Environment International 83 (2015) 63–71

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Exposure to phthalates, bisphenol A and metals in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC study

G.D. Shapiro [a,b], L. Dodds [c,*], T.E. Arbuckle [d], J. Ashley-Martin [c], W. Fraser [b,e], M. Fisher [d], S. Taback [f], E. Keely [g], M.F. Bouchard [b], P. Monnier [h], R. Dallaire [i], AS. Morisset [b], A.S. Ettinger [j]

[a] Department of Social and Preventive Medicine, Université de Montréal, Montréal, Quebec, Canada
[b] CHU Sainte-Justine Research Centre, Université de Montréal, Montréal, Quebec, Canada
[c] Dalhousie University, Halifax, Nova Scotia, Canada
[d] Health Canada, Ottawa, Ontario, Canada
[e] Department of Obstetrics and Gynecology, Université de Montréal, Montréal, Quebec, Canada
[f] University of Manitoba, Winnipeg, Manitoba, Canada
[g] University of Ottawa, Ottawa, Ontario, Canada
[h] McGill University, Montréal, Quebec, Canada
[i] Laval University, Québec City, Quebec, Canada
[j] Yale University, New Haven, CT, USA

ARTICLE INFO

Article history:
Received 16 December 2014
Received in revised form 11 May 2015
Accepted 24 May 2015
Available online 20 June 2015

Keywords:
Metals
Phthalates
Gestational diabetes
Cohort study
Pregnancy
Arsenic

ABSTRACT

Background: Studies from several countries report increases in rates of gestational diabetes mellitus (GDM) over recent decades. Exposure to environmental chemicals could contribute to this trend.
Objectives: To determine the associations between plasticisers and metals measured in early pregnancy with impaired glucose tolerance (IGT) and GDM in a Canadian pregnancy cohort.
Methods: Women enrolled in the Maternal–Infant Research on Environmental Chemicals (MIREC) Study were included if they had a singleton delivery and did not have pre-existing diabetes. Eleven phthalate metabolites and total bisphenol A (BPA) were measured in first-trimester urine samples, and four metals (lead, cadmium, mercury and arsenic) were measured in first-trimester blood samples. IGT and GDM were assessed in accordance with standard guidelines by chart review. Chemical concentrations were grouped by quartiles, and associations with outcomes were examined using logistic regression with adjustment for maternal age, race, pre-pregnancy BMI, and education. Restricted cubic spline analysis was performed to help assess linearity and nature of any dose–response relationships.
Results: Of 2001 women recruited into the MIREC cohort, 1274 met the inclusion criteria and had outcome data and biomonitoring data measured for at least one of the chemicals we examined. Elevated odds of GDM were observed in the highest quartile of arsenic exposure (OR = 3.7, 95% CI = 1.4–9.6) in the adjusted analyses. A significant dose–response relationship was observed in a cubic spline model between arsenic and odds of GDM ($p < 0.01$). No statistically significant associations were observed between phthalates or BPA or other metals with IGT or GDM.
Conclusions: Our findings add to the growing body of evidence supporting the role of maternal arsenic exposure as a risk factor for gestational diabetes.

Abbreviations: BMI, body mass index; BPA, bisphenol A; CRP, C-reactive protein; DEHP, di(2-ethylhexyl)phthalate; EDC, endocrine disrupting chemical; GCT, glucose challenge test; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; LOD, limit of detection; MBP, mono-n-butyl phthalate; MBzP, mono-benzyl phthalate; MCHP, monocyclohexyl phthalate; MCPP, mono-3-carboxypropyl phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, monoethylhexyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutylphthalate; MIREC, Maternal–Infant Research on Environmental Chemicals; MMP, monomethyl phthalate; MNP, mono-isononyl phthalate; MOP, mono-n-octyl phthalate; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; OGTT, oral glucose tolerance test; PPAR, peroxisome proliferator–activated receptor; SG, specific gravity; UPLC, ultra performance liquid chromatography.

* Corresponding author at: Perinatal Epidemiology Research Unit, 7th Floor Women's Site, IWK Health Centre, 5980 University Ave. PO Box 9700, Halifax, NS B3H 6R8, Canada.
E-mail address: L.Dodds@dal.ca (L. Dodds).

http://dx.doi.org/10.1016/j.envint.2015.05.016

1. Introduction

Studies from Canada, the U.S. and Australia report increases in the prevalence of gestational diabetes mellitus (GDM) in recent decades (Davenport et al., 2010; Feig et al., 2014; Galtier, 2010). Although the causes of increasing rates of GDM are likely multifactorial, exposure to environmental chemicals may be partly responsible for this trend (Bezek et al., 2008; Kuo et al., 2013; Thayer et al., 2012). Some epidemiologic research has found associations between environmental chemicals and GDM (Ettinger et al., 2009; Saldana et al., 2007), but there have not been enough studies on this issue to draw definitive conclusions. Roughly 4.5% of pregnant women in Canada experience GDM (Public Health Agency of Canada, 2011). Another group of pregnant women exhibits impaired glucose tolerance (IGT), or hyperglycemia, but not meeting the criteria to warrant a diagnosis of GDM (Canadian Diabetes Association, 2008).

A number of animal toxicity and some human studies have implicated endocrine disrupting chemicals (EDCs) in the etiology of obesity and diabetes (Diamanti-Kandarakis et al., 2010; Legler et al., 2015). Several epidemiologic studies have found associations between exposure to bisphenol A (BPA) and diabetes (Sun et al., 2014; Lang et al., 2008; Melzer et al., 2010; Silver et al., 2011; Shankar and Teppala, 2011). Phthalates have also been associated with type 2 diabetes (Sun et al., 2014) and insulin resistance (James-Todd et al., 2012; Lind et al., 2012; Stahlhut et al., 2007) in human populations. However, there are limited epidemiologic data assessing the risk of metabolic dysfunction associated with exposure to endocrine disrupting chemicals during pregnancy (Ettinger et al., 2009; Robledo et al., 2013).

Metals have been a public health concern for many years because they can persist in the environment and some heavy metals such as cadmium and lead have biological half-lives of more than ten years (Health Canada, 2010). Metals including arsenic, cadmium, lead and mercury are thought to have estrogenic activity and, as such, are classified as EDCs (Choi et al., 2004; Dyer, 2007; Iavicoli et al., 2009; Watson and Yager, 2007). In addition to such naturally-occurring EDCs as these metals, some manufactured chemicals such as phthalates and BPA may also have endocrine disrupting properties (Caserta et al., 2011; Diamanti-Kandarakis et al., 2009). Many of the above-mentioned chemicals are either naturally occurring or are used extensively in everyday consumer products and are, therefore, ubiquitous in our environment.

Because of the potential for long-term consequences of GDM in both mother and offspring, it is important to better characterize the potential role that environmental chemicals may play in the development of glucose disorders during pregnancy. Using data from a Canadian birth cohort, this study sought to determine whether exposure to phthalates, BPA or metals, assessed by measurements made in blood and urine, were associated with increased risk of GDM or IGT during pregnancy.

2. Methods

2.1. Study population

The Maternal–Infant Research on Environmental Chemicals (MIREC) study is a longitudinal birth cohort study conducted in Canada. Further details concerning inclusion and exclusion criteria and study objectives and procedures have been published elsewhere (Arbuckle et al., 2013). Women at least 18 years of age (n = 2001) were recruited during the first trimester of pregnancy (6 to <14 weeks gestation), between 2008 and 2011 at 10 sites in 6 Canadian provinces. Contacts during each trimester of pregnancy were made with each participant to collect questionnaire data, medical history, and maternal blood and urine. Detailed clinical information was collected in a post-delivery chart review. The present analysis focused on MIREC participants with a singleton fetus that resulted in a live birth, who had sufficient data from a glucose challenge test (GCT) and/or oral glucose tolerance test (OGTT) to determine diagnoses of GDM and IGT, and for whom a first-trimester measurement of phthalates, BPA and/or metals was available. All participants signed informed consent forms and the study received ethical approval from the IWK Health Centre (Halifax, NS), Health Canada, and all the study centers.

Of 2001 women recruited into the MIREC study, 18 withdrew and asked that all their data and biospecimens be destroyed (0.9%). Of the remaining 1983 women, a total of 98 were excluded (4.9%) because of a multiple pregnancy (n = 48), stillbirth (n = 21), pre-existing diabetes (n = 24), or having no biological samples available for the measurement of any of the contaminants of interest (n = 5), leaving 1885 who contributed data to the study (Fig. 1).

