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Prenatal exposure to phthalates, bisphenol A and perfluoroalkyl substances and cord blood levels of IgE, TSLP and IL-33 ☆

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ABSTRACT

The fetal time period is a critical window of immune system development and resulting heightened susceptibility to the adverse effects of environmental exposures. Epidemiologists and toxicologists have hypothesized that phthalates, bisphenol A (BPA) and perfluoroalkyl substance have immunotoxic properties. Immunotoxic effects of chemicals may manifest in an altered immune system profile at birth. Immunoglobulin E, thymic stromal lymphopoietin (TSLP), and interleukin-33 (IL-33) are integral in the etiology of childhood allergy and detectable at birth. The objective of this study was to determine the association between maternal levels of phthalates, bisphenol A (BPA), and perfluoroalkyl substances and elevated umbilical cord blood levels of IgE, TSLP, and IL-33. This study utilized data collected in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a trans-Canada cohort study of 2001 pregnant women. Of these women, 1258 had a singleton, term birth and cord blood sample. A Bayesian hierarchical model was employed to determine associations between log-transformed continuous variables and immune system biomarkers while adjusting for potential confounding from correlated environmental contaminants. Inverse, nonlinear associations were observed between maternal urinary MCPP levels and elevated levels of both IL-33/TSLP and IgE and between maternal urinary BPA levels and elevated levels of IL-33/TSLP. In this primarily urban Canadian population of pregnant women and their newborns, maternal urinary and plasma concentrations of phthalate metabolites, BPA, and perfluoroalkyl substances were not associated with immunotoxic effects that manifest as increased odds of elevated levels of IgE, TSLP or IL-33.

1. Introduction [1]

The fetal time period is a critical window of immune system development and heightened susceptibility to the adverse effects of environmental exposures (Dietert et al., 2000; Holsapple et al., 2004; Selgrade, 2007). This susceptibility stems from

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[1] TSLP=thymic stromal lymphopoietin, IL-33=interleukin-33, IgE-=immunoglobulin E, BPA=bisphenol A, MEP=mono ethyl phthalate, MBP=mono butyl phthalate, MBzP=mono benzyl phthalate, MCPP=mono-3-carboxypropyl phthalate, MEHP=mono-2-ethylhexyl phthalate, MEHHP=mono-(2-ethyl-5-hydroxylhexyl phthalate), MEOHP=mono-(2-ethyl-5-oxohexyl) phthalate, MCHP=mono cyclohexyl phthalate, MOP=mono-n-octyl phthalate, MNP=mono-isoonyl phthalate, PFOA= Perfluorooctanoic acid, PFOS= Perfluorooctane sulfonate, PFHxS= Perfluorohexane sulfanoate.

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the immaturity of fetal organ systems and undeveloped detoxification systems (Barr et al., 2007). Exposure to environmental contaminants during this time can promote permanent, irreversible changes to immune system development and increase risk of an allergic phenotype (Holladay and Smialowicz, 2000; Martino and Prescott, 2011). Exploration of in utero exposures that may precipitate these changes is, therefore, critical to understanding the etiology of childhood allergic disease (Prescott and Clifton, 2009).

Epidemiologists and toxicologists have hypothesized that phthalates (Bornehag and Nanberg, 2010; Kimber and Dearman, 2010), bisphenol A (BPA) (Midoro-Horiuti et al., 2009) and perfluoroalkyl substances (Dewitt et al., 2012; Fletcher et al., 2009) may have immunotoxic properties. These contaminants are ubiquitous in the environment; the majority of adults have detectable concentrations in their urine or plasma (NHANES, 2013; Saravanabhavan et al., 2013; Health Canada, 2013). Moreover, maternal urinary or plasma concentrations of phthalates, BPA, and perfluoroalkyl substances results in fetal exposure as these contaminants are known to cross the placenta (Mørck et al., 2010; US DHHS, 1995; Li et al., 2013).

Despite the ubiquity of these contaminants and potential for immunotoxic effects, the epidemiologic literature regarding the association between prenatal exposure to these contaminants and childhood allergic diagnoses is limited. Moreover, validity of studies that examine childhood allergic diagnosis is challenged by: (1) confounding from childhood exposures to allergy risk factors and (2) outcome misclassification inherent in the diagnosis of childhood allergic disease (Ballmer-Weber, 2014; Lipozencić and Wolf, 2010; Reed, 2006).

The immunotoxic effects of in utero environmental contaminant exposure may manifest in altered levels of immune system biomarkers at birth. An altered immune system profile at birth is a risk factor for childhood allergy (Dietert, 2009; Martino and Prescott, 2011; Warner, 2004). The immune system biomarkers, immunoglobulin E (IgE), interleukin-33 (IL-33) and thymic stromal lymphopoietin (TSLP), are detectable in cord blood (Ashley-Martin et al., 2015). Elevated levels are associated with inflammatory processes and allergic disease in later life (Bartemes and Kita, 2012; Lambrecht and Hammad, 2013). Cord blood IgE levels have been previously used as a means of assessing the immunotoxic effects of in utero environmental contaminant exposure (Herr et al., 2011; Okada et al., 2012; Wang et al., 2011). TSLP and IL-33 have recently been recognized for their etiologic role in atopic dermatitis, the earliest manifestation of childhood allergy (Brandt and Sivaprasad, 2011; Lee et al., 2010). Unlike other cytokines that are produced from hematopoietic cells (Abbas et al., 2013), epithelial cell production of TSLP and IL-33 is not dependent on the presence of a functioning, developed immune system function (Oliphant et al., 2011). Analysis of TSLP and IL-33 levels in cord blood provides a novel means for examining the susceptibility of the newborn immune system to the potential adverse effects of in utero exposure to environmental contaminants.

