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Associations between maternal triclosan concentrations in early pregnancy and gestational diabetes mellitus, impaired glucose tolerance, gestational weight gain and fetal markers of metabolic function

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ABSTRACT

Background: Triclosan is a phenolic biocide used in a multitude of consumer products and in health care settings. It is widely detected in the American and Canadian populations and has been shown in animal models to act as an endocrine disrupting agent. However, there has been little examination to date of the effects of triclosan exposure in pregnancy on perinatal metabolic outcomes in human populations.

Methods: Using data from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a Canadian pregnancy cohort, we measured associations of first-trimester urinary triclosan concentrations with total gestational weight gain, gestational diabetes mellitus and impaired glucose tolerance in pregnancy, and fetal markers of metabolic function. Leptin and adiponectin were measured in plasma from umbilical cord blood samples in term neonates and categorized into low (< 10th percentile), intermediate (10th–90th percentile) and high (> 90th percentile) levels. Triclosan concentrations were grouped into quartiles and associations with study outcomes were examined using logistic regression models with adjustment for maternal age, race/ethnicity, pre-pregnancy BMI, education and urinary specific gravity. Restricted cubic spline analysis was performed to help assess linearity and shape of any dose-response relationships. All analyses for leptin and adiponectin levels were performed on the entire cohort as well as stratified by fetal sex.

Results: Triclosan measures were available for 1795 MIREC participants with a live born singleton birth. Regression analyses showed a non-significant inverse association between triclosan concentrations and leptin levels above the 90th percentile that was restricted to female fetuses (OR for highest quartile of triclosan compared to lowest quartile = 0.4 (95% CI 0.2–1.1), p-value for trend across quartiles = 0.02). Triclosan concentrations in the second quartile were associated with elevated odds of adiponectin below the 10th percentile in male fetuses (OR for Q2 compared to Q1 = 2.5, 95% CI 1.1–5.9, p-value for trend across quartiles = 0.93). No significant linear associations between triclosan concentrations and leptin or adiponectin levels in overall or sex-specific analyses were observed from restricted cubic spline analyses. No significant associations were observed in adjusted analyses between triclosan concentrations and gestational diabetes mellitus, impaired glucose tolerance or gestational weight gain.

Abbreviations: CV, coefficient of variation; GCT, glucose challenge test; GDM, gestational diabetes mellitus; GWG, gestational weight gain; IGT, impaired glucose tolerance; IOM, Institute of Medicine; MCPP, mono-(3-carboxypropyl) phthalate; MIREC, Maternal-Infant Research on Environmental Chemicals; OGTT, oral glucose tolerance test; SG, specific gravity

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Conclusions: This study does not support an association between triclosan concentrations in pregnancy and fetal metabolic markers, glucose disorders of pregnancy, or excessive gestational weight gain.

1. Introduction

Triclosan is a broad-spectrum, phenolic biocide with activity against bacteria and fungi and is used in consumer products (Health Canada and Environment Canada, 2012) and health care settings (Jones et al., 2000; MacIsaac et al., 2014). Triclosan is widely detected in the American (Calafat et al., 2008) and Canadian (Health Canada, 2013) populations, with primary exposure through ingestion or dermal contact (Wittassek et al., 2011; Environment and Climate Change Canada and Health Canada, 2016). It has a similar structure to known endocrine disrupting chemicals (Dann and Hontela, 2011), and some studies in animals suggest it may act as an endocrine disrupting agent (Health Canada and Environment Canada, 2012; Wang and Tian, 2015) and may impact metabolism (Guo et al., 2012; Lankester et al., 2013). Triclosan may also affect thyroid function (Lankester et al., 2013), which in turn has been associated with gestational diabetes mellitus (GDM) and low birth weight (Karakosta et al., 2012). While triclosan has been associated with metabolic outcomes in non-pregnant adults (Lankester et al., 2013; Li et al., 2015), examination to date of its effects on perinatal outcomes has been limited and has been mostly related to neonatal size and growth parameters (Wolff et al., 2008; Philippat et al., 2012, 2014; Geer et al., 2016; Lassen et al., 2016), with little attention given to maternal and fetal metabolic outcomes (Buckley et al., 2016).

Evidence has shown sex-specific effects of triclosan in animal (Wang and Tian, 2015) and human (Wolff et al., 2008) studies. In addition, studies examining leptin and adiponectin have found differences by fetal sex (Kajantie et al., 2004; Mantzoros et al., 2009; Karakosta et al., 2013; Luo et al., 2013; Volberg et al., 2013). Accordingly, the objective of the present study was to assess associations between triclosan concentrations, as measured in first-trimester pregnancy urine samples, and perinatal metabolic outcomes including gestational weight gain (GWG), glucose disorders in pregnancy (GDM and impaired glucose tolerance (IGT) in pregnancy) and fetal markers of metabolic function (leptin and adiponectin, as measured in venous umbilical cord blood), and to examine these associations with stratification by infant sex.

