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Original Contribution

Association Between Gestational Exposure to Toxicants and Autistic Behaviors Using Bayesian Quantile Regression

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Autism spectrum disorder, which is characterized by impaired social communication and stereotypic behaviors, affects 1%–2% of children. Although prenatal exposure to toxicants has been associated with autistic behaviors, most studies have been focused on shifts in mean behavior scores. We used Bayesian quantile regression to assess the associations between $\log_2$-transformed toxicant concentrations and autistic behaviors across the distribution of behaviors. We used data from the Maternal–Infant Research on Environmental Chemicals study, a pan-Canadian cohort (2008–2011). We measured metal, pesticide, polychlorinated biphenyl, phthalate, bisphenol-A, and triclosan concentrations in blood or urine samples collected during the first trimester of pregnancy. Using the Social Responsiveness Scale (SRS), in which higher scores denote more autistic-like behaviors, autistic behaviors were assessed in 478 children aged 3–4 years old. Lead, cadmium, and most phthalate metabolites were associated with mild increases in SRS scores at the 90th percentile of the SRS distribution. Manganese and some pesticides were associated with mild decreases in SRS scores at the 90th percentile of the SRS distribution. We identified several monotonic trends in which associations increased in magnitude from the bottom to the top of the SRS distribution. These results suggest that quantile regression can reveal nuanced relationships and, thus, should be more widely used by epidemiologists.

autism; Bayesian statistics; children; endocrine-disrupting chemicals; quantile regression

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; DEHP, di(2-ethylhexyl) phthalate; MCPP, mono-3-carboxypropyl phthalate; MEP, mono-ethyl phthalate; MIREC, Maternal–Infant Research on Environmental Chemicals; PCB, polychlorinated biphenyl; SRS, Social Responsiveness Scale.

Autism spectrum disorders (ASDs), a spectrum of neurodevelopmental disorders affecting 1%–2% of children, are distinguished by social impairments and repetitive behaviors (1, 2). Although ASD diagnosis is relatively uncommon, all children demonstrate varying degrees of autistic behaviors (3). Genetics is an important risk factor for ASD, but it cannot explain ASD etiology entirely (4–6). A growing body of research shows that environmental factors, especially those that affect the developing fetus, play an important role in ASD (2).

The impact of toxicants on ASD diagnosis and autistic behaviors (measured with the Social Responsiveness Scale (SRS)) varies across studies. Several studies have linked certain phthalate metabolites (7–11), polychlorinated biphenyl (PCB) congeners (12–15), and certain organochlorine pesticides (13–16) with ASD diagnosis or autistic behaviors, but a consensus has yet to emerge. The associations of bisphenol-A with autistic behaviors are mixed, although it has been shown to affect neurodevelopment (10, 13, 17, 18). Although lead and mercury have been linked with ASD in some studies, there is less research on their associations with ASD at lower concentrations (19–22). It is unclear whether organophosphate pesticides are associated with ASD, but they are associated with neurodevelopmental outcomes (23–25). There is insufficient research on the associations between triclosan and ASD, but some evidence suggests triclosan may be associated with aspects of neurodevelopment, like a child's intelligence quotient or externalizing behaviors (26–28).

Epidemiologists frequently use ordinary least squares regression (e.g., linear regression) to report the average association between variables. In contrast, quantile regression is used to assess the relationship between exposure and the dependent variables for specified quantiles of the dependent variable's distribution (29–33). This alternative approach can detect associations that would have gone unnoticed had one only modeled the average associations (29, 30). Using quantile regression, Magzamen et al. (34) found that childhood lead exposure had the strongest impact on reading and math test scores in children with the lowest test scores. Meanwhile, the average associations were weaker. Quantile regression has been used elsewhere in environmental epidemiology, particularly in air pollution studies (35–40).

We set out to systematically analyze the relationships of exposure to an array of toxicants during the first trimester of pregnancy with ASD-associated behaviors in preschool-aged children in a Canadian birth cohort, using Bayesian quantile regression.

METHODS

Study participants

We used data from the Maternal–Infant Research on Environmental Chemicals (MIREC) Study, a pregnancy cohort from 10 Canadian cities. Study staff recruited women during the first trimester of pregnancy between 2008 and 2011. Eligibility criteria included being at least 18 years old, being able to communicate in French or English, and consenting to cord blood collection. We excluded women who carried a fetus with a known abnormality, had a major chronic disease, used illicit drugs, or threatened abortion (41). We approached 8,716 women, of whom 5,108 (59%) were eligible, and 1,861 (36%) provided consent and delivered singleton live births. Follow-up was restricted to 7 of the 11 study sites for logistical and financial reasons. In children born to the cohort of women, we measured child development outcomes in a convenience subsample of 600 when they were 3–4 years old. We further restricted our analysis to mothers who had complete information on the confounders and toxicants included in our analysis (Web Figure 1) (available at https://doi.org/10.1093/aje/kwab065).

