Canadian Journal of Public Health (2020) 111:333–341
https://doi.org/10.17269/s41997-020-00322-5

SPECIAL SECTION ON EPIDEMIOLOGY AND BIOSTATISTICS: QUANTITATIVE RESEARCH

Associations of prenatal urinary phthalate exposure with preterm birth: the Maternal-Infant Research on Environmental Chemicals (MIREC) Study

Janice M. Y. Hu[1] · Tye E. Arbuckle[2] · Patricia Janssen[3] · Bruce P. Lanphear[1] · Joseph M. Braun[4] · Robert W. Platt[5] · Aimin Chen[6] · William D. Fraser[7] · Lawrence C. McCandless[1]

Received: 11 July 2019 / Accepted: 13 April 2020 / Published online: 21 May 2020

Abstract

Objectives To examine the relation between prenatal urinary phthalate metabolite concentrations and preterm birth (PTB).

Methods The data were drawn from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a pan-Canadian cohort of 1857 pregnant women enrolled between 2008 and 2011. We quantified urinary concentrations of 7 phthalate metabolites that were detected in > 70% of urine samples collected during the first trimester. Gestational age was obtained from either the last menstrual period or early ultrasound. We used Cox proportional hazard models to examine the associations of urinary phthalate metabolite concentrations, plus the molar sum of di-2-ethylhexyl phthalate metabolites (∑DEHP), with time to delivery before 37 weeks of gestation. We also examined PTB by clinical presentation. PTBs presented with either spontaneous labour or premature rupture of the membrane were considered spontaneous PTB (sPTB). Additionally, we used multiple linear regression to model changes in mean gestational age in relation to phthalate exposure.

Results We found no evidence of an association between first trimester phthalate metabolite concentrations and PTB among the MIREC study participants. For example, each 2-fold increase in any of the 7 phthalate concentrations or ∑DEHP was associated with hazard ratios (HRs) for PTB ranging from 0.95 to 1.07 with 95% confidence intervals including the null. An assessment of non-linear trends showed some evidence of non-monotonic dose-response relationships between phthalates and PTB. Furthermore, male infants exposed to MCPP showed higher sPTB risk compared with female infants.

Conclusion Phthalate exposure during early pregnancy is not clearly associated with the risk of PTB among this Canadian population.

Résumé

Objectifs Examiner la relation entre les concentrations prénatales des métabolites urinaires des phtalates et les naissances avant terme (NAT).

Méthode Les données proviennent de l'Étude mère-enfant sur les composés chimiques de l'environnement (MIREC), une étude de cohorte pancanadienne de 1 857 femmes enceintes inscrites entre 2008 et 2011. Nous avons chiffré les concentrations

Electronic supplementary material The online version of this article (https://doi.org/10.17269/s41997-020-00322-5) contains supplementary material, which is available to authorized users.

✉ Lawrence C. McCandless
lmccandl@sfu.ca

[1] Faculty of Health Sciences, Simon Fraser University, 8888 University Drive, Burnaby, BC V5A 1S6, Canada

[2] Population Studies Division, Environmental Health Science and Research Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Canada

[3] School of Population and Public Health, University of British Columbia, Vancouver, BC V6T 1Z4, Canada

[4] Department of Epidemiology, Brown University, Providence, RI, USA

[5] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada

[6] Department of Environmental Health, University of Cincinnati, Cincinnati, OH 45221, USA

[7] Department d'obstétrique et gynécologie, Université de Sherbrooke, Quebec, Canada

urinaires de 7 métabolites phtaliques détectés dans > 70 % des échantillons d'urine prélevés au cours du premier trimestre. L'âge gestationnel a été obtenu d'après la date des dernières menstruations ou d'une échographie précoce. Nous avons utilisé le modèle à risques proportionnels de Cox pour examiner les associations entre les concentrations des métabolites urinaires des phtalates, plus la somme des moles des métabolites phtaliques de bis(2-éthylhexyle) (∑DEHP), et une date d'accouchement avant 37 semaines de grossesse. Nous avons aussi examiné les NAT selon leur tableau clinique. Les NAT se présentant avec un travail spontané ou avec la rupture prématurée des membranes ont été considérées comme étant spontanées (NATs). De plus, nous avons procédé par régression linéaire multiple pour modéliser les changements de l'âge gestationnel moyen en lien avec l'exposition aux phtalates.

Résultats Nous n'avons relevé aucun signe d'association entre les concentrations en métabolites phtaliques au premier trimestre et les NAT chez les participantes de l'étude MIREC. Par exemple, chaque multiplication par deux de l'une des 7 concentrations de phtalates ou de la ∑DEHP était associée à des coefficients de danger de NAT allant de 0,95 à 1,07 avec des intervalles de confiance de 95 % incluant les valeurs nulles. Une évaluation des tendances non linéaires a montré des signes de relations dose-réponses non monotones entre les phtalates et les NAT. De plus, les nourrissons de sexe masculin exposés aux phtalates de mono(3-carboxypropyle) (MCPP) présentaient un risque de NATs plus élevé que les nourrissons de sexe féminin.

Conclusion L'exposition aux phtalates en début de grossesse n'est pas clairement associée au risque de naissance avant terme dans cette population canadienne.

