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Metals exposure and risk of small-for-gestational age birth in a Canadian birth cohort: The MIREC study

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ARTICLE INFO

Article history:

Received 12 January 2015

Received in revised form

23 April 2015

Accepted 28 April 2015

Available online 15 May 2015

Keywords:

Biomonitoring

Pregnancy cohort study

Small for gestational age

Mercury

Cadmium

Lead

Arsenic

ABSTRACT

Background: Lead, mercury, cadmium and arsenic are some of the most common toxic metals to which Canadians are exposed. The effect of exposure to current low levels of toxic metals on fetal growth restriction is unknown.**Objective:** The aim of this study was to examine relationships between exposure to lead, mercury, cadmium and arsenic during pregnancy, and risk of small for gestational age (SGA) birth.**Methods:** Lead, mercury, cadmium and arsenic levels were measured in blood samples from the first and third trimesters in 1835 pregnant women from across Canada. Arsenic species in first trimester urine were also assessed. Relative risks and 95% confidence intervals were estimated using log binomial multivariate regression. Important covariates including maternal age, parity, pre-pregnancy BMI, and smoking, were considered in the analysis. An exploratory analysis was performed to examine potential effect modification of these relationships by single nucleotide polymorphisms (SNPs) in GSTP1 and GSTO1 genes.**Results:** No association was found between blood lead, cadmium or arsenic and risk for SGA. We observed an increased risk for SGA for the highest compared to the lowest tertile of exposure for mercury ($> 1.6 \mu\text{g/L}$, RR=1.56; 95% CI=1.04–2.58) and arsenobetaine ($> 2.25 \mu\text{g/L}$, RR=1.65; 95% CI=1.10–2.47) after adjustment for the effects of parity and smoking. A statistically significant interaction was observed in the relationship between dimethylarsinic acid (DMA) levels in urinary arsenic and SGA between strata of GSTO1 A104A (p for interaction=0.02). A marginally significant interaction was observed in the relationship between blood lead and SGA between strata of GSTP1 A114V (p for interaction=0.06).**Conclusions:** These results suggest a small increase in risk for SGA in infants born to women exposed to mercury and arsenic. Given the conflicting evidence in the literature this warrants further investigation in other pregnant populations.Crown Copyright © 2015 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Pregnant women and their fetuses are especially susceptible to the effects of exposure to a variety of environmental toxicants including lead, mercury, cadmium, and arsenic.

Metals are ubiquitous in the environment, and exposure occurs through ingestion of food, water, soil, or dust; inhalation from air; and through direct contact with consumer products (Health Canada, 2004, 2008, 2006). Some known consequences of high level

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<http://dx.doi.org/10.1016/j.envres.2015.04.018>

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exposures to these metals in the general population include: neurological deficits, cancer, renal impairment, convulsions, coma, and bone disease (Jarup, 2003; Duruibe et al., 2007). Only a few guidelines exist for metals (e.g., methylmercury) (Legrand et al., 2010), with more research needed on potential health effects, if any, of exposure to the low levels of metals to which most of the general Canadian populations are exposed.

Physiologic changes that occur during pregnancy can alter toxicokinetics and toxicodynamics of environmental chemicals, such as metals, in the pregnant woman's body. For example, bone resorption to help meet calcium demands can increase during pregnancy (Kovacs and Kronenberg, 1997) and release cumulative lead stores from bone into circulation resulting in an endogenous source of prenatal exposure (Gulson et al., 2003; Manton et al.,

2003; Téllez-Rojo et al., 2004). Increased maternal plasma volume, body fat, and body water, coupled with increased excretion, are designed for optimal nutrient supply and waste removal from the fetus (Mattison et al., 1991). However, little is known about the impact of these changes on metabolism and excretion of these substances during pregnancy and lactation, but they likely will differ depending on the chemical class or nature of the substance. Pregnancy is a period of dynamic growth and change for the developing embryo and fetus, thus, any insults to the *in utero* environment could result in suboptimal fetal development (Rice and Barone, 2000).

Growth restricted fetuses fail to reach their full genetic growth potential due to a decreased nutrient supply from the utero placental circulation (Cetin et al., 2004). Intrauterine growth restriction (IUGR) manifests as small for gestational age (SGA), defined as an infant weighing less than the 10th percentile for their gestational age and sex (Canadian Institute for Health Information, 2009). Size relative to gestational age is an established predictor of early childhood mortality and morbidity (Rahman et al., 2009). Children who are born SGA are more likely to have birth complications and are at increased risk for excessive weight gain, cardiovascular disease and insulin resistance syndrome later in life (Clayton et al., 2007). Metals are potential risk factors for SGA births, and are hypothesized to induce growth restriction through oxidative stress mediated pathways (Myatt, 2006). Specifically, when toxic metals are present in the maternal bloodstream, they may cause abnormal placental function and impair nutrient transport to the fetus through the indirect formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that cause oxidative stress by reacting with macromolecules and damaging them. When the vascular endothelium is damaged, endothelins are released, causing the smooth muscle around the blood vessels to contract. This vasoconstriction causes maternal blood pressure to increase and decreases the blood flow to the fetus (Pollock and Pollock, 2005). This reduced blood flow may cause ischemic damage, which could lead to fetal growth restriction and subsequent low birthweight (Llanos and Ronco, 2009).