This research was approved by ethics review boards from the University Hospital of Quebec, Health Canada, Sainte-Justine Research Center, and Simon Fraser University. All women provided informed consent for their own and their child's participation in the study.

Biomarkers of toxicant exposure

Biospecimens were stored at −20°C before being analyzed using gas chromatography/mass spectrometry at the Institut national de santé publique du Québec's toxicology laboratory using previously described methods (42–45). We measured toxicant concentrations during the first trimester of pregnancy (6–13 weeks' gestation) and included the 25 that were detectable in more than 60% of our sample (excluded toxicants are listed in Web Appendix 1). This included metals, measured in whole blood; organochlorine pesticides and PCBs measured in in plasma; and organophosphate pesticides, phthalates, bisphenol-A, and triclosan, measured in in urine. We quantified free plus conjugated bisphenol-A and triclosan concentrations using analytical chemistry methods described by Arbuckle et al. (44, 45). Concentrations below the limit of detection were estimated using single imputation. The mean and standard deviation of a truncated lognormal distribution were estimated for each toxicant, using existing data (with below the limit of detection concentrations being temporarily assigned a concentration of the limit of detection divided by $\sqrt{2}$ to allow for a more accurate distribution). Concentrations below the limit of detection were randomly assigned from this distribution (46).

To address the high correlation between certain toxicants, we calculated their molar sum. We did this for 4 PCB congeners: PCB118, PCB138, PCB153, and PCB180 (Pearson $r = 0.56$–0.95; 2-sided $P < 0.01$), and for 3 di(2-ethylhexyl) phthalate (DEHP) metabolites: mono-(2-ethyl-5-hydroxyhexyl) phthalate, mono-(2-ethylhexyl) phthalate, and mono-(2-ethyl-5-oxo-hexyl) phthalate ($r = 0.79$–0.97; $P < 0.01$) (Web Figure 2). Because these individual DEHP metabolites are derived from the same parent compound (7), we did not include these individual metabolites in our analysis. Because plasma-lipid concentrations affect the concentration of lipophilic toxicants in blood tests (47), we divided the concentrations of organochlorine pesticides and PCBs by maternal lipid concentrations. Furthermore, we addressed variability in urine dilution for the toxicants measured in the urine by standardizing by specific gravity using the following formula: $C_{stan} = C \times [(1.015-1) \div (SG-1)]$, where C_{stan} denotes an individual mother's standardized concentration, C denotes the unstandardized concentration, SG represents an individual mother's specific gravity reading, and 1.015 was the median specific gravity among study participants (48).

Autistic behaviors

When participating children were 3–4 years old (median, 40 months old), 1 parent of each child completed the preschool-aged version of the Social Responsiveness Scale-2 (SRS-2) questionnaire (Western Psychological Services, Torrance, California), which consists of 65 Likert-scale queries (49, 50). The sum of these responses gives a child's T-score, with higher scores indicating a greater number and intensity of ASD-like behaviors (3). The SRS is a valid and reliable measure of reciprocal social, repetitive, and stereotypic behaviors that are typically seen in ASD (50–53). The SRS also can be used to accurately assess autistic behaviors in a nonclinical population, making it well suited for population cohort studies like ours (3).

Confounders

We conducted background research to identify factors that confound the relationship between gestational exposure to toxicants and SRS scores and created a directed acyclic

graph to visualize our assumptions (Web Figure 3) (2, 6, 54–56). We adjusted for the following: child sex, folic acid supplementation, caregiver environment score, household income, relationship status, maternal ethnicity, age, education, parity, and city of residence (see Web Table 1 for more details). This information was collected via questionnaires administered upon study enrollment. Caregiver environment scores, a systematic assessment of the caring environment in which a child is reared, were determined using the Home Observation for Measurement of the Environment test at the childhood follow-up. These scores were determined by in-home observations and interviews with the child's caregiver(s) conducted by a trained interviewer (57).

Statistical analysis

Toxicants may not have equal associations with SRS scores along the entire distribution of SRS scores (30, 32). Thus, we used Bayesian quantile regression to determine the relationship between gestational exposure to toxicants and child SRS scores throughout the SRS distribution. We created separate models for each individual toxicant (or group of correlated toxicants, i.e., the sum of the PCBs and the sum of the DEHPs), and for each of the following quantiles of the SRS distribution (denoted by the Greek letter τ): 0.1, 0.3, 0.5, 0.7, and 0.9. Thus, our estimands were the change in SRS score per 2-fold increase in concentrations at the 10th (lowest), 30th, 50th, 70th, and 90th (highest) percentiles of SRS scores. For comparison purposes, we also created frequentist linear regression models to assess the average change in SRS score per 2-fold increase in toxicant concentrations. We plotted both sets of results alongside each other to allow for easy comparisons, even though linear regression uses 95% confidence intervals and Bayesian quantile regression uses 95% posterior credible intervals. All analyses were adjusted for confounders, performed with R, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria), and with the package "bayesQR" (29).

