HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2021 June 01.

Published in final edited form as:

Environ Int. 2020 June ; 139: 105716. doi:10.1016/j.envint.2020.105716.

Methylparaben in Meconium and Risk of Maternal Thyroid Dysfunction, Adverse Birth Outcomes, and Attention-Deficit Hyperactivity Disorder (ADHD)

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Abstract

Background—Parabens, which are used as a preservative in foods and personal care products, are detected in nearly 100% of human urine samples. Exposure to parabens is associated with DNA damage, male infertility, and endocrine disruption in adults, but the effects of prenatal exposure are unclear. In part, this is due to inadequate assessment of exposure in maternal urine, which may only reflect maternal rather than fetal exposure. To address this gap, we examined the association of prenatal methylparaben measured in meconium with preterm birth, gestational age, birthweight, maternal thyroid hormones, and child Attention-Deficit Hyperactivity Disorder (ADHD) at 6-7 years.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Design—Data come from the GESTation and the Environment (GESTE) prospective observational pregnancy cohort in Sherbrooke, Quebec, Canada. Participants were 345 children with data on ADHD among 394 eligible pregnancies in women age ≥18 years with no known thyroid disease before pregnancy and meconium collected at delivery. Methylparaben was measured in meconium. Birthweight, gestational age, and maternal thyroid hormones at <20 weeks gestation were measured at the Centre Hospitalier Universitaire de Sherbrooke. Preterm birth was defined as vaginal birth before the 37th week of gestation. Physician diagnosis of ADHD was determined at a scheduled cohort follow-up when children were 6-7 years old or from medical records. Associations between meconium methylparaben and outcomes were estimated with logistic and linear regressions weighted on the inverse probability of exposure to account for potential confounders, including child sex, familial income, maternal education, pre-pregnancy body mass index, age, and smoking and alcohol consumption during pregnancy.

Results—Methylparaben was detected in 65 meconium samples (19%), 33 children were diagnosed with ADHD (10%), and 13 children were born preterm (4%). Meconium methylparaben was associated with preterm birth (odds ratio [OR] = 4.81; 95% CI [2.29, 10.10]), decreased gestational age (beta [β] = −0.61 weeks; 95% CI [−0.93, −0.29]) and birthweight (β = −0.12 kilograms; 95% CI [−0.21, −0.03]), altered maternal TSH (relative concentration [RC] = 0.76; 95% CI [0.58, 0.99]), total T3 (RC = 0.84; 95% CI [0.75, 0.96]) and total T4 (RC = 1.10; 95% CI [1.01, 1.19]), maternal hypothyroxinemia (OR = 2.50, 95% CI [1.01, 6.22]), and child ADHD at age of 6-7 (OR = 2.33, 95% CI [1.45, 3.76]). The effect of meconium methylparaben on ADHD was partially mediated by preterm birth (20% mediation) and birthweight (13% mediation).

Conclusions—Meconium methylparaben was associated with preterm birth, decreased gestational age and birthweight, maternal thyroid hormone dysfunction, and child ADHD. Parabens are a substantial health concern if causally related to these adverse outcomes.

Keywords

Attention-Deficit Hyperactivity Disorder (ADHD); birth outcomes; thyroid hormones; endocrine disruption; prenatal exposure; parabens

Introduction

Parabens are used as a preservative in a wide range of human goods, with detection rates of >50% in personal care products and >90% in food.[1,2] Estimates of daily human exposure to parabens range from 76 to 142 milligrams per day, and detection of parabens in urine is nearly ubiquitous.[3] An examination of the health-related consequences of such widespread exposure is critical, as parabens can induce oxidative stress and act as endocrine disruptors.[3–5]