The elimination half-lives of mercury, lead and cadmium in blood are 18 days, 30 days and 100 days respectively (Bernard, 1995). These metals are cumulative toxicants, and previous exposure can be detected after long periods of non-exposure (Bernard, 1995). A proportion of lead in the blood may be present

because of bone remodeling mobilizing lead that has been stored from previous exposure (Smith et al., 2002). In contrast, inorganic arsenic is rapidly cleared from blood. In humans, it has a half-life of 10 h (Hughes, 2006). Measurement of urinary arsenic levels is generally accepted as the most reliable indicator of recent arsenic exposure, given that arsenic absorbed from the lungs or the gastrointestinal tract is excreted in the urine within one to two days, while arsenic is cleared from blood within a few hours (ASTDR, 2007). However some papers have shown good correlation between urinary and blood arsenic (Hall et al., 2006).

The effects of lead, cadmium, mercury and arsenic have all been studied to varying degrees in the context of their effect on fetal growth outcomes such as small for gestational age (SGA) and low birthweight (LBW). In general, the literature regarding metal exposure and fetal growth outcomes is inconsistent. Some studies report an association (Rahman et al., 2009; Llanos and Ronco, 2009; Bellinger et al., 1991; Chen et al., 2006; Foldspang and Hansen, 1990; Hopenhayn et al., 2003; Kippler et al., 2011; Lee et al., 2010; Lin et al., 2011; Nishijo et al., 2004; Odland et al., 1999; Osman et al., 2000; Ramón et al., 2009; Shirai et al., 2010; Tian et al., 2009; Xie et al., 2013; Yang et al., 2003; Zhu et al., 2010) while others report no association (Odland et al., 1999; Osman et al., 2000; Ding et al., 2013; Daniels et al., 2007; Galicia-García et al., 1997; Jones et al., 2010; Sowers et al., 2002; Menai et al., 2012; Loiacono et al., 1992; Lucas et al., 2004). Few studies have examined low-level exposure as currently experienced in most developed countries such as Canada, thus any resultant health effects are relatively unknown. The aim of this study was to examine relationships between exposures to lead (Pb), mercury (Hg), cadmium (Cd) (as measured in blood) or arsenic (As) (as measured in blood and urine) during pregnancy and the risk of small for gestational age birth. Single nucleotide polymorphisms (SNPs) in GSTP1 and GSTO1 genes were explored as a potential modifier of the relationship between lead, cadmium, mercury or arsenic and SGA.

2. Methods

2.1. Study population

The Maternal–Infant Research on Environmental Chemicals

Table 1
Distribution of metal exposure in study population ($n=1835$).

	Below LOD ^a N (%)	Minimum	25th percentile	50th percentile	75th percentile	Maximum
Blood						
Lead (µg/dL)	0 (0)	0.17	0.43	0.59	0.81	4.04
Cadmium (µg/L)	11 (0.6)	< LOD	0.13	0.20	0.30	4.65
Mercury (µg/L)	141 (7.1)	< LOD	0.32	0.64	1.19	6.80
Arsenic (µg/L)	48 (2.5)	< LOD	0.51	0.75	1.13	33.00
Urine						
DMA(µg As/L)	261 (14.6)	< LOD	1.1	2.4	4.5	64.4
Arsenobetaine (µg As/L)	917 (51.2)	< LOD	< LOD	< LOD	3.4	1573.0
MMA (µg As/L)	1654 (92.4)	< LOD	< LOD	< LOD	< LOD	11.2
Arsenate (µg As/L)	1506 (84.1)	< LOD	< LOD	< LOD	< LOD	24.0
Arsenite (µg As/L)	1762 (98.4)	< LOD	< LOD	< LOD	< LOD	22.5
DMA (µg As/L) ^b	261 (14.6)	< LOD	1.6	2.4	3.8	44.1
Arsenobetaine (µg As/L) ^b	917 (51.2)	< LOD	< LOD	1.0	37.7	889.1
MMA (µg As/L) ^b	1654 (92.4)	< LOD	< LOD	< LOD	< LOD	7.7
Arsenate (µg As/L) ^b	1506 (84.1)	< LOD	< LOD	< LOD	0.8	24.1
Arsenite (µg As/L) ^b	1762 (98.4)	< LOD	< LOD	< LOD	< LOD	15.6

^a Limits of detection in blood: lead (0.10 µg/dL), cadmium (0.04 µg/L), mercury (0.12 µg/L), arsenic (0.23 µg/L); and in urine: DMA (0.75 µg As/L) and arsenobetaine (0.75 µg As/L).

^b Adjusted for specific gravity.

Table 2
Relative risk of SGA according to maternal characteristics.

