-person assessment, mothers completed the Social Responsiveness Scale-2 (SRS-2).

Complete data on maternal blood PFAS and covariates were available for 744–756 participants who completed the BASC-2, and for 496 participants who completed the SRS-2.

All participants signed informed consent forms before participation, and the MIREC studies were approved by the Research Ethics Boards of Health Canada/Public Health Agency of Canada, Sainte-Justine University Hospital, and the ethics committees of all study site hospitals.

2.2. Prenatal PFAS concentrations

Concentrations of PFOA, PFHxS and PFOS were measured in maternal blood plasma collected in the first trimester of pregnancy (6–13 weeks of gestation) using 10-ml sterile vacutainer tubes. Samples were centrifuged and the aliquoted plasma was frozen and stored at -80 °C within 2 h of collection. Laboratory analyses were conducted at the Toxicology Laboratory of the Institut national de santé publique du Québec (INSPQ), which is accredited by the Standards Council of Canada. The compounds were quantified using ultra-high-pressure liquid chromatography (ACQUITY UPLC System; Waters Corporation, Milford, MA, USA) coupled with tandem mass spectrometry, operated in the multiple reaction monitoring mode with an electrospray ion source in negative mode (INSPQ, 2009). Between-assay coefficients of variation for PFOA, PFOS and PFHxS were 5.8, 3.6, and 10.0%, respectively. The limits of detection (LODs) were 0.1 μg/L for PFOA, and 0.3 μg/L for

PFOS and PFHxS (Fisher et al., 2016).

2.3. Child neurobehavioral assessment

When children were between 3 and 4 years old, caregivers reported on their child's emotional and behavioral difficulties using the BASC-2 Parent Rating Scale-Preschool Form (Reynolds, 2004). Social impairment was assessed through completion of the SRS-2 Preschool Form, an instrument designed to examine impairments associated with autism spectrum disorder (ASD) (Bruni, 2014). Trained researchers and parents were unaware of the examinees' prenatal PFAS concentrations at the time of administration.

The BASC-2 was completed by parents from all 10 study sites. Nine subscales relevant to our research objectives were administered (Hyperactivity, Aggression, Anxiety, Depression, Somatization, Atypicality, Withdrawal, Attention Problems, and Social Skills). The BASC-2 also provides three composite scores: Behavioral Symptoms Index (BSI), comprised of Hyperactivity, Aggression, Depression, Atypicality, Withdrawal, and Attention Problems subscales, Externalizing Problems (Hyperactivity and Aggression subscales), and Internalizing Problems (Anxiety, Depression and Somatization subscales). The 134-item questionnaire, used for children between 2.5 and 5 years of age, takes approximately 15–20 min to complete. For each item, parents rated how often a behavior or symptom occurred on a 4-level Likert scale ranging from 0 (Never) to 3 (Almost always).

The SRS-2 was completed during an at-home assessment by parents from 6 study sites. The instrument generates 5 subscale scores (Social Awareness, Social Cognition, Social Communication, Social Motivation, Restricted Interests, and Repetitive Behavior), 1 summary score (Total Score), and 2 Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) compatible subscales (Social Communication and Interaction, Restricted Interests and Repetitive Behavior). The 65-item instrument takes 15 min to complete and is intended for children aged between 2.5 and 4 years old. Parents reported on their child's behavior over the past 6 months using a 4-level Likert scale ranging from 1 (Not true) to 4 (Almost always true).

BASC-2 and SRS-2 raw scores were converted into T-scores standardized by sex and age, with a mean of 50 points and a standard deviation of 10 points. Higher BASC-2 T-scores indicate greater problems for all scales but Social Skills scale, for which elevated T-scores suggest fewer problems. For the SRS-2, higher T-scores are also indicative of poorer social development for all scales.

