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Manuscript Title:

Assessing the Relation Between Plasma PCB concentrations and Elevated Autistic Behaviours using Bayesian Predictive Odds Ratios

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impaired social communication and repetitive or stereotypic behaviours. *In utero* exposure to environmental chemicals, such as polychlorinated biphenyls (PCBs), may play a role in the etiology of ASD. We examined the relation between plasma PCB concentrations measured during pregnancy and autistic behaviours in a subset of children aged 3-4 years old in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a pregnancy and birth cohort of 546 mother-infant pairs from Canada (enrolled: 2008-2011). We quantified the concentrations of 6 PCB congeners that were detected in >40% of plasma samples collected during the 1st trimester. At age 3-4 years, caregivers completed the Social Responsiveness Scale-2 (SRS), a valid and reliable measure of children's reciprocal social and repetitive behaviors and restricted interests. We examined SRS scores as both a continuous and binary outcome, and we calculated Bayesian predictive odds ratios for more autistic behaviours based on a latent variable model for SRS scores >60. We found no association between plasma PCB concentrations and autistic behavior, However, we found small and imprecise increases in the mean SRS score and odds of more autistic behaviour for the highest quartile of plasma PCB concentrations compared with the lowest quartile; for instance, an average increase of 1.1 [95%PCI: -0.5, 2.6] in the mean SRS (exposure contrast 4^{th} versus 1^{st} quartile) for PCB138 translated to an odds ratio of 1.6 [95%PCI: 1.0, 2.5]. Our findings illustrate the importance of measuring associations between PCBs and autistic behaviour on both continuous and binary scales.

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition affecting 1-2% of children that is characterized by impaired social communication and repetitive or stereotypic behaviours that manifest during early childhood [1]. It has been suggested that maternal exposure to some environmental chemicals during fetal development may play a role in the etiology of ASD [2–8]. The first and third trimesters of pregnancy have been identified as important developmental windows for chemical exposure [9]. One such class of chemicals is the polychlorinated biphenyls (PCBs), which have well-established neurotoxic properties [10]. PCBs are persistent organic pollutants that were widely used in coolant fluids for different heating and electrical systems and industrial applications [11]. In Canada, action on PCBs has been taken since the late 1970s [12]. Globally, the Stockholm Convention on Persistent Organic Pollutants and PCBs came into force in 2004 [13]. Still, PCBs continue to persist in the environment [11]. Many studies have found that PCBs can affect several mechanisms thought to be involved in the etiology of ASD, including immune response and functions, neuronal development, neuroexcitability, oxidative stress, and steroid hormones [8,14–17].

The impact of prenatal PCB exposure on neurodevelopment in children has been studied extensively [16,18–22]. However, only a few studies have examined PCBs in relation to ASD, and the effects of low-level PCB exposure are uncertain. Braun et al. [22] reported modest, but imprecise differences in autistic behaviours associated with gestational exposure to several endocrine disrupting chemicals, including some PCBs. A small case-control study by Cheslack-Postava et al. [20] reported weak associations between *in utero* PCB exposure and ASD. More recently, in a large population-based case-control study, Lyall et al. [21] reported that several PCB congeners were associated with increased ASD risk in children. Overall, the effects of low-level PCB exposure on ASD and autistic behaviour remain unclear.

The purpose of this study was to examine the relation between plasma PCB concentrations measured during the first trimester of pregnancy and elevated autistic behaviour in 3- to 4-year-old children using the social responsiveness scale (SRS). We used Bayesian statistics to analyze data from 546 mother and child pairs who completed the child follow-up and neurobehavioural assessments component of the Maternal Infant Research on Environmental Chemicals (MIREC) Study, a prospective cohort study of Canadian women and children.

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METHODS

Maternal-Infant Research on Environmental Chemicals (MIREC) Study

We used data from the MIREC study, a prospective pregnancy and birth cohort study from ten Canadian cities between 2008 and 2011. The goal of the MIREC Study was to obtain national biomonitoring data on pregnant women and their infants to examine the effects of prenatal exposure to environmental chemicals on pregnancy and child health outcomes [23]. Study criteria and further details about participant eligibility and exclusions are discussed in the cohort profile by Arbuckle et al. [23]. For this study, we employed the subsample of participants in the MIREC follow-up neurodevelopment study when the children were 3 to 4 years old (average: 3.4 years). We included mothers who had socio-demographic and child neurodevelopment information, as well as plasma PCB concentrations and total lipid concentrations measured during the first trimester of the pregnancy. A total of 546 met all the above criteria for inclusion in our analysis (Table 1). This research was approved by ethics review boards from Health Canada, Sainte-Justine Research Center, and Simon Fraser University. All women provided informed consent for their and their child's participation in the study.