Risk factor	SGA (%)	Total births	Crude RR (95% CI)	Adjusted RR (95% CI) ^a
Age				
< 29	36 (6.3)	568	Reference	
30–35	33 (5.1)	644	0.81 (0.51–1.28)	
36+	37 (5.9)	623	0.94 (0.60–1.46)	
Ethnicity				
White	83 (5.6)	1,496	Reference	
Not White	23 (6.8)	339	1.22 (0.78–1.91)	
Country of birth				
Foreign	25 (7.2)	348	Reference	
Canadian	81 (5.5)	1487	0.76 (0.49–1.17)	
Parity				
0	65 (8.1)	802	Reference	
1+	41 (4.0)	1,031	0.49 (0.34–0.72)	0.51 (0.35–0.74)
Education				
College/trade diploma or less	38 (5.5)	691	Reference	
Undergraduate degree	36 (5.4)	673	0.97 (0.62–1.52)	
Graduate degree	32 (6.8)	469	1.24 (0.79–1.96)	
Household Income				
\$100,000 or more	36 (5.1)	708	Reference	
\$70,001–100,000	31 (6.0)	514	1.19 (0.74–1.89)	
\$40,001–\$70,000	19 (6.2)	305	1.23 (0.71–2.10)	
< \$40,000	13 (5.8)	222	1.15 (0.62–2.13)	
Marital status				
Married or common law	97 (5.5)	1,747	Reference	
Single	9 (10.2)	88	1.84 (0.96–3.52)	
Pre-pregnancy BMI				
Underweight or normal	72 (6.6)	1,085	Reference	
Overweight or obese	25 (4.1)	613	0.61 (0.39–0.96)	
Smoking during pregnancy				
Never	59 (5.2)	1,129	Reference	
Former	27 (5.5)	487	1.06 (0.68–1.65)	1.08 (0.70–1.67)
Current	20 (9.2)	218	1.80 (1.08–2.85)	1.72 (1.07–2.77)
Alcohol consumption				
No alcohol	76 (5.5)	1,379	Reference	
Any alcohol	22 (7.6)	289	1.38 (0.87–2.18)	

^a This column contains results for covariates included in the final model (parity and smoking) using backward selection (p -value < 0.15).

Table 3
Association between metal exposure and SGA.

	SGA n (%)	Total births N	Crude RR (95% CI)	Adjusted RR (95% CI) ^a
Lead				
< 0.52 µg/dL	35 (4.7)	744	Reference	Reference
0.52–1.04 µg/dL	57 (6.6)	862	1.41 (0.93–2.12)	1.33 (0.88–1.99)
> 1.04 µg/dL	14 (6.1)	229	1.30 (0.71–2.37)	1.19 (0.65–2.18)
Mercury				
< 0.8 µg/L	59 (5.4)	1,086	Reference	Reference
0.8–1.6 µg/L	23 (4.8)	479	0.88 (0.55–1.41)	0.89 (0.55–1.42)
> 1.6 µg/L	24 (8.9)	270	1.64 (1.04–2.56)	1.56 (1.04–2.58)
Cadmium^b				
< 0.15 µg/L	31 (5.2)	593	Reference	Reference
0.15–0.3 µg/L	44 (5.5)	804	1.05 (0.67–1.64)	1.00 (0.64–1.56)
> 0.3 µg/L	31 (7.1)	438	1.35 (0.84–2.19)	1.26 (0.78–2.04)
Arsenic				
< 0.525 µg/L	30 (6.0)	498	Reference	Reference
0.525–1.05 µg/L	42 (5.1)	818	0.85 (0.54–1.34)	0.85 (0.54–1.34)
> 1.05 µg/L	34 (6.6)	519	1.09 (0.68–1.75)	1.08 (0.68–1.74)
DMA				
< 1.87 µg As/L	40 (6.5)	612	Reference	Reference
1.87–3.75 µg As /L	19 (4.2)	453	0.77 (0.43–1.37)	0.74 (0.42–1.32)
> 3.75 µg As /L	43 (5.9)	726	1.23 (0.69–2.22)	1.18 (0.66–2.12)
Arsenobetaine				
< 0.75 µg As/L	46 (4.8)	958	Reference	Reference
0.75–2.25 µg As/L	9 (5.1)	177	1.14 (0.56–2.28)	1.20 (0.60–2.41)
> 2.25 µg As/L	47 (7.2)	656	1.64 (1.10–2.47)	1.65 (1.10–2.47)

^a Adjusted for the effect of smoking and parity; DMA and arsenobetaine also adjusted for specific gravity.

^b Analysis of cadmium exposure is not adjusted for smoking.

(MIREC) Study is a prospective cohort study, described in detail elsewhere (Arbuckle et al., 2013) and summarized here. Between 2008 and 2011, 2001 pregnant women were recruited in the first trimester of pregnancy from 10 study sites across Canada. Exclusion criteria included: inability to communicate and consent in either French or English, greater than 14 weeks gestation at the time of recruitment, less than 18 years of age, diagnosed with a fetal anomaly or a history of major chronic disease. Excluded from this analysis are: 18 women who withdrew during the study, 51 women who gave birth to multiples, 9 stillbirths, 32 spontaneous abortions, 13 therapeutic abortions, 28 with no metal exposure data, and 15 with no infant sex, weight, or gestational age recorded. The final sample size for this analysis was 1835 mother–infant pairs.