Keywords Preterm birth · Gestational age · Phthalates · Environmental chemicals

Mots-clés Naissance avant terme · Âge gestationnel · Phtalates · Produits chimiques dans l'environnement

Introduction

Preterm birth (PTB) is a public health priority. Complications of PTB are the largest contributor to infant mortality, responsible for more than two thirds of all perinatal deaths and three quarters of all serious neonatal morbidity (Martin et al. 2018). In the United States (US), from 1981 to 2006, PTB risk increased by 33%. It peaked in 2006 with an average rate of 12.8% and declined steadily until 2014. Between 2014 and 2017, PTB rate increased steadily from 9.5% to 9.9% (Martin et al. 2018). Meanwhile, in Canada, PTB rate increased by 20% in the past two decades and peaked in 2008 with an average rate of 8.0%. By 2013, the average rate decreased minimally where it accounted for 7.8% of live births (Martin et al. 2018). Many risk factors, including advanced maternal age, race, and low pre-pregnancy body-mass index (BMI), have been implicated in PTB, but risk factors for most PTBs are unknown (Institute of Medicine et al. 2007; Simhan et al. 2014). There is a growing concern that environmental contaminants may play a role in PTB.

Phthalates, synthetic chemicals used in a wide variety of consumer and industrial products, have been linked to the risk of PTB (Boss et al. 2018; Ferguson et al. 2014b; Meeker et al. 2009). Phthalates are plasticizers used in food packaging, vinyl flooring, and medical devices. They are also used as excipients in time-release drugs, and as solvents to retain scents in personal care products. Human exposure to phthalates is widespread and the routes of exposure include ingestion, inhalation, dermal contacts, and in utero transfer from mother to fetus via the placenta (Ferguson et al. 2013). Phthalates may affect PTB via three possible mechanisms: endocrine disruption, oxidative stress, and inflammation. Phthalates are endocrine disruptors that can interfere with key endogenous hormones critical in maintaining uterine quiescence during pregnancy (Challis et al. 2000; McLean et al. 1995; Wadhwa et al. 2004). Phthalate exposure may increase oxidative stress levels which can result in poor placentation or cause damage leading to premature rupture of the membranes (PROM) (Longini et al. 2007; Meeker et al. 2009). Finally, phthalate exposure may heighten systemic or intrauterine inflammatory responses, which could increase oxidative stress and induce a sequence of events leading to premature parturition (Challis et al. 2009; Ferguson and Chin 2017).

Studies of the impact of prenatal phthalate exposure on PTB or gestational age (GA) have produced inconsistent results according to a comprehensive review by Ferguson et al. (2013) and the 7 additional studies published since 2012 (Figures S1 in the Supplementary Materials) (Bloom et al. 2019; Boss et al. 2018; Ferguson et al. 2014b; Gao et al. 2019; Shoaff et al. 2016; Watkins et al. 2016; Weinberger et al. 2014). The studies were mostly US-based and varied by sample size (from fewer than 100 births up to 500), timing of exposure, choice of measured phthalate metabolites, outcome assessment, and statistical methods. Therefore, this study aimed to further the knowledge, especially within a Canadian context, by examining the associations between urinary phthalate metabolite concentrations measured during the first trimester of pregnancy and PTB in a large cohort of Canadian women in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study.

Methods

Study participants

Data were drawn from the MIREC Study, a national-level cohort study of 1857 pregnant women recruited between 2008 and 2011 from ten Canadian cities. The goal of the MIREC Study was to obtain Canadian biomonitoring data on pregnant women and to examine associations between prenatal exposure to environmental chemicals and pregnancy and child health outcomes (Arbuckle et al. 2013). Eligibility criteria and exclusions are described in Arbuckle et al. (2013). For the present study, we included all women who had complete socio-demographic information, provided biological samples during the first trimester of the pregnancy, and delivered singleton live births.

Preterm birth and duration of gestation

Gestational age (GA) at delivery was calculated based on last menstrual period (LMP) or first trimester ultrasound. If LMP and ultrasound date differed by less than or equal to seven days, the LMP date was used; otherwise, the ultrasound date was used (Kieler et al. 1993). Births less than 37 completed gestational weeks were considered preterm. We also examined PTB by clinical presentation. We defined spontaneous PTB (sPTB) as either spontaneous preterm labour or with preterm PROM (pPROM). All information was obtained from medical records.

Prenatal phthalate exposure assessment

We measured eleven phthalate metabolite concentrations in urine samples collected from MIREC participants during the first trimester of pregnancy. Biomarker analysis took place at the Toxicology Laboratory of the Institut national de santé publique du Québec using methods previously described (Langlois et al. 2014). We retained the seven phthalate metabolites that were detected in at least 70% of the samples analyzed (Lubin et al. 2004) including mono-2-ethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(3-carboxypropyl) phthalate (MCPP), mono-benzyl phthalate (MBzP), mono-ethyl phthalate (MEP), and mono-n-butyl phthalate (MnBP). Measurements below the limit of detection (LOD) were replaced using the single imputation "fill-in" approach where the log2-phthalate concentrations <LOD were randomly sampled from a truncated lognormal distribution with mean and standard deviation estimated from the observed data (Lubin et al. 2004). The "fill-in" approach for missing biomarkers yields unbiased regression coefficient estimates if the imputation distribution is correct, although standard errors may be biased.

To account for individual-level variability in urinary hydration levels, all phthalate metabolite concentrations were standardized by specific gravity (SG) using the following formula:

$$P_c = P\,[(SG_{median}-1)/(SG-1)],$$

where P_c represents the SG-standardized phthalate metabolite concentration (μg/L), P represents the measured urinary concentration, SG_{median} (i.e., 1.013) is the median SG of all samples measured, and SG represents the SG of the individual sample (Meeker et al. 2009). Standardization by the formula was only applied when presenting the descriptive statistics on the metabolite concentrations. Otherwise, SG was included as a covariate in all regression models (Barr et al. 2005).