Our implementation of Bayesian quantile regression used an asymmetric Laplace working likelihood with identical and independently distributed error terms (29, 58). We used the default vague prior that came with the bayesQR package (29). We sampled from the posterior distribution of regression coefficients using Markov chain Monte Carlo methods with 27,000 iterations and the initial 2000 iterations discarded. The model is further described in Web Appendix 2. This model assumes 1) there is a homoscedastic relationship between each toxicant and SRS scores; 2) the relationship between each toxicant and SRS scores at 1 quantile of the SRS distribution is independent of any other quantile; and 3) there is a linear dose–response relationship between each SRS quantile and $\log_2$-transformed toxicant concentrations (29). To test the first assumption, we used a Breusch-Pagan test to detect the toxicants with statistically significant deviations from homoscedasticity (59). Next, the posterior variance correction of Yang et al. (60) was applied to these toxicants, which adjusted their 95% posterior credible intervals to account for violations of the first assumption (Web Appendix 2).

We opted to use a Bayesian approach to quantile regression because the frequentist approach to point and interval estimation, which comes from the "quantreg" package (61), was unsuitable for our data. Frequentist quantile regression assumes that the dependent variable has a smooth (nongranular) distribution (37). This is not the case for SRS scores, which can only take on whole number values. This unmet assumption caused error messages and implausible results. For this reason, researchers who wish to use quantile regression with a dependent variable with ties should consider using a Bayesian approach instead (37). We did not adjust our findings for multiple comparisons. Doing so would decrease type I errors but increase type II errors (62). Because it is certainly plausible that gestational exposure to toxicants will be associated with SRS scores (7–28), we deemed this to be an inappropriate tradeoff (62). Furthermore, parameter estimation was prioritized over null hypothesis significance testing.

Supplementary and exploratory analyses

Because child sex has been shown to modify the associations of certain toxicants, and ASD is more common in boys (2, 8, 13), we repeated our primary analysis stratifying by sex. We also performed a supplementary analysis adjusting for self-reported smoking during pregnancy. Next, we repeated our primary analysis removing outlier concentrations in each toxicant. Outliers were defined using Tukey fences with $k = 1.5$ (63). The relationship between gestational exposure to toxicants and SRS scores may be nonlinear. Accordingly, we conducted a supplementary analysis in which the range of toxicant concentrations was divided into quartiles, and the change in the SRS score was measured by comparing the bottom (first) quartile with the other 3 quartiles. There is some uncertainty about the validity of single imputation with toxicants that are detectable less than 70% of the time (46). To examine the performance of single imputation on 4 toxicants that were detectable 50%–70% of the time, we repeated single imputation 10 times and analyzed each of these imputations as described earlier in this section.

RESULTS

Descriptive statistics

Of the 600 mother–child pairs for which SRS scores were measured, 478 (79.7%) were included in our analysis. We excluded 89 for missing data on 1 or more of the toxicants, and an additional 33 were removed for missing data on confounders (Web Figure 1). These excluded mothers who were younger and less likely to live with their partner than were the mothers in our sample (Table 1). Most of the mothers in our sample were nonsmokers (91%), aged 30 years or older (80%), had at least an undergraduate degree (68%), and had an annual household income of at least $80,000 (61%) (Table 1). Ten (2.1%) of the children in our sample had an SRS T-score of 60 or higher, indicating at least mild autistic behaviors (51). The distribution of SRS scores is depicted in Web Figure 4. SRS scores were higher in children with

Table 1. Sociodemographic Characteristics of MIREC Study Participants With In-Person Follow-Up Who Were and Were Not Included in Our Sample (n = 600), Canada, 2008–2011