2. Material and methods

2.1. Study sample

The Maternal-Infant Research on Environmental Chemicals (MIREC) Study is a longitudinal birth cohort study conducted across Canada. Further details concerning inclusion and exclusion criteria and study objectives and procedures have been published elsewhere (Arbuckle et al., 2013). Briefly, women were recruited before 14 weeks gestation from 10 Canadian cities between 2008 and 2011. The present analyses were limited to participants who had not withdrawn from the study (18 women excluded) and who had a live singleton birth (49 live multiple births, 32 spontaneous abortions, 13 therapeutic abortions and 9 stillbirths excluded). During the first visit (< 14 weeks gestation), participants provided a urine and blood sample and completed a questionnaire requesting information on demographic and lifestyle factors. For associations with GDM and IGT, participants with pre-existing diabetes (n = 24) and women who did not have a glucose challenge test (GCT) or an oral glucose tolerance test (OGTT) to determine a diagnosis of GDM and IGT (n = 586) were excluded. Leptin and adiponectin analyses were conducted only for women who had a cord blood sample collected after delivery (708 women without cord blood samples excluded). Preterm infants (n = 54) were excluded from these analyses, as leptin and adiponectin levels were notably lower prior to 37 weeks gestation, as has been reported previously (Kajantie et al., 2004).

2.2. Triclosan measurement

For triclosan analyses, sensitive LC-MS/MS methods were developed for the analysis of free and conjugated forms of triclosan in urine. The intraday coefficients of variation (CV) ranged from 2.5% (free triclosan and triclosan sulfate) to 4.5% (triclosan glucuronide), and the interday CVs ranged from 4.3% (triclosan sulfate) to 13% (triclosan glucuronide) (Provencher et al., 2014). Detailed quality assurance/quality control procedures are described in Provencher et al. (Provencher et al., 2014). To account for urine dilution, the specific gravity was measured in thawed urine samples by a refractometer (UG-1, Atago 3461; Atago U.S.A.). Statistical analyses were conducted based on total triclosan concentrations, obtained by summing free triclosan, triclosan glucuronide, and triclosan sulfate. Machine readings were used for 12 samples below the limit of detection (0.12 μg/L), as has been done in previous studies (Zhang et al., 2015; Holland et al., 2016). Further details on triclosan analyses in the MIREC cohort have been previously published (Arbuckle et al., 2015).

2.3. Study outcomes

Total GWG was categorized as defined by the U.S. Institute of Medicine (IOM) (Institute of Medicine US and National Research Council US Committee to Reexamine IOM Pregnancy Weight Guidelines, 2009). For approximately 10% of MIREC study participants, the last measured weight prior to delivery was four or more weeks prior to the delivery date and, therefore, not a reliable proxy for delivery weight. Accordingly, we calculated GWG based on the rate of weekly gain during the second and third trimesters, as this method does not rely on the last measured weight prior to delivery being an accurate representation of delivery weight. The rate of weekly weight gain was calculated by dividing the weight gain between the first trimester visit and the last measured weight before delivery by the number of weeks intervening between these two measures (Ashley-Martin et al., 2016). Further details on the calculation of GWG are described in Dzakpasu et al. (2015).

IGT and GDM were assessed by chart review based on the results of a 50 g GCT and a 75 or 100 g 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 Clinical Practice Guidelines Expert Committee, 2008) and as described in our previous work with this cohort (Shapiro et al., 2015). Briefly, if the result of the 1-h 50 g GCT was ≥ 10.3 mmol/L or if at least two of the cut-off values were met or exceeded on a 75 g or 100 g OGTT, a diagnosis of GDM was assigned. Gestational IGT was diagnosed if one of the OGTT cut-off values was met or exceeded.

Leptin and adiponectin were measured in plasma from umbilical cord blood samples. Analysis was done by ELISA at Mt. Sinai Laboratory (Toronto, ON, Canada) using assay kits from Meso Scale Discovery (MSD) (Rockville, MD, USA). All samples with coefficient of variation (CV) greater than 15% were repeated. The inter- and intra-assay CVs were 11.8% and 9.3% respectively for leptin and 8% and 9% respectively for adiponectin. All samples were in the range of detection.

Umbilical cord blood levels of leptin and adiponectin were categorized into < 10th percentile, 10th–90th percentile, and > 90th percentile. Due to differing leptin levels among male and female neonates,

sex-specific cut-off points were used to calculate leptin percentiles (10th percentile: males 1.87 μg/mL, females 3.51 μg/mL; 90th percentile: males 32.28 μg/mL, females 60.52 μg/mL). Adiponectin levels did not vary by sex (median for males = 16.64 μg/mL, n = 651; females = 16.71 μg/mL, n = 571), thus cut-off points were calculated based on the overall sample (10th percentile: 6.62 μg/mL, 90th percentile: 32.06 μg/mL). As a sensitivity analysis, we also ran all models for leptin and adiponectin using the 25th and 75th percentiles as cut-off points.