The objective of this study was to determine the association between maternal levels of phthalates, bisphenol A (BPA), and perfluoroalkyl substances and elevated umbilical cord blood levels of IgE, TSLP, and IL-33 in Canadian birth cohort. A secondary objective was to determine how relationships may differ by infant sex. Due to the co-occurrence of phthalate metabolites within common household products (e.g. cosmetics, plastics), individuals are routinely exposed to multiple phthalate metabolites simultaneously (Dodson et al., 2012). The concentrations of multiple perfluoroalkyl substances in household dust have been shown to be correlated (D'Hollander et al., 2010). We employed an analytical approach to account for the potential effects of correlated exposures.

2. Materials and methods

2.1. Study population and data sources

This study used data and biospecimens from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study Biobank, a trans-Canada cohort study of 2001 pregnant women from 10 Canadian cities recruited during 2008–2011 (Arbuckle et al., 2013). The target population was pregnant women and their newborns who reside in these 10 urban regions and surrounding catchment areas. Approximately 6% of study participants live in a rural area according to postal forward sortation area. Study participants were contacted throughout pregnancy at pre-specified time points to obtain data and biospecimens. Briefly, women were eligible for inclusion if they were <14 weeks gestation at time of recruitment, ≥ 18 years of age, able to communicate in French or English, and planning on delivering at a local hospital (Arbuckle et al., 2013). The population in the present investigation was mothers who had a singleton, live, term birth (≥ 37 weeks) and a cord blood sample suitable for analysis. Cord blood samples ($n=5$) that were determined to be contaminated with maternal blood based on an elevated immunoglobulin A (IgA) level ($\geq$ 10 μg/mL) were excluded from the analysis (Ownby et al., 1996). A comparison of the full cohort with chemical data and the analytical sample demonstrated no notable differences in age, smoking or chemical concentrations between the two groups. Mean birth weight (g) was higher in the analytical sample (mean (SD) $=3530$ (454)) compared to the whole cohort (mean (SD) $=3433.2$ (583.5)). As the analytical sample did not include preterm or multiple births, this difference is expected. This study received ethical approval from Health Canada, St. Justine's Hospital (Montreal, QC), and the IWK Health Centre (Halifax, NS) and all participants signed informed consent forms.

2.2. Environmental contaminant exposure

BPA and 11 phthalate metabolites were measured in maternal urine collected during the 1st trimester as shown in Table 1 and as previously described (Arbuckle et al., 2014). Briefly, chemical analysis of urine samples was carried out at the Laboratoire de Toxicologie, Institut National de Santé Publique du Québec (Québec, QC, Canada), accredited by the Standards Council of Canada. Phthalates in urine were analyzed by LC–MS/MS with an Ultra Performance Liquid Chromatography (UPLC) coupled with a Quattro Premier XE tandem mass spectrometer following enzymatic deconjugation. Total BPA in urine were measured with a GC Agilent 6890 N GC–MS–MS instrument (Agilent Technologies; Mississauga, ON, Canada) coupled with a Quattro Micro GC tandem mass spectrometer (Waters; Milford, Massachusetts, USA). An enzymatic hydrolysis freed the conjugated compounds in the urine, the samples were then derivatized and the derivatives extracted and analyzed. Perfluoroalkyl substances were measured in study participant 1st trimester plasma using a Water Acquity UPLC–MS–MS operated in the MRM mode with an electrospray ion source in negative mode.

2.3. Fetal markers of immune system function

Immune system biomarkers were measured in the plasma of umbilical cord blood samples in the Department of Microbiology & Immunology, Dalhousie University, Halifax, NS using ELISA. TSLP concentrations were determined using a commercial antibody kit (Biolegend; San Diego, CA, USA). IL-33 concentrations were assessed using antibodies from an R & D systems duoset (Minneapolis, MN, USA). ELISA kits (EBioscience; San Diego, CA, USA) were also used to assess both total IgE and IgA concentrations. ELISA

Table 1
Geometric mean of environmental contaminants (μg/L) by categories of TSLP, IL-33, and IgE (MIREC study, 2008–2011).