Characteristic	Included			Excluded			*P* Value
	No.	%	Mean SRS Score (SD)	No.	%	Mean SRS Score (SD)	
Total	478	100	45.3 (5.9)	122	100	45.5 (6.8)	
Child sex							0.387
Male	235	49.2	46.4 (6.2)	54	44.3	47.7 (8.0)	
Female	243	50.8	44.3 (5.4)	68	55.7	43.7 (5.1)	
Mother's age at enrollment, years							0.034[a]
18–24	7	1.5	45.6 (6.3)	7	5.7	53.4 (2.2)	
25–29	88	18.4	46.1 (5.3)	29	23.8	47.2 (5.8)	
30–34	189	39.5	45.5 (6.3)	45	36.9	45.1 (7.7)	
35–39	155	32.4	44.9 (5.9)	33	27.0	42.9 (5.6)	
≥40	39	8.2	44 (4.7)	8	6.6	44.6 (6.0)	
Living with spouse							>0.001[a]
Yes	468	97.9	45.2 (5.8)	111	91.0	45.1 (6.7)	
No	10	2.1	48.5 (8.3)	11	9.0	49.1 (6.7)	
Maternal race							0.195
White	433	90.6	45.1 (5.9)	105	86.1	45.5 (7.0)	
Other	45	9.4	47.7 (5.7)	17	13.9	45.6 (5.7)	
Education level							0.129
High school or less	25	5.2	47.8 (7.3)	5[b]	4.1	47.6 (7.1)	
College or trade school	128	26.8	46 (5.9)	39[b]	32.0	46.8 (5.7)	
Undergraduate degree	185	38.7	45.4 (6.2)	53[b]	43.4	45.4 (7.7)	
Graduate degree	140	29.3	44.1 (5.0)	23[b]	18.9	42.8 (5.6)	
Household annual income, Canadian $							0.118
≤40,000	43	9.0	48 (6.1)	17[b]	13.9	47.8 (6.1)	
40,001–80,000	142	29.7	46.2 (6.4)	31[b]	25.4	46.9 (5.8)	
80,001–100,000	99	20.7	45.2 (6.2)	17[b]	13.9	44.1 (5.6)	
>100,000	194	40.6	44.1 (4.9)	37[b]	30.3	44.4 (8.5)	
Smoked during pregnancy							0.249
Yes	41	8.6	47.9 (6.8)	6	4.9	50.2 (7.3)	
No	437	91.4	45.1 (5.7)	116	95.1	45.2 (6.7)	
Parity							0.679
Nulliparous	209	43.7	45.9 (5.5)	51	41.8	47.0 (8.0)	
Primiparous	196	41.0	44.6 (5.8)	55	45.1	44.6 (5.3)	
Multiparous	73	15.3	45.5 (7.0)	16	13.1	43.6 (6.3)	
Took supplement with folic acid?							0.713
Yes	452	94.6	45.3 (5.9)	117	95.9	45.4 (6.8)	
No	26	5.4	45.5 (5.7)	5	4.1	46.4 (8.1)	
HOME score							0.094
≥45	383	80.1	44.6 (5.3)	75[b]	61.5	44.9 (5.3)	
<45	95	19.9	48.4 (7)	29[b]	23.8	47.7 (9.3)	

Abbreviations: HOME, Home Observation for Measurement of the Environment; MIREC, Maternal–Infant Research on Environmental Chemicals Study; SD, standard deviation; SRS, Social Responsiveness Scale.

[a] $P < 0.05$ for χ^2 test comparing the included mothers and the excluded mothers. *P* values are 2-sided.

[b] Counts do not add up to 122, because some participants were missing data with respect to these variables.

the following characteristics: were male, had mothers who smoked, were socioeconomically disadvantaged, and grew up in a less-stimulating home environment (Table 1).

Many toxicants, including PCB138, PCB153, dichlorodiphenyldichloroethylene, all metals, and most phthalate metabolites, were detectable in more than 90% of our sample (Table 2). Geometric means for biomarker concentrations were similar or slightly lower than those of Canadian women aged 20–39 years who participated in cycle 1 (2007–2009) of the Canadian Health Measurement Survey (64) (Table 2). In addition to the PCBs and DEHPs, some toxicants were correlated with each other. This was true for oxychlordane and *trans*-nonachlor; dimethylphosphate and dimethylthiophosphate; and the organochlorine pesticides and the PCBs ($P < 0.01$) (Web Figure 2).

Frequentist linear regression analyses

Before presenting our Bayesian quantile regression results, we present our findings using linear regression. Overall, we found negligible confounder-adjusted changes in SRS scores using this method (Figure 1). Higher gestational levels of lead, cadmium, bisphenol-A, mono-3-carboxypropyl phthalate (MCPP), mono-butyl phthalate, and the molar sum of 4 PCBs were associated with higher mean SRS scores. Meanwhile, *trans*-nonachlor, mono-ethyl phthalate (MEP), and manganese were associated with lower mean SRS scores (Figure 1).

The *P* values for linear and quadratic deviations from homoscedasticity are presented in Web Table 2. Arsenic, cadmium, lead, dichlorodiphenyldichloroethylene, and MCPP had statistically significant deviations from homoscedasticity after adjusting for confounders. We adjusted their 95% posterior credible intervals to account for their heteroscedasticity.