2.2. Chemical biomonitoring data

Eleven phthalate metabolites and total BPA were measured in first-trimester urine samples, as previously described (Arbuckle et al., 2014), and four metals (lead, cadmium, mercury and arsenic) were measured from first-trimester blood samples. Phthalate metabolites included monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), mono-3-carboxypropyl phthalate (MCPP), monoethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), monocyclohexyl phthalate (MCHP), mono-n-octyl phthalate (MOP), mono-isononyl phthalate (MNP) and monomethyl phthalate (MMP). All chemical analyses of urine and blood samples were carried out at the Toxicology Centre of the Quebec Institute of Public Health (Institut national de santé publique du Québec), 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 tandem mass spectrometer and Quattro Premier XE following enzymatic deconjugation, as described in detail elsewhere (Arbuckle et al., 2014; Langlois et al., 2014). Total BPA in urine was measured with a GC–MS–MS instrument with a GC Agilent 6890 N (Agilent Technologies; Mississauga, Ontario, Canada) coupled with a tandem mass spectrometer Quattro Micro GC (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. Metals were measured in whole blood using inductively coupled plasma mass spectrometry (PerkinElmer ELAN ICP-MS DRC II).

Concentrations below the limit of detection (LOD) were substituted as one half the LOD. Due to the exploratory nature of our study, we examined each chemical separately for the principal analyses. However, three of the phthalates 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 (≥0.85) between these metabolites, these were not analyzed as individual metabolites, but summed to create an index of DEHP exposure, as has been previously carried out (Hoppin et al., 2013). Four of the phthalate metabolites (MCHP, MOP, MNP and MMP) had a high degree of non-detect (more than 75%) in the urine and were not examined further in the present analyses.

2.3. Impaired glucose tolerance and gestational diabetes mellitus

IGT and GDM were assessed by chart review based on the results of a 50 g glucose challenge test (GCT) and 75 or 100 g oral glucose tolerance test (OGTT), in accordance with guidelines from the Canadian Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada (Berger et al., 2002; Canadian Diabetes Association, 2008). These guidelines specify cut-off values of 5.3 mmol/L for fasting glucose, 10.6 mmol/L 1 hour post glucose, and 8.9 mmol/L 2 hour post glucose for a 75-g OGTT. Cut-off values for a 100-g OGTT are 5.8 mmol/L for fasting glucose, 10.6 mmol/L 1 hour post glucose, 9.2 mmol/L 2 hour post glucose, and 8.0 mmol/L 3 hour post glucose. Subjects were

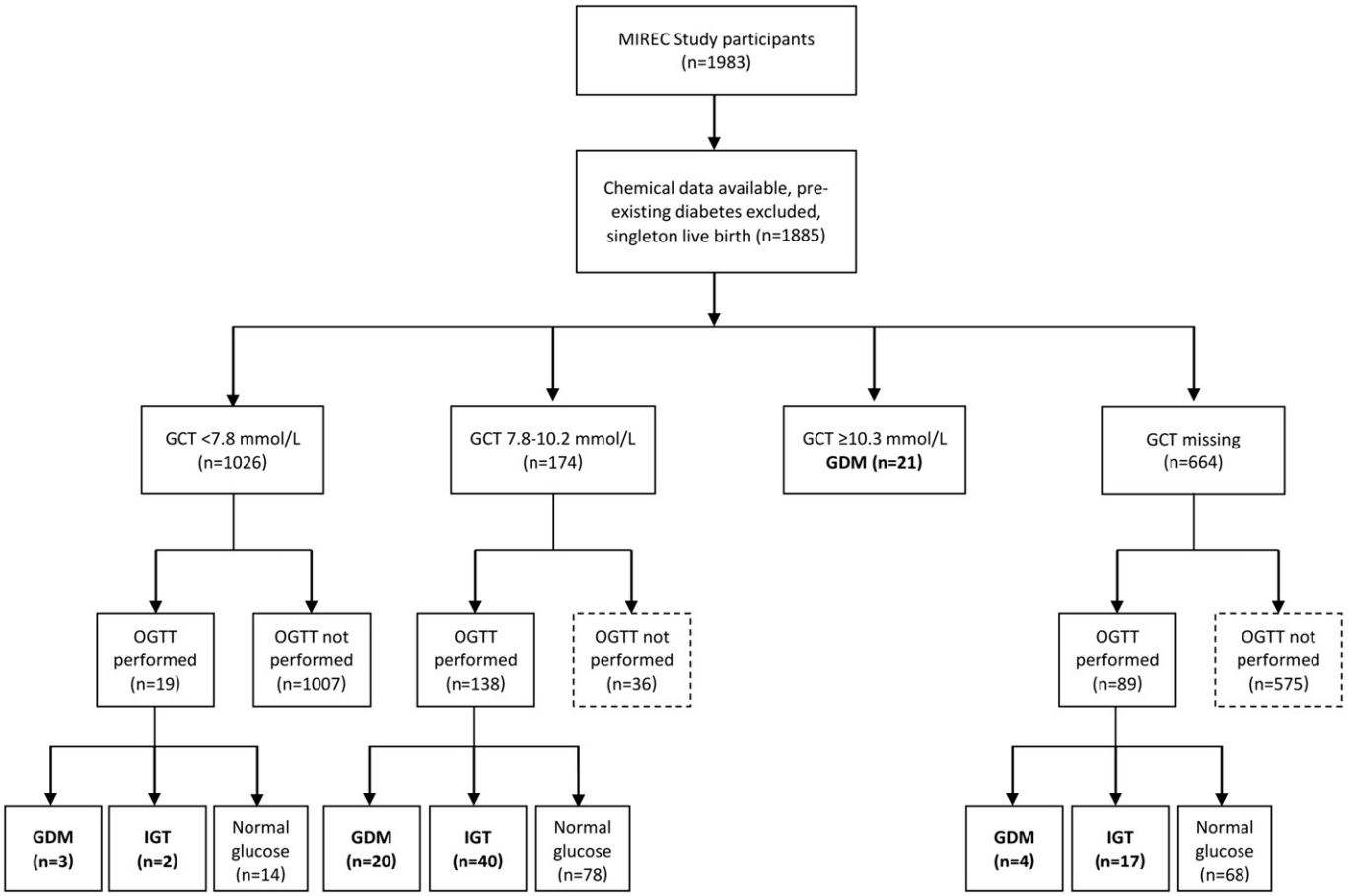

Fig. 1. Study participants and outcome classification.

assigned a diagnosis of IGT if one of the OGTT cut-off values was met or exceeded. If the result of the 1-hour 50 g GCT was ≥10.3 mmol/L, or if at least 2 of the cut-off values were met or exceeded on a 75 g or 100 g OGTT, a diagnosis of GDM was assigned.

Some of the MIREC study centers screened only high-risk patients for GDM. Of the 1885 subjects meeting inclusion criteria and having exposure data, 575 had no information from a GCT or OGTT, and a further 36 had a GCT result between 7.8 and 10.2 mmol/L but no information on an OGTT (Fig. 1). In accordance with the guidelines, we could not make a determination of GDM or IGT for 611 women, leaving 1274 women for our principal analyses.

2.4. Statistical analyses

Descriptive statistics for maternal demographic and clinical characteristics were calculated according to study outcomes (normal blood glucose, IGT, GDM) using frequency distributions and chi-square tests of significance. Geometric means and standard deviations were calculated for chemical concentrations according to study outcomes. In determining the geometric mean, concentrations of phthalate metabolites and BPA were adjusted for urinary specific gravity (SG) 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).

All blood and urine contaminant concentrations were grouped into quartiles for analyses, and logistic regression models were used to examine associations between quartiles and study outcomes. In calculating odds ratios for these outcomes, we examined subjects with GDM vs. normal blood glucose, IGT vs. normal glucose, and subjects with either IGT or GDM grouped together vs. normal blood glucose. We examined the following maternal variables as potential confounders: age at delivery (≤29, 30–34, ≥35), pre-pregnancy BMI (<25, 25–29.9, ≥30 kg/m^2), parity (nulliparous vs. parous), household income ($ ≤ 30,000, 30,001–50,000, 50,001–100,000, >100,000), education (high school diploma or less, some college or trade school, undergraduate university degree, graduate university degree), race (White, non-White), and smoking (never or quit before pregnancy, quit when knew pregnant, current smoker). Variables were selected a priori for inclusion in multivariable models on the basis of association with IGT and GDM in univariable analyses ($p < 0.1$) or on the basis of evidence of an association from the literature. As model results were not substantially different with adjustment for both income and education vs. adjustment for education only, we did not adjust for income in the final models. Specific gravity was included as a covariate in all adjusted models for chemicals measured in urine to account for heterogeneity in urinary dilution. For models with statistically significant association estimates, we used restricted cubic spline analysis to further examine the dose–response relationship (Desquilbet and Mariotti, 2010). This technique is applicable when there is no a priori hypothesis regarding the shape of the dose–response association, and it overcomes the inherent limitations of the categorical analyses. Knots were set at the 5th, 50th, and 95th percentiles and the referent value was set to the median.