2.2. Metals exposure

Maternal blood was collected during the first and third trimesters of pregnancy and analyzed for total lead, cadmium, mercury, and arsenic concentrations. Speciated levels of arsenic (arsenite (As+3) (generally considered to be of most toxicological significance (Hughes, 2006)), arsenate (As+5), monomethylarsenic

Table 4
Gene-environment interaction in relation to risk for SGA.

GSTP1 A114V = CC				GSTP1 A114V = TC+TT			
	SGA (%)	Not SGA (%)	Adjusted RR		SGA (%)	Not SGA (%)	Adjusted RR
Pb > 0.08 µg/dL	24 (5.3)	430 (94.7)	0.90 (0.57–1.41)	Pb > 0.08 µg/dL	9 (14.3)	54 (85.7)	2.25 (0.95–5.16)
Pb ≤ 0.08 µg/dL	62 (5.6)	1050 (94.4)	Reference	Pb ≤ 0.08 µg/dL	11 (6.2)	167 (93.8)	Reference
P for interaction 0.06							
Cd > 0.30 µg/L	24 (5.9)	383 (94.1)	1.06 (0.67–1.68)	Cd > 0.30 µg/L	7 (12.5)	49 (87.5)	1.69 (0.71–4.00)
Cd ≤ 0.30 µg/L	62 (5.4)	1097 (94.7)	Reference	Cd ≤ 0.30 µg/L	13 (7.0)	172 (93.0)	Reference
P for interaction 0.35							
Hg > 1.20 µg/L	31 (7.7)	372 (92.3)	1.65 (1.08–2.52)	Hg > 1.20 µg/L	5 (10.4)	43 (89.6)	1.24 (0.47–3.22)
Hg ≤ 1.20 µg/L	55 (4.7)	1108 (95.3)	Reference	Hg ≤ 1.20 µg/L	15 (7.8)	178 (92.2)	Reference
P for interaction = 0.59							
As > 0.79 µg/L	36 (4.8)	711 (95.2)	0.77 (0.51–1.17)	As > 0.79 µg/L	9 (8.9)	92 (91.1)	1.12 (0.48–2.56)
As ≤ 0.79 µg/L	50 (6.1)	769 (93.9)	Reference	As ≤ 0.79 µg/L	11 (7.9)	129 (92.1)	Reference
P for interaction = 0.45							
DMA > 1.50 µg As/L	24 (4.8)	472 (95.2)	0.87 (0.55–1.38)	DMA > 1.50 µg As/L	8 (10.4)	69 (89.6)	1.32 (0.57–3.08)
DMA ≤ 1.50 µg As/L	58 (5.6)	977 (94.4)	Reference	DMA ≤ 1.50 µg As/L	12 (7.6)	145 (92.4)	Reference
P for interaction = 0.39							
AsBe > 5.64 µg As/L	41 (6.4)	598 (93.6)	1.43 (0.94–2.18)	AsBe > 5.64 µg As/L	11 (11.8)	82 (88.2)	1.77 (0.77–4.8)
AsBe ≤ 5.64 µg As/L	41 (4.6)	851 (95.4)	Reference	AsBe ≤ 5.64 µg As/L	9 (6.4)	132 (93.6)	Reference
P for interaction = 0.66							
GSTP1 I105V = AA				GSTP1 I105V = AG+GG			
	SGA (%)	Not SGA (%)	Adjusted RR		SGA (%)	Not SGA (%)	Adjusted RR
Pb > 0.08 µg/dL	17 (7.3)	217 (92.7)	1.22 (0.69–2.15)	Pb > 0.08 µg/dL	16 (5.7)	266 (94.3)	0.95 (0.54–1.66)
Pb ≤ 0.08 µg/dL	31 (5.6)	526 (94.4)	Reference	Pb ≤ 0.08 µg/dL	42 (5.7)	691 (94.3)	Reference
P for interaction = 0.53							
Cd > 0.30 µg/L	17 (8.3)	188 (91.7)	1.51 (0.86–2.66)	Cd > 0.30 µg/L	14 (5.5)	243 (94.5)	0.90 (0.50–1.61)
Cd ≤ 0.30 µg/L	31 (5.3)	555 (94.7)	Reference	Cd ≤ 0.30 µg/L	44 (5.8)	714 (94.2)	Reference
P for interaction = 0.21							
Hg > 1.20 µg/L	20 (9.6)	188 (90.4)	1.98 (1.15–3.43)	Hg > 1.20 µg/L	16 (6.6)	227 (93.4)	1.21 (0.69–2.11)
Hg ≤ 1.20 µg/L	28 (4.8)	555 (95.2)	Reference	Hg ≤ 1.20 µg/L	42 (5.4)	730 (94.6)	Reference
P for interaction 0.23							
As > 0.79 µg/L	23 (5.9)	366 (94.1)	0.93 (0.54–1.60)	As > 0.79 µg/L	22 (4.8)	437 (95.2)	0.73 (0.44–1.22)
As ≤ 0.79 µg/L	25 (6.2)	377 (93.8)	Reference	As ≤ 0.79 µg/L	36 (6.5)	520 (93.5)	Reference
P for interaction = 0.53							
DMA > 1.50 µg As/L	17 (6.9)	231 (93.2)	1.23 (0.70–2.19)	DMA > 1.50 µg As/L	15 (4.6)	310 (95.4)	0.76 (0.43–1.35)
DMA ≤ 1.50 µg As/L	30 (5.7)	497 (94.3)	Reference	DMA ≤ 1.50 µg As/L	40 (6.0)	624 (94.0)	Reference
P for interaction = 0.24							
AsBe > 5.64 µg As/L	24 (7.4)	299 (92.6)	1.54 (0.89–2.67)	AsBe > 5.64 µg As/L	28 (6.8)	381 (93.2)	1.46 (0.88–2.43)
AsBe ≤ 5.64 µg As/L	23 (5.1)	429 (94.9)	Reference	AsBe ≤ 5.64 µg As/L	27 (4.7)	553 (95.3)	Reference
P for interaction = 0.89							
GSTO1 A104A = CC				GSTO1 A104A = CA+AA			
	SGA (%)	Not SGA (%)	Adjusted RR		SGA (%)	Not SGA (%)	Adjusted RR
Pb > 0.08 µg/L	15 (5.7)	248 (94.3)	0.94 (0.52–1.69)	Pb > 0.08 µg/dL	18 (7.1)	235 (92.9)	1.20 (0.70–2.06)
Pb ≤ 0.08 µg/dL	36 (5.6)	609 (94.4)	Reference	Pb ≤ 0.08 µg/dL	37 (5.8)	604 (94.2)	Reference
P for interaction = 0.54							
Cd > 0.30 µg/L	18 (7.9)	210 (92.1)	1.55 (0.89–2.70)	Cd > 0.30 µg/L	13 (5.5)	222 (94.5)	0.84 (0.46–1.54)
Cd ≤ 0.30 µg/L	33 (4.8)	647 (95.2)	Reference	Cd ≤ 0.30 µg/L	42 (6.4)	617 (93.6)	Reference
P for interaction = 0.14							
Hg > 1.20 µg/L	19 (8.0)	218 (92.0)	1.70 (0.98–2.93)	Hg > 1.20 µg/L	17 (7.9)	197 (92.1)	1.47 (0.85–2.55)

