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Impact of exposure to phenols during early pregnancy on birth weight in two Canadian cohort studies subject to measurement errors☆

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ABSTRACT

Background: It is of interest to know whether early pregnancy exposure to phenols such as bisphenol-A (BPA) or triclosan (TCS) negatively impacts birth weight outcomes. Exposure to these chemicals is widespread in the Canadian population but obtaining accurate measurements of average exposure is difficult because these chemicals are rapidly excreted from the body, causing body levels to fluctuate both within and between days, as observed in a recent Canadian study (P4). This measurement error can attenuate the estimated effects of exposures.

Methods: Data from two Canadian cohort studies, the Plastics and Personal-care Products use in Pregnancy (P4) Study and the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, such that all participants with complete BPA or TCS exposure and outcome data were used (MIREC $n = 1822$, P4 $n = 68$). We used regression calibration to correct for the attenuating effects of exposure measurement error when modeling the effect of first trimester BPA or TCS exposure on four birth weight outcomes: birth weight (BW), low birth weight (LBW), small for gestational age (SGA) and large for gestational age (LGA). Specific gravity, time of day, and time since last urine void were also controlled in the analysis.

Results: TCS exposure has a marginally significant association with SGA only with odds ratio 0.87 and 95% confidence interval (0.74, 1.00). It also has a marginally significant association with LGA in male offspring with odds ratio 1.11 and 95% confidence interval (1.00, 1.25). The effects of BPA on the four birth outcomes were insignificant.

Conclusions: Increased TCS exposure during pregnancy is marginally associated with decreased odds of having SGA offspring. It is possibly associated with decreased BW in males and decreased odds of LBW, though these associations were not present in measurement error corrected models. TCS is possibly associated with increased odds in male offspring of being LGA, though this relationship was not present in models not corrected for measurement error. The study finds no significant effects of BPA on birth weight outcomes, which may be due to more severe measurement error in a single observation of BPA.

1. Introduction

Low birth weight (LBW) and small for gestational age (SGA) are well-known risk factors for perinatal illness and death, and are associated with long-term morbidity (Kidder et al., 2000). There are many known risk factors for LBW (e.g. young maternal age, low education level) and SGA (e.g. maternal smoking during pregnancy, gestational hypertension), but it is of interest to increase understanding of additional potential risk factors for adverse birth weight outcomes (McCowan and Horgan, 2009; Shmueli and Cullen, 1999). Exposure to various environmental chemicals such as triclosan (TCS) and bisphenol-A (BPA) during early pregnancy is a proposed risk factor.

Exposure to the chemical BPA is common in the Canadian population. Detectable concentrations of BPA were present in the urine of 92% of Canadians in the most recent Canadian Health Measures Survey (Health Canada, 2015). Exposure occurs through materials such as

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polycarbonate plastic, epoxy resins that coat cans, and dental fillings (Arbuckle et al., 2014). Research into the potential endocrine disrupting effects of BPA has been extensive over the past decade but studies display conflicting results specific to the effect of maternal exposure on pregnancy outcomes (Birks et al., 2016; Casas et al., 2016; Chou et al., 2011; Ferguson et al., 2016; Huo et al., 2015; Philippat et al., 2012, 2014; Tang et al., 2013; Troisi et al., 2014; Snijder et al., 2013; Wolff et al., 2008).

Triclosan (TCS) is also a common chemical, with about 65% of the Canadian population exposed to detectable concentrations in urine (Health Canada, 2015). TCS is anti-microbial and is therefore found in products such as soap, toothpaste, mouthwash, deodorant, lotion, and acne face washes. It is also used as a preservative in materials such as textiles, rubber, and plastic (Government of Canada, 2013). TCS has been less investigated in the literature, with fewer existing studies investigating associations between maternal exposures and pregnancy outcomes and only one to our knowledge reporting any significant association between TCS exposure and birth weight or gestational age (Etzel et al., 2017; Geer et al., 2017; Lassen et al., 2016; Philippat et al., 2012, 2014; Wolff et al., 2008). Etzel et al. (2017) averaged urinary TCS exposure over two samples at 16 weeks and 26 weeks for 378 pregnant women and found that increased TCS was associated with decreased birth weight. The remainder of the studies utilized a single urine sample to quantify TCS exposure and found no association with birth weight.