3. Results

Table 1 shows the maternal characteristics of the study population and the distribution of IGT and GDM cases with respect to these characteristics. Less than 5% of study subjects smoked during pregnancy, and more than a third of the study population was overweight or obese.

Forty eight participants (3.1%) were identified as GDM cases and 59 (4.6%) were identified as having IGT. As expected, rates of GDM and IGT were higher among overweight and obese women than among women with normal or low pre-pregnancy BMI. A total of 611 participants were excluded from analyses due to insufficient outcome data (Fig. 1). This group included a lower proportion of women who were obese (10.3% vs. 15.0% of included participants, p = .05) and a higher proportion of Caucasian women (88.1% vs. 84.5%, p = .04). Excluded participants were also more frequently current smokers (7.5% vs. 4.4%, p = .04).

Table 2 shows the percentage of samples below the LOD and the geometric mean for each chemical analyzed, stratified by the three outcome categories (normal blood glucose, IGT, GDM). The Pearson correlation coefficients between the various phthalates and BPA were all statistically significant (p < .01) and ranged from 0.30 (between MEP and BPA) to 0.71 (between MBP and MBzP). For metals, correlations ranged from −0.04 (between cadmium and arsenic) to 0.34 (between mercury and arsenic). The correlations between cadmium and mercury and between cadmium and arsenic were not statistically significant (p > .13), while correlations between all other metals were statistically significant (p < .01).

Table 3 shows the crude and adjusted odds of each individual outcome (GDM vs. normal glucose; IGT vs. normal glucose) and for the two outcomes of interest combined (IGT or GDM vs. normal glucose) by quartile of phthalates and BPA urinary concentrations. In comparing odds of GDM in the upper three quartiles vs. the lowest quartile for phthalates and BPA, no statistically significant associations were observed in the adjusted models. Increased odds of IGT were observed for the third and fourth quartiles of MBzP in unadjusted analyses (third quartile: OR = 2.8, 95% CI = 1.0–7.8; fourth quartile: OR = 2.8, 95% CI = 1.0–8.0). After adjusting for confounders, point estimates were similar to the crude analyses but the confidence interval no longer excluded the null effect (third quartile: OR = 2.9, 95% CI = 0.9–9.4; fourth quartile: OR = 2.9, 95% CI = 0.9–10.4). A similar pattern but with attenuated odds ratios was observed for the combined GDM/IGT outcome (adjusted OR for third quartile = 2.0, 95% CI = 0.9–4.4; adjusted OR for fourth quartile = 2.0, 95% CI = 0.9–4.8).

In comparing the odds of GDM in the upper three quartiles vs. the lowest quartile for metals (Table 4), elevated odds of GDM were observed in the highest quartile of arsenic (adjusted OR = 3.7, 95% CI = 1.4–9.6). In the cubic spline models, there was a significant relationship between arsenic level and odds of GDM (p < .01) (Fig. 2). A test of the null hypothesis that the effect of arsenic level and odds of GDM is linear was not rejected (p = .92), suggesting a linear association.

Elevated odds of combined GDM/IGT were also observed for the highest quartile of arsenic (adjusted OR = 1.9, 95% CI = 1.1–3.5). Cubic spline analysis showed a statistically significant relationship between arsenic and odds of GDM/IGT combined (p = 0.03) (Fig. 3), while a test of the null hypothesis of linearity was not rejected (p = .09). Elevated odds of GDM were observed in the highest quartile of cadmium in unadjusted analyses (OR = 2.9, 95% CI = 1.2–7.0) but after adjustment, the confidence interval included the null effect. (OR = 2.5, 95% CI = 1.0–6.4). No statistical evidence of associations with GDM or IGT was observed for the other metals.

4. Discussion

In this longitudinal birth cohort study of Canadian women, we evaluated the association between maternal concentrations of phthalates, BPA and metals with IGT and GDM. After adjustment for confounding variables, we observed statistical evidence of relationships between blood arsenic concentration with GDM and GDM or IGT combined, but not IGT alone. We found no statistical evidence of a relationship between levels of the other chemicals we examined and GDM or IGT in adjusted analyses.

While statistical evidence of an association between arsenic exposure and GDM was found only for the top quartile in regression analyses, the spline curve suggested a linear relationship with no evidence of a threshold. Two previous studies, a U.S. based cohort study (Ettinger et al., 2009) and a Chinese case–control study (Peng et al., 2015), both found significant associations between arsenic exposure and gestational diabetes. Other studies have examined arsenic exposure in relation to type 2 diabetes. Two cross-sectional analyses from the U.S. National Health and Nutrition Examination Survey (NHANES) showed

Table 1
Study population characteristics by glycemic status (N = 1274).

		Total subjects (%)	Normal glucose (%)	IGT cases (%)	p-Value [a]	GDM cases (%)	p-Value [a]
N		1274	1167	59		48	
Age	≤29	308 (24.2)	289 (93.8)	13 (4.2)	0.26	6 (1.9)	0.20
	30–34	447 (35.1)	406 (90.8)	19 (4.3)		22 (4.9)	
	≥35	515 (40.4)	469 (91.1)	26 (5.0)		20 (3.9)	
	Missing	4 (0.3)	3 (75.0)	1 (25.0)		0 (0.0)	
Pre-pregnancy BMI (kg/m^2)	Underweight or normal (<25)	752 (59.0)	713 (94.8)	20 (2.7)	<.01	19 (2.5)	0.02
	Overweight (25–29.9)	257 (20.2)	230 (89.5)	14 (5.4)		13 (5.1)	
	Obese (≥30)	191 (15.0)	163 (85.3)	16 (8.4)		12 (6.3)	
	Missing	74 (5.8)	61 (82.4)	9 (12.2)		4 (5.4)	
Parity	Nulliparous	563 (44.2)	518 (92.0)	22 (3.9)	0.53	23 (4.1)	0.86
	Parous	709 (55.7)	647 (91.3)	37 (5.2)		25 (3.5)	
	Missing	2 (0.2)	2 (100.0)	0 (0.0)		0 (0.0)	
Education	High school diploma or less	106 (8.3)	99 (93.4)	1 (0.9)	<.01	6 (5.7)	0.74
	Some college, or trade school	352 (27.6)	304 (86.4)	33 (9.4)		15 (4.3)	
	Undergraduate university degree	477 (37.4)	446 (93.5)	15 (3.1)		16 (3.4)	
	Graduate university degree	338 (26.5)	317 (93.8)	10 (3.0)		11 (3.3)	
	Missing	1 (0.1)	1 (100.0)	0 (0.0)		0 (0.0)	
Household Income ($CAD)	≤50,000	209 (16.4)	185 (88.5)	13 (6.2)	0.20	11 (5.3)	0.47
	50,001–100,000	505 (39.6)	458 (90.7)	27 (5.3)		20 (4.0)	
	≥100,000	506 (39.7)	475 (93.9)	16 (3.2)		15 (3.0)	
	Missing	54 (4.2)	49 (90.7)	3 (5.6)		2 (3.7)	
Race	White	1077 (84.5)	997 (92.6)	50 (4.6)	0.88	30 (2.8)	<.01
	Non-White	197 (15.5)	170 (86.3)	9 (4.6)		18 (9.1)	
Smoking	Never or quit before pregnancy	1124 (88.2)	1035 (92.1)	50 (4.4)	0.19	39 (3.5)	0.42
	Quit when knew pregnant	93 (7.3)	79 (84.9)	8 (8.6)		6 (6.5)	
	Current smoker	56 (4.4)	52 (92.9)	1 (1.8)		3 (5.4)	
	Missing	1 (0.1)	1 (100.0)	0 (0.0)		0 (0.0)	

Percentages shown in the Total subjects column reflect the entire study population, while those for the three outcome groups reflect each population stratum.
[a] vs. normal glucose.

Table 2
Geometric mean (SD) concentrations of urinary phthalate metabolites and bisphenol A (BPA) and blood metals in first trimester pregnancy specimens by glycemic status.