Finally, we summed di-2-ethylhexyl phthalate (DEHP) metabolites (i.e., MEHHP, MEHP, and MEOHP) by dividing each metabolite concentration by its molecular weight and then summing them to calculate the molar sums of DEHP metabolites (∑DEHP). The formula is given by (Hauser et al. 2016)

$$[MEHP \times (1/278.34)] + [MEHHP \times (1/294.34)] + [MEOHP \times (1/292.33)]$$

Covariates

We examined variables that may potentially confound the relationship between urinary phthalate metabolite concentrations and PTB. We created a directed acyclic graph (Figure S2) to identify predictors of PTB and factors associated with both phthalate exposure and PTB (Hernan 2002). The following covariates derived from the baseline questionnaire were examined: maternal age (under 25, ≥ 25 to < 30, ≥ 30 to < 35, ≥ 35 to < 40, and ≥ 40), race (white, non-white), education (high school diploma or less, college or trade school diploma, undergraduate university degree, and graduate university degree), marital status (married, same partner ≥ 1 year, single, and others), smoking status (never, current, former, and quit during pregnancy), parity (0, 1, 2, ≥ 3), and pre-pregnancy BMI (underweight, normal, overweight, and obese). The same set of covariates was used in all analyses.

Analytical approach

Participant characteristics were tabulated and geometric means (GM) and percentiles of the phthalate metabolite concentrations were calculated. To reduce the effects of the right skewed distributions, the metabolite concentrations were log2 transformed before inclusion in the regression models. Log2-transformation was specifically chosen for easy interpretation (i.e., a two-fold increase).

Our primary analysis involved analyzing gestational age (GA) as a time-to-event outcome to examine the relationship

between urinary phthalate metabolite concentrations and PTB. We used Cox proportional hazards regression, adjusted for potential confounders, to examine the relationship of the 7 individual urinary phthalate metabolite concentrations plus ∑DEHP with time to delivery before 37 weeks. We computed the hazard ratios (HRs) to compare the hazard of PTB relative to a two-fold increase in phthalate metabolite concentrations (Yau Fu and Liu 2002). If GA was less than 37 weeks, then GA was taken as the time to event. Full-term births at 37 weeks or later were treated as censored observations. The analysis assumed that the effects of the exposure upon survival are constant over time for GA < 37 weeks, and we tested the proportional hazards assumption using a test of the scaled Schoenfeld residuals (Fox 2002). Prior studies have examined GA as a time-to-event outcome in the analysis of PTB with no censoring of births at 37 weeks (e.g., Mitchell et al. 2016). However, this approach assumes proportional hazards throughout the entire range of GA (e.g., using a parametric proportional hazards model) unless time-dependent covariates are included.

We also examined the risk of sPTB. In this case, sPTB was the event, whereas indicated PTBs, PTBs with missing clinical presentation, and full-term births were censored observations. To check for non-linear trends, we repeated the Cox proportional hazards regression analysis with phthalate metabolite exposure concentrations considered in quartiles. Additionally, we conducted stratified analysis to examine the potential modifying effects of infant sex on the relationship between phthalate metabolite concentrations and both PTB and sPTB.

Our secondary analysis examined all GAs as a continuous outcome variable in relation to phthalate metabolite concentrations using multiple linear regression adjusted for confounders. The beta coefficient describes the change in mean GA, measured in weeks, associated with a 2-fold increase in urinary phthalate metabolite concentration. We used residual plots to check for violations of assumptions.

All analyses were conducted using R version 3.6.0 (2019-04-26).

Ethics approval

This research was approved by the ethics review boards from Health Canada, Sainte-Justine Research Centre, and Simon Fraser University. All study participants provided informed consent.

Results

Descriptive statistics

A total of 1857 MIREC participants were included in the analysis (Table 1). The women were generally white (81.7%), ≥ 30 years of age (69.6%) with at least an undergraduate degree (62.3%), either married or in a stable relationship (95.3%), had never smoked (61.3%), and had normal BMI (60.5%). Characteristics that were predictive of lower GA included being non-white, advanced maternal age, underweight or obese, having lower educational attainment, and increased parity. The missing observations for all socio-demographic variables were less than 1% except for pre-pregnancy BMI with 138 (7.4%) observations missing. Of the participants, 127 (6.8%) were PTB and 86 (67.7%) of these were sPTB. There were 77 sPTB events after 297 (16.0%) MIREC participants were deleted from the analysis due to missing information on socio-demographic characteristics, chemical concentrations, and clinical presentation. There is some evidence that a number of risk factors such as maternal age, marital status, maternal educational attainment, parity, and pre-pregnancy BMI (Institute of Medicine et al. 2007; Simhan et al. 2014) may be associated with PTB and sPTB, although caution is warranted in the interpretation due to imprecise CIs (Table S1).

Primary analysis of Cox proportional hazards regression and PTB

In the Cox proportional hazards regression analyses (Table 3), a 2-fold increase in urinary phthalate metabolite concentrations was associated with unadjusted HRs for PTB that ranged from as low as 0.92 to as high as 1.07. The HRs changed minimally and remained close to 1 when comparing adjusted with unadjusted models. For instance, a two-fold increase in ∑DEHP resulted in an HR of 0.98 (95% CI: 0.83, 1.14) in the unadjusted model versus 0.99 (95% CI: 0.83, 1.16) in the adjusted model.

We also estimated the HRs for the probability of sPTB that were associated with a 2-fold change in phthalate metabolite concentrations (Table 3). The unadjusted models had HRs for sPTB ranging from 0.98 to 1.12, whereas the adjusted HRs ranged from 0.98 to 1.10. For both PTB and sPTB, no departures from proportional hazards in relation to log2-transformed phthalate metabolite concentrations were detected with Schoenfeld residual-based tests.