Chemical (μg/L)	LOD (μg/L)	% > LOD	IL-33/TSLP (pg/mL)		IgE (ku/L)	
			≥ 80% GM (SD)	< 80% GM (SD)	≥ 0.5 ku/L GM (SD)	< 0.5 ku/L GM (SD)
Phthalate metabolites & BPA (n=1137)[a]						
Mono-ethyl phthalate (MEP)	0.5	99.8	33.9 (3.9)	39.0 (4.1)	32.4 (3.8)	39.3 (4.1)
Mono-n-butyl phthalate (MBP)	0.2	99.7	12.6 (2.5)	13.3 (2.3)	12.9 (2.4)	13.2 (2.3)
Mono-benzyl phthalate (MBzP)	0.2	99.5	5.5 (2.8)	6.0 (2.7)	6.4 (3.0)	5.9 (2.6)
Mono-3-carboxyypropyl phthalate (MCPP)	0.2	83.9	0.9 (2.6)	1.0 (3.0)	0.9 (2.7)	1.0 (3.0)
Mono-2-ethylhexyl phthalate (MEHP)	0.2	98.3	2.5 (2.6)	2.7 (2.5)	2.6 (2.7)	2.6 (2.5)
Mono-(2-ethyl-5-hydroxyhexyl) (MEHHP)	0.4	99.3	9.4 (2.6)	10.7 (2.5)	10.4 (2.7)	10.6 (2.4)
Mono-(2-ethyl-5-oxohexyl) (MEOHP)	0.2	99.7	6.8 (2.5)	7.5 (2.3)	7.4 (2.5)	7.4 (2.3)
Bisphenol A (BPA)	0.2	86.6	0.9 (2.6)	0.9 (2.8)	0.9 (2.6)	0.9 (2.8)
Mono cyclohexyl phthalate (MCHP)	0.2	7.4				
Mono-n-octyl phthalate (MOP)	0.6	3.0				
Mono-isononyl phthalate (MNP)	0.4	1.1				
Mono-methyl phthalate (MMP)	5	14.0				
Perfluoroalkyl substances (n=1242)						
Perfluorooctanoic acid (PFOA)	0.3	99.8	1.7 (1.9)	1.7 (1.8)	1.7 (1.9)	1.6 (1.8)
Perfluorooctane sulfonate (PFOS)	0.1	99.8	4.7 (1.9)	4.5 (1.8)	4.6 (1.9)	4.6 (1.8)
Perfluorohexane sulfanoate (PFHxS)	0.3	96.0	1.0 (2.2)	1.0 (2.3)	1.0 (2.4)	1.0 (2.3)

[a] Geometric means and standard deviations are adjusted for specific gravity; LOD=limit of detection, GM=geometric mean, SD=standard deviation.

assays were performed according to manufacturer's instructions with the exception that plates were coated with sodium bicarbonate buffer (pH 8.3–8.5) and blocked with 2% BSA in PBS instead of using the manufactures coating and blocking buffers. The inter-assay and intra-assay CVs for IL-33 were 5.9% and 11.3% respectively; for TSLP inter and intra-assay CVs were 6.0% and 8.1% respectively. The inter-assay and intra-assay CVs were 3.2% and 6.5% respectively for IgE and 5.2% and 10.4% respectively for IgA. These coefficients of variation were determined empirically in our study using the standard curves and sample controls on each ELISA plate.

2.4. Statistical analysis

Due to the high percentage of samples below the limit of detection (LOD), each immune system biomarker was categorized as a binary variable. A composite variable was developed to identify samples with elevated concentrations of both TSLP and IL-33 (IL-33/TSLP) as these cytokines are highly correlated (Spearman correlation coefficient=0.8). TSLP and IL-33 were categorized at the 80th percentile (TSLP=554 pg/mL; IL-33=879 pg/mL) because there are no pre-existing thresholds. Elevated concentrations of the composite IL-33/TSLP variable were defined as those samples that had elevated concentrations (≥80%ile) of both TSLP and IL-33. The cut-off percentile for IgE was defined at 1.2 ng/mL (0.5 kU/L), a cut-off point previously used in studies of cord blood IgE (Pesonen et al., 2009; Sadeghnejad et al., 2004).

Maternal urinary measures of 11 phthalate metabolites and BPA collected from a spot urine sample in the 1st trimester were available in the MIREC study (Table 1). Four phthalate metabolites (MCHP, MOP, MNP, MMP) were not examined in multivariate analysis due to the low proportion of values above the limit of detection (% >LOD MCHP=7.4, MOP=3.0, MNP=1.1, MMP=14.0). Three of the phthalate metabolites are primary (MEHP) and secondary (MEHHP, MEOHP) metabolites of the parent compound Di(2-ethylhexyl) phthalate (DEHP) (Hauser and Calafat, 2005). Considering the high correlation (Pearson correlation coefficient=0.9) between these metabolites, they were not analyzed as individual metabolites. Rather, metabolite concentrations were summed to create an index of DEHP metabolite exposure as previously reported (Hoppin et al., 2013). Maternal measures of three perfluoroalkyl substances were collected from 1st trimester plasma (Table 2). All values less than the LOD were substituted as LOD/2.

As the distribution of the environmental contaminants was non-normal, chemical concentrations were log-transformed to calculate descriptive statistics and perform multivariate analysis. Geometric means and standard deviations were calculated for the all environmental contaminants according to high and low levels of the immune system biomarkers. Concentrations of phthalate metabolites and bisphenol A were adjusted for urinary specific gravity according to the following formula $P_c=P_i$ [$(SG_m-1)/(SG_i-1)$] where: P_c=SG adjusted metabolite concentration (μg/ml), P_i =observed metabolite concentration, SG_i =specific gravity of the urine sample, and SG_m=median SG for the cohort (Just et al., 2010).

As the distribution of the environmental contaminants was normal upon log-transformation, the Pearson correlation coefficient was used to examine correlation among the chemicals. The Pearson correlation coefficients of log-transformed phthalate metabolites and bisphenol A ranged from 0.3 (between MEP and BPA) to 0.6 (between MBP and DEHP metabolites). The correlation coefficients of the log-transformed perfluoroalkyl substances ranged from 0.5 (between PFOA and PFHxS) to 0.6 (between PFOA and PFOS). Bayesian hierarchical logistic regression models were, therefore, employed to estimate odds ratios (OR) and 95% credible intervals (CI) for the association between the environmental contaminants and immune system biomarkers. The outcome variables were elevated IL-33/TSLP and elevated IgE (as defined above). This approach facilitates inclusion of correlated exposures and is not subject to the challenges of convergence and unstable estimates faced by maximum likelihood regression models (Maclehose et al., 2007). A separate hierarchical model was developed for each chemical class (e.g. phthalates,perfluoroalkyl substances) and outcome (IL-33/TSLP and IgE). As the correlation between BPA and phthalate metabolites was comparable to the within-phthalate correlation (e.g. MBP–BPA correlation coefficient=0.5), BPA was included in the phthalate model.