2.4. Covariates

We identified determinants of maternal PFAS exposure and child neurodevelopmental outcomes through a review of the literature. Using DAGitty (Version 3.1), we developed a directed acyclic graph (DAG) to visualize the relations between candidate variables, exposure, and outcomes, as presented in Supplemental Fig. 1. The models were adjusted for the following confounding variables: maternal age at enrollment in years (continuous), parity (0, 1, ≥2), ethnicity (White, non-White), education level (college/trade school diploma or less, undergraduate university degree, graduate university degree), household income in CAD (≤$60 000, $60 001-$100 000, >$100 000), and monthly fish consumption during first trimester of pregnancy (low [0–2 times], moderate [3–7 times], high [≥8 times]). These confounding variables have been consistently associated in the literature with both PFAS exposure (McAdam and Bell, 2023) and child neurobehavior (Lebeña et al., 2024; Pinborough-Zimmerman et al., 2011). Additionally, we adjusted for variables associated with child neurobehavior to increase the precision of our coefficient estimates. These included: maternal pre-pregnancy body mass index in kg/m^2 (continuous), child's breastfeeding duration in months (continuous), first-trimester maternal alcohol consumption (no, yes) and cigarette smoking status (never, former, quit during pregnancy/current), and sex identified at birth (Lebeña et al., 2024; Pinborough-Zimmerman et al., 2011).

2.5. Statistical analysis

We computed descriptive statistics for exposure and outcome variables, as well as sociodemographic and lifestyle characteristics. PFAS concentration values below the limit of detection were imputed using a robust and reliable semiparametric method, referred to as regression on order statistics (ROS) (Lee and Helsel, 2005). Using R Statistical Software (Version 4.2.1; R Core Team, 2022), PFAS measures were $\log_2$-transformed to normalize distributions and to limit the potential influence of outliers. The sum of PFAS (ΣPFAS) for each participant was calculated by summing their untransformed PFOA, PFOS and PFHxS concentrations. This sum was then $\log_2$-transformed. We then performed covariate-adjusted multivariable linear regressions to estimate variations in BASC-2 and SRS-2 scales' T-scores for each doubling of individual and summed prenatal PFAS concentrations. Regression model assumptions, such as normality of residuals, linearity, collinearity, and homoscedasticity, were evaluated using visual diagnostic methods. Upon inspection, no violations of these assumptions were detected, indicating that the models were well-specified, and the data adhered to the expected conditions for reliable regression analysis. The statistical significance level threshold was set at 0.05. Further analyses were conducted to examine potential effect modification by child sex. This involved introducing an interaction term between child sex and PFAS concentrations into the models, and by conducting stratified analyses. We considered an interaction term of $p < 0.1$ as indicative of effect modification.

3. Results

3.1. Descriptive statistics

Most of the mothers at the time of enrollment were between 26 and 35 years old (64.3%) (Table 1). The majority were White (89.7%), and had a pre-pregnancy BMI within the normal range according to the Canadian body weight classification system (61.6%) (Health Canada, 2003). Most had a university degree (68.3%), a household income of at least $60 000 CAD (83.3%), and were at least primiparous (55.0%). On average, the children were 3.37 years old (range = 2.92–4.21) at the time of the neurobehavioral assessment.

Mothers included in this study presented comparable sociodemographic characteristics with those of the original MIREC cohort. For instance, the average age of initially recruited mothers was 32.2 years, with the majority being White (81.3%), having a university degree (62.3%) and having a household income exceeding $50,000 (77.8%) (Arbuckle et al., 2013).

Table 2 presents the summary of first-trimester maternal PFAS blood plasma concentrations. Among the PFAS measured, PFOS showed the highest median concentration, followed by PFOA and PFHxS. Spearman's rank correlations between the different PFAS were moderate, ranging from 0.52 to 0.55 (Supplemental Table 1).

The median prenatal PFAS concentrations of the participants in this study closely mirrored those measured in the original MIREC cohort (i.e., PFOA = 1.7, PFOS = 4.6 and PFHxS = 1 μg/L) (Fisher et al., 2016).

Descriptive statistics of children's BASC-2 and SRS-2 T-scores are presented in Supplemental Tables 2 and 3, respectively.

3.2. Associations between maternal PFAS concentrations and child BASC-2 T-scores

Overall, the association estimates between maternal blood PFAS concentrations and children's BASC-2 T-scores were generally small and had large confidence intervals (CI) for most PFAS. Associations are presented graphically in Fig. 1, and numerical beta estimates with 95% CI are presented in Supplemental Table 2. In the total sample (both

Table 1
Mother and child descriptive statistics stratified by child sex (n = 757).