2.6. Statistical analysis

Spearman's correlation coefficients were calculated to examine the relationship between the first and third trimester blood concentrations of the metals. Relative risks and 95% confidence intervals controlling for important covariates were estimated using log binomial regression. A parsimonious covariate model predicting SGA was created using backward stepwise deletion at a p -value of 0.15. Relative risks for each metal were adjusted for this covariate model.

Smoking is the single most important known predictor of SGA (McCowan and Horgan, 2009; Valero De Bernabé et al., 2004), and so should be considered; however, this analysis is complicated by the fact that cigarette smoke is also a major source of cadmium exposure. Including smoking in a model may obscure any effect of cadmium on SGA. Therefore the effect of cadmium was modeled in three ways: with and without controlling for smoking, and by excluding smokers from the analysis. All analysis was performed using SAS enterprise guide version 4.2.

3. Results

Lead, cadmium, mercury and arsenic were detectable in the blood of 100%, 99%, 93% and 97% of participants respectively (Table 1). In maternal urine DMA and arsenobetaine were detectable in 85% and 49% of the sample. Since arsenate, arsenite, and MMA were not detectable in > 85% of the study population, they were not included in the analysis of SGA.

First and third trimester concentrations of lead, mercury and cadmium in maternal blood were significantly and highly correlated with coefficients of 0.74, 0.63 and 0.79, respectively. The correlation coefficient for arsenic in blood between first and third trimester was 0.21.

3.1. Factors associated with SGA

Table 2 describes the characteristics of the study population, bivariate analysis between the covariates and SGA, and the relationships with covariates included in the final parsimonious model. Among the births, 5.8% were SGA. Mothers in this study were mostly white, never smokers, Canadian born and of higher socioeconomic status. Infant gender was 52.7% male and 47.3% female. Independent of other factors, only parity and smoking were associated with SGA. Parous women had a decreased risk for a SGA birth (RR=0.51, 95% CI=0.35–0.74) compared to nulliparous women. Smoking at any time during pregnancy was associated with a 72% increased risk of SGA birth (RR 1.72, 95% CI 1.07–2.77). Pre-pregnancy BMI was associated with decreased risk of SGA (RR 0.61, 95% CI 0.39–0.96); however, this association was not significant when other factors were considered.