The assessment of non-linear trends in the relationship between phthalate metabolite concentrations and PTB showed non-monotonic associations with wide 95% CIs (Table S2 and Figure S3). The adjusted HRs of PTB in the second quartile (Q2) of MBP, MEHHP, and ∑DEHP were higher compared with the first quartile (Q1) and had significant HRs ranging from 2.0 to 2.5 for PTB. For MCPP, the adjusted HRs of PTB for all quartiles were at least twice as high compared with Q1 with HRs ranging from 2.00 to 2.72. When the quartiles were examined in relation to sPTB risk, some of the trends became stronger and some HRs associated with Q2 versus Q1 increased.

Table 1 Preterm birth (PTB) and duration of gestation by maternal demographic and pregnancy-related characteristics among MIREC study participants in Canada, 2008–2011

	n (%)	PTB (%)	Duration of gestation 25th percentile	Duration of gestation Median (IQR)
Total	1857 (100%)	115 (100%)	38.6	39.6 (1.8)
Maternal age				
19–24	117 (6.3%)	9 (7.8%)	38.4	39.9 (1.9)
25–29	443 (24.0%)	18 (15.7%)	38.9	39.9 (1.7)
30–34	656 (35.5%)	38 (33.0%)	38.6	39.6 (2.0)
35–39	502 (27.2%)	39 (33.9%)	38.6	39.3 (1.8)
40+	127 (6.9%)	10 (8.7%)	38.8	39.4 (1.5)
Education				
High school diploma or less	161 (8.7%)	11 (9.6%)	38.4	39.4 (1.9)
Some college, trade school, or college diploma	538 (29.0%)	40 (34.8%)	38.4	39.4 (1.9)
Undergrad degree	681 (36.7%)	37 (34.8%)	38.7	39.7 (1.9)
Graduate degree	475 (25.6%)	27 (23.5%)	38.7	39.6 (1.9)
Race				
White	1517 (81.7%)	91 (79.1%)	38.6	39.6 (2.0)
Other	340 (18.3%)	24 (20.9%)	38.4	39.3 (1.7)
Marital status				
Married	1337 (72.0%)	78 (67.8%)	38.6	39.6 (1.8)
Same partner for ≥ 1 year	432 (23.3%)	30 (26.1%)	38.6	39.7 (2.0)
Single	78 (4.2%)	6 (5.2%)	38.5	39.6 (1.7)
Others	10 (0.5%)	1 (0.9%)	38.9	39.1 (0.4)
Parity				
0	812 (43.7%)	52 (45.2%)	38.9	39.9 (1.8)
1	751 (40.4%)	47 (40.9%)	38.6	39.4 (1.7)
2	222 (12.0%)	13 (11.3%)	38.3	39.3 (1.8)
3+	72 (3.9%)	3 (2.6%)	38.4	39.0 (1.6)
Smoking status				
Never	1137 (61.3%)	71 (61.7%)	38.6	39.4 (1.8)
Former	498 (26.8%)	30 (26.1%)	38.7	39.7 (1.9)
Quit during pregnancy	115 (6.2%)	8 (7.0%)	38.6	39.6 (2.0)
Current	106 (5.7%)	6 (5.2%)	38.6	39.6 (1.8)
BMI				
Underweight	49 (2.9%)	2 (1.7%)	38.6	39.4 (1.8)
Normal	1040 (60.5%)	52 (45.2%)	38.9	39.6 (1.7)
Overweight	372 (21.6%)	20 (17.4%)	38.6	39.6 (2.0)
Obese	258 (15.0%)	33 (28.7%)	38.1	39.1 (2.2)

Numbers may not sum to total as a result of missing data

Tables S3 and S4 show that a 2-fold increase in MCPP concentration was associated with adjusted HRs of 1.19 (95% CI: 1.00, 1.41) and 0.85 (95% CI: 0.65, 1.13) for male and female infants, respectively, with a product interaction *p* value of 0.57.

Secondary analysis of linear regression and GA

The associations between a two-fold increase in phthalate metabolite concentrations and the change in the mean GA in weeks are summarized in Table 4. All phthalate metabolites and ∑DEHP were associated with small changes in the mean GA. A doubling of phthalate metabolite concentrations was associated with changes in GA ranging from − 0.03 to 0.01 weeks and the adjusted estimates differed minimally. For example, for ∑DEHP, the shift in mean GA was − 0.03 weeks (95% CI: − 0.09, 0.04) and the adjusted effect decreased slightly to − 0.04 weeks (95% CI: − 0.10, 0.03). The multiple regression analysis assumptions were checked and met.

Discussion

We found no evidence of a dose-response association between individual maternal urinary phthalate metabolite concentrations or ∑DEHP measured during the first trimester of pregnancy and PTB among MIREC study participants. The HRs for PTB ranged from 0.95 to 1.07 with 95% confidence intervals (CIs) ranging from 0.81 to 1.21 for a doubling of urinary phthalate metabolite concentrations. In a relatively recent study, when asked about the minimal clinically meaningful effect sizes, Canadian obstetricians reported that a minimum of one week increase in GA was required before they would consider changing their current treatment methods to prevent PTB (Ross et al. 2012). Small relative effect sizes and an exposure shift of < 1 day in GA are arguably not clinically meaningful (Olivier et al. 2017; Ross et al. 2012). Consequently, the 95% CIs in Tables 3 and 4 rule out important differences in the association between phthalate exposure and PTB. However, the HRs in Table 3 are scale dependent, and we would obtain larger effect estimates using other log transformations of the metabolite concentrations (e.g., log10). Furthermore, small effects may have important significance when we consider the entire populations (Bellinger 2007; Rose 1981).