2.4. Statistical analysis

We began by describing the demographic and clinical characteristics of the overall study sample and the sub-sample with data available for GDM and IGT. We then calculated geometric mean triclosan concentrations based on categories of the three groups of outcome variables (GDM/IGT, GWG, fetal adipokines). In determining geometric means, triclosan concentrations 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 triclosan concentration (μg/L), P_i = observed concentration, SG_i = SG of the urine sample, and SG_m = median SG for the cohort (Just et al., 2010). We ran logistic regression models with triclosan divided into quartiles as the independent variable estimating associations with the outcome variables with adjustment for specific gravity. In addition to testing quartile-specific associations, we tested trends across quartiles using an ordinal variable representing quartile. We established a common set of confounding variables identified for the study outcomes based on previous work with the MIREC cohort. Final models for the principal analyses included adjustment for maternal age, race/ethnicity, pre-pregnancy BMI and education, all according to the categories in Table 1. We included maternal age and pre-pregnancy BMI as continuous variables along with their squared terms in a sensitivity analysis. We also tested all models with adjustment for parity and maternal smoking. However, these variables did not confound the associations between triclosan and any of the outcome variables (change in adjusted OR < 10%) and were not retained in adjusted analyses. Finally, we ran restricted cubic spline models for outcomes showing statistically significant associations in the regression models (Desquilbet and Mariotti, 2010). Knots were set at the 5th, 50th and 95th percentiles and the referent value was set to the median. Specific gravity was included in all adjusted models (regressions and cubic spline models) to account for heterogeneity in urinary dilution. Given previous evidence of sex differences in associations between environmental contaminants and fetal adipokines (Chou et al., 2011; Ashley-Martin et al., 2014), we ran analyses for leptin and adiponectin levels for the entire cohort as well as stratified by fetal sex. Finally, given that triclosan exposure levels likely exhibit some collinearity with other phenols, we ran all models with adjustment for bisphenol A (BPA), a more frequently studied phenol that was also measured in first-trimester urine samples in the MIREC cohort, as well as with adjustment for mono-(3-carboxypropyl) (MCPP) phthalate, a metabolite associated with umbilical cord leptin in a previous MIREC analysis (Ashley-Martin et al., 2014).

All analyses were carried out using SAS 9.4. All participants gave written, informed consent and Research Ethics Board Approval was obtained at all study sites and from Health Canada.

3. Results

Of the 1914 women with a live born singleton birth in the MIREC cohort, triclosan measures were available for 1795 MIREC participants. The subsample of 1209 participants with data available for GDM and IGT did not differ substantially from the overall sample on any of the demographic or clinical measures we examined. As has been reported previously (Arbuckle et al., 2013), roughly 40% of women in the study sample were at least 35 years old, more than 40% were nulliparous, approximately 85% reported white race/ethnicity, and fewer than 6% smoked during pregnancy. Importantly, pre-pregnancy BMI and GWG were similar between the main sample and the GDM/IGT subsample. In both groups, roughly 20% of participants were overweight, 15% were obese, half had higher than recommended GWG, and 15% had insufficient GWG (Table 1).

The overall geometric mean triclosan concentration was 14.28 μg/L (IQR: 2.24–71.73). Mean triclosan concentrations were highest in participants meeting or exceeding IOM recommendations for GWG, those with normal glucose tolerance, those with leptin levels between the 10th and 90th percentiles, and those with adiponectin levels below the 90th percentile (Table 2). No significant association were observed in adjusted analyses between triclosan concentrations and GWG or glucose disorders of pregnancy (Table 3). Regression analyses showed a non-significant inverse association, in female fetuses only, between triclosan concentrations and high leptin levels (OR for highest quartile of triclosan compared to lowest quartile = 0.4 (95% CI 0.2–1.1), p-value for trend across quartiles = 0.02, Table 4). However, this association was not observed in the sensitivity analysis for leptin above the 75th percentile (Appendix Table S3). Triclosan concentrations in the second quartile were associated with elevated odds of adiponectin below the

Table 1
Characteristics of Study Cohort.