Chemical concentration (μg/L) [a, b]	LOD	% < LOD		Geometric mean (SD)		
			Total N [c]	Normal glucose N = 1167	IGT cases N = 59	GDM cases N = 48
Monoethyl phthalate (MEP)	0.50	0.1	1152	38.8 (4.1)	34.5 (2.9)	34.5 (4.0)
Mono-n-butylphthalate (MBP)	0.20	0.1	1152	13.3 (2.2)	12.6 (2.4)	12.3 (1.9)
Mono-benzyl phthalate (MBzP)	0.20	0.7	1152	5.8 (2.7)	5.9 (2.8)	6.3 (2.9)
Mono-3-carboxypropyl phthalate (MCPP)	0.20	16.0	1152	1.0 (3.0)	0.9 (2.8)	0.8 (3.2)
Monoethylhexyl phthalate (MEHP)	0.20	1.7	1143	2.6 (2.5)	2.3 (2.4)	2.7 (2.9)
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	0.40	0.6	1152	10.6 (2.5)	10.4 (2.4)	11.4 (3.0)
Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	0.20	0.2	1152	7.4 (2.3)	6.9 (2.2)	7.8 (2.7)
Bisphenol A (BPA)	0.20	12.7	1247	0.9 (2.7)	0.9 (2.6)	0.9 (2.7)
Lead (μg/dL)	0.10	0.0	1259	0.6 (1.6)	0.6 (1.7)	0.6 (1.7)
Cadmium	0.04	2.9	1259	0.2 (2.2)	0.2 (2.5)	0.3 (2.4)
Mercury	0.10, 0.12	9.3	1259	0.6 (3.0)	0.5 (3.3)	0.9 (3.0)
Arsenic	0.22	6.1	1259	0.8 (2.2)	0.7 (2.5)	1.1 (2.1)

[a] Geometric mean concentrations for phthalate metabolites and BPA are adjusted for specific gravity (Just et al., 2010).
[b] The following phthalate metabolites had more than 75% of non-detect and were not further examined: Monocyclohexyl phthalate (MCHP), mono-n-octyl phthalate (MOP), mono-isononyl phthalate (MNP), monomethyl phthalate (MMP).
[c] Number of subjects with data for at least one exposure measurement.

strong associations between total arsenic and diabetes prevalence (Navas-Acien et al., 2008, 2009). Several mechanisms have been proposed to support the associations between arsenic and diabetes. Arsenic is hypothesized to increase the risk of diabetes through oxidative stress, upregulation of inflammatory markers (tumor necrosis factor alpha and interleukin 6), and inhibition of peroxisome proliferator-activated receptor-γ (PPAR-γ) (Tseng, 2004). Experimental studies have shown inorganic arsenic to impair insulin-dependent glucose uptake and glucose-stimulated insulin secretion (Huang et al., 2011). Arsenic may also increase diabetes risk through endocrine-disrupting mechanisms (Davey et al., 2007) and by altering methylation patterns of diabetes-related genes (Smeester et al., 2011).

Despite some studies suggesting a positive association between arsenic exposure and development of diabetes and proposed mechanisms to support associations, several literature reviews have emphasized the inconclusive nature of overall evidence (Huang et al., 2011; Navas-Acien

Table 3
Odds ratios (95% CI) for GDM, IGT, and GDM or IGT by quartiles of phthalate metabolites and bisphenol A in first trimester urine.

Chemical (μg/L)		GDM (N = 43) vs. normal glucose (N = 1080) [a]		IGT (N = 47) vs. normal glucose (N = 1080) [a]		GDM or IGT (N = 90) vs. normal glucose (N = 1080) [a]	
		Unadjusted OR (95% CI)	Adjusted OR [b] (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
MEP	Q1 (0.3–11.0)	1	1	1	1	1	1
	Q2 (12.0–28.0)	0.7 (0.3–1.8)	0.7 (0.3–1.8)	1.6 (0.7–3.7)	1.5 (0.6–3.8)	1.1 (0.6–2.0)	1.0 (0.5–2.0)
	Q3 (29.0–90.0)	1.0 (0.5–2.4)	0.8 (0.3–2.1)	1.0 (0.4–2.7)	0.8 (0.3–2.4)	1.0 (0.6–2.0)	0.8 (0.4–1.7)
	Q4 (91.0–6600.0)	0.8 (0.3–2.0)	0.5 (0.2–1.4)	1.3 (0.5–3.2)	1.0 (0.4–3.0)	1.0 (0.5–1.9)	0.7 (0.3–1.5)
	p-Value [c]		0.25		0.72		0.29
MBP	Q1 (0.1–5.0)	1	1	1	1	1	1
	Q2 (5.1–11.0)	1.7 (0.7–4.2)	1.7 (0.6–4.4)	1.8 (0.7–4.7)	1.9 (0.7–5.2)	1.8 (0.9–3.4)	1.8 (0.9–3.6)
	Q3 (12.0–24.0)	1.5 (0.6–3.7)	1.0 (0.3–3.2)	1.8 (0.7–4.7)	1.7 (0.5–5.4)	1.6 (0.8–3.2)	1.3 (0.6–3.0)
	Q4 (25.0–1500.0)	1.2 (0.4–3.1)	0.6 (0.1–2.2)	1.6 (0.6–4.3)	1.2 (0.3–4.6)	1.4 (0.7–2.8)	0.8 (0.3–2.2)
	p-Value [c]		0.29		0.95		0.51
MBzP	Q1 (0.1–2.1)	1	1	1	1	1	1
	Q2 (2.2–4.8)	0.7 (0.2–1.9)	0.7 (0.2–2.2)	2.2 (0.8–6.5)	2.3 (0.8–7.2)	1.2 (0.6–2.6)	1.3 (0.6–2.8)
	Q3 (4.9–12.0)	1.5 (0.7–3.6)	1.5 (0.6–4.2)	2.8 (1.0–7.8)	2.9 (0.9–9.4)	2.0 (1.0–3.8)	2.0 (0.9–4.4)
	Q4 (13.0–420.0)	1.5 (0.6–3.7)	1.5 (0.5–4.7)	2.8 (1.0–8.0)	2.9 (0.8–10.4)	2.0 (1.0–3.9)	2.0 (0.9–4.8)
	p-Value [c]		0.28		0.13		0.07
MCPP	Q1 (0.1–0.3)	1	1	1	1	1	1
	Q2 (0.3–0.9)	1.3 (0.6–3.1)	1.2 (0.5–2.9)	1.8 (0.7–4.4)	1.8 (0.7–4.5)	1.5 (0.8–2.9)	1.5 (0.7–2.8)
	Q3 (0.9–2.0)	0.9 (0.4–2.2)	0.6 (0.2–1.8)	0.6 (0.2–1.9)	0.5 (0.1–1.8)	0.8 (0.4–1.6)	0.6 (0.2–1.3)
	Q4 (2.1–100.0)	1.1 (0.4–2.7)	0.6 (0.2–1.9)	2.2 (0.9–5.2)	1.6 (0.5–4.8)	1.6 (0.8–3.0)	1.0 (0.4–2.3)
	p-Value [c]		0.27		0.70		0.63
∑ DEHP	Q1 (0.4–8.0)	1	1	1	1	1	1
	Q2 (8.0–17.4)	1.1 (0.5–2.7)	1.0 (0.4–2.5)	1.3 (0.5–3.1)	1.1 (0.4–2.8)	1.2 (0.6–2.3)	1.0 (0.5–2.0)
	Q3 (17.5–36.5)	0.6 (0.2–1.7)	0.4 (0.1–1.5)	1.1 (0.5–2.8)	0.9 (0.3–2.7)	0.9 (0.4–1.7)	0.6 (0.3–1.5)
	Q4 (36.8–2470.0)	1.5 (0.7–3.5)	0.9 (0.3–2.9)	1.4 (0.6–3.5)	1.0 (0.3–3.4)	1.5 (0.8–2.7)	0.9 (0.4–2.3)
	p-Value [c]		0.72		0.91		0.75
BPA	Q1 (0.1–0.4)	1	1	1	1	1	1
	Q2 (0.4–0.8)	1.9 (0.8–4.7)	1.8 (0.7–4.5)	1.4 (0.6–3.3)	1.2 (0.5–2.9)	1.6 (0.9–3.1)	1.5 (0.8–2.9)
	Q3 (0.8–1.6)	1.6 (0.6–4.0)	1.5 (0.5–4.5)	0.7 (0.3–2.0)	0.6 (0.2–1.7)	1.1 (0.6–2.2)	0.9 (0.4–2.0)
	Q4 (1.7–95.0)	1.2 (0.5–3.2)	1.1 (0.3–3.6)	1.8 (0.8–4.1)	1.3 (0.5–3.6)	1.6 (0.8–2.9)	1.2 (0.5–2.7)
	p-Value [c]		0.99		0.79		0.92

[a] Number of subjects with data for at least one exposure measurement and all covariates.
[b] Adjusted for maternal age, race, pre-pregnancy BMI, education and specific gravity.
[c] p-Value from linear test across exposure categories.