Bayesian quantile regression analyses

After adjusting for confounders, we found that many toxicants were associated with mild changes in SRS scores in at least some part of the SRS distribution (Figure 1). We identified monotonic trends for some toxicants, where the associations increased in magnitude across the SRS distribution. The associations between gestational levels of mono-butyl phthalate, MCPP, the sum of the DEHPs, bisphenol-A, arsenic, cadmium, and β-hexachlorocyclohexane steadily increased as we modeled the 10th to the 90th percentiles of the SRS distribution. In contrast, the associations between gestational levels of manganese, *trans*-nonachlor, and MEP steadily decreased as we modeled the 10th to the 90th percentiles of the SRS distribution.

Bayesian quantile regression allowed us to identify relatively strong associations at the 90th percentile of the SRS distribution compared with the mean. Each 2-fold increase in gestational urinary MCPP concentrations at the upper tail of the SRS distribution was associated with increased SRS scores ($\beta_{\tau=0.9}$ = 0.79, 95% adjusted posterior credible interval: 0.24, 1.34). In contrast, we found relatively weaker associations using linear regression to model the mean of the SRS distribution (β_{LR} = 0.37, 95% CI: 0.08, 0.67) (Figure 1). We observed a similar phenomenon for lead ($\beta_{\tau=0.9}$ = 0.99, 95% adjusted posterior credible interval: −1.05, 3.02 vs. β_{LR} = 0.54, 95% CI: −0.25, 1.32), *trans*-nonachlor ($\beta_{\tau=0.9}$ = −0.51, 95% posterior credible interval: −1.21, 0.2 vs. β_{LR} = −0.24, 95% CI: −0.90, 0.42), and the sum of the DEHPs ($\beta_{\tau=0.9}$ = 0.70, 95% posterior credible interval: 0.14, 1.26 vs. β_{LR} = 0.06, 95% CI: −0.43, 0.55).

We identified positive associations between plasma PCB concentrations and SRS scores throughout the SRS distribution (Figure 1). Urinary organophosphate pesticide concentrations were associated with slightly decreased SRS scores at the upper tail of SRS scores (τ = 0.90). Associations were weak and mixed in the other parts of the SRS distribution. Our findings suggest there are no associations between urinary triclosan concentrations and SRS scores (Figure 1). Convergence was reached for all toxicants for the range of τ values used in this study (Web Figure 5).

Supplementary analyses

We found that child sex modified some of the associations between gestational exposure to several toxicants and SRS scores. For boys, the associations were relatively stronger for mono-butyl phthalate, MEP, and mono-benzyl phthalate. For girls, the associations were relatively stronger for oxychlordane, and *trans*-nonachlor (Web Figure 6). Differences in associations between the sexes were pronounced at the 90th percentile of SRS scores. Adding each mother's smoking status to the model did not meaningfully change the effect estimates (Web Figure 7). Removing outlier toxicant concentrations changed our results in an inconsistent manner, especially at the 90th percentile of SRS scores. This caused associations to increase for lead, MCPP, and especially the sum of the DEHPs. Associations decreased for arsenic, β-hexachlorocyclohexane, PCB153, and especially oxychlordane (Web Figure 8). To assess nonlinearity in the dose–response relationship between toxicant concentration and SRS scores, we repeated our primary analysis using concentrations broken down into quartiles of exposure. Comparing the top and bottom quartiles, we found similar trends to our main analysis, but we did not find clear evidence of a dose–response relationship for any individual toxicant (Web Figure 9). The results from 10 imputations of low-level toxicant exposure are shown in Web Figure 10. The variation in parameter estimates between imputations was particularly high for cotinine, which led us to conclude that toxicants must be detectable at least 60% of the time to be included in our study.

DISCUSSION

We assessed the relationship between gestational exposure to various toxicants and autistic behaviors measured with SRS in preschool-aged Canadian children, using Bayesian quantile regression. We found that associations between SRS scores and maternal concentrations of cadmium, lead, and some phthalate metabolites in blood or urine were the strongest at the high end of the SRS distribution.