Both BPA and TCS are excreted primarily through urine and do not accumulate in the body (Sandborgh-Englund et al., 2006; Völkel et al., 2002). BPA has a reported half-life of 5.3 h, whereas TCS has a slightly longer half-life of around 11 h (Genuis et al., 2012; Sandborgh-Englund et al., 2006). Substances with short half-lives are rapidly eliminated from the body and therefore their levels in urine samples exhibit high variability when measured repeatedly in the same subject throughout the day. This leads to increased measurement error when single spot urine samples are used to capture average exposure levels (Lin et al., 2005). Additionally, BPA and TCS exposure occur episodically throughout the day, which further increases the measurement error that can occur when single spot urine samples are used.

As the ratio of between-individual variance to within-individual variance decreases, the ability to accurately reflect a long-term average exposure using a single measurement decreases (Lin et al., 2005). This is often quantified using an intra-class correlation coefficient (ICC), defined as the ratio of the variance between individuals to the sum of the variance between and within individuals (Pleil and Sobus, 2013). ICCs, which fall between 0 and 1 with higher values representing more reliable exposure measurements, therefore, tend to be higher for substances with longer half-lives. Past studies analyzing repeated spot-urine samples show that TCS and BPA exhibit very different ICCs. For BPA, reported ICCs typically range from 0.1 (e.g. 389 pregnant women sampled at 16 weeks, 26 weeks, and delivery (Braun et al., 2011)) to 0.5 (e.g. 25 children, 4 samples over 2 days (Heffernan et al., 2014)), with a greater proportion falling closer to 0.1 (Fisher et al., 2015). Fewer studies have investigated TCS ICCs. Lassen et al. (2013) measured 4 samples over 3 months in men and found ICCs between 0.55 and 0.9. Koch et al. (2014) measured every void over 6 days and calculated an ICC of 0.934. Philippat et al. (2014) measured 3 samples at least 2 weeks apart in 71 women and obtain ICCs of 0.56, 0.58, and 0.60 respectively, depending on whether the ICC was unadjusted, adjusted for specific gravity alone, or adjusted for specific gravity (a measure that attempts to control for differences in the hydration status of the participants at the time of sampling) and hour of sampling.

Therefore, measurement error is an important concern when using a measurement from a single spot urine sample as a proxy for average exposure to BPA or, to a lesser extent, TCS. Recent studies suggested that some of the variability in TCS and BPA exposure is due to differences in time of day of the sample and how recently the participant last urinated. Specifically, samples collected after 16:00 showed higher levels of both TCS and BPA, and samples collected when the time since the participant's last urine void was greater than 90 min showed higher levels of TCS (Fisher et al., 2015; Weiss et al., 2015). Therefore these variables, along with specific gravity, could explain some of the variation in exposure levels within participants.

In this paper we explore the variability of repeated BPA and TCS measurements within individuals over the course of one or two days during early pregnancy (< 20 weeks gestation) using the Plastics and Personal-care Products use in Pregnancy (P4) Study, a recent Canadian study (Arbuckle et al., 2015b). We also look for association between TCS or BPA exposure in early pregnancy and four birth weight outcomes (birth weight (BW), LBW, SGA, and large for gestational age (LGA)) using combined data from both the P4 Study and the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, another recent Canadian study (Arbuckle et al., 2013). We use the regression calibration technique to correct for the attenuating effects of the measurement error in BPA and TCS when modeling their effects on birth weight outcomes.

2. Methods

The MIREC Study was designed as a Canadian biomonitoring study for pregnant women and their babies to investigate possible adverse health effects of exposure to a wide range of environmental chemicals during pregnancy. One of the specific objectives of the MIREC Study was to assess if exposure to either BPA or TCS during early pregnancy has negative impacts on birth outcomes. MIREC recruited participants from 2008 to 2011 and obtained a single spot urine sample from a cohort of 2000 pregnant women (Arbuckle et al., 2013). Since the explanatory variable of interest in our study was mean exposure over all of early pregnancy, there was likely considerable measurement error in using this single observation as a proxy. The P4 Study was designed to evaluate the variability in BPA and TCS measurements. P4 recruited participants from 2009 to 2010 and collected multiple urine samples from each of the 80 pregnant women during the early pregnancy (< 20 weeks) as well as information about the pregnancy outcome. It is possible that other exposure measures may alternatively be the relevant exposure, such as median or maximum early pregnancy exposure, but these were not explored here. Informed consent was obtained from all subjects of the MIREC and P4 studies.