3.2. Relationship between metal exposure and SGA

Mercury and arsenobetaine exposures were each associated with increased risk for SGA with relative risks for highest versus lowest exposure tertiles: 1.56 (95% CI 1.04–2.58) and 1.65 (95% CI 1.10–2.47) respectively (Table 3). No relationship was observed between blood lead or arsenic and SGA. The relative risk of SGA from moderate and high exposure to cadmium were close to the null value when adjusted for smoking (0.15–0.3 $\mu\text{g/L}$: RR=0.97) (95% CI: 0.62–1.52); > 0.3 $\mu\text{g/L}$: RR=1.03 (95% CI: 0.60–1.78). Cadmium was also not a significant risk factor for SGA when smoking was not adjusted for or when smokers were excluded from the analysis.

3.3. Exploratory gene–environment interactions

The GSTP1 and GSTO1 genes have never been studied in the context of fetal growth prior to this analysis. Stronger relative risks were hypothesized in genotype categories with decreased detoxification capacity. The relative risks of SGA for DMA exposure differed across strata defined by the GSTO1 A104A SNP (p -value interaction 0.02). The relative risk for those with a variant allele was in the direction of increased risk (RR=1.48 95% CI 0.87–2.51), while the relative risk for those with a homozygous wildtype genotype was in the direction of a protective effect (RR=0.56 95% CI 0.29–1.08). There was a marginally significant interaction between lead exposure and the GSTP1 A114V SNP (p =0.06) (Table 4). No other interactions approached statistical significance.

4. Discussion

In the MIREC Study detectable levels of lead, cadmium, mercury and arsenic were found in first and third trimester blood samples for over 90% of women. This is an indication of the sensitivity of the analytical method used and not an indication of any increased risk. The median blood lead (0.59 $\mu\text{g/dL}$) and arsenic (0.75 $\mu\text{g/L}$) concentrations in this analysis were lower than those reported in the general population of Canadian women aged 20–39 in the Canadian Health Measures Survey (CHMS) (0.83 $\mu\text{g/dL}$, 0.88 $\mu\text{g/L}$, respectively), but fairly consistent with the measures for mercury (0.64 vs. 0.69 $\mu\text{g/L}$ in the CHMS) and cadmium (0.2 vs. 0.28 $\mu\text{g/L}$ in the CHMS) (Health Canada, 2010, 2013). Blood lead, cadmium or arsenic at the levels observed in this study were not associated with increased risk of SGA.

Women in the highest tertile of mercury exposure (> 1.6 $\mu\text{g/L}$) had an increased risk for SGA infants. In vitro studies have shown that mercury can interfere with nutrient transfer across the placenta (Urbach et al., 1992). Mercury has a very high affinity for fetal hemoglobin (Jedrychowski et al., 2006) and methylmercury can quickly be transported into the fetal bloodstream through the neutral amino acid carrier system (Kajiwara et al., 1996). Several epidemiological studies have reported an association between mercury and birth weight (Foldspang and Hansen, 1990; Lee et al., 2010; Ramón et al., 2009). However, later analysis of a more complete dataset disproved Foldspang and Hansen's (1990) original findings (Bjerregaard and Hansen, 1996), and the analysis by Ramón et al. (2009) lacked statistical power. Only two of the previous studies of mercury exposure and SGA have had sample sizes greater than 1000 (Daniels et al., 2007; Hujoel et al., 2005). Of the studies that reported geometric mean concentrations of mercury in blood, all 5 (Lee et al., 2010; Ding et al., 2013; Guo et al., 2013; Lederman et al., 2008; Bjerregaard and Hansen, 2000) have higher exposure levels than those seen in the MIREC sample (geometric mean=0.57 $\mu\text{g/L}$). Of the studies examining the relationship between mercury and SGA, four used measures of mercury in both cord blood and maternal blood (Lee et al., 2010; Guo et al., 2013; Lederman et al., 2008; Bjerregaard and Hansen, 2000). The remaining studies of mercury and SGA looked at mercury in cord blood, cord tissue, or amalgam fillings, and did not use maternal blood. Differences in the associations reported in these studies may in part be due to these differences in exposure matrices.

Several small studies have reported an association between urinary arsenic (primarily inorganic) and birthweight, including a study in Bangladesh (Rahman et al., 2009), in Romania (Gelmann et al., 2013), in New Hampshire USA (Fei et al., 2013). However, no significant association between urinary arsenic levels and SGA was reported in a study in Japan (Shirai et al., 2010). We found urinary arsenobetaine levels > 2.25 $\mu\text{g As/L}$ to be associated with an

increased risk of SGA. Arsenobetaine is an organic arsenic species excreted in urine and is perceived to be less toxic than inorganic arsenic (Vahter, 2009; Francesconi, 2010). There is no literature to suggest that arsenobetaine would be related to fetal size independent of other arsenic metabolites. A study in rats reported no teratogenic or deleterious effects of arsenobetaine by gavage on reproductive development (Taylor et al., 2013). It is possible that this association was due to chance, or that urinary arsenobetaine concentrations are a proxy for an unknown risk factor that is truly associated with SGA. There have been no studies to date of associations between individual urinary arsenic metabolites and SGA.