	Female (n = 387)	Male (n = 370)	Total (n = 757)
Maternal characteristics			
Age at inclusion in years			
18–25	20 (5.2%)	20 (5.4%)	40 (5.3%)
> 25–35	257 (66.4%)	230 (62.2%)	487 (64.3%)
> 35	110 (28.4%)	120 (32.4%)	230 (30.4%)
Mean (SD)	32.8 (4.5)	33.0 (4.9)	32.9 (4.7)
Ethnicity			
White	348 (89.9%)	331 (89.5%)	679 (89.7%)
Other	39 (10.1%)	39 (10.5%)	78 (10.3%)
Pre-pregnancy BMI			
Underweight	8 (2.1%)	8 (2.2%)	16 (2.1%)
Normal	246 (63.6%)	220 (59.5%)	466 (61.6%)
Overweight	79 (20.4%)	80 (21.6%)	159 (21.0%)
Obese	54 (14.0%)	62 (16.8%)	116 (15.3%)
Education level			
College/trade school diploma or less	120 (31.0%)	120 (32.4%)	240 (31.7%)
Undergraduate university degree	160 (41.3%)	134 (36.2%)	294 (38.8%)
Graduate university degree	107 (27.6%)	116 (31.4%)	223 (29.5%)
Household income in CAD			
≤ $60 000	56 (14.5%)	71 (19.2%)	127 (16.8%)
$60 001 - $100 000	166 (42.9%)	144 (38.9%)	310 (41.0%)
> $100 000	165 (42.6%)	155 (41.9%)	320 (42.3%)
Parity			
0	181 (46.8%)	160 (43.2%)	341 (45.0%)
1	151 (39.0%)	153 (41.4%)	304 (40.2%)
≥ 2	55 (14.2%)	57 (15.4%)	112 (14.8%)
Monthly fish consumption during first trimester			
Low (0–2 times)	143 (37.0%)	136 (36.8%)	279 (36.9%)
Moderate (3–7 times)	139 (35.9%)	129 (34.9%)	268 (35.4%)
High (≥8 times)	105 (27.1%)	105 (28.4%)	210 (27.7%)
Cigarette smoking status during first trimester			
Never	252 (65.1%)	240 (64.9%)	492 (65.0%)
Former	105 (27.1%)	95 (25.7%)	200 (26.4%)
Current/Quit during pregnancy	30 (7.8%)	35 (9.5%)	65 (8.6%)
Alcohol consumption during first trimester			
No	313 (80.9%)	307 (83.0%)	620 (81.9%)
Yes	74 (19.1%)	63 (17.0%)	137 (18.1%)
Child characteristics			
Breastfeeding duration in months			
< 6	89 (23.0%)	89 (24.1%)	178 (23.5%)
6-12	152 (39.3%)	141 (38.1%)	293 (38.7%)
> 12	146 (37.7%)	140 (37.8%)	286 (37.8%)
Child age at assessment in years			
Mean (SD)	3.37 (0.31)	3.38 (0.31)	3.37 (0.31)
Median [Min, Max]	3.28 [2.92, 4.16]	3.30 [2.93, 4.21]	3.29 [2.92, 4.21]
Missing (%)	0 (0%)	2 (0.5%)	2 (0.3%)

Abbreviations: SD = Standard deviation; CAD = Canadian dollar; Min = Minimum; Max = Maximum.

Table 2
PFAS concentrations (μg/L) in first-trimester maternal blood plasma (n = 757).

PFAS (μg/L)	% < LOD	GM	Median	Min, Max	IQR
PFOA	0.13	1.64	1.70	0.16, 11.00	1.10, 2.50
PFOS	0.13	4.57	4.60	0.37, 29.00	3.30, 6.80
PFHxS	4.76	1.04	1.00	0.10, 24.00	0.65, 1.60
∑PFAS	5.02	7.62	7.70	0.95, 39.50	5.45, 11.00

Abbreviations: LOD = limit of detection; GM = geometric mean; Min = Minimum; Max = Maximum; IQR = interquartile range.

sexes), maternal PFAS did not show significant associations with children's BASC-2 T-scores.