The Bayesian model was run with three chains and 5000 iterations with the first 500 iterations discarded as a burn-in period. The prior distribution for the parameter estimates of the exposure variables was modeled as a normal distribution (0, Φ) where Φ was modeled as a half-normal distribution (mean=0,

Table 2
Maternal demographic characteristics, MIREC Study, Canada, 2008–2011 ($n=1258$).[a]

Characteristic	N (%)
Maternal demographic	
Maternal age (yr)	
≤ 24	60 (4.8)
25–29	270 (21.5)
30–34	452 (35.9)
≥ 35	476 (37.8)
Household Income ($CAD)	
≤ 30,000	90 (7.4)
30,001–50,000	117 (9.7)
50,001–100,000	515 (42.6)
> 100,000	487 (40.3)
Parental smoking[b]	
No	1008 (80.1)
Yes	249 (19.9)
Pet ownership	
No	560 (44.5)
Yes	698 (55.5)
Maternal reproductive & medical history	
Pre-pregnancy BMI[c]	
Underweight (< 18.5)	27 (2.3)
Normal (18.5–24.9)	718 (60.4)
Overweight (25 –29.9)	272 (22.9)
Obese (≥ 30)	171 (14.4)
Maternal allergy[d]	
No	1204 (95.7)
Yes	54 (4.3)
Parity	
Nulliparous	526 (41.9)
Primiparous	512 (40.8)
Multiparous	217 (17.3)
Infant characteristics	
Infant sex	
Male	672 (53.5)
Female	585 (46.5)
Birth weight (g)	
< 2500	11 (0.9)
2500– < 3500	606 (48.2)
3500– < 4000	449 (35.7)
≥ 4000	192 (15.3)

[a] Subgroup total may not equal 1258 due to missing data.
[b] Defined as either the mother or father smoking during pregnancy.
[c] World Health Organization Classification (WHO, 2000).
[d] Defined as use of maternal allergy medication.

variance = 100) (Spiegelhalter et al., 2004). This uninformative prior distribution was chosen to reflect lack of prior knowledge regarding the association between these chemicals and newborn immune system development. The distribution is uninformative due to the large variance. In comparison to models that apply a fixed variance and resulting fixed degree of estimate shrinkage toward the prior mean, this approach allows the degree of shrinkage to vary depending on how closely the data fit the prior distribution (Maclehose et al., 2007). Model convergence was assessed by visual assessment of trace plots and by convergence diagnostic tests (Gelman–Rubin convergence test < 1.05; R-hat = 1)(Yau, 2014). Details on the model are provided in Appendix A (available in Supplementary material).

Prior to inclusion in the hierarchical models, the linearity of each contaminant-immune system biomarker association was assessed using restricted cubic spline models (Desquilbet and Mariotti, 2010). Knots were set at the 5th, 50th, and 95th percentiles. Environmental contaminants that met the criteria for linearity were log-transformed and those that did not were modeled with a quadratic term.

Potential covariates were identified using a causal model (Greenland et al., 1999). The causal models were constructed using evidence regarding predictors of the exposures (Arbuckle et al., 2014; Kudo and Kawashima, 2003) and predictors of the immune system biomarkers (Ashley-Martin et al., 2015; Scirica et al., 2007). The minimal adjustment sets for confounding were identified using DAGitty (Textor and Hardt, 2011). Specific gravity was forced into the adjusted phthalate/BPA model to account for heterogeneity in urinary dilution (Arbuckle et al., 2014). As childhood allergy prevalence differs by sex (Kynyk et al., 2011), analyses were also stratified by sex.

Descriptive statistics were performed in SAS V.9.2 (Cary, NC). Bayesian modeling was performed using R v.3.0.3 (The R Foundation for Statistical Computing) and Openbugs (v 3.2.1 Members of OpenBUGS Project Management Group).

3. Results

Of the 2001 women recruited, 18 withdrew and asked that all their data and biospecimens be destroyed. Of the remaining 1983 subjects, 1363 women had a cord blood sample. Of these 1363 samples, a total of 105 samples were excluded for a high IgA concentration, pre-term birth (< 37 weeks), multiple birth, or samples with insufficient sample for analysis, and no chemical data for either phthalates, BPA and the perfluoroalkyl substances leaving 1258 subjects for inclusion in the statistical analysis. An additional 121 women did not have maternal urinary measurements of phthalates and an additional 16 women did not have maternal plasma measurements of perfluoroalkyl substances.

Table 1 depicts geometric mean first trimester concentrations of phthalates and perfluoroalkyl substances according to categories of the immune system biomarkers. Maternal demographic, reproductive, and infant characteristics are depicted in Table 2. The majority of study participants were greater than 30 years of age, had a household income greater than $50,000, were non-smokers, and of normal BMI.