Biomarkers of PCB Exposure

We measured concentrations of 24 congeners in plasma samples collected during the first trimester of the pregnancy, at an average of 12.0 weeks gestation (range: 6.0-14.0 weeks). Biomarker analysis occurred at the Toxicology Laboratory of the Institut national de santé publique du Québec, and all samples were stored at -20°C [24]. We quantified PCB congener concentrations (International Union for Pure and Applied Chemistry no. 28, 52, 66, 74, 99, 101, 105, 118, 128, 138, 146, 153, 156, 163, 167, 170, 178, 180, 183, 187, 194, 201, 203, 206) using gas chromatography/mass spectrometry at the Toxicology Laboratory of the Institut national de santé publique du Québec, and all samples were stored at -20°C [24]. We retained PCB congeners that were detected in at least 40% of samples. We also calculated the sum of the six PCBs to estimate the relation between combined exposure to multiple PCBs and the SRS score (Table 2). We did not consider summations weighted using toxic equivalency factor (TEF) calculation, because the only dioxin-like congener that was detected in >40% of samples was PCB118. Axelrad et al. [25] examined different PCB body burden metrics and recommended using the sum of the most frequently detected congeners. We replaced measurements below the LOD with LOD/sqrt(2) [26]. To account for individual-level variability in plasma lipid levels, we standardized all PCB concentrations by total plasma lipid concentrations and expressed in

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units of ng/g lipids [26,27]. Additionally, we conducted further sensitivity analyses related to LOD and plasma lipid dilution, which are detailed below.

Social Responsiveness Scale Score

The Social Responsiveness Scale-2 (SRS-2) was the dependent variable in our analysis, a valid and reliable caregiver-reported questionnaire that provides a quantitative measure of autistic behaviour and, at higher scores, differentiates autism from other disorders [28]. The SRS score has been cross-validated in a large European sample of clinical ASD cases [29], and it has been compared with the Diagnostic and Statistical Manual of Mental Disorders (DSM) [30]. The SRS consists of a series of 65 questions on a Likert Scale that measure a child's behavioural characteristics during the previous 6 months. The sum of the questions gives a total T-score, where higher scores describe greater deficiencies in reciprocal social behaviour (i.e. interpersonal, repetitive, or stereotypic behaviours) that are more likely to indicate clinically diagnosed autism spectrum disorder [29,31,32]. SRS score cut-offs have been defined to denote the range of autistic behaviours. Scores from 60 to 65 are categorized as 'Mild', 66 to 75 as 'Moderate', and above 75 as 'Severe'. The SRS has two DSM-V subscales for ASD and five treatment subscales (social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behaviour), which measure receptive, cognitive, expressive and motivational aspects of social behaviour as well as autistic preoccupations.

Covariates

We included variables that may potentially confound the relationship between plasma PCB concentrations and autistic behaviours. We created a Directed Acyclic Graph (DAG) (Supplementary Figure 1) to identify factors that are common causes of PCB exposure and autistic behaviour [33]. Our final set of covariates included: child sex, mother's age in years, maternal race, maternal education, annual income, marital status, ever smoked/consumed alcohol during pregnancy, and pre-pregnancy BMI. We used the same set of covariates in all analyses.

Analytic Approach

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We used Bayesian linear regression to estimate the confounder-adjusted associations between mother plasma PCB concentrations and child mean SRS scores. Each PCB concentration was included in a single-pollutant model using indicator variables to create four sub-groups, separated into quartiles at the 25th, 50th and 75th percentiles, along with measured covariates. Comparisons based on PCB quartiles are easier to interpret than incremental plasma PCB concentrations changes. We did not adjust for co-pollutant confounding from multiple PCBs. An autoregressive prior on the regression coefficients was used to smooth the dose-response relationship. We used Markov Chain Monte Carlo (MCMC) with the software Stan [34] to generate a sample from the posterior distribution [35]. Further details are given in the Supplementary Materials.