Child sex modified several associations, particularly for PFOA and PFOS, as suggested by interaction term p-values below 0.1. PFOA, PFOS and ∑PFAS were associated with slightly lower T-scores in boys, indicative of fewer problem behaviors, whereas the reverse was observed for girls (Fig. 1). In boys for instance, PFOA was associated with decreases of 1.03 points on the Behavioral Symptoms Index (BSI) (95% CI: -1.98, -0.08) and 1.32 points on the Externalizing Problems scale (95% CI: -2.43, -0.22). The latter association was driven by results on the subscales of Hyperactivity (B = -1.14, 95% CI: -2.23, -0.05) and Aggression (B = -1.30, 95% CI: -2.51, -0.10). PFOS was associated with a 1.01-point decrease on the Aggression subscale (95% CI: -2.14, 0.12) in boys, but the CIs included the null.

In girls, most PFAS were associated with higher T-scores of most scales but associations were small and the CIs included the null, with the exception of PFOA being significantly associated with higher T-scores for Anxiety (B = 1.84, 95% CI: 0.36, 3.32). PFAS were related to increased scores on the scales of Externalizing Problems (PFOS: B = 0.97, 95% CI: -0.09, 2.03; ΣPFAS: B = 1.17, 95% CI: -0.03, 2.38) and Hyperactivity (PFOA: B = 1.08, 95% CI: -0.13, 2.30; PFOS: B = 0.95, 95% CI: -0.09, 2.00; ∑PFAS: B = 1.17, 95% CI: -0.03, 2.38), although the associations did not reach statistical significance.

3.3. Associations between maternal PFAS concentrations and child SRS-2 T-scores

The association estimates for most PFAS and children's SRS-2 T-scores were negative, indicating less problems of social development with higher exposure, but estimates were imprecise. Results for the analyses on SRS-2 scores are depicted graphically in Fig. 2, and numerical estimates are provided in Supplemental Table 3. In the overall sample (both sexes), a doubling of maternal PFOA was associated with decreases of 1.08 points on the Social Motivation scale (95% CI: -2.01, -0.16), 0.79 point on the DSM-Social Communication scale (95% CI: -1.54, -0.04), and 0.78 point on the SRS Total scale (95% CI: -1.54, -0.02), suggesting fewer deficits with higher exposure. In addition, PFOS and ∑PFAS were associated with significantly lower scores on the Social Motivation subscale (B = -1.11, 95% CI: -2.01, -0.21 and B = -1.09, 95% CI: -2.08, -0.10, respectively).

The associations did not seem to differ significantly between boys and girls, as indicated by p-values for interaction terms between exposures and sex above 0.1 for nearly all associations. PFOA, PFOS and ∑PFAS tended to be associated with a slight decrease in SRS-2 T-scores in both sexes, whereas for PFHxS, the pattern differed: small positive associations were observed for girls, and negative associations were seen in boys. The only result reaching statistical significance was for PFHxS, which was associated with a 0.68-point increase (95% CI: 0.01, 1.35) on the Social Cognition scale in girls.

4. Discussion

The present study examined the relation between maternal PFAS exposure during the first trimester of pregnancy and parent-reported neurobehavioral problems and social impairments in young children living in Canada. We observed largely null associations, although increased PFOA, PFOS and ∑PFAS were related to a subtle decrease in social difficulties in the overall sample. When examining the modifying effect of sex, higher concentrations of PFOA were associated with slightly less behavioral problems in boys, whereas it was related to more anxiety and externalizing problems in girls.

Similar to our results, a previous smaller American study from the Health Outcomes and Measures of the Environment (HOME) cohort also reported inverse associations between prenatal PFOA and SRS-2 T-scores in children aged 4 to 5 (n = 175) (Braun et al., 2014). However, another study that combined 10 American cohorts from the Environmental influences on Child Health Outcomes (ECHO) Program reported that most maternal PFAS were not associated with SRS scores (n = 1429) (Ames et al., 2023). Several epidemiological studies have also reported sex-specific differences that suggest more adverse associations in girls. For example, a meta-analysis that pooled data from 9 European studies found that early-life exposure to PFOS and PFOA was associated with a