Significant non-linear associations were observed between the

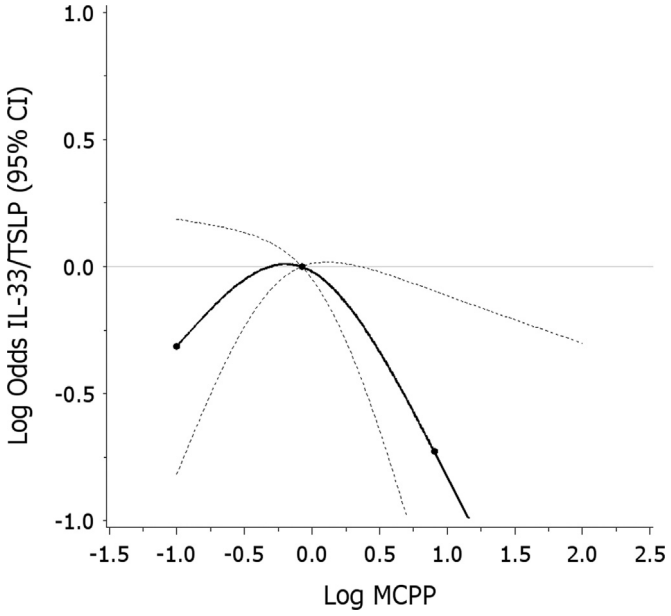

Fig. 1. Restricted cubic spline curve of association between maternal urinary $\log_{10}$ MCPP concentrations and high IL-33/TSLP cord blood concentrations (MIREC study, 2008–2011). *Adjusted for maternal age, specific gravity. Dotted lines represent 95% confidence interval, dots represent knots defined at the 5th, 50th, and 95th percentiles.

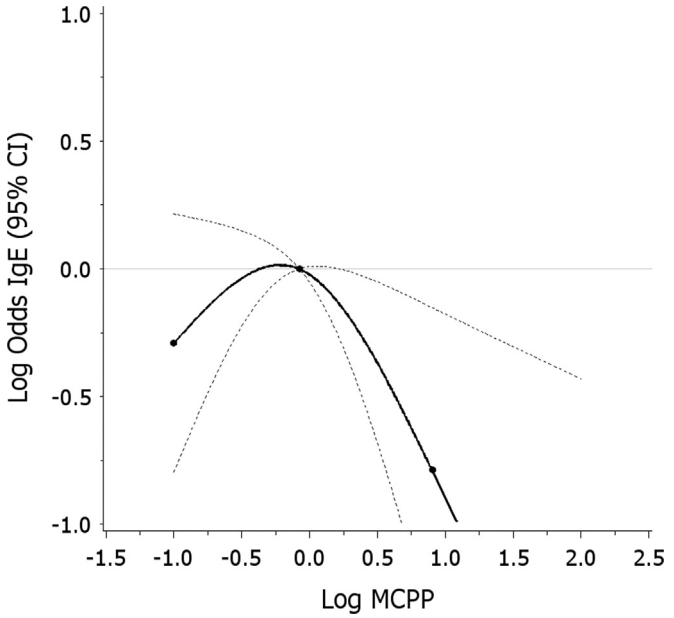

Fig. 2. Restricted cubic spline curve of association between maternal urinary $\log_{10}$ MCPP urinary concentrations and high IgE cord blood levels (MIREC study, 2008–2011). *Adjusted for maternal age, specific gravity. Dotted lines represent 95% confidence interval, dots represent knots defined at the 5th, 50th, and 95th percentiles.

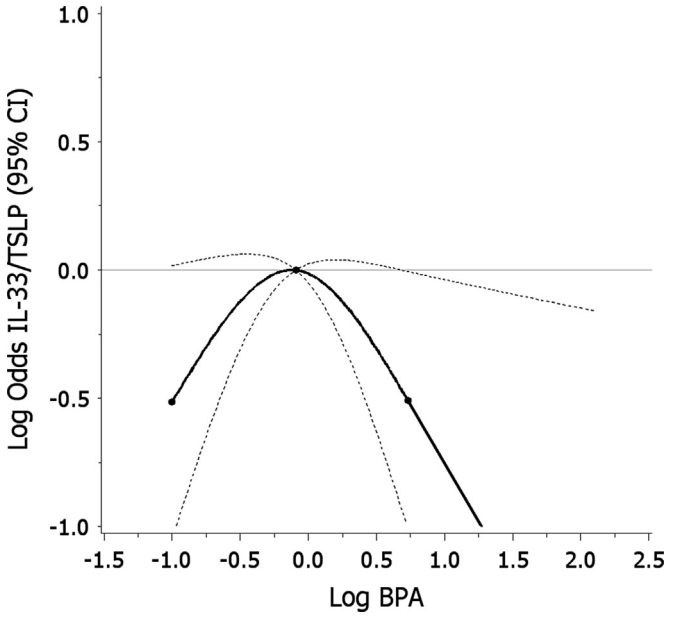

Fig. 3. Restricted cubic spline curve of association between maternal urinary $\log_{10}$ BPA concentrations and high IL-33/TSLP cord blood concentrations (MIREC study, 2008–2011). *Adjusted for maternal age, specific gravity. Dotted lines represent 95% confidence interval, dots represent knots defined at the 5th, 50th, and 95th percentiles.

phthalate metabolite MCPP (*P*-value=0.008 test for linearity; *P*-value =0.01 test for association) and BPA (*P*-value test for linearity=0.02, *P*-value test for association 0.05) and odds of elevated IL-33/TSLP (Figs. 1–2). MCPP was also observed to have a significant, non-linear association with odds of elevated IgE (*P*-value linearity=0.01, *P*-value association=0.02) (Fig. 3). Thus, quadratic terms for both MCPP and BPA were included in the IL-33/TSLP model and a quadratic term for MCPP was included in the IgE model. There were no significant non-linear associations between

Table 3
Bayesian odds ratios of elevated (≥ 80%) cord blood IL-33/TSLP (pg/mL) and maternal concentrations of $\log_{10}$ environmental contaminants (μg/L) (MIREC study, 2008–2011).