Table 2. Distribution[a] of Toxicants in MIREC Participants (n = 478), Canada, 2008–2011

Chemical Name	% >LOD	GM (GSD)	Percentile				Maximum	CHMS GM[b]
			25th	50th	75th	95th		
Metals, μg/L[c]								
Arsenic	96.44	0.82 (1.95)	0.57	0.82	1.20	2.26	34.5	0.88
Cadmium	97.07	0.20 (2.10)	0.13	0.19	0.29	0.68	5.06	0.36
Lead	100.00	6.33 (1.62)	4.56	6.22	8.50	14.3	41.4	8.90
Manganese	100.00	8.56 (1.36)	7.14	8.79	10.4	13.7	26.9	9.17
Mercury	91.00	0.62 (2.77)	0.34	0.66	1.34	2.81	7.82	0.70
Organochlorine pesticides, ng/g lipid[d]								
β-HCH	65.48	2.29 (2.67)	<LOD	2.15	3.39	9.01	500	4.83
DDE	99.58	55.3 (2.14)	35.4	49.1	74.5	211	2,660	102
Oxychlordane	93.31	2.05 (1.79)	1.55	2.17	3.02	4.50	8.44	2.31
trans-Nonachlor	87.03	2.99 (1.82)	2.08	3.09	4.38	7.88	18.3	3.07
Organophosphate pesticides, μg/L[e]								
DEP	73.01	2.49 (2.21)	<LOD	2.50	4.07	9.54	36.8	2.00[f]
DMP	76.57	3.13 (2.62)	1.73	3.29	5.89	14.1	71.5	2.60[f]
DMTP	79.71	3.52 (3.95)	1.33	3.84	8.65	30.9	87.8	1.80[f]
Phenols, μg/L[e]								
BPA	84.31	0.84 (2.64)	0.46	0.81	1.39	4.46	79.1	1.20[f]
Phthalates, μg/L[e]								
MBP	99.79	12.7 (2.33)	7.80	12.0	19.0	54.8	526	NR
MBzP	99.37	5.45 (2.52)	3.12	4.77	9.05	26.2	182	9.30[f]
MCPP	80.13	0.89 (3.28)	0.47	0.89	1.71	7.52	72.0	1.01[f]
MEHHP	99.37	9.55 (2.18)	6.18	9.10	14.5	34.7	356.	20.0[f]
MEHP	98.12	2.34 (2.21)	1.43	2.21	3.71	9.12	53.0	3.40[f]
MEOHP	99.58	6.78 (2.03)	4.51	6.50	9.61	22.6	171	13.0[f]
MEP	99.79	32.2 (4.05)	12.3	24.8	67.5	462	20,800	50.0[f]
Sum of DEHPs[g]		18.8 (2.07)	12.5	18.0	26.7	63.8	551	NA
Polychlorinated biphenyls, ng/g lipid[d]								
PCB118	77.82	2.46 (1.87)	1.74	2.48	3.43	6.56	30.2	3.09
PCB138	94.77	4.51 (2.03)	2.99	4.52	6.61	15.0	46.8	5.46
PCB153	99.79	8.11 (2.00)	5.00	7.82	12.0	28.1	80.8	8.22
PCB180	96.86	5.55 (2.20)	3.28	5.26	8.44	21.4	115	5.79
Sum of PCBs[h]		21.0 (1.96)	13.2	20.1	30.7	70.7	221	NA
Triclosan, μg/L[e]								
Triclosan	99.79	15.4 (8.74)	2.62	9.29	97.2	569	1740	19.0[f]

Abbreviations: BPA, bisphenol-A; CHMS, Canadian Health Measures Survey; DDE, p,p′-dichlorodiphenyldichloroethylene; DEHP, di-2-ethylhexyl phthalate; DEP, diethylphosphate; DMP, dimethylphosphate; DMTP, dimethylthiophosphate; GM, geometric mean; GSD, geometric standard deviation; LOD, limit of detection; MBP, monobutyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MEP, mono-ethyl phthalate; MIREC, Maternal–Infant Research on Environmental Chemicals; NA, not applicable; NR, not reported; PCB, polychlorinated biphenyl; β-HCH, β-hexachlorocyclohexane.

[a] Concentrations are rounded to 3 significant digits when greater than 1.00. Otherwise, concentrations are rounded to the nearest hundredth to reflect the precision of the gas chromatography/mass spectrometry procedure.

[b] Concentration in Canadian women aged 20–39 years from Canadian Health Measures Survey (CHMS) cycle 2, 2009–2011 for triclosan; CHMS cycle 1, 2007–2009 for the remaining toxicants.

[c] Whole-blood concentration.

[d] Plasma concentration.

[e] Urinary concentration standardized by specific gravity.

[f] Not standardized by specific gravity in CHMS.

[g] Sum of MEHHP, MEHP, MEOHP, weighted by molecular weight.

[h] Sum of PCB118, PCB138, PCB153, PCB180, weighted by molecular weight.