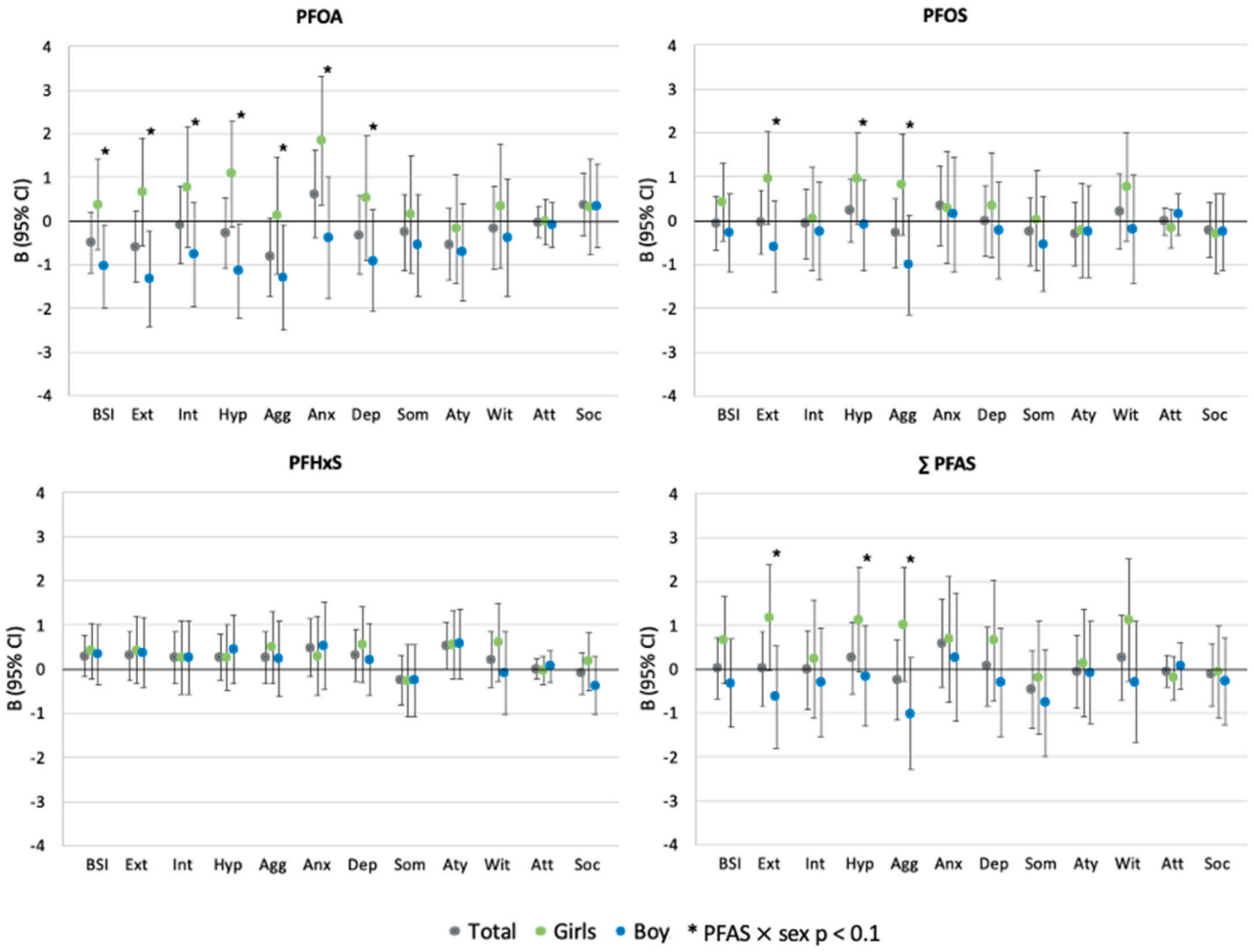

Fig. 1. Change in children's BASC-2 T-scores for a two-fold increase in maternal blood PFAS, for the total group and stratified by sex
Abbreviations: BSI = Behavioral Symptoms Index; Ext = Externalizing Problems; Int = Internalizing Problems; Hyp = Hyperactivity; Agg = Aggression; Anx = Anxiety; Dep = Depression; Som = Somatization; Aty = Atypicality; Wit = Withdrawal; Att = Attention Problems; Soc = Social Skills.
Higher association estimates indicate that PFAS are associated with more behavioral problems, apart from the Social Skills scale which is reversed.