Contaminant	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)
Phthalates & BPA[a] (*n*=1137)		
MEP	0.9 (0.7–1.1)	0.9 (0.7–1.1)
MBP	1.0 (0.6–1.4)	1.0 (0.7–1.4)
MBzP	1.0 (0.7–1.3)	0.9 (0.7–1.3)
MCPP	0.9 (0.7–1.2)	0.9 (0.7–1.2)
MCPP*MCPP	0.8 (0.5–1.0)	0.8 (0.5–1.1)
∑ DEHP	0.9 (0.6–1.2)	0.9 (0.7–1.3)
BPA	1.0 (0.7–1.3)	1.0 (0.7–1.3)
BPA*BPA	0.8 (0.5–1.0)	0.8 (0.5–1.0)
Perfluoroalkyl substances[b] (*n*=1242)		
PFOA	1.1 (0.6–1.9)	1.1 (0.6–1.8)
PFOS	1.1 (0.6–1.9)	1.1 (0.6–1.9)
PFHxS	1.0 (0.7–1.4)	1.0 (0.7–1.4)

[a] Adjusted for maternal age, specific gravity.
[b] Adjusted for maternal age, sex.

Table 4
Bayesian odds ratio of elevated (≥ 0.5 ku/L) cord blood IgE (ku/L) and maternal concentrations of $\log_{10}$ environmental contaminants (μg/L) (MIREC study, 2008–2011).

Contaminant	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Phthalates & BPA[a] (*n*=1137)		
MEP	0.8 (0.6–1.0)	0.8 (0.6–1.0)
MBP	1.0 (0.6–1.4)	0.9 (0.6–1.3)
MBzP	1.3 (0.9–1.8)	1.2 (0.9–1.7)
MCPP	0.8 (0.6–1.1)	0.8 (0.6–1.1)
MCPP*MCPP	0.7 (0.5–1.0)	0.7 (0.5–1.0)
∑ DEHP	1.0 (0.7–1.4)	1.0 (0.7–1.5)
BPA	1.0 (0.8–1.4)	1.0 (0.7–1.3)
Perfluoroalkyl substance[b] (*n*=1242)		
PFOA	1.1 (0.6–2.0)	1.1 (0.6–1.9)
PFOS	1.1 (0.6–2.0)	1.1 (0.6–1.9)
PFHxS	1.0 (0.7–1.4)	1.0 (0.7–1.4)

[a] Adjusted for maternal age, specific gravity.
[b] Adjusted for maternal age, sex.

the perfluoroalkyl substances and either IL-33/TSLP or IgE.

Tables 3 and 4 depict results of the Bayesian hierarchical models. The quadratic term for maternal urinary BPA concentrations was inversely associated with odds of elevated IL-33/TSLP (aOR=0.8; 95% CI: 0.5–1.0) (Table 3). The quadratic term for MCPP was inversely associated with odds of elevated IgE (aOR=0.7; 95% CI: 0.5–1.0) (Table 5). Credible intervals for all other phthalates and perfluoroalkyl substances included the null value (Tables 3 and 4). Results were similar among male and female infants in all statistical models (Supplementary Tables 1–4).

4. Discussion

In this study, we sought to determine the association between first trimester maternal levels of phthalates, BPA, and perfluoroalkyl substances and elevated umbilical cord blood levels of IgE, TSLP and IL-33. This question was motivated by the fact that in utero environmental contaminant exposure may alter newborn immune system development and promote risk of an allergic phenotype (Luebke et al., 2006; Martino and Prescott, 2011). Consistent with the inverted U-shaped curve observed in the restricted cubic spline analyses, we found an inverse, non-linear association between maternal urinary MCPP levels and elevated

Table 5
Birth cohort studies examining the association between prenatal exposure to phthalates, BPA or perfluoroalkyl substances and measures of childhood allergy.

Study	Target population	Maternal exposure concentrations (median)	Outcome measures	Major finding
MIREC	Primarily Caucasian, urban women residing in Canada	BPA=0.8 ug/L MBzP =5.0 ug/L MCPP=0.9 ug/L PFOA=1.7 ug/L, PFOS=4.6 ug/L, PFHxS=1.0 ug/L	Cord blood IgE, TSLP, IL-33	
Whyatt et al., 2014	Dominican African American womenresiding in New York city	MBzP=13.6 ug/L MnBP=37.5 ug/L (GM)	Diagnosed asthma	MBzP asthma RR =1.17 95% CI:1.01–1.35 MnBP asthma RR=1.25 95% CI:1.04–1.51
Just et al., 2012 Donohue et al., 2013	Dominican African American womenresiding in New York city	MBzP =13 ng/mL BPA =1.8 ng/mL (GM)	Atopic eczema ages 2,5 Wheeze in childhood	MBzP and eczema age 2 RR=1.595% CI:1.2–1.9 BPA and wheeze age 5 OR= 0.7 95% CI:0.5–0.9
Wang et al., 2014	Taiwanese women	MBzP =1.84 ug/g creatinine (GM)	Cord blood IgE	MBzP and IgE Males β (*p*-value)=0.3(0.3) Females β (*p*-value)=−0.4(0.3)
Spanier et al., 2012	Mid-West US	BPA =2.2 ug/g creatinine	Wheeze	BPA and wheeze birth to age 3OR=1.2 95% CI:1.0–1.5
Okada et al., 2012	Japanese	PFOS= 5.2 ng/mL PFOA= 1.3 ng/mL	Cord blood IgE	PFOA and IgE Males β (95% CI)=1.3 (−2.2,4.7) Females β (95% CI)=−3.1(−5.4, 0.7)
Wang et al., 2011	Taiwanese	PFOA=1.7 ng/mL, PFOS=5.5 ng/mL PFHxS=0.035 ng/mL	Cord blood IgE	PFOA and IgE Males β (*p*-value)=0.2(0.02) Females β (*p*-value)=0.06(0.8)