Table 4
Odds ratios (95% CI) for GDM, IGT, and GDM or IGT by quartiles of metals in first trimester blood.

Metal		GDM (N = 44) vs. normal glucose (N = 1088) [a]		IGT (N = 49) vs. normal glucose (N = 1088) [a]		GDM or IGT (N = 93) vs. normal glucose (N = 1088) [a]	
		Unadjusted OR (95% CI)	Adjusted OR [b] (95% CI)	Unadjusted OR (95% CI)	Adjusted OR [b] (95% CI)	Unadjusted OR (95% CI)	Adjusted OR [b] (95% CI)
Lead (μg/dL)	Q1 (0.2–0.4)	1	1	1	1	1	1
	Q2 (0.5–0.6)	0.8 (0.3–1.8)	0.8 (0.3–1.9)	0.7 (0.3–1.5)	0.8 (0.4–1.8)	0.7 (0.4–1.3)	0.8 (0.4–1.5)
	Q3 (0.6–0.9)	0.6 (0.2–1.4)	0.6 (0.2–1.6)	0.4 (0.2–1.0)	0.6 (0.2–1.3)	0.5 (0.3–0.9)	0.6 (0.3–1.1)
	Q4 (0.9–4.1)	1.1 (0.5–2.3)	1.1 (0.5–2.6)	0.7 (0.3–1.6)	0.9 (0.4–2.1)	0.9 (0.5–1.5)	1.0 (0.6–1.8)
	p-Value [c]		0.87		0.62		0.76
Cadmium (μg/L)	Q1 (0.0–0.1)	1	1	1	1	1	1
	Q2 (0.2–0.2)	2.1 (0.8–5.4)	2.1 (0.8–5.4)	0.8 (0.4–1.9)	0.9 (0.4–2.1)	1.3 (0.7–2.3)	1.3 (0.7–2.4)
	Q3 (0.2–0.3)	1.3 (0.5–3.7)	1.4 (0.5–3.9)	0.8 (0.3–1.8)	0.8 (0.3–1.8)	1.0 (0.5–1.8)	1.0 (0.5–1.8)
	Q4 (0.3–5.1)	2.9 (1.2–7.0)	2.5 (1.0–6.4)	1.1 (0.5–2.3)	1.0 (0.5–2.3)	1.6 (0.9–2.9)	1.5 (0.8–2.7)
	p-Value [c]		0.13		0.95		0.38
Mercury (μg/L)	Q1 (0.1–0.3)	1	1	1	1	1	1
	Q2 (0.4–0.7)	1.2 (0.5–3.2)	1.1 (0.4–2.9)	1.2 (0.5–2.5)	1.1 (0.5–2.3)	1.2 (0.6–2.2)	1.1 (0.6–2.1)
	Q3 (0.7–1.4)	1.7 (0.7–4.2)	1.4 (0.6–3.7)	0.8 (0.4–1.9)	0.9 (0.4–2.1)	1.2 (0.6–2.2)	1.1 (0.6–2.1)
	Q4 (1.4–10.0)	1.8 (0.8–4.5)	1.7 (0.7–4.5)	1.0 (0.4–2.2)	1.2 (0.5–2.7)	1.3 (0.7–2.4)	1.4 (0.7–2.7)
	p-Value [c]		0.21		0.88		0.34
Arsenic (μg/L)	Q1 (0.1–0.5)	1	1	1	1	1	1
	Q2 (0.5–0.8)	0.7 (0.2–2.5)	0.7 (0.2–2.3)	0.8 (0.4–1.8)	0.8 (0.4–1.8)	0.8 (0.4–1.6)	0.8 (0.4–1.5)
	Q3 (0.9–1.2)	2.5 (0.9–6.7)	2.5 (0.9–6.9)	0.7 (0.3–1.7)	0.8 (0.3–1.9)	1.3 (0.7–2.4)	1.3 (0.7–2.5)
	Q4 (1.3–34.5)	3.8 (1.5–9.5)	3.7 (1.4–9.6)	1.0 (0.5–2.3)	1.2 (0.5–2.6)	1.9 (1.0–3.3)	1.9 (1.1–3.5)
	p-Value [c]		<.01		0.76		0.01

[a] Number of subjects with data for at least one exposure measurement and all covariates.
[b] Adjusted for maternal age, race, pre-pregnancy BMI, and education.
[c] p-Value from linear test across exposure categories.

et al., 2006; Andra et al., 2013). A 2011 U.S. National Toxicological Program workshop concluded that epidemiological evidence was inconclusive at lower exposure levels and did not reach the threshold for a 'sufficient' classification at high arsenic exposure levels (Maull et al., 2012). A later updated systematic review reached a similar conclusion (Kuo et al., 2013).

Although several epidemiologic studies have investigated the relationship between BPA exposure and type 2 diabetes, only one small pilot study has looked at BPA exposure and GDM and found no evidence of an association (Robledo et al., 2013). Analysis from nested case–control studies found significant associations between urinary BPA and incident type 2 diabetes within the Nurses' Health Study II (NHSII) but not the NHS (Sun et al., 2014). The different finding between these cohorts may be explained by the age differences of participants at the time of sample collection; stronger effects were observed in younger women. Moderate associations were found between urinary BPA and self-reported diabetes in the 2003–2004 wave of NHANES (Lang et al., 2008) as well as in a pooled analysis from 2003–2006 (Melzer et al., 2010). In larger pooled analyses from 2003–2008, significant associations were found between BPA levels and diabetes prevalence as assessed by hemoglobin A1c and self-report (Silver et al., 2011), laboratory-diagnosed prediabetes (Sabanayagam et al., 2013), and diabetes (Shankar and Teppala, 2011). Despite this body of literature, two recent systematic reviews examined the relationship between BPA exposure and type 2 diabetes and concluded that there is insufficient evidence to confirm a causal link between BPA exposure and type 2 diabetes (Kuo et al., 2013; LaKind et al., 2014).

A number of experimental studies have demonstrated potential mechanisms underlying the association between BPA exposure and diabetes. BPA has been associated with altered β-cell function (Diamanti-Kandarakis et al., 2009; Kuo et al., 2013; Alonso-Magdalena et al., 2006; Soriano et al., 2012), adiponectin release (Diamanti-

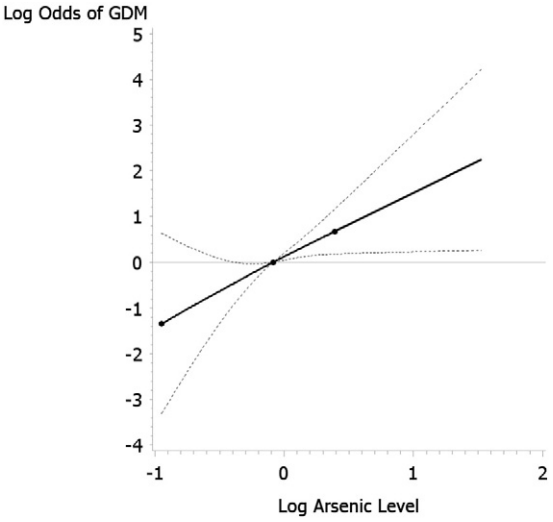

Fig. 2. Restricted spline curve association between log10 arsenic (μg/L) and odds of GDM, adjusted for maternal age, race, pre-pregnancy BMI and education. Knots were located at the 5th, 50th and 95th percentiles. Dashed lines = 95% CI; dots = knots.

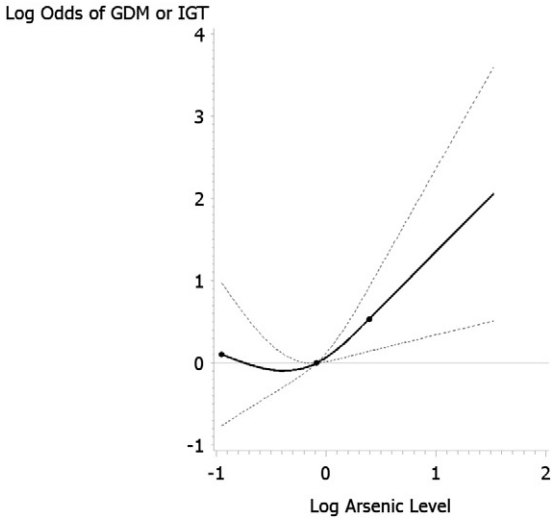

Fig. 3. Restricted spline curve association between log10 arsenic (μg/L) and odds of GDM or IGT, adjusted for maternal age, race, pre-pregnancy BMI and education. Knots were located at the 5th, 50th and 95th percentiles. Dashed lines = 95% CI; dots = knots.