slight increase in attention-deficit/hyperactivity disorder (ADHD) and associated symptoms in girls aged 4 to 11, but not in boys (n = 4826) (Forns et al., 2020). Sex-stratified analysis from Ames et al. (2023)'s study reported that prenatal PFOS was related to higher SRS scores in girls of preschool and school-age, but not in boys. Another study conducted in China among 4-year-old children found that most gestational PFAS, including PFOA and PFOS, were associated with more personal-social skills problems in girls evaluated with the Ages and Stages Questionnaires (ASQ) (n = 533) (Niu et al., 2019). Furthermore, in a study conducted in 5 and 8-year-old children from the Health Outcomes and Measures of the Environment (HOME) cohort, the adverse associations between maternal PFOS and PFHxS and BASC-2 externalizing and internalizing problems were stronger in girls compared to boys, and PFHxS was related to increased conduct problems only among girls within the sample (n = 240) (Vuong et al., 2021). A smaller study from the Netherlands found that, in 18-month-old boys, higher prenatal PFOA exposure was related to fewer externalizing problems as evaluated with the Child Behavior Checklist (CBCL), and the sum of prenatal PFOS and PFOA was associated with more externalizing problems in girls (n = 76) (Quaak et al., 2016). In contrast, a few studies reported adverse associations predominantly in boys. Sex-stratified analysis from Braun et al. (2014)' s study observed that PFOS was associated with more autistic behaviors in boys but not girls, and another study reported that prenatal PFHxS was associated with greater Strengths and Difficulties Questionnaire (SDQ) scores in 6–10 years old boys (n = 933) (Harris et al., 2021). Lastly, other studies found no evidence of sex-specific associations between prenatal PFOA, PFOS and PFHxS and neurobehavioral outcomes (Oulhote et al., 2016; Xie et al., 2023).

The results of the present study support the relevance of analyzing the neurodevelopmental effects of chemical contaminants according to the child's sex. Indeed, in the present study several associations were only apparent in sex-stratified analyses. The biological underpinnings of these sex-specific differences are not clear. However, a possible explanation behind the sex-specific associations observed in our study and in others may be related to PFAS endocrine-disrupting properties, such as the thyroid hormone imbalances documented in animal and human studies (Piekarski et al., 2020). Several studies have indicated that prenatal exposure to PFAS could disrupt the balance of gestational thyroid-stimulating hormone (TSH), triiodothyronin (T3), and thyroxine (T4), although findings diverge regarding which specific PFAS congener and thyroid hormone are affected (Boesen et al., 2020; Kato et al., 2016; Kim et al., 2011; Piekarski et al., 2020). Fetal brain maturation, particularly during the first weeks of gestation, depends on an