We focused on four outcomes: BW, LBW, SGA, and LGA. LBW was defined as a birth weight less than 2500 g (World Health Organization, 1992) for both male and female babies. LBW encompassed both babies who were small because they were born preterm and those who were small because of restricted intrauterine growth. In order to specifically investigate LBW caused by restricted intrauterine growth, gestational age (GA) must be controlled for. Babies with low BW, controlling for gestational age, are referred to as SGA (Kidder et al., 2000). Conversely, babies with high BW for their gestational age are called LGA. The sex-specific 10th and 90th percentile values from the fetal growth references of Kramer et al. (2001) were used as our cut-off values for defining SGA and LGA, respectively, and these dichotomous outcomes were analyzed separately from each other.

A spot urine sample to measure TCS and BPA was taken 6–13 weeks after conception in the MIREC study, while in the P4 study, all urine voids during a 24-h period before 20 weeks of pregnancy were collected. Some participants in the P4 study chose to participate in two separate 24-h collection days. Urine samples were measured for TCS and BPA concentration using a gas chromatographic tandem mass spectrometric method. At delivery, BW was recorded. GA at delivery was calculated using both first trimester ultrasound and last menstrual period. If the GA calculated by first trimester ultrasound differed by more than 7 days from the GA calculated by the last menstrual period, then the ultrasound GA was used and otherwise the last menstrual period GA was used. Ultrasound GA was calculated by adding gestational age in days as recorded at first ultrasound to the number of days between the first ultrasound and delivery. Other confounders, such as

Table 1
Demographical characteristics and auxiliary variables in P4 and MIREC.

Characteristic	P4 Mean (SD) or n (%)	MIREC Mean (SD) or n (%)
Age (years)	32.61 (4.75)	32.20 (5.02)
Missing	1 (1.5%)	0 (0%)
BMI		
> 30	5 (7.4%)	270 (4.8%)
25–30	14 (20.6%)	386 (21.2%)
18.5–24.9	40 (58.8%)	1079 (59.2%)
< 18.5	1 (1.5%)	55 (3.0%)
Missing	8 (11.8%)	32 (1.8%)
Education		
< High school	0 (0%)	42 (2.3%)
High school diploma	3 (4.4%)	117 (6.4%)
College classes	4 (5.9%)	92 (5.0%)
College or trades diploma	13 (19.1%)	426 (23.4%)
University undergraduate degree	29 (42.6%)	669 (36.7%)
MSc/ PhD degree	19 (27.9%)	474 (26.0%)
Missing	0 (0%)	2 (0.1%)
Household income ($)		
< 20 000	1 (1.5%)	71 (3.9%)
20–40 000	2 (2.9%)	141 (7.7%)
40–60 000	3 (4.4%)	187 (10.3%)
60–80 000	10 (14.7%)	278 (15.3%)
80–100 000	10 (14.7%)	356 (19.5%)
> 100 000	38 (55.9%)	709 (38.9%)
Missing	4 (5.9%)	80 (4.4%)
Parity		
Previous child	47 (69.1%)	1015 (55.7%)
Mother birthplace		
Canada	53 (77.9%)	1478 (81.1%)
Missing	1 (1.5%)	0 (0%)
Smoker		
Current or past	21 (30.9%)	712 (39.1%)
SG	1.016 (0.007)	1.014 (0.008)
Missing	0 (0%)	3 (0.2%)
TOD		
Midnight–16:00	44 (64.7%)	1658 (91.0%)
16:00–midnight	21 (30.9%)	162 (8.9%)
Missing	3 (4.4%)	0 (0%)
TSLV		
< 90 min	17 (25%)	673 (36.9%)
> 90 min	43 (63.2%)	1062 (58.3%)
Missing	8 (11.8%)	87 (4.8%)

the mother's country of birth and income level, were collected through questionnaires. Three auxiliary variables that may affect observed exposure and could vary within repeated samples of an individual were also recorded, and included time of day of the spot urine sample (TOD), time since last urine void (TSLV), and specific gravity (SG). We assumed that the confounders and auxiliary variables were measured without error. We formulated our list of confounding variables from those examined in previous Health Canada analyses on these datasets (Arbuckle et al., 2014, 2015a,b); it included mother's age, BMI, education level, nulliparity status, place of birth (Canada or elsewhere), income level (greater or less than $100 000), and smoking status (ever or never smoker). Education level, nulliparity status, place of birth, income level, and smoking status were all categorical variables, with categories specified in Table 1. BMI was a variable coded as 0,1,2, and 3 for BMI < 18.5, 18.5–24.9, 25–30, and > 30 respectively. Details of the MIREC and P4 studies can be found in Arbuckle et al. (Arbuckle et al., 2013) and Fisher et al. (Fisher et al., 2015).