Several recent studies have reported that maternal paraben exposure may alter thyroid hormone levels during pregnancy.[6–9] While thyroid hormones are crucial to fetal brain development, fetal thyroid hormone synthesis does not begin until mid-gestation.[10,11] As a result, early fetal brain development is heavily dependent on thyroid hormones supplied by the mother. In fact, there is a well-known relationship between maternal thyroid dysfunction and neurodevelopmental disorders. A recent meta-analysis of 39 studies showed that

maternal subclinical hypothyroidism more than doubled the odds of intellectual disability in offspring,[12] and several studies have shown that altered maternal thyroid hormone function may increase the odds of Attention-Deficit Hyperactivity Disorder (ADHD).[13–16]

In addition to their impact on thyroid hormones, paraben exposures may affect birth outcomes such as gestational age, preterm birth, and birthweight.[17–20] Adverse birth outcomes such as preterm birth may severely impair neurodevelopment, as shorter gestation interferes with the four-fold increase in cerebral cortex volume that occurs during the last 10 weeks of pregnancy.[21] Indeed, preterm birth is known to increase the risk of neurodevelopmental disorders,[22,23] and both preterm birth and low birthweight are associated with ADHD.[24]

Prior studies examining the relation between maternal paraben exposures and child neurodevelopment have found no associations.[25–27] These null results could be due to the use of maternal urinary paraben measurements. While a single sample collected during gestation may accurately classify maternal exposure through pregnancy,[28] urinary measurements may reflect excretion and/or levels in the maternal blood, while not accurately reflecting fetal exposure. Indeed, exposure assessment in maternal urine may result in misclassification of exposure to the fetus owing to differential placental transfer across individuals. A more accurate measurement of fetal exposure should capture parabens the fetus experiences *In utero*. One novel way to measure fetal paraben exposure is in meconium. Chemicals in meconium accumulate throughout the last two thirds of pregnancy and are known to have passed through the fetus and into the fetal intestinal tract.[29–32] In addition, owing to the stability of individual paraben exposure over time, parabens measured in meconium should accurately estimate exposure during the entire gestational period.[28]

Despite prior studies showing that maternal thyroid hormone function, birthweight, and preterm birth are risk factors for child ADHD, and that these risk factors may be negatively impacted by paraben exposure, no study has examined the association between prenatal paraben exposure and ADHD. In an ongoing prospective cohort, we investigated the association between prenatal methylparaben exposure and child ADHD, along with the potential mediating role of maternal thyroid dysregulation, gestational age, preterm birth, and birthweight.

Methods

Study population

This analysis was conducted in the GESTation and the Environment (GESTE) cohort in Sherbrooke, Quebec, Canada. Women age ≥18 years and with no known thyroid disease before pregnancy enrolled at the Research Center of the CHUS (Centre Hospitaller Universitaire de Sherbrooke) between September 2007 and 2009 at their first prenatal care visit or delivery and were followed up when children were 6-7 years old. Only individuals with meconium samples collected at delivery were eligible for inclusion in this analysis (N=394). We excluded 49 individuals for whom ADHD status was unknown due to loss to follow up or lack of medical record if they had moved out of the hospital system the final sample size was 345.

Meconium methylparaben

A recent study in this cohort measured 72 multiclass organic compounds and selected elements in meconium.[33] The goal of the study was to measure a broad range of chemicals that may cause prenatal harm, including pesticides, heavy metals, caffeine, and nonsteroidal anti-inflammatory drugs. Only methylparaben was included in this meconium analysis, as it was unknown at the time of the study whether parabens could be detected in meconium. Thus, other forms of parabens including ethyl-, propyl-, and butyl-paraben were not measured.

Meconium was collected from the diapers of newborn infants after delivery and stored at −80 °C until analysis. Methylparaben was extracted from < 120 mg meconium and analyzed with ultraperformance liquid chromatography mass spectrometry following the methods described elsewhere.[33,34] At the time of the study, it was unknown whether parabens could be detectable in meconium, so it did not make sense to analyze this class of chemicals in depth. Methylparaben was detected in roughly 20% of the samples, with a recovery of 91% and repeatability of ±22%. The limit of detection (LOD) and limit of quantification (LOQ) were 5 ng/g and 10 ng/g respectively.