levels of both IL-33/TSLP and IgE in the Bayesian hierarchical model. An inverse, non-linear association was also observed between maternal urinary BPA levels and elevated levels of IL-33/TSLP in the Bayesian hierarchical model, similarly consistent with the association observed in the restricted cubic spline analysis. These findings suggest that traditional monotonic assumptions regarding dose–response relationships may not be an appropriate characterization of endocrine disruptor related health effects. Clinical interpretation of the observed non-linear relationships requires evaluation in a cohort of children with allergic disease data. We did not observe any associations between the contaminants of interest and elevated levels of IgE, or IL-33/TSLP where the credible interval did not include the null.

4.1. Prenatal exposure to phthalate metabolites and measures of childhood allergy

The potential role of phthalate exposure in childhood allergy etiology is supported by experimental evidence demonstrating that these chemicals exhibit adjuvant-like properties (Kimber and Dearman, 2010). Epidemiological evidence regarding prenatal phthalate exposure is, however, equivocal. To our knowledge, authors of two birth cohort studies in New York (Just et al., 2012; Whyatt et al., 2014) and Taiwan (Wang et al., 2014) have examined the association between prenatal urinary phthalate exposure measurements and measures of childhood allergy. One recent cohort study examined the association between a proxy measure of exposure and childhood allergy (Shu et al., 2014). The Taiwanese birth cohort reported no statistically significant associations between phthalate metabolites and cord blood IgE (Wang et al., 2014). Investigators of the New York city cohort reported a significant association between maternal urinary phthalate metabolite (MBzP) concentrations and eczema at two but not five years of age (Just et al., 2012). In a later follow-up of this cohort, authors report a significant association between prenatal MBzP exposure and childhood asthma diagnosed between the ages of 5 and 11 (Whyatt et al., 2014). Considering that the present study also identified a slight positive association between cord blood IgE levels and MBzP exposure (OR=1.2 95% CI: 0.9–1.7), further investigation into the role of this metabolite in childhood allergy etiology is warranted. Divergence in other results among the New York (Just et al., 2012), Taiwanese (Wang et al., 2014) and present study may be explained by the heterogeneity in target populations, exposure levels, or outcome measures (Table 5). The different units of measurement in MIREC (μg/L) and the Taiwanese study (μg/g creatinine) preclude direct comparison of exposure levels. Median levels in the MIREC study were, however, lower than those reported in the New York cohort. This difference may be one explanation for the lack of observed effect in the present study. Authors of the Dampness in Buildings and Health study in Sweden reported that the presence of polyvinyl chloride flooring in children's homes at age 1–5 years was associated with a two-fold increased risk of self-reported childhood asthma after 10 years of follow-up (Shu et al., 2014). The lack of direct phthalate metabolite measurements in this study precludes comparison of exposure levels with other birth cohort studies.

4.2. Prenatal exposure to BPA and measures of childhood allergy

Experimental evidence has demonstrated that BPA may induce an asthmatic pshenotype by elevating IgE levels and promoting eosinophilic inflammation (Midoro-Horiuti et al., 2009; Nakajima et al., 2012). However, epidemiological literature regarding prenatal BPA exposure and childhood allergy is limited and inconsistent. A birth cohort study from the mid-west US (Spanier et al., 2012) reported a positive association between maternal urinary

BPA levels and childhood wheeze whereas the NY birth cohort investigators (Donohue et al., 2013) reported an inverse association. In contrast, in the present study we identified a non-linear association between BPA and elevated IgE. In addition to differences outlined in Table 5, a possible explanation for the heterogeneity in results is exposure misclassification. The short half-life (Stahlhut et al., 2009), complexity of metabolism (Zalko et al., 2003), and potential contamination of urinary samples with external sources of BPA (e.g. laboratory equipment) (Ye et al., 2013) create material challenges to accurately estimating fetal BPA levels.

4.3. Prenatal exposure to perfluoroalkyl substances and measures of childhood allergy

In experimental models, perfluorinated compounds have been shown to induce immune system profile changes indicative of an allergic phenotype (Dewitt et al., 2012; Fairley et al., 2007). Two previous birth cohort studies reported that the association between gestational perfluorinated compound exposure and cord blood IgE levels differed by infant sex (Table 5) (Okada et al., 2012; Wang et al., 2011). These findings may be explained by the fact that PFOA has a longer half-live and slower renal clearance in males (Kudo and Kawashima, 2003). The lack of notable differences by sex in the PFOA and IgE model in the present study may be due to the relatively low percentage of cord blood samples with levels of IgE above 0.5 ku/L.