In the MIREC study, arsenobetaine was measured in a spot urine sample collected during the first trimester, without seafood abstinence. This sample may not represent long-term exposure to arsenic as arsenobetaine is thought to have a very short half-life in urine and is excreted rapidly and unchanged in urine (Lai et al., 2004). Arsenobetaine was detected in almost half the women in MIREC and when it was detected it was at relatively elevated levels. Confusion remains on how to interpret arsenobetaine concentrations in urine. While correlations have been reported between fish and shellfish consumption and urinary concentrations (Lovreglio et al., 2012; Rivera-Núñez et al., 2012), one study of volunteers fed a diet with no known sources of arsenobetaine suggested that either accumulated arsenobetaine in the tissues was slowly released over time or that arsenobetaine is a human metabolite of dimethylarsinic acid or inorganic arsenic from the trial food, or both (Newcombe et al., 2010). The authors hypothesized that the long-term excretion pattern was dependent on the individual volunteer. Data from another feeding study indicated that arsenobetaine may be formed as a result of biotransformation of other organic arsenicals of seafood origin and reported large individual variations in the estimated absorption and excretion of arsenobetaine that depended on the dietary source (Molin et al., 2014).

We found no association with maternal cadmium exposure and SGA. When smokers are included in the analysis, there is no significant effect on SGA both before and after controlling for the effect of smoking. When smokers are removed from the dataset, there are very few people in the high exposure category. This is to be expected as smokers have much higher blood cadmium levels than nonsmokers. Because of this, the risk estimate between the highest and lowest exposure groups in this analysis has such a wide confidence interval that this risk estimate and dose response pattern are difficult to interpret. The results of these three analyses do not support the case for an association between cadmium exposure and SGA, independent of smoking status.

Maternal blood, cord blood, placental tissue and urine are all matrices that have been used to study the association between cadmium exposure and fetal growth. This fact may be a contributing factor to the conflicting findings in the literature regarding cadmium exposure and fetal growth. Cadmium concentrations in blood are likely to be more transient in nature than urinary levels, reflecting recent exposure and may not be as directly correlated with the key toxic responses (World Health Organization, 2001; Hays et al., 2008). Two studies found no effect of cadmium on fetal growth outcomes (Odland et al., 1999; Loiacono et al., 1992) while others found relationships with birth weight or length (Kippler et al., 2011; Nishijo et al., 2004; Tian et al., 2009; Galicia-García et al., 1997). Most studies of cadmium exposure and SGA have similar exposure ranges as the MIREC sample, however 2 studies in Taiwan (Lin et al., 2011; Tian et al., 2009) and one in Bangladesh (Kippler et al., 2011) had exposure ranges higher than those observed in this study. Many of these studies had very small sample sizes; only one analysis (Kippler et al., 2011) was larger than 1000 subjects.

Lead has been extensively studied using a variety of matrices

(Andrews et al., 1994), with most of the more recent studies of the relationship with SGA using maternal blood, cord blood and placenta. Multiple studies have found an association with SGA (Chen et al., 2006; Odland et al., 1999; Xie et al., 2013; Gundacker et al., 2010; Jelliffe-Pawlowski et al., 2006; Berkowitz et al., 2006; González-Cossío et al., 1997) while others report no relationship (Shirai et al., 2010; Jones et al., 2010; Sowers et al., 2002). The different matrices used and the varying exposure levels may explain the conflicting results. The lead exposure in the Taiwanese study (Chen et al., 2006) was very high, with a maximum exposure of 62 µg/dL. Studies conducted in the U.S. (Bellinger et al., 1991; Zhu et al., 2010; Jones et al., 2010; Sowers et al., 2002; Jelliffe-Pawlowski et al., 2006; Berkowitz et al., 2006) and in Nordic countries (Osman et al., 2000; Odland et al., 2004) had levels of exposure closer to those measured in the MIREC study, with maximum exposure levels ranging from ~10 to 12 µg/dL (still considerably higher than the levels in the MIREC cohort). Only the Taiwanese study had a sample size greater than 1000 (Chen et al., 2006). Two studies have had sample sizes greater than 4000 (Bellinger et al., 1991; Berkowitz et al., 2006).

An examination of potential interactions of metal concentrations and the GSTP1 and GSTO1 genes on the risk of SGA found a significant interaction between DMA levels and the GSTO1 A104A SNP, as well as a marginally significant interaction between blood lead concentrations and the GSTP1 A114V SNP. The GSTO1 enzyme has been shown to catalyse the reduction of MMA, the rate-limiting step in arsenic detoxification (Zakharyan et al., 2001), making it a candidate enzyme in the modification of arsenic exposure and SGA. If the effect of lead on SGA is real, but only certain sub-populations are at risk for this effect, then genetic variation may be the reason that some studies report significant associations while others do not. Epidemiological studies using biomarkers have found associations between GSTP1 polymorphisms and differential metabolism/elimination of arsenic, mercury and lead (Custodio et al., 2004; Goodrich and Basu, 2012; Gundacker et al., 2010; Marcos et al., 2006; Gundacker et al., 2009). One study found GSTP1 to have no effect on fetal growth (Yamada, 2004), however the study simply compared frequencies using a fisher's exact test, and genotype was analyzed as the exposure rather than an effect modifier of a relationship with an environmental exposure.