For comparisons with odds ratios for ASD observed in other studies, we examined SRS scores as both a continuous and a binary outcome using Bayesian analysis (Lyall [21] and Cheslack-Postava [20]). Bayesian statistics is an approach to statistics where uncertainty about the results is represented using probability distributions on model parameters. One advantage of Bayesian methods is that we can calculate the probability of any model parameter output (e.g. the probability that SRS >60). We calculated Bayesian predictive odds ratios (BPORs) for more autistic behavior using SRS scores >60 and calculated from Equation (1) in the Supplementary Material with logistic errors. We obtained 95% posterior credible intervals (PCIs), which are the Bayesian equivalent of frequentist confidence intervals (CIs). The abbreviation CI is specific to frequentist confidence intervals. The parameters are interpreted as random variables and the boundaries indicate a 95% probability range for the unknown quantity. The BPOR approach gives much narrower 95% interval estimates for the OR of ASD compared to logistic regression directly on the dichotomized SRS score because it uses the underlying linear model for SRS to predict the probability that SRS >60. Additionally, we used the MCMC samples to calculate the posterior probability that the odds ratios were greater than 1.0.

We conducted additional multiple linear regression analyses to estimate differences in subscales of the SRS score (Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behaviour). We conducted a sex stratified analysis for males and females because ASD is more prevalent in boys, and matched case-control studies of ASD underestimates any effects in girls [3,36–38].

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Sensitivity Analyses

Because some PCBs were detected in fewer than 50% of participants, we conducted a sensitivity analysis that repeated the regression analyses using the single imputation "fill-in" approach where the logarithm PCB concentrations <LOD were randomly sampled from a truncated lognormal distribution with mean and standard deviation estimated from the data [39]. Additionally, building on the work of O'Brien et al. [24], we conducted a sensitivity analysis to compare results when plasma lipid concentrations were included as a covariate in our regression models for SRS.

RESULTS

The women were generally ≥30 years of age (77.5%) with a post-secondary degree (94.7%), and had an annual household income ≥ $80,000 (59.0%) (Table 1). Eight (6 boys and 2 girls) out of 546 children in the MIREC sample (1.5%) had SRS scores >60. Characteristics that were predictive of lower SRS scores included: higher maternal age, higher education, an annual income ≥ $100,000, and having a female child.

Six (118, 138, 153, 170, 180, 187) of 24 PCB congeners were detected in >40% of participants; PCB153, which was the most prevalent, was detected in 100% of participants (Table 2). Geometric mean concentrations (ng/g lipid) among the 6 PCBs were as high as 7.9 (range: 1.7-80.9) for PCB153 and as low as 1.8 (range: 0.5-26.9) for PCB187. The geometric means of PCBs for pregnant women in MIREC were generally lower than the Canadian women of childbearing age (20-39 years) from Canadian Health Measures Survey (CHMS) [40,41]. PCB153 had the highest geometric mean for MIREC and CMHS, at 7.9 and 8.2 ng/g lipids, respectively.

The Cronbach's alpha for all SRS scores (i.e. total SRS, two DSM-V subscales and five treatment subscales) were all greater than 0.90, which indicates a high internal consistency. To calibrate our inferences about the strength of the association between plasma PCB exposure and SRS, we used preliminary frequentist regression analyses to show the relation between each participant characteristic and SRS score (Supplementary Table 1). Children who were male and had mothers who were not married had higher mean SRS scores, with mean differences in SRS score of 2.3 [95%CI: 1.3, 3.3] versus female and 1.5 [95%CI: 0.3, 2.7]

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versus married mothers, respectively.

Higher plasma PCB concentrations were associated with subtle non-monotonic differences in continuous SRS scores, meaning that we saw a change in direction of the response between the quartiles of ng/g lipid PCB concentrations (Table 3). PCBs 138, 153, 170, 187, and the sum of the 6 PCBs were associated with weak and imprecise increases in the mean SRS when comparing the fourth quartile with the first quartile. For instance, mean SRS scores were 1.1-points [95%PCI: -0.5, 2.6] higher among children born to women in the 4th PCB138 quartile compared to children born to women in the 1st quartile. In a Bayesian analysis, the word imprecise means a large posterior standard deviation for the parameter. In other settings, comparisons of the 2nd or 3rd PCB quartile to the lowest quartile were associated with reductions in the mean SRS score (e.g. PCB153 in Table 3).