4.4. Strengths and limitations

This study benefited from the relatively large sample size in the MIREC study, the comparatively rich covariate data, and the use of novel immune system biomarkers. The study population was predominantly from urban regions in Canada. We employed analytical methods to control for correlated exposures (Maclehose et al., 2007) and assess non-linear associations. Furthermore, by shrinking effect estimates towards each other, Bayesian hierarchical models lower the likelihood of identifying a significant association by chance (Gelman et al., 2004).

This study was subject to at least five limitations common to observational studies. First, the short half life and rapid elimination of phthalates and BPA creates a source of potential misclassification bias as the body burden of these chemicals may vary on a daily basis (Braun et al., 2011; Ye et al., 2011; Stahlhut et al., 2009; Volkel et al., 2002). In pregnant women, the reported intraclass correlation (ICCs) for serial measurements of BPA throughout pregnancy has been very low, ranging from 0.11 to 0.32 ([Braun et al., 2011,Meeker et al., 2014,Quirós-Alcalá et al., 2013,Jusko et al., 2014]). A Canadian study of pregnant women reported an ICC of 0.33 for BPA based on first trimester 24 h urine voids (Fisher et al., 2014). Given the similarities in timing of measurement and study population, this value may be representative of the variability in MIREC measurements. The phthalate metabolite MCPP was reported to have considerable within person variability based on an ICC of 0.20 in a study of serial measurements in pregnant women (Cantonwine et al., 2014). Considering, however, that (1) that exposure misclassification is non-differential and (2) this study employed continuous rather than polytomous exposure variables, any potential misclassification bias likely attenuated effect estimates towards the null (Rothman et al. 2008; Wacholder, 1995). Reproduction of the present findings in cohort studies with serial phthalate and BPA measurements would be valuable in investigating the influence of this potential information bias. As our findings pertain to first trimester phthalate and BPA exposure only, reproduction in cohort studies with serial measurements would also be valuable in ascertaining the role of exposure during other trimesters. Due to their longer half-life, perfluoroalkyl acids are not subject to the degree of variability observed with the phthalates and BPA. First and second trimester maternal PFOA levels have been shown to be highly correlated ($r=0.9$) (Fei et al., 2007), suggesting that first trimester exposure levels may be indicative of exposure throughout pregnancy. Second, the MIREC study population was of higher income and more educated than the target population. This potential selection bias is unlikely to have biased the observed associations because the associations did not seem to be confounded by income or education. The socioeconomic characteristics of the MIREC population did, however, preclude our ability to assess associations among certain population subgroups including low income women with minimal secondary education. Third, the influence of residual confounding cannot be ruled out. We did not have information on certain risk factors for childhood allergy such as vitamin D (Muehleisen and Gallo, 2013) and maternal stress (Von Hertzen, 2002). Considering that an association between these variables and exposure to the contaminants of interest is not well established, it is unlikely that our observed associations are invalidated by lack of control for these variables. Fourth, the potential for non-differential misclassification of the immune system biomarkers exists. However, since within-person variability primarily occurs longitudinally (Rothers et al., 2011) rather than at birth, the extent of type 2 error resulting from this potential misclassification is thought to be minimal. Last, though the Bayesian hierarchical model facilitated analysis of correlated exposures, this model does not provide estimates of the potential health related effects of exposure mixtures or potential synergistic or antagonistic effects among chemicals.

4.5. Public health interpretations

Due to the lack of Canadian health-based biomonitoring guidelines for the contaminants of interest, interpretation of the present findings within a public health context is a challenge. On average, the phthalate and BPA exposure levels observed within the MIREC study are lower than other birth cohorts discussed (Table 5) and consistent with the temporal trend of declining body burden levels of many phthalates and BPA (NHANES, 2013; Zota et al., 2014). Health Canada recently took regulatory action to minimize exposure levels of BPA and certain phthalates to children (Health Canada, 2010, 2011). Though these actions are unlikely to directly affect prenatal exposure levels in the current study, the regulations may promote heightened consumer awareness and subsequent attempts to minimize use of BPA and phthalate-laden products.

Plasma concentrations of PFOA and PFOS have also been decreasing over time, but concentrations of other perfluoroalkyl substances (e.g. perfluorononanoic acid (PFNA)) have been on the rise (Glynn et al., 2012; NHANES, 2013; Okada et al., 2013). The decrease in PFOA and PFOS concentrations is explained by the cessation of PFOA and PFOS production within the last 10 years (Prevedouros et al., 2006; Health Canada, 2007). The persistent nature and long half-life of these compounds (Kudo and Kawashima, 2003) explains the continued presence of detectable concentrations of these chemicals in maternal plasma. The second cycle of the Canadian Health Measures Study reported that the majority of Canadians have detectable concentrations of some of these less common compounds such as PFNA (Health Canada, 2013). As such, continuing biomonitoring efforts could help to determine trends in levels and sources of exposure as well as investigate potential health effects.

The novel finding of a non-linear association between first trimester measures of MCPP and BPA and the immune system biomarkers of interest in this study is consistent with evidence

that endocrine disrupting chemicals may operate in a non-monotonic manner (Vandenberg et al., 2012). Further elucidation of these dose–response relationships and underlying biological mechanisms will be a valuable contribution to the development of health based biomonitoring guidelines for these contaminants.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.04.010.

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