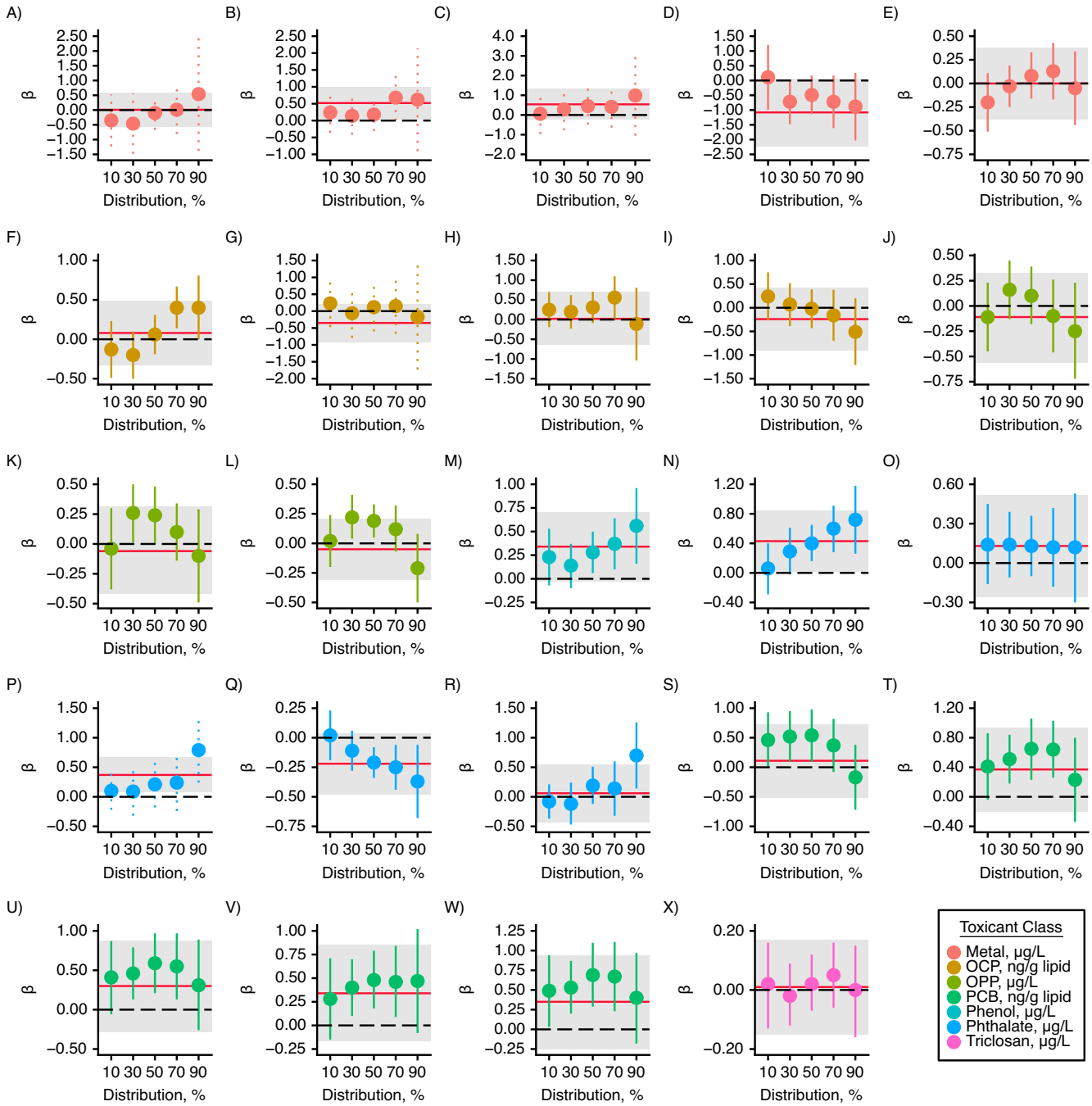

Figure 1. Effect estimates for the association between maternal toxicant concentrations and SRS scores using linear regression and Bayesian quantile regression, from the MIREC study (n = 478), Canada, 2008–2011. Effect estimates were adjusted for child sex, folate supplementation status, Home Observation for Measurement of the Environment score, and maternal characteristics (ethnicity, age, income, education, parity, city of residence). Coefficients describe the change in Social Responsiveness Scale score per 2-fold increase in concentration of the specified toxicant. Horizontal red lines in the gray boxes represent linear regression coefficients and their 95% confidence intervals. Circles and their whiskers depict the Bayesian quantile regression coefficients for the specified percentile of the SRS distribution and their 95% posterior credible intervals. Solid whiskers denote unadjusted posterior credible intervals, dotted whiskers denote adjusted posterior credible intervals. Toxicants include: A) arsenic; B) cadmium; C) lead; D) manganese; E) mercury; F) β-hexachlorocyclohexane (β-HCH); G) p,p′-dichlorodiphenyldichloroethylene (DDE); H) oxychlordane; I) *trans*-nonachlor; J) diethylphosphate (DEP); K) dimethylphosphate (DMP); L) dimethylthiophosphate (DMTP); M) bisphenol-A (BPA); N) monobutyl phthalate (MBP); O) mono-benzyl phthalate (MBzP); P) mono-3-carboxypropyl phthalate (MCPP); Q) mono-ethyl phthalate (MEP); R) sum of mono-(2-ethyl-5-hydroxy-hexyl) phthalate (MEHHP), mono-(2-ethylhexyl) phthalate (MEHP), and mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP), weighted by molecular weight; S) polychlorinated biphenyl (PCB)118; T) PCB138; U) PCB153; V) PCB180; W) sum of PCB118, PCB138, PCB153, and PCB180, weighted by molecular weight; and X) triclosan. OCP, organochlorine pesticide; OPP, organophosphorus pesticide.