		All participants (%)	Participants with data available for GDM/IGT (%)
N		1795	1209
Age (years)	≤ 29	440 (24.5)	292 (24.2)
	30–34	623 (34.7)	432 (35.7)
	≥ 35	684 (38.1)	481 (39.8)
	missing	48 (2.7)	4 (0.3)
Parity	Nulliparous	780 (43.5)	539 (44.6)
	Parous	1011 (56.3)	668 (55.3)
	missing	4 (0.2)	2 (0.2)
Education	High school diploma or less	157 (8.8)	99 (8.2)
	Some college, or trade school	514 (28.6)	335 (27.7)
	Undergraduate university degree	667 (37.2)	461 (38.1)
	Graduate university degree	455 (25.4)	313 (25.9)
	missing	2 (0.1)	1 (0.1)
Household Income ($CAD)	≤ 50,000	304 (16.9)	196 (16.2)
	50,001–100,000	725 (40.4)	485 (40.1)
	> 100,000	687 (38.3)	479 (39.6)
	missing	79 (4.4)	49 (4.1)
Race/ethnicity	White	1543 (86.0)	1027 (85.0)
	Non-white	252 (14.0)	182 (15.1)
Maternal smoking	Never or quit before pregnancy	1570 (87.5)	1064 (88.0)
	Quit when knew pregnant	129 (7.2)	91 (7.5)
	Current Smoker	95 (5.3)	53 (4.4)
	missing	1 (0.1)	1 (0.1)
Pre-pregnancy BMI (kg/m2)	Underweight or Normal (< 25)	1067 (59.4)	709 (58.6)
	Overweight (25–29.9)	368 (20.5)	246 (20.4)
	Obese (≥ 30)	255 (14.2)	182 (15.1)
	missing	105 (5.9)	72 (6.0)
Gestational weight gain[a]	Below IOM recommendation	267 (14.9)	193 (16.0)
	IOM recommendation	399 (22.2)	258 (21.3)
	Above IOM recommendation	879 (49.0)	628 (51.9)
	missing	250 (13.9)	130 (10.8)

[a] Gestational weight gain was calculated based on a rate of weekly gain during the second and third trimesters and was categorized as defined by the U.S. Institute of Medicine (IOM) (Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines, 2009).

Table 2
Geometric mean triclosan concentrations (adjusted for urinary specific gravity) by gestational weight gain, glucose status in pregnancy, and fetal markers of metabolic function.

		N	Triclosan geometric mean (μg/L)	Triclosan geometric standard deviation (μg/L)
	Overall	1795	14.28	8.78
Gestational weight gain[a]	Below IOM	267	11.66	1.52
	IOM recommendation	399	15.41	1.72
	Above IOM	879	14.25	1.07
Glucose status	Normal glucose	1107	15.90	1.07
	IGT	55	11.49	3.35
	GDM	47	13.74	4.52
	missing	563	11.65	1.07
Leptin	< 10th percentile	122	12.29	2.33
	10th–90th percentile	976	15.86	1.14
	> 90th percentile	122	11.11	2.09
Females	< 10th percentile	57	12.50	3.64
	10th–90th percentile	456	17.05	1.76
	> 90th percentile	57	8.73	2.42
Males	< 10th percentile	65	12.10	3.02
	10th–90th percentile	520	14.87	1.49
	> 90th percentile	65	13.83	3.51
Adiponectin	< 10th percentile	122	15.09	3.12
	10th–90th percentile	979	15.39	1.10
	> 90th percentile	122	11.61	2.19
Females	< 10th percentile	61	15.68	4.39
	10th–90th percentile	445	15.76	1.65
	> 90th percentile	65	13.06	3.55
Males	< 10th percentile	61	14.50	4.46
	10th–90th percentile	533	15.14	1.48
	> 90th percentile	57	10.20	2.66

[a] Gestational weight gain was calculated based on a rate of weekly gain during the second and third trimesters and was categorized as defined by the U.S. Institute of Medicine (IOM) (Institute of Medicine (US) and National Research Council (US) Committee to Reexamine IOM Pregnancy Weight Guidelines, 2009).

10th percentile in male fetuses (OR for Q2 compared to Q1 = 2.5, 95% CI 1.1–5.9, p-value for trend across quartiles = 0.93, Table 4). This association was attenuated and not statistically significant when age was adjusted for continuously rather than categorically (OR = 2.1, 95% CI 0.9–4.6) and was of borderline statistical significance in the sensitivity analysis for adiponectin below the 25th percentile (Appendix Table S3).

Restricted cubic spline analysis did not show statistically significant associations between triclosan concentrations and leptin in the overall cohort (p-value for overall association = 0.89, Fig. 1a), or with the analysis restricted to female (p = 0.36, Fig. 1b) or male fetuses (p = 0.71, Fig. 1c). Spline analyses of triclosan and adiponectin also did not show statistically significant associations in the overall cohort (p = 0.53) or in male fetuses (p = 0.86). The linear correlation between log-transformed triclosan and log-transformed BPA was 0.18 (p < 0.01), and that between log-transformed triclosan and log-transformed MCPP was 0.23 (p < 0.01). Results were not substantially changed by adjustment for BPA or for MCPP (data not shown).