Machine readings were used for exposure values below the instrument limit of detection (LOD), which is a common practice when investigating these chemicals (Bloom et al., 2015; Fisher et al., 2015; Weiss et al., 2015). For BPA, the LOD was 0.2 μg/L for both the MIREC and P4 study. For TCS, the LOD was 0.12 μg/L for the MIREC study and 3 μg/L for the P4 study. Any machine readings of zero in the data were set to half of the lowest machine reading occurring in the data for that chemical. Thus, 12 values of 0 were set to 0.0034 for TCS and 4 values of 0 were set to 0.0053 for BPA. Exposure measurements were then natural log transformed prior to further analysis. After log transformation the exposure data better fit the assumptions for classical measurement error, specifically the assumption of constant variance of the error.

The ICC was calculated using the combined dataset (P4 and MIREC) for each log transformed exposure by obtaining within-individual and between-individual variance estimates from a linear mixed model with one chemical exposure as the outcome, participant ID as a random intercept, and the confounding and auxiliary variables as covariates. An unadjusted ICC and ICCs calculated using only the P4 participants were also calculated for comparison. The confidence intervals for the ICC estimates were calculated using a parametric bootstrapping procedure with 3000 bootstrap replicates, as recommended in Nakagawa and Schielzeth (2010).

For each exposure, the regression calibration was carried out by using a best linear unbiased predictor (BLUP) approach (Kipnis et al., 2009). In this approach, we assumed that after log transformation the measurement error was classical in nature and thus additive and non-differential. We used the repeated exposure measurements in the P4 study combined with the single exposure measurements in the MIREC study as the response variable in a linear mixed model, with participant as the random effect, to estimate the expected value of the true exposure for each of the participants. The variables SG, TOD and TSLV were included in the model as auxiliary variables to explain some of the variations in repeated exposure measurements within a participant. The confounders were also included as covariates. The baby's sex was also included as a covariate in the linear BW model, but not in the SGA and LGA models where it was implicitly controlled for in the formulation of the SGA and LGA outcomes. The LBW model does not control for the baby's sex. Because the effect of TCS and BPA on birth weight may differ depending on the baby's sex, due to possible endocrine disrupting mechanisms, we additionally ran a baby's sex stratified analysis. The BLUP estimate of the exposure for each subject in the combined P4 and MIREC dataset, obtained from this linear mixed model, was used in place of exposure in the various exposure-outcome models: linear regression for BW and logistic regression for the other outcomes. As a comparison and a sensitivity analysis, we also estimated the effects of TCS/BPA based on naïve models that ignored the measurement error in TCS/BPA. The single MIREC sample and the first P4 sample for each individual was used as the naïve exposure measurements to mimic an analysis where no effort was made to account for measurement error. The percentage of the first observations occurring after 16:00 (9%) was the same as the percentage of observations occurring after 16:00 among all P4 observations. Similarly, the percentage of the first observations with TSLV > 90 min(72%) was comparable to the percentage of all P4 observations with TSLV > 90 min(74%). Therefore, using the first observation from individuals in the P4 study was suitably representative of the sample that would exist for a naïve analysis.

Both regression calibration and naïve methods were adjusted for the list of identified confounders (mother's age, BMI, education level, nulliparity status, place of birth (Canada or elsewhere), income level (greater or less than $100 000), and smoking status (ever or never smoker)) and auxiliary variables (SG, TOD and TSLV). Bootstrapped 95% confidence intervals, calculated using 3000 replicates and the bias-corrected and accelerated interval in R, are also reported (Efron and Tibshirani, 1993). All analyses were performed in R 3.2.0 (R Core Team, 2015).

3. Results

There were 1822 participants from MIREC and 68 from P4 who had recorded exposure information for either TCS or BPA during the early

Table 2
Description of birth outcomes for singleton live births.