Kandarakis et al., 2009; Kuo et al., 2013; Hugo et al., 2008), insulin release (Soriano et al., 2012) and insulin levels (Alonso-Magdalena et al., 2006). Gestational BPA exposure was associated with insulin resistance and glucose tolerance in mice (Alonso-Magdalena et al., 2010). Moreover, BPA has been shown to be associated with altered insulin release in human tissue samples (Soriano et al., 2012).

Positive associations between phthalates and type 2 diabetes were found in the NHSII (Sun et al., 2014) and NHANES (James-Todd et al., 2012) cohorts, as well as in cross-sectional studies from Mexico (Svensson et al., 2011) and Sweden (Lind et al., 2012). Biological evidence supports a possible role for phthalates in the development of diabetes, principally through activation of PPARs, which in turn affect adipogenesis, lipid storage and the control of insulin sensitivity (Casals-Casas and Desvergne, 2011; Hurst and Waxman, 2003).

There is some biological evidence linking diabetes with metals other than arsenic. Cadmium (Kawakami et al., 2010; Kuo et al., 2013) and mercury (Chen et al., 2006; Kuo et al., 2013) are hypothesized to increase diabetes risk through impacts on pancreatic β-cell function and adiponectin release. Our negative findings regarding lead, cadmium and mercury are consistent with most existing literature examining these exposures in relation to diabetes. It should be noted that most of these studies were not conducted in pregnant women. A 2003 cross-sectional study using data from the U.S. NHANES III found a positive association between urinary cadmium and both diabetes and impaired fasting glucose (Schwartz et al., 2003). However, subsequent studies (Barregard et al., 2013; Moon, 2013; Swaddiwudhipong et al., 2010), including those measuring cadmium in blood (Barregard et al., 2013; Moon, 2013), have failed to confirm this finding (Kuo et al., 2013). One long-term prospective study found an association between toenail mercury and diabetes (He et al., 2013), but research to date on mercury and diabetes is limited and the majority of studies have not found a significant association (Moon, 2013; Mozaffarian et al., 2013). The Chinese case–control study, in which metals were measured in meconium, reported significant dose–response trends across exposure quartiles of mercury and cadmium. The third and fourth quartiles of cadmium exposure were associated with a significantly increased risk of gestational diabetes. Interestingly, they found significantly reduced odds ratios for the second and third quartile of lead compared to the first quartile (Peng et al., 2015).

In light of the varied findings in the literature, it is not clear whether the lack of association for BPA, phthalates and most metals observed in our study reflects true null findings, or possibly rather is a function of the low overall exposure levels or other unmeasured characteristics of the MIREC study population. Urinary concentrations of phthalates and BPA observed in the MIREC study are substantially lower than those found in several other pregnancy cohorts (Casas et al., 2011; Engel et al., 2009; Woodruff et al., 2011). Our observed concentrations of lead, cadmium, and mercury are comparable or slightly lower than those for women age 20–39 in the Canadian Health Measures Survey (CHMS) (Health Canada, 2010), and are comparable to those found in the NHANES (Woodruff et al., 2011). Our observed average arsenic levels were comparable to those from a small study assessing metals and glucose tolerance in a non-pregnant population (Serdar et al., 2009), and somewhat lower than blood arsenic levels from a U.S. study of arsenic exposure and glucose tolerance during pregnancy (Ettinger et al., 2009). In comparing the levels of arsenic observed in our study with those of women age 20–39 in the CHMS, the 10th, 25th and 50th percentiles were similar, while the 75th, 90th, and 95th percentiles from the MIREC cohort were somewhat lower than the corresponding percentiles in the CHMS (Health Canada, 2010). Nevertheless, our highest observed arsenic concentrations were substantially above the 95th percentile from the CHMS. In order to account for the possible effects of these outliers, we conducted a sensitivity analysis in which values more than three standard deviations from the arithmetic mean (12 participants) were removed. The observed odds of GDM were similar to the overall study group (highest quartile of arsenic: crude OR = 3.6 (95% CI 1.4–9.2); adjusted OR = 3.5 (95% CI 1.3–9.2)). Similarly, the ORs for IGT and IGT/GDM were essentially unchanged.

New guidelines for GDM have recently been adopted by the International Association of Diabetes and Pregnancy Study Groups and the Canadian Diabetes Association (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee et al., 2013; International Association Diabetes and Pregnancy Study Groups Consensus Panel, 2010), but were not used in this study because they had not been adopted when the MIREC subjects were being tested for GDM. Under these new guidelines, a diagnosis of GDM will require only 1 abnormal result from the OGTT. Thus, the new definition of GDM will be similar to the combined GDM/IGT category used in the current study. Although we observed an increased risk of GDM/IGT with the highest quartile of blood arsenic exposure, the odds ratio was attenuated from that observed with GDM alone (i.e., not including IGT). If a gradient exists between the level of glucose intolerance and the risks associated with chemical exposures, future studies evaluating the association between chemical exposure and GDM (under the new criteria) may fail to detect significant associations.

An important limitation of our analysis is the use of a single urinary measure for BPA and phthalates. As these chemicals have short elimination half-lives (Koch et al., 2005; Volkel et al., 2002), within-person variability in urinary BPA concentrations (Fisher et al., 2014; Kuo et al., 2013; Robledo et al., 2013) and phthalates (Fisher et al., 2014; Kuo et al., 2013) has been reported to be low, with intraclass correlation coefficients ranging from 0.11 to 0.31 (Braun et al., 2011; Jusko et al., 2014; Fisher et al., 2014; Meeker et al., 2013; Quiros-Alcala et al., 2013). However, as within-person BPA and exposure variability is unlikely to be related to our study outcomes, we expect any resulting bias would be non-differential. Future studies incorporating multiple measurements are needed to better illuminate variation in levels and effects of BPA and phthalates across pregnancy. Although a critical exposure window in gestation is not known, it is reassuring that the dates of urine sample collection preceded measurement of glucose tolerance for 1117 (99%) of participants for whom data were available.

There were a substantial number of subjects for whom a GCT was not performed and who were therefore excluded from our analyses. Notably, current smokers were more frequently excluded, which may have biased our results towards the null, particularly for cadmium. However, given the small magnitude of the differences between included and excluded participants, we do not expect that selection bias would strongly affect our findings. Our study has several notable strengths, including the prospective nature of the study design, which overcomes the limitations of the previous cross-sectional research, and individual-level exposure measurement. We were also able to account for a rich variety of potential confounding variables using the comprehensive questionnaire data and anthropometric measurements collected in the MIREC study.

5. Conclusions

Using a prospective cohort design, we evaluated the relationships between phthalates, BPA and metals measured during the first trimester of pregnancy with IGT and GDM based on published national guidelines. We did not find evidence of associations between the new emerging chemicals we examined (phthalates and BPA) and glucose tolerance disorders in pregnancy, though our use of a single exposure measurement for these chemicals constitutes a limitation. We observed a strong association between elevated first-trimester blood arsenic levels and GDM, as well as a significant association between blood arsenic and GDM and IGT combined. These findings add to previous epidemiologic research showing associations between arsenic and diabetes, and are consistent with the other studies of arsenic exposure and glucose tolerance disorders in pregnant women. Finally, we did not find evidence of an association between other metals and IGT or GDM.

Acknowledgments

We would like to acknowledge the MIREC Study Group as well as the MIREC study participants and staff for their dedication. This study was funded by a grant from the Canadian Diabetes Association (OG-2-11-3424-LD). The MIREC study was funded by the Chemicals Management Plan of Health Canada, the Canadian Institutes for Health Research (MOP-81285), and the Ontario Ministry of the Environment.

The authors declare they have no actual or potential competing financial interests.

References

Alonso-Magdalena, P., Morimoto, S., Ripoll, C., Fuentes, E., Nadal, A., 2006. The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. Environ. Health Perspect. 114, 106–112.

Alonso-Magdalena, P., Vieira, E., Soriano, S., Menes, L., Burks, D., Quesada, I., et al., 2010. Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ. Health Perspect. 118, 1243–1250.