4. Discussion

In a national pregnancy and birth cohort study with first-trimester triclosan measurements for 1795 women who went on to deliver a singleton live birth, we did not find statistically significant associations

Table 3
Odds ratios (95% CI) for gestational weight gain and glucose status in pregnancy, by quartiles of exposure to triclosan in first trimester urine.

Triclosan quartile (μg/L)	GWG below IOM (N = 256) vs. IOM recommendation (N = 373)		GWG above IOM (N = 844) vs. IOM recommendation (N = 373)		GDM (N = 42) vs. Normal Glucose (N = 1005)		IGT (N = 43) vs. Normal Glucose (N = 1005)		GDM or IGT (N = 85) vs. Normal Glucose (N = 1005)	
	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Q1 (0.007–2.23)	1	1	1	1	1	1	1	1	1	1
Q2 (2.24–8.68)	0.9 (0.6–1.4)	1.0 (0.6–1.6)	1.0 (0.7–1.4)	1.0 (0.7–1.4)	1.7 (0.8–4.0)	1.7 (0.7–4.2)	0.6 (0.3–1.3)	0.3 (0.1–1.0)	1.0 (0.6–1.7)	0.8 (0.4–1.5)
Q3 (8.70–71.73)	0.8 (0.6–1.3)	0.9 (0.6–1.5)	0.9 (0.6–1.2)	0.8 (0.5–1.2)	1.2 (0.5–2.8)	0.9 (0.3–2.5)	0.6 (0.3–1.3)	0.5 (0.2–1.3)	0.8 (0.4–1.4)	0.7 (0.3–1.3)
Q4 (71.90–6874.30)	0.6 (0.4–0.9)	0.7 (0.4–1.1)	0.9 (0.6–1.3)	0.9 (0.6–1.2)	1.2 (0.5–2.9)	0.9 (0.4–2.5)	0.7 (0.4–1.5)	0.7 (0.3–1.5)	0.9 (0.5–1.6)	0.8 (0.4–1.5)
p-value for trend[a]		0.11		0.28		0.54		0.55		0.40

[a] Adjusted for maternal age, race/ethnicity, pre-pregnancy BMI, education and urinary specific gravity.

Table 4
Odds ratios (95% CI) for fetal markers of metabolic function by quartiles of exposure to triclosan in first trimester urine.

Triclosan quartile (μg/L)	Leptin < 10th percentile (N = 112) vs. 10th–90th percentile (N = 881)		Leptin > 90th percentile (N = 105) vs. 10th–90th percentile (N = 881)		Adiponectin < 10th percentile (N = 112) vs. 10th–90th percentile (N = 875)		Adiponectin > 90th percentile (N = 114) vs. 10th–90th percentile (N = 875)	
	Unadjusted OR (95% CI)	Adjusted OR[a] (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
All								
Q1 (0.007–2.23)	1	1	1	1	1	1	1	1
Q2 (2.24–8.68)	1.0 (0.6–1.6)	1.0 (0.5–1.7)	1.3 (0.8–2.1)	1.2 (0.7–2.1)	1.3 (0.8–2.2)	1.7 (0.9–3.0)	0.9 (0.5–1.4)	1.0 (0.6–1.7)
Q3 (8.70–71.73)	0.8 (0.5–1.3)	0.9 (0.5–1.5)	0.9 (0.5–1.6)	0.8 (0.4–1.5)	1.0 (0.6–1.7)	1.4 (0.7–2.5)	0.6 (0.3–1.0)	0.7 (0.4–1.2)
Q4 (71.90–6874.30)	0.6 (0.3–1.0)	0.7 (0.4–1.3)	0.6 (0.4–1.1)	0.6 (0.3–1.1)	0.9 (0.5–1.6)	1.4 (0.7–2.5)	0.7 (0.4–1.1)	0.8 (0.4–1.4)
p-value for trend		0.24		0.04		0.55		0.25
Female fetuses								
Q1 (0.007–2.22)	1	1	1	1	1	1	1	1
Q2 (2.24–8.68)	0.8 (0.4–1.7)	0.8 (0.3–1.8)	1.0 (0.5–2.0)	1.0 (0.4–2.4)	0.9 (0.4–2.0)	1.1 (0.5–2.6)	0.6 (0.3–1.2)	0.6 (0.3–1.4)
Q3 (8.70–71.60)	0.8 (0.4–1.6)	0.7 (0.3–1.7)	0.5 (0.2–1.1)	0.4 (0.2–1.1)	0.9 (0.4–1.9)	1.2 (0.5–2.8)	0.6 (0.3–1.2)	0.6 (0.3–1.4)
Q4 (73.00–6874.30)	0.5 (0.2–1.2)	0.7 (0.3–1.6)	0.5 (0.2–1.1)	0.4 (0.2–1.1)	1.0 (0.5–2.1)	1.3 (0.6–3.2)	0.8 (0.4–1.6)	0.9 (0.4–2.0)
p-value for trend		0.37		0.02		0.50		0.82
Male fetuses								
Q1 (0.01–2.23)	1	1	1	1	1	1	1	1
Q2 (2.28–8.65)	1.2 (0.6–2.3)	1.1 (0.5–2.5)	1.7 (0.8–3.5)	1.4 (0.6–3.3)	1.7 (0.8–3.5)	2.5 (1.1–5.9)	1.2 (0.6–2.5)	1.5 (0.7–3.2)
Q3 (8.73–71.73)	0.8 (0.4–1.6)	0.9 (0.4–2.2)	1.6 (0.7–3.3)	1.6 (0.7–3.7)	1.0 (0.5–2.2)	1.4 (0.6–3.5)	0.6 (0.2–1.3)	0.6 (0.3–1.5)
Q4 (71.90–3351.49)	0.7 (0.3–1.4)	0.7 (0.3–1.7)	0.8 (0.3–1.8)	0.8 (0.3–2.1)	0.9 (0.4–2.0)	1.4 (0.6–3.5)	0.5 (0.2–1.2)	0.7 (0.3–1.6)
p-value for trend		0.43		0.70		0.93		0.14