Birth outcome	Mean (SD) or n(%)
Sex	
Female	867 (45.9%)
Male	966 (51.1%)
Missing	57 (3%)
Gestation	
GA (weeks)	39.32 (1.76)
Preterm delivery	116 (6.1%)
Missing	71 (3.8%)
Birth weight	
Weight (g)	3451.18 (533.06)
LBW	63 (3.3%)
Missing	59 (3.1%)
Weight for GA	
SGA	107 (5.7%)
LGA	242 (12.8%)
Missing	75 (4%)

pregnancy and had a singleton live birth. These 1890 participants formed the basis of our analyses. Of these individuals, 1866 participants (1798 MIREC and 68 P4) had recorded TCS exposure information and were used in our analyses focussing on TCS; our analyses of BPA exposure were based on the 1880 participants (1812 MIREC and 68 P4) with recorded BPA exposure information. Participants were only included if they had complete information on all of the exposure, outcome, confounding, and observation-level variables included in the analysis.

Characteristics and auxiliary variables of all mothers from P4 and MIREC can be found in Table 1. The distributions of the birth outcomes from the two studies are presented in Table 2. The maternal characteristics appeared to be similar between the two studies, with both study populations being generally well-educated and high-income and with an average age of around 32. LBW was the rarest outcome, with only 3.3% of babies falling into this category. SGA was slightly more common, with 5.7% occurrence. LGA was more common, with 12.8% occurrence. The average BW of all babies included in analysis was 3451.18 g.

A summary of the exposures is presented in Table 3. Both BPA and TCS exposures tended to be larger in P4 than in MIREC. When compared to MIREC, P4 tended to have fewer BPA measurements and more TCS measurements less than the LOD. The LOD was higher for TCS in the P4 study than in the MIREC study so this explains the larger number of TCS values below the LOD in P4. It should be noted that the collection of urine samples in these two studies occurred in slightly different time windows during pregnancy (< 14 weeks for MIREC, 6–19 weeks for P4), which may contribute to the differences observed in Table 3.

Table 3
Distribution of urinary maternal exposure to BPA and TCS, measured in $\mu g/L$.

Exposure	n(%) < LOD	Mean (SD)	Min	Quartile	Max
BPA					
MIREC	199 (11%)	2.29 (7.91)	0.01	0.39, 0.88, 1.91	137.82
P4[a]	42 (5%)	2.75 (12.07)	0	0.63, 1.20, 2.21	297.85
Overall	241 (9%)	2.44 (9.48)	0	0.45, 0.99, 2.03	297.85
TCS					
MIREC	11 (1%)	130.91 (364.07)	0.01	2.20, 8.73, 72.80	6784.30
P4[a]	142 (16%)	181.43 (328.28)	0	5.31, 31.53, 203.7	2629.95
Overall	153 (6%)	147.54 (353.43)	0	2.87, 14.43, 121.15	6784.30

LOD - limit of detection.
[a] All urine samples from each P4 participant were used.

Table 4
Estimated ICCs for TCS and BPA (machine readings are used for values < LOD). Confidence intervals are calculated using parametric bootstrap with 3000 bootstrap replicates.

		MIREC & P4		P4 Only	
Chemical	Variables adjusted	ICC	95% CI	ICC	95% CI
BPA	-	0.38	(0.32, 0.44)	0.35	(0.25, 0.44)
	SG,TOD,TSLV & Confounders[a]	0.29	(0.21, 0.37)	0.33	(0.22, 0.44)
TCS	-	0.77	(0.74, 0.79)	0.78	(0.74, 0.86)
	SG,TOD,TSLV & Confounders[a]	0.78	(0.76, 0.81)	0.79	(0.72, 0.87)

ICC - intraclass correlation coefficient, LOD - limit of detection, SG - specific gravity, TOD - time of day, TSLV - time since last void.
[a] Confounders: mother's age, BMI, education level, nulliparity status, place of birth (Canada or elsewhere), income level (greater or less than $100 000), and smoking status (ever or never smoker).

Calculated ICCs for BPA and TCS based on the linear mixed model built using the combined dataset as well as using only the P4 participants are reported in Table 4. BPA showed very high intra-individual variability and TCS showed moderate to low intra-individual variability. The unadjusted ICC based on the combined dataset for TCS was 0.77 (95% CI: 0.74 − 0.79) while the adjusted ICC for TCS was 0.78 (95% CI: 0.76 − 0.81). The similarity between adjusted and unadjusted ICC values suggests that controlling for SG, TOD, and TSLV did not explain a large amount of the variation among TCS measurements within an individual. There likely exist variables not controlled for in this study that are causing a large amount of the intra-individual variability. The unadjusted ICC for BPA was 0.38 (95% CI: 0.32–0.44) while the adjusted ICC decreased to 0.29 (95% CI: 0.21–0.37). The small ICC values suggest that there is large variability in BPA measurements within a participant regardless of whether TOD, TSLV, or SG are controlled or not. ICCs based on the combined dataset are similar to those based on the P4 participants.