ADHD

At a scheduled cohort follow-up when children were 6-7 years old, parents were asked on a questionnaire if their child had physician-diagnosed ADHD. In total, 176 parents provided information at the 6-7 year follow up. For those that did not complete the 6-7-year-old follow-up visit (n=169), physician diagnosis of ADHD was obtained from reviewing medical charts from CHUS pediatric clinics, which are available in the hospital database.

Thyroid Hormones

For a subsample of 123 among the full study sample of 345 individuals, maternal blood was collected during the first prenatal care visit at <20 weeks gestational age at the CHUS (mean gestational age = 11.2 weeks, standard deviation = 2.9). Levels of thyroid stimulating hormone (TSH), thyroperoxidase antibodies (TPO), free triiodothyronine (T3), and free thyroxine (T4) were measured using the Advia Centaur immunoassay system (Bayer), while total T3 and T4 were measured using Coat-A-Count radioimmunoassay kits purchased from DPC Inc. (Los Angeles, USA). Maternal TSH, TPO, and total and free T3 and T4 were modeled continuously (log_2transformed). Free T4 was additionally categorized as below or above the 10th percentile to reflect subclinical maternal hypothyroxinemia,[35] although lower cutoffs are also used in some clinical settings.[16]

Birth outcomes

Data for birthweight and gestational age were obtained from CHUS medical records. Newborn babies were weighed on Scale-tronix pediatrics scale 4802 by obstetricians. Gestational age was determined via ultrasound in the first trimester and used along with birthdate to calculate gestational age at birth. Preterm birth was defined as vaginal birth before the 37th week of gestation (no caesarean sections occurred before 37 weeks gestation in this study sample). Birthweight and gestational age were modeled continuously while preterm birth was modeled as a binary factor.

Covariates

Covariate data were obtained from questionnaires given during the first prenatal care visit and after delivery. Covariates were child sex and familial income (dichotomized at the sample median), along with maternal characteristics including age at delivery, education status (College/University vs. no College/University), pre-pregnancy BMI, smoking during pregnancy (yes/no), and alcohol during pregnancy (yes/no). Post-pregnancy BMI was used for 53 individuals for whom pre-pregnancy BMI was unavailable. A sensitivity analysis including ADHD of the mother (self-reported, obtained from questionnaire) as an additional covariate was conducted, but this variable was excluded from the final models because data were only available for 155 individuals. Missing covariate data were imputed with the median of continuous variables and the mode of categorical variables.

Statistical analysis

To control for potential confounders, we employed inverse probability weighting (IPW) using propensity scores[36–39] using the 'CBPS' R package.[40] Propensity scores (p, the likelihood of detectable meconium methylparaben) were estimated using logistic regression models in which exposure (meconium methylparaben detected vs not detected) was regressed on child sex and maternal covariates described above. Weights were estimated as 1/p for exposed individuals, and 1/(1 – p) for unexposed individuals. Study sample weighting creates a pseudo-population balanced on measured baseline covariates.[36–38] Balancing of covariates between the exposed and unexposed groups in the weighted sample was confirmed with chi-square goodness of fit tests for binary variables and two-sample t-tests for continuous variables (eTable 1).

To test for an effect of meconium methylparaben on ADHD, we estimated odds ratios and 95% confidence intervals (CIs) using logistic regression on the study sample weighted by the inverse probability of exposure. In sensitivity analyses, we ran additional IPW models as described above, but weighted on probability of loss to follow-up (missing vs. nonmissing ADHD data) and tested for effect modification by method of ADHD diagnosis (6-7-year-old follow-up versus medical record) by including an interaction term in weighted and crude logistic regression models.

We modeled the associations of meconium methylparaben with each birth outcome and thyroid hormone, and the associations of univariate birth outcomes and thyroid hormones with child ADHD. We employed inverse probability weighting as described above on linear models for continuous outcomes and logistic regressions for binary outcomes. Weighting accounted for maternal covariates discussed above. When birthweight was the outcome, the model was repeated with and without additional adjustment for gestational age. Thyroid hormone models were additionally weighted for TPO, along with all thyroid hormones other than each model's hormone of interest. In models where $\log_2$ transformed thyroid hormones were the outcome, the beta value was re-exponentiated as 2^{beta} and interpreted as a relative concentration (RC), the relative change in thyroid hormone concentration attributable to methylparaben exposure.