[a] Adjusted for maternal age, race/ethnicity, pre-pregnancy BMI, education and urinary specific gravity.

between triclosan concentrations and gestational weight gain or glucose disorders of pregnancy. We found that among female neonates, triclosan concentrations were inversely and non-significantly associated with odds of having high leptin levels, after adjustment for maternal age, race/ethnicity, education and prepregnancy BMI. Among male neonates, triclosan concentrations in the second quartile were associated with elevated odds of low adiponectin levels in adjusted analyses.

Leptin and adiponectin play critical roles in the metabolic function of neonates as well as adults (Trujillo and Scherer, 2005; Karakosta et al., 2011; Walsh et al., 2014). Leptin is secreted by adipose tissue to signal satiety, thus regulating appetite and bodyweight (Koerner et al., 2005; Antuna-Puente et al., 2008; Walsh et al., 2014). Adiponectin suppresses immune cells and secretion of inflammatory cytokines, as well as lowering dyslipidemia and improving insulin resistance (Fasshauer et al., 2004; Gil-Campos et al., 2004; Koerner et al., 2005; Mazaki-Tovi et al., 2005; Trujillo and Scherer, 2005; Antuna-Puente et al., 2008; Sheng and Yang, 2008). These hormones may in turn provide insight on future risk of childhood obesity (Mantzoros et al., 2009; Karakosta et al., 2011; Volberg et al., 2013; Romano et al., 2014).

A small number of studies have investigated triclosan concentrations in relation to perinatal outcomes. Third-trimester urinary triclosan was measured in a cohort of 404 women in New York City. Analyses showed inverse, though non-significant, associations between triclosan concentrations and birth weight and birth length for boys only (Wolff et al., 2008). In a retrospective study of male newborns in France, triclosan concentrations as measured across pregnancy were collected on 191 women. No significant associations were found between triclosan concentrations and birth weight, length or head circumference (Philippat et al., 2012). In another French study of 520 women who gave birth to boys, triclosan was measured between 22 and 29 weeks and fetal/child growth parameters were assessed throughout pregnancy and up to 36 months of age. Inverse associations were observed between triclosan and growth parameters for all measures from the third-trimester ultrasound (biparietal diameter, head circumference, femoral length, abdominal circumference, and weight) with statistically significant estimates observed only for abdominal circumference and fetal weight (Philippat et al., 2014). A recent cohort study from Denmark found a statistically significant association between prenatal urinary triclosan concentrations and smaller head circumference in boys, with trends towards lower abdominal circumference and anogenital distance among boys as well (Lassen et al., 2016). In a recent cohort study from Cincinnati, OH of 378 mother-infant pairs, maternal prenatal triclosan concentrations were inversely associated with infants' birth weight, length, head circumference, and gestational age in adjusted analyses, although some of the associations were of marginal statistical significance. Notably, that study did not find evidence of effect modification by child sex (Etzel et al., 2017). A cohort study from New York City investigating prenatal levels of several phenols did not find evidence of an association between triclosan concentrations and childhood percent fat mass among girls or boys (Buckley et al., 2016). Another cohort study of an immigrant population in New York that examined associations between several phenols and birth outcomes found no associations between maternal triclosan concentrations and length of gestation, birth weight, or birth length (Geer et al., 2016).

Unlike several previous investigations of prenatal triclosan in relation to metabolic outcomes (Wolff et al., 2008; Philippat et al., 2014; Buckley et al., 2016; Geer et al., 2016; Lassen et al., 2016), triclosan concentrations were measured in the MIREC cohort in the first trimester of pregnancy. While exposures in early pregnancy are by definition most relevant to GWG and GDM, it is unknown whether there is a critical exposure period for fetal metabolic effects of prenatal triclosan exposure. Our study thus contributes to the current body of research in providing evidence that triclosan concentrations in early pregnancy are not associated with fetal adipokine levels.