Andra, S.S., Makris, K.C., Christophi, C.A., Ettinger, A.S., 2013. Delineating the degree of association between biomarkers of arsenic exposure and type-2 diabetes mellitus. Int. J. Hyg. Environ. Health 216, 35–49.

Arbuckle, T.E., Fraser, W.D., Fisher, M., Davis, K., Liang, C.L., Lupien, N., et al., 2013. Cohort profile: the maternal–infant research on environmental chemicals research platform. Paediatr. Perinat. Epidemiol. 27, 415–425.

Arbuckle, T.E., Davis, K., Marro, L., Fisher, M., Legrand, M., Leblanc, A., et al., 2014. Phthalate and bisphenol A exposure among pregnant women in Canada — results from the MIREC study. Environ. Int. 68, 55–65.

Barregard, L., Bergstrom, G., Fagerberg, B., 2013. Cadmium exposure in relation to insulin production, insulin sensitivity and type 2 diabetes: a cross-sectional and prospective study in women. Environ. Res. 121, 104–109.

Berger, H., Crane, J., Farine, D., Armson, A., De La Ronde, S., et al., 2002. Screening for gestational diabetes mellitus. J. Obstet. Gynaecol. Can. 24, 894–912.

Bezek, S., Ujhazy, E., Mach, M., Navarova, J., Dubovicky, M., 2008. Developmental origin of chronic diseases: toxicological implication. Interdiscip. Toxicol. 1, 29–31.

Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Bernert, J.T., Ye, X., Silva, M.J., et al., 2011. Variability and predictors of urinary bisphenol A concentrations during pregnancy. Environ. Health Perspect. 119, 131–137.

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can. J. Diabetes 32 (Suppl. 1), S1–S201.

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Thompson, D., Berger, H., Feig, D., Gagnon, R., Kader, T., et al., 2013. Diabetes and pregnancy. Can. J. Diabetes 37 (Suppl. 1), S168–S183.

Casals-Casas, C., Desvergne, B., 2011. Endocrine disruptors: from endocrine to metabolic disruption. Annu. Rev. Physiol. 73, 135–162.

Casas, L., Fernandez, M.F., Llop, S., Guxens, M., Ballester, F., Olea, N., et al., 2011. Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children. Environ. Int. 37, 858–866.

Caserta, D., Mantovani, A., Marci, R., Fazi, A., Ciardo, F., La Rocca, C., et al., 2011. Environment and women's reproductive health. Hum. Reprod. Update 17, 418–433.

Chen, Y.W., Huang, C.F., Tsai, K.S., Yang, R.S., Yen, C.C., Yang, C.Y., et al., 2006. The role of phosphoinositide 3-kinase/Akt signaling in low-dose mercury-induced mouse pancreatic beta-cell dysfunction in vitro and in vivo. Diabetes 55, 1614–1624.

Choi, S.M., Yoo, S.D., Lee, B.M., 2004. Toxicological characteristics of endocrine-disrupting chemicals: developmental toxicity, carcinogenicity, and mutagenicity. J. Toxicol. Environ. Health B Crit. Rev. 7, 1–24.

Davenport, M.H., Campbell, M.K., Mottola, M.F., 2010. Increased incidence of glucose disorders during pregnancy is not explained by pre-pregnancy obesity in London, Canada. BMC Pregnancy Childbirth 10, 85–91.

Davey, J.C., Bodwell, J.E., Gosse, J.A., Hamilton, J.W., 2007. Arsenic as an endocrine disruptor: effects of arsenic on estrogen receptor-mediated gene expression in vivo and in cell culture. Toxicol. Sci. 98, 75–86.

Desquilbet, L., Mariotti, F., 2010. Dose–response analyses using restricted cubic spline functions in public health research. Stat. Med. 29, 1037–1057.

Diamanti-Kandarakis, E., Bourguignon, J.P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., et al., 2009. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr. Rev. 30, 293–342.

Diamanti-Kandarakis, E., Palioura, E., Kandarakis, S.A., Koutsilieris, M., 2010. The impact of endocrine disruptors on endocrine targets. Horm. Metab. Res. 42, 543–552.

Dyer, C.A., 2007. Heavy metals as endocrine-disrupting chemicals. In: Gore, A.C. (Ed.), Endocrine-disrupting Chemicals: From Basic Science to Clinical Practice. NJ Humana Press Inc., Totowa.

Engel, S.M., Zhu, C., Berkowitz, G.S., Calafat, A.M., Silva, M.J., Miodovnik, A., et al., 2009. Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. Neurotoxicology 30, 522–528.

Ettinger, A.S., Zota, A.R., Amarasiriwardena, C.J., Hopkins, M.R., Schwartz, J., Hu, H., et al., 2009. Maternal arsenic exposure and impaired glucose tolerance during pregnancy. Environ. Health Perspect. 117, 1059–1064.

Feig, D.S., Hwee, J., Shah, B.R., Booth, G.L., Bierman, A.S., Lipscombe, L.L., 2014. Trends in incidence of diabetes in pregnancy and serious perinatal outcomes: a large, population-based study in Ontario, Canada, 1996–2010. Diabetes Care 37, 1590–1596.

Fisher, M., Arbuckle, T.E., Mallick, R., LeBlanc, A., Hauser, R., Feeley, M., et al., 2014. Bisphenol A and phthalate metabolite urinary concentrations: daily and across pregnancy variability. J. Expo. Sci. Environ. Epidemiol. http://dx.doi.org/10.1038/jes.2014.65.

Galtier, F., 2010. Definition, epidemiology, risk factors. Diabetes Metab. 36, 628–651.

Hauser, R., Calafat, A.M., 2005. Phthalates and human health. Occup. Environ. Med. 62, 806–818.

He, K., Xun, P., Liu, K., Morris, S., Reis, J., Guallar, E., 2013. Mercury exposure in young adulthood and incidence of diabetes later in life: the CARDIA Trace Element Study. Diabetes Care 36, 1584–1589.

Health Canada, 2010. Report on Human Biomonitoring of Environmental Chemicals in Canada: Results of the Canadian Health Measures Survey Cycle 1 (2007–2009). (Available: http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/chms-ecms/index-eng.php [accessed 24 September 2014]).

Hoppin, J.A., Jaramillo, R., London, S.J., Bertelsen, R.J., Salo, P.M., Sandler, D.P., et al., 2013. Phthalate exposure and allergy in the U.S. population: results from NHANES 2005–2006. Environ. Health Perspect. 121, 1129–1134.

Huang, C.F., Chen, Y.W., Yang, C.Y., Tsai, K.S., Yang, R.S., Liu, S.H., 2011. Arsenic and diabetes: current perspectives. Kaohsiung J. Med. Sci. 27, 402–410.

Hugo, E.R., Brandebourg, T.D., Woo, J.G., Loftus, J., Alexander, J.W., Ben-Jonathan, N., 2008. Bisphenol A at environmentally relevant doses inhibits adiponectin release from human adipose tissue explants and adipocytes. Environ. Health Perspect. 116, 1642–1647.

Hurst, C.H., Waxman, D.J., 2003. Activation of PPARalpha and PPARgamma by environmental phthalate monoesters. Toxicol. Sci. 74, 297–308.

Iavicoli, I., Fontana, L., Bergamaschi, A., 2009. The effects of metals as endocrine disruptors. J. Toxicol. Environ. Health B Crit. Rev. 12, 206–223.

International Association of Diabetes and Pregnancy Study Groups Consensus Panel, 2010. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 33, 676–682.

James-Todd, T., Stahlhut, R., Meeker, J.D., Powell, S.G., Hauser, R., Huang, T., et al., 2012. Urinary phthalate metabolite concentrations and diabetes among women in the National Health and Nutrition Examination Survey (NHANES) 2001–2008. Environ. Health Perspect. 120, 1307–1313.

Jusko, T.A., Shaw, P.A., Snijder, C.A., Pierik, F.H., Koch, H.M., Hauser, R., et al., 2014. Reproducibility of urinary bisphenol A concentrations measured during pregnancy in the Generation R Study. J. Expo. Sci. Environ. Epidemiol. 24, 532–536.

Just, A.C., Adibi, J.J., Rundle, A.G., Calafat, A.M., Camann, D.E., Hauser, R., et al., 2010. Urinary and air phthalate concentrations and self-reported use of personal care products among minority pregnant women in New York city. J. Expo. Sci. Environ. Epidemiol. 20, 625–633.

Kawakami, T., Sugimoto, H., Furuichi, R., Kadota, Y., Inoue, M., Setsu, K., et al., 2010. Cadmium reduces adipocyte size and expression levels of adiponectin and Peg1/Mest in adipose tissue. Toxicology 267, 20–26.