Finally, we considered for mediation analysis the birth outcomes that were associated with both meconium methylparaben and ADHD at $P < 0.05$, which were preterm birth and birthweight. We estimated the total effect, the natural direct effect (NDE), and the natural indirect effect (NIE) using an imputation-based method implemented in the 'medflex' R package, which is embedded within the counterfactual framework.[41,42] The NDE was interpreted as the unmediated effect of prenatal methylparaben on ADHD, and the NIE was interpreted as the effect of prenatal methylparaben on ADHD that is mediated through preterm birth or birthweight. We calculated the percent mediated as the natural indirect effect divided by the total effect×l00%.

Thyroid hormone measurements were only available for a subset of 123 individuals in the cohort. Meconium methylparaben was not associated with ADHD in this subset, precluding a full mediation analysis (eTable 2). Statistical analyses were conducted with R version 3.5.1.[43]

Results

Methylparaben was detected in the meconium of 65 individuals and ADHD was diagnosed in 33 individuals among the total study sample of 345. The 9.6% ADHD prevalence mirrors that of the underlying Quebec population.[44] Baseline maternal characteristics stratified by methylparaben detection are presented in Table 1.

Methylparaben detection in meconium was associated with a more than doubling in the odds of ADHD at 6–7 years in the weighted sample balanced on baseline covariates (OR = 2.33; 95% CI [1.45, 3.76]) (Table 2). This odds ratio was not appreciably different in an IPW model accounting for selection bias (OR = 2.14; 95% CI [1.00, 4.55]), nor in a sensitivity analysis controlling for maternal ADHD (OR = 2.23; 95% CI [0.94, 5.29]). There was no effect modification of methylparaben exposure by method of ADHD diagnosis (crude interaction term P=0.80; weighted P=0.69).

In the weighted sample balanced on measured covariates, meconium methylparaben was associated with 24% decreased TSH (RC = 0.76; 95% CI [0.58, 0.99]), 16% decreased total T3 (RC = 0.84; 95% CI [0.75, 0.96]), and higher odds of low free T4 (OR = 2.50; 95% CI [1.01, 6.22]), but 10% increased total T4 (RC = 1.10; 95% CI [1.01, 1.19]) in maternal blood at <20 weeks gestation (Table 3). Methylparaben was non-significantly associated with decreased free T3 (RC = 0.97; 95% CI [0.94, 1.00]), while there was no clear trend in the association between methylparaben and continuously modeled free T4 (Table 3). Meconium methylparaben was also associated with all birth outcomes. Detection of methylparaben was associated with decreased gestational age by more than half a week (β = −0.61; 95% CI [−0.93, −0.29]) and nearly 5-fold increased odds of preterm birth (OR = 4.81; 95% CI [2.29, 10.10]) in weighted models (Table 3). All preterm births were spontaneous other than two, which were complicated by pre-eclampsia and occurred in individuals not exposed to methylparaben. Methylparaben was also associated with decreased birthweight by 0.12 kg (β = −0.12; 95% CI [−0.21, −0.03]) in models weighted for all confounders, but further adjusting for gestational age resulted in a smaller, non-significant association (β = −0.04; 95% CI [−0.13, 0.05]) (Table 3).

Total T3 and low free T4 in maternal blood at <20 weeks gestation were associated with ADHD, while continuously modeled TSH, free T3, free T4, and total T4 were not (Table 4). Relationships between methylparaben exposure, low free T4, and ADHD were consistent with the potential for mediation. Compared to no methylparaben detection in meconium, methylparaben exposure was associated with more than 2-fold increased odds of low maternal free T4, and low maternal free T4 was associated with nearly 9-fold increased odds of child ADHD (OR = 8.33; 95% CI [3.28, 21.18]) (Table 4).