Nonetheless, Table S2 showed some evidence of a non-monotonic dose-response relationship between phthalate metabolite concentrations and PTB. When the analysis was limited to modelling the hazards of sPTB, some of the trends became stronger. However, due to the small sample size of each quartile, the effect estimates were imprecise and caution is warranted in the interpretation of results. In our analysis of effect modification, we found that infant sex modified the relationship between MCPP and sPTB (p value = 0.57). In the literature, among studies that modeled associations of phthalate exposure with PTB stratified by infant sex, inconsistent results were reported (Shoaff et al. 2016; Watkins et al. 2016; Weinberger et al. 2014).

Watkins et al. (2016) found that first trimester phthalate metabolite concentrations, which were generally lower than that of MIREC's (Table 2), were associated with decreases in mean GA of – 0.75 to – 2.18 days. Other studies also reported reductions in GA or increased odds of PTB in relation to phthalate metabolite concentrations (Boss et al. 2018; Ferguson et al. 2014b; Gao et al. 2019; Meeker et al. 2009; Whyatt et al. 2009). Ferguson et al. (2014b) found that a ln-unit increase in MEHP or ∑DEHP was associated with increased odds of PTB while a ln-unit increase in MEHP, MEOHP, DEHP, MBP, or MCPP was associated with increased odds of sPTB (Ferguson et al. 2014b). Whyatt et al. (2009) observed among ethnic women in America a decrease of up to − 0.18 weeks (95% CI: − 0.32, − 0.03) in GA per log-unit increase in DEHP or its metabolites. Meanwhile, Meeker et al. (2009), in a small nested case-control study in Mexico, found increased odds of PTB with third trimester MBP and MCPP. Furthermore, Gao et al. (2019) reported increased odds of PTB with increasing phthalate metabolite concentrations and Boss et al. (2018), using survival analysis, reported an increase in probability for PTB in women with higher MBzP, MBP, or MCPP concentrations compared with those with lower concentrations.

Our results are contrary to prior studies where increasing phthalate metabolite concentrations during pregnancy were associated with small increases in GA. For example, Wolff et al. (2008) found that third trimester phthalate metabolite concentrations were associated with increasing GA. For instance, a ln-unit increase in MEHP was associated with a 0.15-week (95% CI: 0.02, 0.29) increase in GA. Adibi et al. (2009) also reported an association between a ln-unit increase in DEHP metabolites and a 0.16 to 0.19 week increase in GA. Recently, Shoaff et al. (2016) reported that MCPP was associated with increases in GA.

Differences in study design, statistical methodology, and exposure assessment such as the timing of the urinary phthalate metabolite measurements and the differences in exposure levels could account for the discrepancies between our findings and those of previous studies. Women in the MIREC Study had lower phthalate metabolite concentrations during the first trimester compared with the levels previously reported such as those in the nested case-control study (n = 130 cases; 352 controls) of Ferguson et al. (2014b). Nonetheless, the 75th percentile of phthalate levels in the MIREC Study were equal to or greater than the geometric mean (GM) from earlier studies (Adibi et al. 2009; Ferguson et al. 2014b; Whyatt et al. 2009). For example, for MBP, which has been associated with PTB in Ferguson et al. (2014b), the 75th percentile concentration was 20.8 μg/L in MIREC versus the GM of 16.7 μg/L in Ferguson et al. (2014b). This suggests that, although study methodology may differ, at least 464 MIREC participants (25% × 1857 participants) had phthalate metabolite concentrations greater than the GM of Ferguson et al. (2014b) where decrements in GA and PTB were previously observed. Despite the overlapping exposure concentrations in our study versus that of Ferguson et al. (2014b), no associations were observed in the MIREC cohort.

This study has several limitations. First, we only had first trimester spot urine phthalate metabolite measurements and had assumed that the measurements reasonably represent the exposure during the critical window of organ development in the first trimester. Phthalates, however, are non-persistent chemicals that metabolize quickly and most of the measured urinary phthalate metabolite concentrations, except for MEP and MBzP, had low reported intraclass correlation throughout pregnancy (Fisher et al. 2015). Therefore, exposure misclassification may exist and repeated urine measurements may better classify gestational exposure. Furthermore, timing of exposure measurements may also be important in the etiology of PTB (Ferguson et al. 2014a).

Table 2 Distributions of first trimester specific gravity standardized urinary phthalate metabolite concentrations among MIREC study participants ($n = 1857$) in Canada, 2008–2011, including geometric means from Canadian Health Measures Survey 2009–2011 and Watkins et al. (2016) for comparison purpose

Phthalates (μg/L)	LOD	%>LOD MIREC	GM[1] MIREC	Min	5th	25th	50th	75th	95th	Max	GM CHMS[2]	GM Watkins[3]
MBP	0.2	99.8	13.5	0.1	4.1	8.5	13.0	20.8	47.7	1831.8	-	6.4
MBzP	0.2	99.5	6.1	0.1	1.5	3.1	5.6	11.2	37.3	342.7	8.2	3.0
MCPP	0.2	84.8	1.1	0.0	0.2	0.6	1.0	1.8	7.5	186.3	1.9	1.9
MEHHP	0.4	99.4	10.8	0.1	3.1	6.4	9.8	16.3	52.1	1114.3	12.0	7.2
MEHP	0.2	98.5	2.6	0.1	0.8	1.5	2.4	4.1	13.0	260.0	1.8	2.0
MEOHP	0.2	99.7	7.5	0.1	2.4	4.6	6.9	11.1	31.4	733.6	7.3	3.5
MEP	0.5	99.9	37.8	0.1	5.7	13.5	31.1	86.3	478.2	20,800.0	44.0	30.5
ΣDEHP (μmol/L)	-	-	0.07	0.00	0.02	0.04	0.07	0.11	0.33	7.22	-	0.07