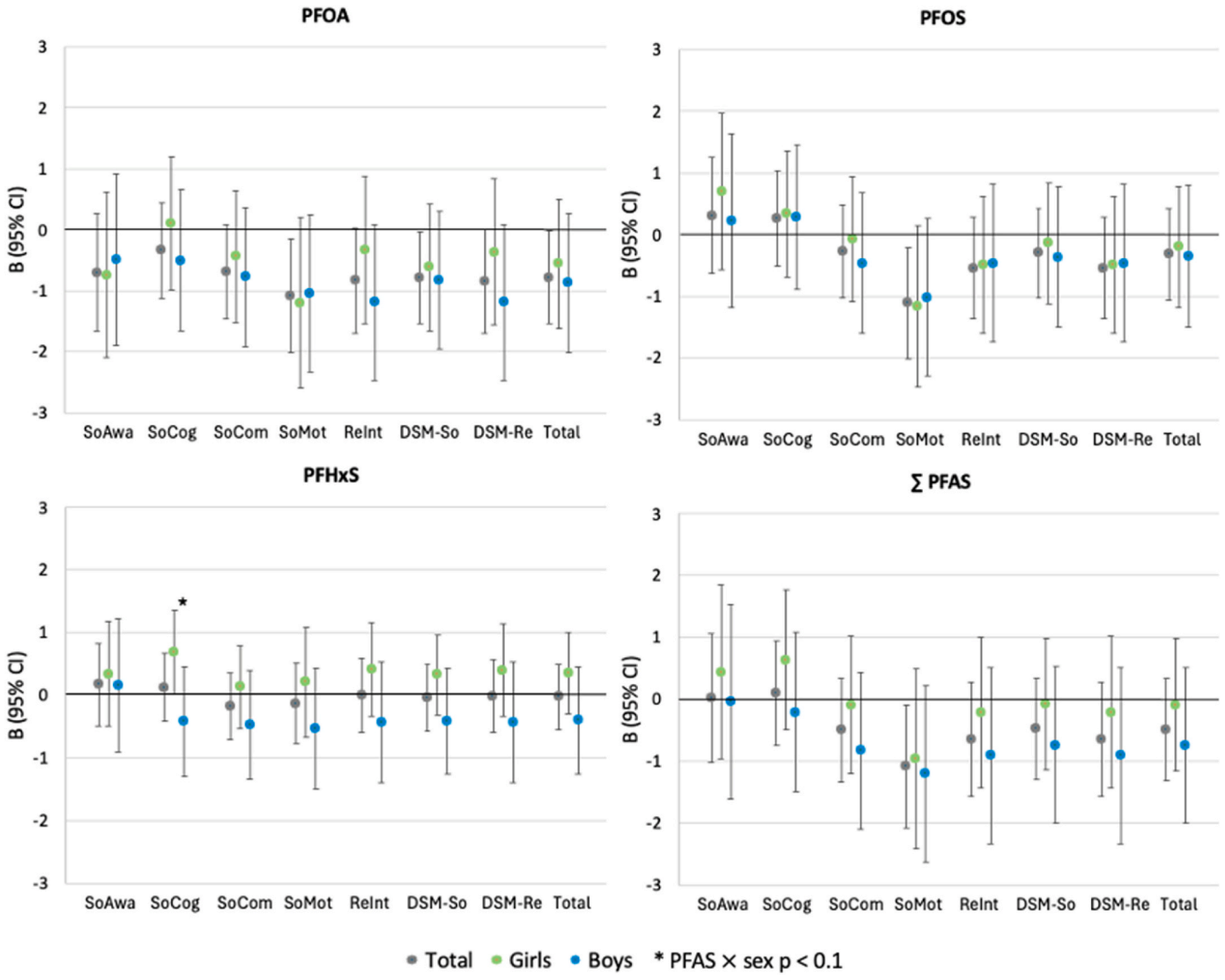

Fig. 2. Change in children's SRS-2 T-scores for a two-fold increase in maternal blood PFAS, for the total group and stratified by sex
Abbreviations: SoAwa = Social Awareness; SoCog = Social Cognition; SoCom = Social Communication; SoMot = Social Motivation; ReInt = Restricted Interests; DSM-So = Diagnostic and Statistical Manual of Mental Disorders-Social Communication; DSM-Re = Diagnostic and Statistical Manual of Mental Disorders-Restricted Interests/Repetitive Behavior; Total = Total Score.
Higher association estimates indicate that PFAS are associated with more social problems.

adequate supply of maternal TH (de Escobar et al., 2004). Even subtle alterations may lead to neurodevelopmental impairments (Moog et al., 2017; Patel et al., 2011). Both high and low concentrations of maternal TH have been associated with increased behavioral and emotional problems in early childhood (Fetene et al., 2017; Ghassabian et al., 2011; Kampouri et al., 2019). Females may be more vulnerable to the effects of altered gestational TH concentrations than males, as a large study observed a rise in ADHD symptoms among females born to mothers with elevated TSH levels during pregnancy, while such finding was not apparent in boys (Päkkilä et al., 2014). Further mechanistic and epidemiological studies are necessary to gain a better understanding of the sex-specific associations in PFAS exposure and thyroid hormone homeostasis and to investigate how these associations may lead to different neurobehavioral outcomes as a function of sex.