4.1. Methodological considerations

The participation rate in the original study was relatively low at only 39% (Arbuckle et al., 2013). A comparison of the sample to Canadian birth statistics reveals that the MIREC participants tended to be older, more educated, included a greater proportion of married or common law, had fewer smokers and higher household income than the general Canadian pregnant population from 2009 (Arbuckle et al., 2013; Public Health Agency of Canada, 2009). Despite the fact that the sample was not representative of the Canadian population of pregnant women, the findings of this study are generalizable to this, and other pregnant populations with similar metal exposure. The relationship being studied is a biologic one and thus it should hold in a population that is not demographically identical.

The low correlation observed between the first and third trimester measures of arsenic in blood is in line with existing literature. It has been shown that arsenic is cleared from the blood rapidly (Hughes, 2006), which means that blood arsenic may not accurately represent arsenic exposure over the course of pregnancy. This is a limitation of using blood arsenic as an exposure measure. A limitation of the urinary arsenic results is that with the high detection limit for the inorganic species, especially MMA, we were not able to examine risks from the sum of the inorganic

species.

There is inherent misclassification in the use of SGA as a surrogate measure of fetal growth restriction. Specifically, not all infants who are SGA are pathologically growth restricted, and not all infants who are pathologically growth restricted are SGA (Mayer and Joseph, 2012). This misclassification is likely to be non-differential based on infants' metal exposure *in utero*.

Another area of uncertainty is the critical period(s) during pregnancy that can affect fetal growth and therefore when exposure to metals should be measured. Fetal weight gain is fastest in the third trimester (Matheus and Sala, 1980); however the determination of the fetus' centile of weight could occur before this period. Similarly, the exact timing for the programming of length is unclear (Norris and Cameron, 2013).

There is possible uncontrolled confounding in this analysis due to lack of information on maternal diet. Dietary factors such as milk and leafy green consumption have been shown to have a positive effect on fetal growth outcomes (Mayer and Joseph, 2012). Maternal under-nutrition is associated with IUGR (Wu et al., 2012), but this is likely not an issue in this study of Canadian women of relatively high socioeconomic status. Of more relevance is maternal over-nutrition, or obesity during/prior to pregnancy, which can also result in IUGR (Wu et al., 2012). While this analysis does not account for nutritional factors, it does examine pre-pregnancy BMI, which may capture some of the variation caused by individual differences in diet. Furthermore, the trace element deficiencies that are associated with IUGR are not typical of people living in developed countries, especially in our sample of pregnant women who are older, more educated, and of higher socioeconomic status. All of these characteristics make them more likely to start prenatal care earlier, to have more prenatal visits, and to take prenatal dietary supplements (Public Health Agency of Canada, 2009).

4.2. Implications

The results indicate that neither blood lead, cadmium nor arsenic at the levels typical of Canadian exposure have a significant measurable effect on birth size by gestational age. However, higher concentrations of maternal blood mercury or urinary arsenobetaine may be associated with increased risk of a fetal growth restricted infant. Furthermore, the null findings of this study do not mean that high levels of these metals are not associated with SGA births.

There is some inconsistency in the existing literature regarding mercury exposure and fetal size and no previous human studies have examined arsenobetaine risks. Canadians are generally exposed to mercury in their diet, primarily from certain types of fish (Health Canada, 2007). A strong correlation exists between fish and shellfish consumption and urinary arsenobetaine concentrations (Rivera-Núñez et al., 2012) and a seafood intervention study has reported that arsenobetaine was the major arsenical excreted followed by DMA (Molin et al., 2014). Arsenobetaine has also been detected in edible mushrooms and hares from contaminated sites in Canada (Koch et al., 2013).

The risk of mercury and arsenobetaine exposure from fish and shellfish must be weighed against the benefits of fish consumption on fetal growth. Fish is an excellent source of omega-3 fatty acids, protein, naturally occurring Vitamin D, and other essential minerals (Health Canada, 2007) that help the fetus to grow. By following fish consumption advice, Canadians can reduce their exposure to these metals while enjoying the health benefits of eating fish (Health Canada, 2007).

5. Conclusions

Increased exposure to mercury and arsenobetaine were associated with increased risk of giving birth to a SGA infant in the MIREC cohort of Canadian women. These findings, in addition to previous work in this area, underscore the need to monitor pregnant populations and to raise education and awareness around chemicals and health (particularly with respect to fish consumption) amongst this target population. Further research is needed to confirm the associations we observed between these metals and fetal growth restriction.

Acknowledgements

The authors thank the MIREC participants, site and coordinating center staff and the MIREC Study Group for their contributions to the success of this study. The MIREC Study was funded by Health Canada's Chemicals Management Plan, the Canadian Institute of Health Research (Grant no. MOP-81285) and the Ontario Ministry of the Environment. ASE was supported by NIEHS K01-ES014907.

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