The estimates of the effects of TCS and BPA on birthweight outcomes based on the BLUP-based regression calibration are presented in Table 5. For BW, the naïve linear regression showed that in males increased TCS exposure is significantly associated with increased BW. However, the effect becomes marginal under the BLUP-based regression calibration. For LBW, the significant effect of TCS on LBW in the naïve linear regression also becomes marginal in the BLUP-based regression calibration, showing that increased TCS exposure is marginally associated with decreased odds of LBW babies, either in the combined infants or in the female infants. Similarly, the naïve logistic regression analysis suggested a significant effect of TCS on SGA while the BLUP-based regression calibration only suggested a marginally significant effect, suggesting that a larger TCS exposure may correspond to a smaller risk of SGA. For LGA, both the BLUP-based regression calibration and the naïve linear regression suggest a marginally significant effect of TCS on LBW in male infants only. Note that given the rarity of LBW and SGA, the reported odds ratios can be interpreted as relative risks too.

Overall, these results suggest that increased TCS exposure during pregnancy is marginally associated with decreased odds of having SGA offspring and increased odds of LGA in male infants, and possibly associated with increased BW in male infants and decreased odds of LBW either in female infants or in combined infants. These associations were less significant than those suggested by the naïve regression analyses.

The estimated effects of BPA on birthweight outcomes were insignificant in both the BLUP-based regression calibration models and the

Table 5
Regression[a] parameter estimates (linear regression for BW) and odds ratio estimates (logistic regression for LBW, SGA, LGA) for TCS and BPA with 95% confidence intervals[b].

		Naïve			BLUP		
Outcome	Sex	Estimate	95% CI	*p*-value	Estimate	95% CI	*p*-value
TCS							
BW	Female	5.82	(−11.7, 23.9)	0.51	6.97	(−0.92, 41.0)	0.55
	Male	18.67	(1.55, 36.0)	0.03	19.11	(−15.2, 33.4)	0.06
	Both	11.85	(0.06, 24.7)	0.05	13.28	(−1.78, 30.5)	0.09
LBW	Female	0.85	(0.70, 1.03	0.11	0.79	(0.56, 1.04)	0.07
	Male	0.88	(0.70, 1.07)	0.22	0.90	(0.67, 1.17)	0.41
	Both	0.86	(0.75, 1.00)	0.04	0.85	(0.70, 1.03)	0.07
SGA	Female	0.85	(0.71, 1.01)	0.07	0.87	(0.66, 1.13)	0.22
	Male	0.89	(0.76, 1.03)	0.11	0.88	(0.72, 1.07)	0.16
	Both	0.86	(0.76, 0.98)	0.02	0.87	(0.74, 1.00)	0.05
LGA	Female	0.99	(0.90, 1.09)	0.81	0.98	(0.85, 1.13)	0.79
	Male	1.09	(0.99, 1.21)	0.07	1.11	(1.00, 1.25)	0.05
	Both	1.04	(0.97, 1.11)	0.30	1.05	(0.96, 1.15)	0.25
BPA							
BW	Female	3.78	(−37.8, 47.8)	0.85	24.17	(−134.1, 254.1)	0.74
	Male	−15.99	(−50.3, 20.1)	0.40	−69.30	(−260.1, 45.8)	0.27
	Both	−9.20	(−36.0, 19.2)	0.51	−34.08	(−143.6, 56.8)	0.43
LBW	Female	0.79	(0.50, 1.23)	0.32	0.43	(0.02, 1.52)	0.29
	Male	1.14	(0.74, 1.66)	0.53	2.51	(0.61, 32.8)	0.18
	Both	0.94	(0.68, 1.21)	0.69	0.96	(0.31, 2.64)	0.93
SGA	Female	0.94	(0.64, 1.34)	0.74	0.87	(0.12, 5.16)	0.84
	Male	1.28	(0.97, 1.69)	0.07	2.44	(0.85, 15.6)	0.06
	Both	1.14	(0.86, 1.46)	0.24	1.62	(0.65, 4.18)	0.21
LGA	Female	0.97	(0.76, 1.21)	0.77	0.83	(0.18, 2.64)	0.62
	Male	0.41	(0.72, 1.15)	0.45	0.81	(0.28, 1.70)	0.60
	Both	0.93	(0.79, 1.11)	0.42	0.81	(0.38, 1.51)	0.44