For all six PCBs, we observed small increases in the odds ratio of SRS >60 in the fourth quartile compared to the first quartile, although the resulting 95% interval estimates were very imprecise (large posterior standard deviation). For instance, PCB138 exhibited a modest odds ratio in the fourth quartile compared to the first quartile, with an odds ratio of 1.6 [95%PCI: 1.0, 2.5]. To recognize the importance of the BPORs and PCIs, we also report the posterior probabilities that the OR is greater than 1.0 (Table 4). This tells the reader that if the model is correct, then for PCB138, there is an estimated 98% probability that the odds ratio (fourth quartile versus first quartile) is greater than 1, emphasizing the value of the BPOR approach and narrower 95% interval estimates.

To demonstrate the advantage of Bayesian methods and the BPOR approach, we included odds ratios for more autistic behavior (SRS>60) calculated from frequentist logistic regression directly on the dichotomized SRS scores (Table 4). A total of 8 (1.5%) out of 546 children (6 boys and 2 girls) had SRS> 60. Because only 1.5% had scores for SRS >60, we see that the ORs from a traditional logistic regression model are imprecise. In contrast, the 95% intervals from BPOR are much narrower than logistic regression because they leverage the underlying linear regression model for SRS to provide more accurate estimation of the probability of elevated autistic behavior (SRS >60). Additionally, to enable comparisons with previous research, Table 4 also includes odds ratios for ASD from Lyall et al. [21].

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We conducted additional analyses to estimate differences in subscales of the SRS score (Supplementary Tables 2-6) and a sex stratified analysis for males (n=261) and females (n=285) (Supplementary Tables 7-8). However the width of the 95% CIs for model parameters were wider, and this makes the interpretation of results more challenging. Changes in PCB concentrations were associated with small increases or decreases in the SRS subscales. In some cases, we saw the same patterns with the Bayesian models for the total SRS score (Supplementary Tables 2-6). For instance, the Social Communication subscale had a mean increase of 1.3 [95%CI: -0.3, 2.9] for PCB138, compared to the first quartile. In the sex stratified analysis for PCB138, we saw an overall increase in the mean SRS score, with increases of 0.3 [95%PCI: -2.3, 2.9] for boys and 0.8 [95%PCI: -1.2, 2.7] for girls (Supplementary Tables 7-8).

In sensitivity analyses, we found that using a single imputation “fill-in” value for PCB<LOD, rather than LOD/sqrt(2) did not meaningfully change the results (Supplementary Table 9). This is unsurprising because PCB exposure was categorized into quartiles. Further sensitivity analyses showed that including plasma lipid concentrations as a covariate did not have an impact on our results (data not shown). For instance, linear regression models showed similar increases in the mean SRS when comparing the fourth quartile with the first quartile for PCB138, with a mean SRS score increase of 0.5 [95%CI: -1.1, 2.0] without the lipid covariate (but PCB adjusted for lipids) versus 0.5 [95%CI: -1.1, 2.1] with lipids as a covariate and adjusted for lipids.

DISCUSSION

We examined the relationship between plasma PCB concentrations and elevated autistic behaviour using a novel Bayesian analytic approach. We found no association between plasma PCB concentrations and autistic behavior. SRS scores differed modestly as plasma PCB concentrations increased; the associations were generally non-monotonic. Most congeners were associated with imprecise increases in mean SRS in the highest PCB quartile compared with the lowest PCB quartile (large posterior standard deviation). However, comparisons of the 2nd or 3rd PCB quartile to the lowest quartile were in some cases associated with reductions in the mean SRS score (e.g. PCB153 in Table 3). The BPORs provided an alternative framework to examine the SRS, and there was a similar pattern of higher odds of elevated autistic behavior in the highest PCB quartile compared with the lowest quartile. Interestingly, the standard errors of the BPORs were smaller than the corresponding standard errors from Lyall et al. [21], even

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though only 8 out of 546 children in the MIREC sample (1.5%) had scores for SRS >60. The reason is because BPORs leverage the underlying linear regression model for SRS from equation (1) (see Supplementary Methods) to enable more accurate Bayesian predictions of the odds ratio compared to logistic regression directly on the dichotomized SRS score data.