Several studies have examined associations between triclosan and metabolic outcomes in non-pregnant populations, though results to date are inconclusive. Analyses from the U.S. NHANES have shown both positive (Lankester et al., 2013) and negative (Li et al., 2015) associations between urinary triclosan and BMI, as well as a negative association with waist circumference (Li et al., 2015). A case-control study of children in India did not find evidence for an association between urinary triclosan and obesity (Xue et al., 2015). One study in humans showed an association between triclosan and pubertal development in girls, (Wolff et al., 2008) though several other studies did not find significant associations (Buttke et al., 2012; Chevrier et al., 2012; Chen et al., 2013).

Research using animal models has found that triclosan influences reproductive endocrine function (Wang and Tian, 2015). Specifically, studies in aquatic species (Ishibashi et al., 2004; Raut and Angus, 2010)

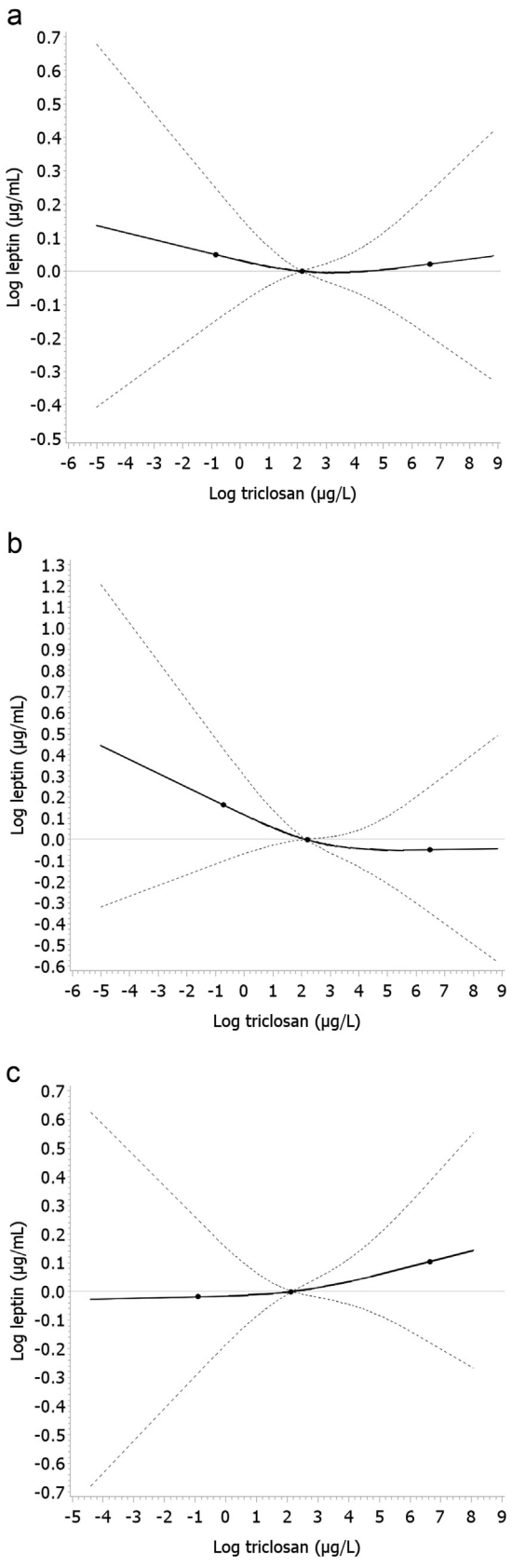

Fig. 1. Restricted spline curve associations between log triclosan and log leptin, all fetuses (a), female fetuses only (b), male fetuses only (c) Model is adjusted for maternal age, race/ethnicity, prepregnancy BMI, education and urinary specific gravity. Knots were located at the 5th, 50th and 95th percentiles. Dashed lines = 95% CI; dots = knots.

and mammals (Jung et al., 2012) suggest possible estrogenic effects of triclosan, which is understood to function through displacement of hormones from hormone receptors and disruption of steroidogenic enzymes (Chen et al., 2007; Ahn et al., 2008; Gee et al., 2008). In addition, triclosan has been associated with impaired lipid metabolism in zebrafish embryos (Ho et al., 2016), with decreased metabolic rate in amphibian larvae (Palenske et al., 2010), and with hepatic metabolic disorder in *Xenopus tropicalis* frogs (Regnault et al., 2016). However, it should be noted that triclosan exposure levels in humans are substantially below those used in animal studies to date, and evidence suggests that many of the species used in experimental models are more sensitive to triclosan than are mammals (Wang and Tian, 2015).