Koch, H.M., Bolt, H.M., Preuss, R., Angerer, J., 2005. New metabolites of di(2-ethylhexyl)phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. Arch. Toxicol. 79, 367–376.

Kuo, C.C., Moon, K., Thayer, K.A., Navas-Acien, A., 2013. Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. Curr. Diabetes Rep. 13, 831–849.

LaKind, J.S., Goodman, M., Mattison, D.R., 2014. Bisphenol A and indicators of obesity, glucose metabolism/type 2 diabetes and cardiovascular disease: a systematic review of epidemiologic research. Crit. Rev. Toxicol. 44, 121–150.

Lang, I.A., Galloway, T.S., Scarlett, A., Henley, W.E., Depledge, M., Wallace, R.B., et al., 2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA 300, 1303–1310.

Langlois, E., Saravanabhavan, G., Arbuckle, T.E., Giroux, S., 2014. Correction and comparability of phthalate metabolite measurements of Canadian biomonitoring studies (2007–2012). Environ. Int. 64, 129–133.

Legler, J., Fletcher, T., Govarts, E., Porta, M., Blumberg, B., Heindel, J.J., Trasande, L., 2015. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European union. J. Clin. Endocrinol. Metab. 100, 1278–1288.

Lind, P.M., Zethelius, B., Lind, L., 2012. Circulating levels of phthalate metabolites are associated with prevalent diabetes in the elderly. Diabetes Care 35, 1519–1524.

Maull, E.A., Ahsan, H., Edwards, J., Longnecker, M.P., Navas-Acien, A., Pi, J., et al., 2012. Evaluation of the association between arsenic and diabetes: a National Toxicology Program workshop review. Environ. Health Perspect. 120, 1658–1670.

Meeker, J.D., Cantonwine, D.E., Rivera-Gonzalez, L.O., Ferguson, K.K., Mukherjee, B., Calafat, A.M., et al., 2013. Distribution, variability, and predictors of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico. Environ. Sci. Technol. 47, 3439–3447.

Melzer, D., Rice, N.E., Lewis, C., Henley, W.E., Galloway, T.S., 2010. Association of urinary bisphenol a concentration with heart disease: evidence from NHANES 2003/06. PLoS One 5, e8673.

Moon, S.S., 2013. Association of lead, mercury and cadmium with diabetes in the Korean population: the Korea National Health and Nutrition Examination Survey (KNHANES) 2009–2010. Diabet. Med. 30, e143–e148.

Mozaffarian, D., Shi, P., Morris, J.S., Grandjean, P., Siscovick, D.S., Spiegelman, D., et al., 2013. Methylmercury exposure and incident diabetes in U.S. men and women in two prospective cohorts. Diabetes Care 36, 3578–3584.

Navas-Acien, A., Silbergeld, E.K., Streeter, R.A., Clark, J.M., Burke, T.A., Guallar, E., 2006. Arsenic exposure and type 2 diabetes: a systematic review of the experimental and epidemiological evidence. Environ. Health Perspect. 114, 641–648.

Navas-Acien, A., Silbergeld, E.K., Pastor-Barriuso, R., Guallar, E., 2008. Arsenic exposure and prevalence of type 2 diabetes in US adults. JAMA 300, 814–822.

Navas-Acien, A., Silbergeld, E.K., Pastor-Barriuso, R., Guallar, E., 2009. Rejoinder: arsenic exposure and prevalence of type 2 diabetes: updated findings from the National Health Nutrition and Examination Survey, 2003–2006. Epidemiology 20, 816–820.

Peng, S.Y., Liu, L.P., Zhang, X.Q., Heinrich, J., Zhang, J., Schramm, K.W., et al., 2015. A nested case–control study indicating heavy metal residues in meconium associate with maternal gestational diabetes mellitus risk. Environ. Health 14, 19.

Public Health Agency of Canada, 2011. Diabetes in Canada: Facts and Figures from a Public Health Perspective. Available:, http://www.phac-aspc.gc.ca/cd-mc/publications/diabetes-diabete/facts-figures-faits-chiffres-2011/index-eng.php (accessed 21 May 2014).

Quiros-Alcala, L., Eskenazi, B., Bradman, A., Ye, X., Calafat, A.M., Harley, K., 2013. Determinants of urinary bisphenol A concentrations in Mexican/Mexican–American pregnant women. Environ. Int. 59, 152–160.

Robledo, C., Peck, J.D., Stoner, J.A., Carabin, H., Cowan, L., Koch, H.M., et al., 2013. Is bisphenol-A exposure during pregnancy associated with blood glucose levels or diagnosis of gestational diabetes? J. Toxicol. Environ. Health A 76, 865–873.

Sabanayagam, C., Teppala, S., Shankar, A., 2013. Relationship between urinary bisphenol A levels and prediabetes among subjects free of diabetes. Acta Diabetol. 50, 625–631.

Saldana, T.M., Basso, O., Hoppin, J.A., Baird, D.D., Knott, C., Blair, A., et al., 2007. Pesticide exposure and self-reported gestational diabetes mellitus in the Agricultural Health Study. Diabetes Care 30, 529–534.

Schwartz, G.G., Il'yasova, D., Ivanova, A., 2003. Urinary cadmium, impaired fasting glucose, and diabetes in the NHANES III. Diabetes Care 26, 468–470.

Serdar, M.A., Bakir, F., Hasimi, A., Celik, T., Akin, O., Kenar, L., et al., 2009. Trace and toxic element patterns in nonsmoker patients with noninsulin-dependent diabetes mellitus, impaired glucose tolerance, and fasting glucose. Int. J. Diabetes Dev. Ctries. 29, 35–40.

Shankar, A., Teppala, S., 2011. Relationship between urinary bisphenol A levels and diabetes mellitus. J. Clin. Endocrinol. Metab. 96, 3822–3826.

Silver, M.K., O'Neill, M.S., Sowers, M.R., Park, S.K., 2011. Urinary bisphenol A and type-2 diabetes in U.S. adults: data from NHANES 2003–2008. PLoS One 6, e26868.

Smeester, L., Rager, J.E., Bailey, K.A., Guan, X., Smith, N., Garcia-Vargas, G., et al., 2011. Epigenetic changes in individuals with arsenicosis. Chem. Res. Toxicol. 24, 165–167.

Soriano, S., Alonso-Magdalena, P., Garcia-Arevalo, M., Novials, A., Muhammed, S.J., Salehi, A., et al., 2012. Rapid insulinotropic action of low doses of bisphenol-A on mouse and human islets of Langerhans: role of estrogen receptor beta. PLoS One 7, e31109.

Stahlhut, R.W., van Wijngaarden, E., Dye, T.D., Cook, S., Swan, S.H., 2007. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environ. Health Perspect. 115, 876–882.

Sun, Q., Cornelis, M.C., Townsend, M.K., Tobias, D.K., Eliassen, A.H., Franke, A.A., et al., 2014. Association of urinary concentrations of bisphenol A and phthalate metabolites with risk of type 2 diabetes: a prospective investigation in the Nurses' Health Study (NHS) and NHSII cohorts. Environ. Health Perspect. 122, 616–623.

Svensson, K., Hernandez-Ramirez, R.U., Burguete-Garcia, A., Cebrian, M.E., Calafat, A.M., Needham, L.L., et al., 2011. Phthalate exposure associated with self-reported diabetes among Mexican women. Environ. Res. 111, 792–796.

Swaddiwudhipong, W., Mahasakpan, P., Limpatanachote, P., Krintratun, S., 2010. Correlations of urinary cadmium with hypertension and diabetes in persons living in cadmium-contaminated villages in northwestern Thailand: a population study. Environ. Res. 110, 612–616.

Thayer, K.A., Heindel, J.J., Bucher, J.R., Gallo, M.A., 2012. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. Environ. Health Perspect. 120, 779–789.

Tseng, C.H., 2004. The potential biological mechanisms of arsenic-induced diabetes mellitus. Toxicol. Appl. Pharmacol. 197, 67–83.

Volkel, W., Colnot, T., Csanady, G.A., Filser, J.G., Dekant, W., 2002. Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. Chem. Res. Toxicol. 15, 1281–1287.

Watson, W.H., Yager, J.D., 2007. Arsenic: extension of its endocrine disruption potential to interference with estrogen receptor-mediated signaling. Toxicol. Sci. 98, 1–4.

Woodruff, T.J., Zota, A.R., Schwartz, J.M., 2011. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ. Health Perspect. 119, 878–885.