We found that small changes in the mean SRS score translated to observably larger changes in the odds of autistic behaviour based on an SRS threshold of 60. For example, for PCB138 an average increase of 1.1 [95%PCI: -0.5, 2.6] in the mean SRS for (Q4 versus Q1) translates to an odds ratio of 1.6 [95%PCI: 1.0, 2.5]. Furthermore, an important property of the logistic error model given in Equation (1) (see Supplementary Methods) is that BPOR is invariant to the choice of threshold used to define ASD [42]. In other words, it can be shown that using a threshold of 60, 75, or any other value will give the same odds ratio for more autistic behavior. These findings have important implications in the study of autistic behavior using the SRS score because seemingly small effect sizes can translate to larger effect sizes on the multiplicative risk scale. This phenomenon has been demonstrated in previous studies looking at the impact of toxicants on children, as depicted by Lanphear et al. in how “Little things matter” [43–46].

This study builds on the existing literature examining *in utero* PCB exposure and autistic behaviours [16,18–22]. Cheslack-Postava et al. [20] found some evidence that higher total PCB levels were associated with high frequency of ASD, whereas Braun et al. [22] found evidence that several PCBs (e.g. PCB138) were associated with more autistic behaviours. The larger case-control study of Lyall et al. [21] presented clearer evidence of monotonic dose-response relationships between PCBs (e.g. PCB 138 and 153) and risk of ASD in offspring. More generally, there is a evidence from human and animal studies that that some PCB congeners are associated with neurotoxic endpoints even at low doses [47,48].

This is one of only a few studies to examine *in utero* PCB exposures and autistic behaviour in a prospective cohort of pregnant women. PCBs have long half-lives and PCB levels in plasma are fairly stable over time; hence, we can rely on accurate and rigorous measurements of PCB exposure [9,49]. Additionally, our study is the first of its kind to estimate predictive odds ratios using Bayesian methods rather than using logistic regression applied directly to the dichotomized SRS score. Bayesian methods in environmental research are accessible and suitable to advance the literature; for example, researchers can create multilevel models and

implement other novel and innovative approaches with their data [50].

The study has some limitations. Although our linear model for SRS given in Equation (1) of the Supplementary Material accounts for non-linear dose-response using PCB quartiles, it is overly simplistic and does not account for co-pollutant confounding or interaction between PCB congeners. The analysis ignores the effect of combined exposure to multiple PCBs on autistic behaviour. The lack of association observed with the sum of the 6 PCB congeners suggests that calculating the sum is not satisfactory to characterize the combined effect of multiple PCBs. Individual congeners or the sum of PCBs with similar chemical properties may play a larger role in associations with autistic behaviour or other neurodevelopmental disorders [21].

Another limitation of our analysis is that SRS scores are not a perfect quantitative measure of autistic traits. Our BPOR analysis defines elevated autistic behavior using an established threshold of >60, which indicates mild, moderate or severe autistic behavior [29], rather than clinical information. The SRS is not a diagnostic test for ASD; it also measures other aspects of social behaviours that tend to co-occur with other behavioural disorders such as attention deficit hyperactivity disorder or language disorders [29,51,52]. Furthermore, SRS may have low specificity for ASD, because of traits related to social motivation and ADHD [51–53].

In conclusion, we found no association between plasma PCB concentrations and autistic behavior. However, we found some evidence that plasma PCB concentrations during pregnancy may be associated with small increases in autistic behaviours in children, as measured by SRS scores. Our findings demonstrate the value of measuring associations between PCBs and autistic behaviour on both continuous and binary scales using Bayesian statistics. Further research is needed to examine the effects of chemical mixtures and combined exposure to multiple PCBs to improve our understanding of the effects of multiple correlated exposures.

DECLARATIONS

Ethics Approval and Consent to Participate:

Health Canada and the Institutional Review Boards of CHU Sainte-Justine Research Centre and Simon Fraser University approved the MIREC Study. All subjects gave their informed consent to participate in the study.

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Competing Interests:

None declared.

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Author's Contributions:

BB and LM designed the study with input from SV, BL, JB, TA. BB conducted the analysis and wrote the bulk of the content with LM. BL, GM, TA and WF provided the data. SV, BL, JB, TA and WF assisted with editing and revising the manuscript.