[a] Regression models under the BLUP-based calibration approach to account for exposure measurement errors in TCS and BPA and under the naïve model not to account for the measurement errors, stratified by baby sex as well as unstratified, all adjusted for confounders (*mother's age, BMI, education level, nulliparity status, place of birth (Canada or elsewhere), income level (greater or less than $100000), and smoking status (ever or never smoker)*), SG, TOD, and TSLV).
[b] 95% bootstrap confidence intervals.

naïve models.

4. Discussion

Contrary to past studies that utilize a single exposure measurement to characterize the association between TCS exposure and birth outcomes, our naïve analysis showed a very small but significant association between increased TCS exposure and decreased BW in males as well as decreased odds of both LBW and SGA offspring, controlling for our identified confounders. After controlling for measurement error, our results still suggest that TCS has a mild effect on SGA and additionally find a marginal association of increased TCS exposure being associated with decreased odds of LGA in male babies. These mild associations are contrary to a large study by Philippat et al. (2014), which found an association between TCS exposure and decreased fetal weight at the time of the third ultrasound, which disappeared when weight at birth was used instead. Lassen et al. (2016) found a significant association between increasing TCS exposure at approximately 28 weeks pregnancy and decreasing head circumference in boys as well as marginal significance association with decreased abdominal circumference in boys at birth. Geer et al. (2017) used a single maternal urine TCS concentration as well as a single neonatal umbilical cord blood plasma TCS concentrations at birth and did not find an association with BW or gestational age. All of these studies utilized single spot urine samples to estimate TCS exposure. Etzel et al. (2017) used the average of two urine samples at 16 and 26 weeks and found that increased TCS exposure was associated with decreased birth weight and gestational age, the opposite of our findings.

It is still unclear what causes the differences between our results and some existing results. One possibility is that we have inadequately controlled for some important confounding variables. An example of a possible confounder we have not controlled for is occupation. Participants in this study who work in the field of health care may be exposed to higher levels of TCS through antibacterial hand wash used frequently throughout their work day (e.g. nurse, physiotherapist, chiropractor, doctor, osteopath). These participants may also be more likely to be exposed to detailed education about the risk factors for LBW/SGA babies, and therefore more likely to avoid other risk factors. This postulation is unlikely though, because the most common hand sanitizers in health care settings are alcohol based and do not contain TCS. We cannot rule out the unlikely possibility that the association is a true effect of TCS such that TCS has some fetal weight gaining properties, perhaps more so in males. It should also be noted that both the MIREC and P4 cohorts have a high proportion of participants who are highly educated and of high socioeconomic status (SES) which are both protective factors against the outcomes of LBW and SGA (Parker et al., 1994). However, although we realize that this could impact our results, we do not see an obvious connection between the high SES in our population and the results we have obtained.

Our study does not demonstrate any significant effects of BPA on the birth outcomes. The past literature is vast but inconclusive on the subject of BPA exposure and birth weight outcomes. Philippat et al. (2014) used a single urinary exposure measurement on 520 women and found no significant effect on BW in boys. Both Tang et al. (2013) and Wolff et al. (2008) used a single urinary exposure measurement and found no association between urinary BPA concentration and BW. Casas et al. (2016) tried to decrease exposure measurement error by using two urine samples (1st and 3rd trimester) while Ferguson et al. (2016) used up to four urine samples but both found no association of BPA exposure with BW. On the contrary, Snijder et al. (2013), who had a study design similar to ours in the sense that their participants had anywhere from one to three repeated urine samples but differing from ours in that these samples were spread across all trimesters of pregnancy, showed an association between increased BPA exposure and decreased BW for