[1] *GM*, geometric mean

[2] Canadian Health Measures Survey (CHMS) 2009–2011 creatinine adjusted urinary phthalate concentration for Canadian females aged 6–49 (Health Canada 2016)

[3] First trimester urinary phthalate concentration for American participants in Watkins et al. (Watkins et al. 2016)

Second, although Cox proportional hazards regression accounted for the effects of time and confounders, it did not account for co-pollutant confounding and interactions among phthalate metabolites or other chemicals the women were exposed to. Our linear regression analysis also ignored the effect of combined exposure to multiple phthalate metabolites on GA. Although we calculated ∑DEHP, it did not fully characterize the combined effect of multiple phthalate metabolites. Instead, we could consider machine learning methods such as the Bayesian Kernel Machine Regression (Bobb et al. 2015), which can incorporate several phthalate metabolites into the same model.

Third, linear regression may not be suitable for examining the association between phthalate exposure and GA, which may not be linear and showed non-monotonic trends in risk of PTB when examined by quartiles (Table S2). However, the drawbacks of categorizing continuous predictors are well known, and, in particular, the choice of cut points is somewhat arbitrary and manipulable (Harrell and Jr. 2015). Furthermore, instead of checking for non-linear trends by categorizing phthalate metabolite concentrations into quartiles, splines could be used which permit hypothesis testing for nonlinearity (Steenland and Deddens 2004).

A further limitation of our analysis is that missing values may bias the effect estimates and the MIREC Study may not

Table 3 Hazard ratios (HRs) for preterm birth (PTB) or spontaneous preterm birth (sPTB) according to 2-fold increase in urinary phthalate metabolite concentrations among MIREC study participants in Canada, 2008–2011, calculated using Cox proportional hazards regression

	HRs for PTB (event = PTB)		HRs for sPTB (event = sPTB)	
Phthalates (2-fold increase in exposure)	Unadjusted*[1] (95% CI)	Adjusted**[2] (95% CI)	Unadjusted*[3] (95% CI)	Adjusted**[4] (95% CI)
MBP	0.97 (0.82, 1.14)	0.99 (0.83, 1.17)	0.98 (0.82, 1.18)	1.01 (0.83, 1.22)
MBzP	1.00 (0.87, 1.14)	0.99 (0.86, 1.15)	1.01 (0.87, 1.18)	1.02 (0.87, 1.20)
MCPP	1.07 (0.95, 1.21)	1.07 (0.94, 1.21)	1.12 (0.97, 1.28)	1.10 (0.95, 1.27)
MEHHP	0.99 (0.85, 1.14)	1.00 (0.85, 1.17)	1.05 (0.89, 1.23)	1.05 (0.88, 1.25)
MEHP	0.92 (0.79, 1.07)	0.95 (0.81, 1.11)	0.98 (0.82, 1.16)	0.98 (0.82, 1.18)
MEOHP	0.98 (0.84, 1.14)	0.98 (0.83, 1.16)	1.05 (0.88, 1.24)	1.05 (0.87, 1.26)
MEP	1.01 (0.91, 1.11)	0.99 (0.90, 1.10)	1.02 (0.91, 1.13)	0.99 (0.88, 1.12)
ΣDEHP	0.98 (0.83, 1.14)	0.99 (0.83, 1.16)	1.04 (0.88, 1.23)	1.04 (0.87, 1.25)

*Adjusted for specific gravity

**Adjusted for specific gravity, maternal age, race, education, pre-pregnancy BMI, smoking status, marital status, and parity

[1] $n = 101$ PTB; $n = 1572$ term births

[2] $n = 92$ PTB; $n = 1454$ term births

[3] $n = 77$ sPTB; $n = 1557$ term births + indicated PTB

[4] $n = 70$ sPTB; $n = 1442$ term births + indicated PTB

Table 4 Urinary phthalate concentrations in relation to gestational age (weeks) among MIREC study participants in Canada, 2008–2011, calculated using multiple linear regression

Phthalates (2-fold increase in exposure)	β unadjusted* (95% CI)	β adjusted** (95% CI)
MBP	− 0.03 (− 0.10, 0.04)	− 0.02 (− 0.09, 0.05)
MBzP	− 0.02 (− 0.07, 0.04)	− 0.02 (− 0.08, 0.04)
MCPP	− 0.01 (− 0.06, 0.05)	− 0.01 (− 0.07, 0.04)
MEHHP	− 0.03 (− 0.09, 0.03)	− 0.04 (− 0.10, 0.03)
MEHP	− 0.01 (− 0.07, 0.05)	− 0.03 (− 0.09, 0.04)
MEOHP	− 0.03 (− 0.09, 0.04)	− 0.03 (− 0.10, 0.03)
MEP	0.01 (− 0.04, 0.05)	0.01 (− 0.04, 0.05)
ΣDEHP	− 0.03 (− 0.09, 0.04)	− 0.04 (− 0.10, 0.03)

*Adjusted for specific gravity

**Adjusted for specific gravity, maternal age, race, education, pre-pregnancy BMI, smoking status, marital status, and parity

have sufficient power to detect a statistically significant association between phthalates and PTB. If a 2-fold increase in phthalate metabolite concentration (e.g., MEHP) multiplies the risk of PTB by 1.5 (estimated from Figure S1), then, when comparing two independent samples with the frequency of PTB among the Canadian population at 8% (Martin et al. 2018), we require 69 PTBs per group (138 in total) to detect a statistically significant difference in proportions with $\beta = 0.2$ and $\alpha = 0.05$ (Rosner 2015). This indicates low power because our analysis included only 115 PTBs, and additionally, the true relative risks may be less than 1.5. Nonetheless, compared with prior studies, the MIREC Study is one of the largest studies available to examine phthalate exposure in relation to GA. MIREC, with its large sample size and a large number of PTB and sPTB events, enables us to obtain, in our primary analysis, more precise estimates of effects with relatively narrow 95% CIs. Results in Table S1 show that we are able to observe the effects of established risk factors for PTB (Institute of Medicine et al. 2007; Simhan et al. 2014), which demonstrates that MIREC is able to measure unbiased estimators of population parameters. Therefore, regardless of the amount of power, the data in Tables 3 and 4 provide unbiased estimates of the relationships in the data and statistical significance should not be the sole criteria for evaluating quantitative research (Amrhein et al. 2019).