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Table 1. Sociodemographic characteristics of MIREC study participants, Canada, 2008-2011 (n=546).

	n (%)	SRS (mean ± SD)	PCB[1] (ng/g lipid) (median (IQR))
Total	546 (100)	45.3 ± 6.2	22.9 (15.4-36.4)
Child Sex			
Male	261 (47.8)	46.6 ± 6.7	24.2 (15.7-35.6)
Female	285 (52.2)	44.2 ± 5.4	22.3 (15.0-36.8)
Mother's Age			
19-29	122 (22.3)	46.7 ± 5.6	15.4 (12.3-22.2)
30-34	205 (37.5)	45.4 ± 6.8	21.8 (15.5-31.5)
35+	219 (40.0)	44.5 ± 5.7	29.1 (21.5-43.6)
Race			
White	491 (89.9)	45.5 ± 5.8	35.7 (22.9-50.4)
Other	55 (10.1)	44.8 ± 6.3	40.6 (25.9-65.9)
Marital Status			
Married	241 (89.9)	45.5 ± 5.8	35.7 (22.9-50.4)
Other	154 (28.2)	45.4 ± 6.2	27.0 (22.9-61.2)
Education Level			
High School Diploma or less	29 (5.3)	47.8 ± 7.1	14.7 (11.9-18.4)
College or Trade School Diploma	154 (28.2)	46.2 ± 5.9	18.4 (13.2-29.6)
Undergraduate University Degree	213 (39.0)	45.5 ± 6.7	22.9 (15.6-35.2)
Graduate University Degree	150 (27.5)	43.8 ± 5.0	29.6 (21.5-43.0)
Annual Household Income			
<= $40,000	73 (13.4)	47.2 ± 6.2	19.0 (12.9-34.8)
$40,001-$80,000	151 (27.7)	46.2 ± 6.5	22.2 (14.6-32.4)
$80,001-$100,000	105 (19.2)	45.1 ± 6.2	19.3 (14.3-33.6)

> $100,000	217 (39.7)	44.2 ± 5.7	26.3 (18.1-39.2)
Has Ever Smoked During Pregnancy			
Yes	189 (34.6)	45.6 ± 6.5	24.4 (16.1-38.4)
No	357 (65.4)	45.2 ± 6.0	22.7 (15.1-34.8)
Has Ever Consumed Alcohol During Pregnancy			
Yes	91 (16.7)	44.7 ± 6.0	23.4 (17.8-38.7)
No	455 (83.3)	45.4 ± 6.2	22.8 (15.0-36.0)
Pre-Pregnancy BMI			
Underweight	14 (2.6)	45.2 ± 4.9	34.7 (14.4-53.7)
Normal	332 (60.8)	45.4 ± 6.5	24.8 (17.0-38.1)
Overweight	112 (20.5)	44.7 ± 5.4	22.9 (14.2-35.5)
Obese	88 (16.1)	45.9 ± 6.1	15.8 (12.8-24.6)

[1] Sum of PCBs 118, 138, 153, 170, 180, and 187.

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Table 2. Distributions of Blood Plasma PCBs (ng/g lipid) during the first trimester for MIREC study participants, Canada, 2008-2011 (n=546).

							MIREC			
Congener	**n**	**%>LOD CHMS[1]**	**%>LOD MIREC**	**GM[2] CHMS[1]**	**GM MIREC**	**SD**	**25th**	**50th**	**75th**	**95th**	**Max**
PCB118	546	83.2	77.5	3.09	2.5	2.5	1.6	2.4	3.4	6.9	30.2
PCB138	546	96.1	95.2	5.46	4.5	5.3	2.9	4.2	6.3	14.5	46.8
PCB153	546	91.6	100	8.22	7.9	9.9	4.9	7.5	11.8	25.6	80.9
PCB170	546	50.2	56.8	NA	2.1	3.6	1.2	1.9	3.1	7.5	40.3
PCB180	546	95.4	97.1	5.79	5.4	9.8	3.2	5.2	8.2	20.1	114.9
PCB187	546	41.1	46.0	NA	1.8	2.3	1.2	1.5	2.5	5.7	26.9
Sum of above PCBs	546	NA	NA	NA	24.8	31	15.4	22.9	36.4	73.3	296

[1] Plasma concentrations (ng/g lipid) for Canadian women of childbearing age (20-39 years), Canadian Health Measures Survey (CHMS) Cycle 1, 2007-2009 [40,41].
[2] GM = Geometric Mean (not calculated in CHMS when %>LOD was less than 60%).

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Table 3. Mother PCB levels (quartiles) in relation to mean child SRS score in MIREC study participants, Canada, 2008-2011 using Bayesian Autoregressive Quantile Regression (n=546).