subjects with 3 measurements, but no association for subjects with only a single exposure measurement. It is interesting how this study demonstrates a significant association using 3 urine samples on $n = 80$ participants, yet the study by Ferguson et al. (2016) with 4 samples on $n = 484$ participants does not. Huo et al. (2015) conducted a case control study and found single maternal urine sample BPA levels at delivery to be significantly associated with risk of LBW, with a stronger effect in female neonates. Other studies have used blood or placental concentrations to calculate BPA exposure. Troisi et al. (2014) found significant correlations between increased placental BPA concentrations and lower birth weight centile, a version of the BW outcome that accounts for maternal height, weight, parity and ethnic group. Additionally, LBW and SGA babies showed significantly higher BPA concentrations. Chou et al. (2011) found that being in the highest quartile for maternal blood BPA concentrations was associated with increased risk of LBW and SGA in male infants. Veiga-Lopez et al. (2015) found higher unconjugated BPA levels in first trimester maternal blood to be significantly associated with decreased BW. The effect was more severe in females. Therefore, studies that measured BPA exposure through placental concentrations or blood concentrations reported that a significant association with birth weight outcomes existed. However, in another study that characterized 20 subjects' BPA exposure through both urine and blood samples it was found that contamination was likely occurring during the analysis of blood BPA concentrations (Teeguarden et al., 2011), a problem not isolated to this study (Markham et al., 2010; Twaddle et al., 2010).

Clearly, accurately measuring BPA exposure is a challenging task, which may play a part in the conflicting results. Other methods should be explored in the future to better analyze BPA exposure effects. Our data setup of repeated measurements for a small subset of subjects over the course of one or two days was not sufficient to draw any conclusions as to the effects of BPA on birth weight outcomes. Although our regression calibration methods are able to decrease bias, this comes at the cost of increased variance. Therefore we would recommend more intensive sampling strategies such as repeated exposure measurements both within a day and over separate days throughout early pregnancy for all individuals in the study. As shown in Perrier et al. (2016), one way to decrease bias and increase power without increasing cost of the study is to pool multiple samples and assay them as a single measurement. Taking the average of these exposure measurements would decrease some of the error introduced due to within-individual exposure variation. This can effectively decrease the within-individual variation and therefore increase the ICC and subsequently decrease attenuation in both linear and logistic exposure-outcome models; if the exposure ICC is closer to one, the effects estimate obtained is closer to the true association (Whitehead et al., 2012). However, this still increases the burden on study participants of having to collect a very large number of samples across multiple days. Perrier et al. (2016) concluded that in order to decrease bias to $< 10\%$ in exposures with ICCs of 0.2, one would need > 30 exposure measurements. Although the ICC for BPA is slightly higher than 0.2 and therefore would require slightly fewer measurements, it would still be a very cumbersome number of urine samples for the participants to collect. Another option recommended by Perrier et al. (2016), if the number of pooled urine samples is the same for each individual, would be to use a posteriori bias disattenuation to decrease bias further, given that the ICC for BPA has been relatively well studied. However, reported ICCs for BPA in the literature range from 0.1 to 0.5 so it may be difficult to decide upon what a good estimate for BPA ICC truly is.

If, due to economic or compliance constraints, the option above of increasing the number of repeated measurements per individual is not feasible, future researchers could attempt to find additional variables that predict some of the variation that occurs between repeated BPA exposures. These variables however have proven difficult to predict for BPA. The ones used in this study (SG, TOD, TSLV) increased the ICC value for TCS but did not increase the ICC value for BPA. An example of a variable that was not used in our study but might be useful in describing some variation in the exposure is *time since last meal*, though Stahlhut et al. (2009) reported decline in BPA exposure to be associated with time since last meal during the 4.5–8.5 h interval only. If one were somehow able to explain a greater amount of the within-individual variation in BPA exposure through controlling for additional variables, one could achieve greater power and precision when using the appropriate regression calibration estimation. However, it should be noted that this is under the assumption that average BPA exposure throughout the first trimester is the pertinent exposure. It is of course possible that other exposure types could be physiologically relevant, such as the peak BPA exposure during the first trimester.

5. Conclusions

Our important findings include:

- Increased TCS exposure did not display any negative impacts on BW, LBW, SGA, or LGA in this study.
- The level of uncertainty in risk estimates for BPA, after correcting for measurement error, was very large and these risk estimates displayed no significant results.

Our recommendations for future analysis of BPA are to:

- Include the same number of repeated measurements of BPA for all individuals throughout the time window of interest and pool these exposure measurements prior to assay and then include a posteriori disattenuation using known ICCs to further decrease bias, as discussed in Perrier et al. (2016).
- Explore different auxiliary variables that may explain some of the within-individual variation in BPA exposure and combine this with regression calibration to minimize the impact of measurement error.

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