In conclusion, our main analysis indicated no evidence of associations between first trimester maternal urinary phthalate exposure and PTB in a large prospective cohort of Canadian pregnant women. However, we found some evidence of non-monotonic dose-response relationships between MCPP quartiles and both PTB and sPTB. We also found limited evidence of increased sPTB risk in male infants exposed to MCPP, although the interaction effect was not statistically significant. Nevertheless, the current scientific evidence of the effects of phthalate exposure on PTB remains inconsistent. Further studies with multiple exposure measurements during the first trimester may reduce within-individual variability and improve the validity of the results.

Acknowledgements We are grateful to all the participants who took part in the MIREC Study, as well as to all study staff.

Funding information This project was funded by a Catalyst Grant from the Canadian Institutes of Health Research (L-CIP-150736). The MIREC Study was funded by Health Canada's Chemicals Management Plan, the Ontario Ministry of the Environment and a research grant from the Canadian Institutes of Health Research (MOP-81285).

Compliance with ethical standards

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

Competing interests JMB was financially compensated for serving as an expert witness for plaintiffs in litigation related to tobacco smoke exposures.

References

Adibi, J. J., Hauser, R., Williams, P. L., Whyatt, R. M., Calafat, A. M., Nelson, H., et al. (2009). Maternal urinary metabolites of di-(2-ethylhexyl) phthalate in relation to the timing of labor in a US multicenter pregnancy cohort study. *American Journal of Epidemiology, 169*(8), 1015–1024.

Amrhein, V., Greenland, S., & McShane, B. (2019). Scientists rise up against statistical significance. *Nature, 567*(7748), 305–307.

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. *Paediatric and Perinatal Epidemiology, 27*(4), 415–425.

Barr, D. B., Wilder, L. C., Caudill, S. P., Gonzalez, A. J., Needham, L. L., & Pirkle, J. L. (2005). Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. *Environmental Health Perspectives, 113*(2), 192–200.

Bellinger, D. C. (2007). Interpretation of small effect sizes in occupational and environmental neurotoxicology: individual versus population risk. *Neurotoxicology, 28*(2), 245–251.

Bloom, M. S., Wenzel, A. G., Brock, J. W., Kucklick, J. R., Wineland, R. J., Cruze, L., et al. (2019). Racial disparity in maternal phthalates exposure; association with racial disparity in fetal growth and birth outcomes. *Environment International, 127*, 473–486.

Bobb, J. F., Valeri, L., Claus Henn, B., Christiani, D. C., Wright, R. O., Mazumdar, M., et al. (2015). Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. *Biostatistics, 16*(3), 493–508.

Boss, J., Zhai, J., Aung, M. T., Ferguson, K. K., Johns, L. E., McElrath, T. F., et al. (2018). Associations between mixtures of urinary phthalate metabolites with gestational age at delivery: a time to event analysis using summative phthalate risk scores. *Environmental Health: A Global Access Science Source, 17*(1), 56.

Challis, J. R. G., Matthews, S. G., Gibb, W., & Lye, S. J. (2000). Endocrine and paracrine regulation of birth at term and preterm. *Endocrine Reviews, 21*(5), 514–550.

Challis, J. R., Lockwood, C. J., Myatt, L., Norman, J. E., Strauss 3rd, J. F., & Petraglia, F. (2009). Inflammation and pregnancy. *Reproductive Sciences, 16*(2), 206–215.

Ferguson, K. K., & Chin, H. B. (2017). Environmental chemicals and preterm birth: biological mechanisms and the state of the science. *Current Epidemiology Reports, 4*(1), 56–71.

Ferguson, K. K., O'Neill, M. S., & Meeker, J. D. (2013). Environmental contaminant exposures and preterm birth: a comprehensive review. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews, 16*(2), 69–113.

Ferguson, K. K., McElrath, T. F., Ko, Y.-A., Mukherjee, B., & Meeker, J. D. (2014a). Variability in urinary phthalate metabolite levels across pregnancy and sensitive windows of exposure for the risk of preterm birth. *Environment International, 70*, 118–124.

Ferguson, K. K., McElrath, T. F., & Meeker, J. D. (2014b). Environmental phthalate exposure and preterm birth. *JAMA Pediatrics, 168*(1), 61–67.

Fisher, M., Arbuckle, T. E., Mallick, R., LeBlanc, A., Hauser, R., Feeley, M., et al. (2015). Bisphenol A and phthalate metabolite urinary concentrations: daily and across pregnancy variability. *Journal of Exposure Science & Environmental Epidemiology, 25*(3), 231–239.

Fox, J. (2002). Cox proportional-hazards regression for survival data *An R and S-PLUS Companion to Applied Regression*, 2002. Retrieved from https://socialsciences.mcmaster.ca/jfox/Books/Companion-2E/appendix/Appendix-Cox-Regression.pdf

Gao, H., Wang, Y.-F., Huang, K., Han, Y., Zhu, Y.-D., Zhang, Q.-F., et al. (2019). Prenatal phthalate exposure in relation to gestational age and preterm birth in a prospective cohort study. *Environmental Research, 176*, 108530.