PCB/quartile	Value (ng/g lipid)	n	SRS Unadjusted mean scores (95% CI)	SRS Adjusted[1] mean scores (95% CI)
PCB118				
Q1	< 1.63	136	0.0 (referent)	0.0
Q2	1.63-< 2.45	137	-0.26 (-1.74, 1.24)	-0.20 (-1.68, 1.26)
Q3	2.45-< 3.41	136	-0.57 (-2.05, 0.91)	-0.05 (-1.57, 1.45)
Q4	>= 3.41	137	-0.68 (-2.17, 0.79)	-0.10 (-1.64, 1.42)
PCB138				
Q1	< 2.86	136	0.0	0.0
Q2	2.86-< 4.23	137	-0.26 (-1.74, 1.23)	0.08 (-1.39, 1.55)
Q3	4.23-< 6.32	136	-0.84 (-2.30, 0.63)	-0.12 (-1.65, 1.42)
Q4	>= 6.32	137	0.11 (-1.34, 1.57)	1.06 (-0.50, 2.62)
PCB153				
Q1	< 4.93	136	0.0	0.0
Q2	4.93-< 7.5	137	-0.95 (-2.41, 0.54)	-0.61 (-2.08, 0.86)
Q3	7.5-< 11.77	136	-1.52 (-2.96, -0.05)	-0.96 (-2.53, 0.57)
Q4	>= 11.77	137	-0.47 (-1.94, 1.02)	0.51 (-1.07, 2.08)
PCB170				
Q1	< 1.22	136	0.0	0.0
Q2	1.22-< 1.85	137	-0.30 (-1.80, 1.17)	-0.60 (-2.06, 0.85)
Q3	1.85-< 3.09	136	-1.54 (-3.01, -0.07)	-1.01 (-2.54, 0.51)
Q4	>= 3.09	137	-0.59 (-2.03, 0.87)	0.05 (-1.52, 1.59)
PCB180				
Q1	< 3.2	136	0.0	0.0

Q2	3.2-< 5.15	137	-1.84 (-3.31, -0.38)	-1.48 (-3.02, 0.07)
Q3	5.15-< 8.24	136	-1.92 (-3.38, -0.48)	-1.26 (-2.88, 0.35)
Q4	>= 8.24	137	-0.99 (-2.45, 0.45)	-0.01 (-1.67, 1.69)
PCB187				
Q1	< 1.18	136	0.0	0.0
Q2	1.18-< 1.46	137	0.45 (-1.01, 1.93)	-0.05 (-1.53, 1.40)
Q3	1.46-< 2.5	136	-0.48 (-1.92, 0.98)	-0.46 (-1.91, 0.98)
Q4	>= 2.5	137	0.00 (-1.45, 1.46)	0.56 (-0.96, 2.08)
Sum of above PCBs				
Q1	< 15.41	136	0.0	0.0
Q2	15.41-< 22.94	137	-0.45 (-1.88, 1.01)	-0.15 (-1.62, 1.34)
Q3	22.94-< 36.42	136	-1.45 (-2.93, 0.05)	-1.02 (-2.58, 0.56)
Q4	>= 36.42	137	-0.12 (-1.58, 1.35)	0.83 (-0.75, 2.41)

[1] Adjusted for child's sex, mother's age, race, marital status, education level, annual income, whether the mother has ever smoked during pregnancy, has ever consumed alcohol during pregnancy, and pre-pregnancy BMI.

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Table 4. Bayesian Predictive Odds Ratios (BPORs) for the relation between mother PCB levels (quartiles) and child autistic behaviours defined by an SRS >60 threshold, in MIREC study participants, Canada, 2008-2011 (n=546).