We observed a non-statistically significant inverse association, in female fetuses only, between maternal triclosan and fetal leptin levels above the 90th percentile, as well as a statistically significant association, in male fetuses only, between second-quartile triclosan and fetal adiponectin levels below the 90th percentile. Findings from previous literature suggest that sex-specific associations between triclosan and fetal adipokines may operate through several potential biological pathways. Sexually dimorphic mechanisms have been found to underlie numerous metabolic processes including energy expenditure, regulation of energy homeostasis, steroid metabolism, xenobiotic metabolism and pharmacokinetics (Heindel et al., 2016). Triclosan has been associated with sex-specific estrogenic activity in the reproductive system in animal studies (Frederiksen et al., 2014; Wang and Tian, 2015) and may have other endocrine disrupting properties and impact on thyroid function as well (Lankester et al., 2013). While the test of trend for the association between triclosan and high leptin across quartiles was statistically significant for female fetuses in our study, there was no statistically significant association for any quartile compared to the referent, nor was there evidence of an association when examining splines or when using the 75th percentile of leptin. Similarly, the association between triclosan concentrations in the second quartile and low adiponectin was not robust to sensitivity analyses and was not accompanied by evidence of an association in cubic spline models. Combined with the large overall number of associations tested in our study and the resulting possibility of type 1 error, our findings do not provide strong evidence for sex-specific associations between triclosan and fetal adipokines.

As an antibiotic, it has been suggested that triclosan may lead to changes in the gut flora which then could alter gastrointestinal metabolism (Lankester et al., 2013). However, a recent small crossover control study found no association between use of triclosan-containing personal care products and gut microbiome composition, metabolic or endocrine markers, or weight, despite marked differences in urinary triclosan concentrations (Poole et al., 2016). In addition, induction of antimicrobial resistance from current triclosan levels has not been identified as a concern for human health (Environment and Climate Change Canada and Health Canada, 2016). Finally, triclosan levels in pregnancy may be related to oxidative stress and inflammation, which could potentially have consequences for birth outcomes, though metabolic consequences remain unclear (Watkins et al., 2015).

The overall geometric mean triclosan concentration in our study was 14.28 µg/L, with an interquartile range of 2.24–71.73. These levels are somewhat lower than in two other studies measuring triclosan in pregnant women (Watkins et al., 2015; Poole et al., 2016), substantially higher than those from one study (Lassen et al., 2016), and in line with levels from several other pregnancy studies (Wolff et al., 2008; Casas et al., 2011; Woodruff et al., 2011; Biomonitoring California, 2013; Philippat et al., 2013; Mortensen et al., 2014; Pycke et al., 2014; Buckley et al., 2016; Geer et al., 2016).

An important potential limitation to our study is the use of a single spot urine sample to measure triclosan levels in early pregnancy. Across pregnancy, intraclass correlation coefficients (ICCs) for triclosan were reported as ranging from 0.38 to 0.58 in a recent study of pregnant women (Stacy et al., 2017) and ≥ 0.47 in several earlier studies

(Meeker et al., 2013; Philippat et al., 2013; Bertelsen et al., 2014; Weiss et al., 2015). In early pregnancy, a study which measured within day variability reported high reproducibility within a week-day (0.77) and week-end day (0.79) (Weiss et al., 2015). Nonetheless, our study may be limited by within-person variability in triclosan concentrations. While it is unlikely that such variation would be differentially related to the study outcomes, measurement error from using a single spot urine sample may have biased results toward the null such that a true association would be undetected. While we explored the possibility that associations between triclosan and our study outcomes may be confounded by exposure to BPA, we did not examine potential joint effects between triclosan and other chemical exposures. Potential synergy between triclosan and other phenols or environmental chemicals remains an important area for future investigation.

We excluded preterm infants from analyses of leptin and adiponectin, as levels of these adipokines were substantially lower among preterm infants. It is plausible that this exclusion criterion may have introduced some degree of selection bias if triclosan were associated with preterm birth. While triclosan was associated with markers of oxidative stress and inflammation among pregnant women, which are important risk factors for preterm birth (Watkins et al., 2015), no associations between maternal urinary (Huo et al., 2017) or maternal or cord blood triclosan levels and preterm birth (Geer et al., 2016) have been reported. Data on BMI were missing for 6% of participants, who were therefore excluded from analyses. It is thus plausible that our findings were biased by excluding these women. In addition, the MIREC study sample has a relatively high education level overall, with more than 60% of participants having a university degree. Caution should therefore be exercised when generalizing findings to other populations. Finally, in light of the exploratory nature of our study and the number of outcomes examined, spurious findings may have arisen by chance.

5. Conclusions

Results from the present study do not support an association between urinary triclosan concentrations in the 1st trimester of pregnancy and markers of adverse maternal or fetal metabolic outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2017.12.001.

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