Harrell, F. E., & Jr. (2015). *Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis*. Springer.

Hauser, R., Gaskins, A. J., Souter, I., Smith, K. W., Dodge, L. E., Ehrlich, S., et al. (2016). Urinary phthalate metabolite concentrations and reproductive outcomes among women undergoing in vitro fertilization: results from the EARTH Study. *Environmental Health Perspectives, 124*(6), 831–839.

Health Canada. (2016). Second report on human biomonitoring of environmental chemicals in Canada - Tables 13.1.1 to 15.12.6 - Canada.ca. Retrieved June 9, 2019, from https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/second-report-human-biomonitoring-environmental-chemicals-canada-tables-13-1-1-15-12-6.html

Hernan, M. A. (2002). Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *American Journal of Epidemiology, 155*, 176–184. https://doi.org/10.1093/aje/155.2.176.

Institute of Medicine, Board on Health Sciences Policy, & Committee on Understanding Premature Birth and Assuring Healthy Outcomes. (2007). Preterm birth: causes, consequences, and prevention. National Academies Press.

Kieler, H., Axelsson, O., And, S. N., & Waldenstrom, U. (1993). Comparison of ultrasonic measurement of biparietal diameter and last menstrual period as a predictor of day of delivery in women with regular 28 day-cycles. *Acta Obstetricia et Gynecologica Scandinavica, 72*(5), 347–349.

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

Longini, M., Perrone, S., Vezzosi, P., Marzocchi, B., Kenanidis, A., Centini, G., et al. (2007). Association between oxidative stress in pregnancy and preterm premature rupture of membranes. *Clinical Biochemistry, 40*(11), 793–797.

Lubin, J. H., Colt, J. S., Camann, D., Davis, S., Cerhan, J. R., Severson, R. K., et al. (2004). Epidemiologic evaluation of measurement data in the presence of detection limits. *Environmental Health Perspectives, 112*(17), 1691–1696.

Martin, J. A., Hamilton, B. E., Osterman, M. J. K., Driscoll, A. K., & Drake, P. (2018). Births: final data for 2017. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, 67*(8), 1–50.

McLean, M., Bisits, A., Davies, J., Woods, R., Lowry, P., & Smith, R. (1995). A placental clock controlling the length of human pregnancy. *Nature Medicine, 1*(5), 460–463.

Meeker, J. D., Hu, H., Cantonwine, D. E., Lamadrid-Figueroa, H., Calafat, A. M., Ettinger, A. S., et al. (2009). Urinary phthalate metabolites in relation to preterm birth in Mexico city. *Environmental Health Perspectives, 117*(10), 1587–1592.

Mitchell, E. M., Hinkle, S. N., & Schisterman, E. F. (2016). It's about time: a survival approach to gestational weight gain and preterm delivery. *Epidemiology, 27*(2), 182–187.

Olivier, J., May, W. L., & Bell, M. L. (2017). Relative effect sizes for measures of risk. *Communications in Statistics - Theory and Methods, 46*(14), 6774–6781.

Rose, G. (1981). Strategy of prevention: lessons from cardiovascular disease. *British Medical Journal, 282*(6279), 1847–1851.

Rosner, B. (2015). Fundamentals of biostatistics. Nelson Education.

Ross, S., Milne, J., Dwinnell, S., Tang, S., & Wood, S. (2012). Is it possible to estimate the minimal clinically important treatment effect needed to change practice in preterm birth prevention? Results of an obstetrician survey used to support the design of a trial. *BMC Medical Research Methodology, 12*(1), 31.

Shoaff, J. R., Romano, M. E., Yolton, K., Lanphear, B. P., Calafat, A. M., & Braun, J. M. (2016). Prenatal phthalate exposure and infant size at birth and gestational duration. *Environmental Research, 150*, 52–58.

Simhan, H. N., Berghella, V., & Iams, J. D. (2014). Preterm labor and birth. *Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice. 7th Ed. Philadelphia, PA: Saunders-Elsevier*, 624–653.

Steenland, K., & Deddens, J. A. (2004). A practical guide to dose-response analyses and risk assessment in occupational epidemiology. *Epidemiology, 15*(1), 63–70.

Wadhwa, P. D., Garite, T. J., Porto, M., Glynn, L., Chicz-DeMet, A., Dunkel-Schetter, C., & Sandman, C. A. (2004). Placental corticotropin-releasing hormone (CRH), spontaneous preterm birth, and fetal growth restriction: a prospective investigation. *American Journal of Obstetrics and Gynecology, 191*(4), 1063–1069.

Watkins, D. J., Milewski, S., Domino, S. E., Meeker, J. D., & Padmanabhan, V. (2016). Maternal phthalate exposure during early pregnancy and at delivery in relation to gestational age and size at birth: a preliminary analysis. *Reproductive Toxicology, 65*, 59–66.

Weinberger, B., Vetrano, A. M., Archer, F. E., Marcella, S. W., Buckley, B., Wartenberg, D., et al. (2014). Effects of maternal exposure to phthalates and bisphenol A during pregnancy on gestational age. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 27*(4), 323–327.

Whyatt, R. M., Adibi, J. J., Calafat, A. M., Camann, D. E., Rauh, V., Bhat, H. K., et al. (2009). Prenatal di(2-ethylhexyl)phthalate exposure and length of gestation among an inner-city cohort. *Pediatrics, 124*(6), e1213–e1220.

Yau Fu, C., & Liu, S. H. (2002). Using survival analysis in preterm birth study. In *Recent advances in statistical methods* (pp. 107–113). Imperial College Press: World Scientific Publishing Co.