			Adjusted Odds Ratio (95% CI)			
			Bayesian Results		Traditional Frequentist Results	
PCB/ quartile	**Value[1] (ng/g lipid)**	**n**	**BPOR[2]**	**Probability OR>1[3]**	**Logistic Regression[4]**	**OR for ASD in Lyall et al. [21][5]**
PCB118						
Q1	< 1.63	136	1.0 (referent)	0%	1.0	1.0
Q2	1.63-< 2.45	137	1.03 (0.65, 1.56)	55%	0.57 (0.09, 3.23)	1.29 (0.86, 1.95)
Q3	2.45-< 3.41	136	1.16 (0.73, 1.73)	75%	0.42 (0.07, 2.20)	1.38 (0.90, 2.11)
Q4	>= 3.41	137	1.23 (0.77, 1.86)	82%	0.00 (NA, 2.78e34)	1.15 (0.72, 1.82)
PCB138						
Q1	< 2.86	136	1.0	0%	1.0	1.0
Q2	2.86-< 4.23	137	0.98 (0.62, 1.48)	46%	2.86 (0.49, 24.1)	1.39 (0.92, 2.10)
Q3	4.23-< 6.32	136	1.03 (0.64, 1.56)	55%	0.75 (0.07, 8.24)	1.34 (0.87, 2.07)
Q4	>= 6.32	137	1.62 (1.00, 2.49)	98%	0.33 (0.01, 4.60)	1.79 (1.10, 2.92)
PCB153						
Q1	< 4.93	136	1.0	0%	1.0	1.0
Q2	4.93-< 7.5	137	0.78 (0.49, 1.18)	13%	2.06 (0.37, 16.4)	1.32 (0.88, 1.99)
Q3	7.5-< 11.77	136	0.81 (0.50, 1.25)	18%	0.21 (0.01, 2.84)	1.24 (0.80, 1.93)
Q4	>= 11.77	137	1.30 (0.79, 2.01)	86%	0.51 (0.05, 5.51)	1.82 (1.10, 3.02)
PCB170						
Q1	< 1.22	136	1.0	0%	1.0	1.0
Q2	1.22-< 1.85	137	0.84 (0.53, 1.25)	21%	0.57 (0.11, 2.91)	1.15 (0.76, 1.76)
Q3	1.85-< 3.09	136	0.82 (0.52, 1.24)	19%	0.08 (0.00, 0.69)	1.17 (0.75, 1.83)
Q4	>= 3.09	137	1.15 (0.71, 1.76)	73%	0.21 (0.02, 1.50)	1.48 (0.88, 2.50)

PCB180						
Q1	< 3.2	136	1.0	0%	1.0	1.0
Q2	3.2-< 5.15	137	0.63 (0.38, 0.97)	27%	0.85 (0.15, 5.24)	1.00 (0.66, 1.50)
Q3	5.15-< 8.24	136	0.76 (0.46, 1.19)	13%	0.10 (0.00, 1.04)	1.17 (0.75, 1.81)
Q4	>= 8.24	137	1.17 (0.68, 1.86)	73%	0.25 (0.02, 2.28)	1.49 (0.89, 2.49)
PCB187						
Q1	< 1.18	136	1.0	0%	1.0	1.0
Q2	1.18-< 1.46	137	1.07 (0.67, 1.61)	62%	0.51 (0.08, 2.72)	0.89 (0.58, 1.36)
Q3	1.46-< 2.5	136	0.96 (0.61, 1.43)	43%	0.11 (0.00, 0.93)	1.22 (0.79, 1.87)
Q4	>= 2.5	137	1.39 (0.87, 2.12)	93%	0.38 (0.06, 2.30)	1.32 (0.79, 2.20)
Sum of above PCBs						
Q1	< 15.41	136	1.0	0%	1.0	NA[5]
Q2	15.41-< 22.94	137	0.91 (0.57, 1.38)	34%	2.22 (0.40, 17.5)	NA[5]
Q3	22.94-< 36.42	136	0.80 (0.50, 1.24)	17%	0.17 (0.01, 2.22)	NA[5]
Q4	>= 36.42	137	1.46 (0.89, 2.30)	94%	0.46 (0.04, 4.98)	NA[5]

[1] Quartiles defined in MIREC are not the same quartiles in Lyall et al. [21], given a different distribution for PCB exposure.
[2] BPORs for autistic behaviour in MIREC using an SRS threshold of 60. Adjusted for child's sex, mother's age, race, marital status, education level, annual income, whether the mother has ever smoked during pregnancy, has ever consumed alcohol during pregnancy, and pre-pregnancy bmi.
[3] The probability the OR>1 was calculated using the posterior mean and posterior standard deviation.
[4] Frequentist logistic regression using the dichotomized SRS data as the dependent variable (SRS >60). Adjusted for child's sex, mother's age, race, marital status, education level, annual income, whether the mother has ever smoked during pregnancy, has ever consumed alcohol during pregnancy, and pre-pregnancy BMI.
[5] ORs for ASD copied directly from Table 3 of Lyall et al. [21]. Lyall et al. did not report ORs for ASD based on the quartiles of the sum of PCB118, 138, 153, 170, 180 and 187.