In other words, our results suggest that children with the most autistic-like behaviors, who are of greater clinical interest, appear to be particularly susceptible to these toxicants. Quantile regression, therefore, allowed us to uncover details about the relationship between toxicants and autistic behaviors that could have been overlooked if we simply examined the mean. In contrast, increased maternal concentrations of manganese, *trans*-nonachlor, many organophosphate pesticide metabolites, and MEP were most strongly associated with decreased SRS scores at the upper tail of the SRS distribution (Figure 1). Child sex modified many of these associations, with associations for several phthalate metabolites being stronger in boys than girls (Web Figure 6). We note that the associations identified in our study were quite mild. A 1-unit increase in SRS score corresponds to just a one-sixth of a standard deviation increase.

Our study builds on the existing literature investigating the link between gestational exposure to toxicants and autistic behaviors. Other researchers have also linked metals (19, 21), organochlorine pesticides, PCBs (12–15), bisphenol-A, and several phthalate metabolites (7–10) with autistic behaviors. There were some inconsistencies with the literature. Although Roberts et al. (21) identified a positive link between gestational mercury concentrations and ASD diagnosis, our findings did not suggest that this was the case (Figure 1). Some of our findings contrast with those of Braun et al. (13), who identified a protective relationship between gestational exposure to PCB153, β-hexachlorocyclohexane, and SRS scores. MEP was most strongly linked with ASD in studies by Shin et al. (8) and Miodovnik et al. (10), yet our results suggest the opposite (Figure 1). These studies (8, 10, 13, 21) may differ from ours in several ways, including the study population, degree of exposure, and the statistical approach.

A key finding of our study is that the relationships of gestational concentrations of many toxicants and SRS scores were not uniform across the distribution of SRS scores. We found monotonic patterns for numerous toxicants where associations were either particularly strong or particularly weak at the 90th percentile of the SRS distribution, which represents children with the most autistic behaviors. This suggests that this subgroup has biological features that could protect them from some toxicants (manganese, *trans*-nonachlor, MEP) and make them more susceptible to other toxicants (several metals and phthalates). We began investigating this by stratifying by child sex, but this did not provide a clear explanation for this phenomenon (Web Figure 6). We recommend that more research be conducted to find a biological explanation for why associations differed among children with more autistic behaviors. Factors that may influence the developing brain's susceptibility to toxicants, such as prenatal micronutrient availability (11), should be scrutinized.

This study has several limitations. First, our use of complete case analysis may have resulted in increased bias and variance (65), especially considering that excluded mothers tended to be of lower socioeconomic status (Table 1). Second, biomarkers of organophosphate pesticide and phthalate exposure have a short half-life (66, 67). We expect that their regression coefficients are biased toward the null due to nondifferential exposure misclassification. Third, the SRS-2 questionnaire may overestimate autistic behaviors in children with lower intelligence quotient scores or behavioral disorders (68–70). Fourth, the participants in the MIREC study may not be representative of the rest of Canada; they are wealthier and more likely to be White (41). Fifth, we used toxicant concentrations at 6–13 weeks' gestation. Gestational exposure at different stages of development may have different consequences (71). Finally, we did not consider the role that combined exposure to several toxicants may have on autistic behaviors. Although we considered the molar sums of some highly correlated toxicants, latent class analysis or weighted quantile sum regression may be a more suitable approach for addressing this question (72, 73).

Our investigation builds on prior research linking endocrine-disrupting chemicals with ASD. It is also, to our knowledge, the first to analyze, using Bayesian quantile regression, the relationship between an array of toxicants and ASD. We have shown that quantile regression can unveil nuances in the relationship between toxicants and neurodevelopmental outcomes that may be overlooked with ordinary least squares regression methods, such as linear regression. Quantile regression thus should receive more attention from environmental epidemiologists, especially when the relationship between a biomarker and the response variable may differ throughout the response's distribution (74).

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The underlying data for this project may not be publicly released.

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