Variability in findings in the literature on the relation between prenatal PFAS exposure and child neurodevelopment can be ascribed to differences in exposure levels across study populations, influenced by various factors such as dietary habits, as well as geographical and temporal variations in sampling. Regions with historical or current PFAS production sites often exhibit higher exposure levels due to contamination of food and water sources, and regulatory measures to restrict PFAS contamination have led to decreasing levels of certain PFAS over the years (Jian et al., 2017; Sonnenberg et al., 2023). For instance, in our cohort from Canada, where PFAS were never manufactured, maternal PFAS concentrations measured from 2008 to 2011 tended to be lower compared to other studies. In this investigation, median concentrations of maternal blood PFOA, PFOS, and PFHxS were 1.7, 4.5, and 1.0 μg/L, respectively. In contrast, Harris et al. (2021) reported median concentrations of 5.6, 24.7, and 2.3 μg/L for the same compounds from 1999 to 2002 in the United States, Niu et al. (2019) found concentrations of 10.9, 10.8, and 2.8 μg/L in China in 2012, and Oulhote et al. (2016) observed concentrations of 27.4, 3.3, and 5.5 μg/L in the Faroese cohort from 1997 to 2000. Variations in timing of prenatal PFAS measurements (1st trimester vs. 2nd or 3rd), ages of children during behavioral assessments (toddlers vs. preschool vs. school-age), demographics (e.g. race/-ethnicity), statistical approaches and covariates choice, and neurobehavioral assessments used across studies (SDQ, CBCL, SRS, BASC-2) may also contribute to the diverse findings in the literature.

The strengths of our study include its prospective design, which allowed us to assess the suspected impact of gestational PFAS exposure on children's neurobehavioral outcomes. The large sample size of our cohort and the inclusion of a broad range of covariates in our models constitute added strengths. To evaluate child neurobehavior, we administered the BASC-2 and the SRS-2, which are well-validated and standardized questionnaires often used in the neurotoxicology field (Braun et al., 2017; McGuinn et al., 2020; Vuong et al., 2021). These assessments, compared to clinical diagnosis, allow us to detect more subtle sub-clinical symptoms. Furthermore, prenatal PFAS exposure was measured early in pregnancy, before significant pregnancy-related physiological changes such as plasma volume expansion occurred.

Some limitations need to be considered in the context of the present investigation. Our results may not be generalizable to other populations since participants of the MIREC cohort were more often white, older, and with higher income and education levels than pregnant Canadians at the time of enrollment (Arbuckle et al., 2013). Additionally, while our findings exhibited a consistent pattern across related scales and between sexes, and were in alignment with numerous other epidemiological studies as previously discussed, we cannot exclude the possibility that some associations may have arisen by chance due to multiple testing. We opted not to correct for multiple comparisons because our hypotheses are supported by biological plausibility derived from experimental evidence of PFAS neurotoxicity (Cao and Ng, 2021), and we investigated specific neurobehavioral issues, like internalizing or somatization problems, that were less commonly studied in epidemiological studies. Moreover, despite adjusting for several known confounders, we cannot rule out that unmeasured confounding factors may have influenced our results as in common in observational studies. Finally, it is important to acknowledge the potential limitations inherent in assessing behavioral and social difficulties in children as young as 3–4 years old, as it may result in outcome misclassification.

5. Conclusions

This is the first study to investigate associations between prenatal exposure to PFAS and neurobehavioral and social development in the Canadian population. Overall, we did not observed strong associations between prenatal exposure to the PFAS evaluated and children's neurobehavioral and social development in this population with low exposure levels. The results show mixed findings, depending on children's sex, neurodevelopmental outcome, and specific PFAS.

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Data availability

The authors do not have permission to share data.

CRediT authorship contribution statement

Trisha Saha: Formal analysis, Writing – original draft, Writing – review & editing. **M. Corinaud J. Gbemavo:** Formal analysis. **Linda Booij:** Writing – review & editing. **Tye E. Arbuckle:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Jillian Ashley-Martin:** Writing – review & editing. **Mandy Fisher:** Writing – review & editing, Data curation. **Gina Muckle:** Writing – review & editing, Methodology. **Bruce Lanphear:** Writing – review & editing, Methodology. **Elizabeth Asztalos:** Writing – review & editing. **Jean Séguin:** Writing – review & editing. **Maryse F. Bouchard:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114469.

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