Adverse birth outcomes were associated with ADHD in a direction consistent with mediation. Each one kilogram increase in birthweight was associated with a nearly 60% decreased odds for ADHD (OR = 0.44; 95% CI [0.20, 0.97]), and preterm birth increased the odds of ADHD more than 3-fold (OR = 3.39; 95% CI [2.27, 5.06]) (Table 4). Gestational age was not associated with ADHD. Causal mediation analyses of the association between meconium methylparaben and ADHD indicated that 20% of the total effect was mediated through preterm birth and 13% was mediated through birthweight (Figure 1) (eTable3).

Discussion

In this prospective Eastern Canadian cohort, prenatal methylparaben measured in meconium was associated with preterm birth, decreased gestational age and birthweight, altered maternal thyroid hormones, and ADHD in children aged 6-7 years. Preterm birth and birthweight partially mediated the effect of prenatal methylparaben exposure on child ADHD. These adverse health effects indicate the possible need to reduce methylparaben exposure during pregnancy.

While parabens have long been purported to negatively impact neurodevelopment via oxidative stress or endocrine disruption,[45] this hypothesis has only been tested in rodent models of autism and behavior.[46,47] To the best of our knowledge, this is the first report of an association between prenatal paraben exposure and child ADHD, or any human neurodevelopmental outcome. Future studies in larger and more diverse cohorts are needed to validate this novel association.

This study adds to the growing body of evidence that parabens may disrupt thyroid hormones during pregnancy,[6–9] and that maternal thyroid hormone dysregulation may influence the development of ADHD.[13–16] Meconium methylparaben was associated with low free T4 indicative of hypothyroxinemia and decreased TSH and total T3 indicative of hypothyroidism. Reductions in these thyroid hormones during gestation may impair fetal brain development by disrupting cell migration and differentiation, synaptogenesis, and myelination.[48] While our data indicate a high potential for mediation by maternal thyroid hormones, a larger sample is needed for a formal mediation analysis. Parabens may also regulate sex hormone signaling[4,49] and promote oxidative stress,[50,51] but the downstream health consequences are poorly understood.

The data also contribute to a small body of evidence that paraben exposure may influence birth outcomes. Controlling for gestational age substantially attenuated the effect of methylparaben on birthweight, suggesting that earlier birth rather than intrauterine growth

restriction was primarily responsible. Consistent with this study, prenatal paraben exposure was associated with preterm birth, decreased gestational age, and low birthweight in an immigrant population in Brooklyn, NY.[19] By contrast, Philippat and colleagues (2014) reported a positive association between prenatal methylparaben exposure and child weight from birth to 3 years,[17] and in another study, methyl and propyl paraben were associated with longer gestation and decreased odds for newborns being small for their gestational age.[20] Thus, the limited data from this and other studies of parabens and birth outcomes is conflicting, and more work in larger and more diverse cohorts is needed.

Birth outcomes partially mediated the effect of prenatal methylparaben exposure on child ADHD. Preterm birth, which was responsible for 20% mediation, has previously been associated with altered gray and white matter brain volumes that may underly neurodevelopmental outcomes.[52] Given the limited mediation by birth outcomes, however, additional independent processes including oxidative stress and hormone signaling may also play a mediating role. In addition to future work on other mediators, an investigation into outcomes other than ADHD is warranted. For instance, preterm birth predicts immune, respiratory, cardiovascular, and neurodevelopmental diseases, along with mortality in some cases.[53] Thus, preterm birth may link prenatal paraben exposure with a multitude of adverse health consequences. Indeed, prenatal ethylparaben exposure was associated with increased childhood asthma and other respiratory outcomes in one study,[54] but research on other health outcomes is lacking.

A considerable strength of this study was our measurement of methylparaben in meconium rather than urine. While parabens are known to cross the placenta,[55] the 20% detection rate of methylparaben in meconium was considerably lower than detection rates of nearly 100% in urine across 14 studies,[3] which may be the consequence of rapid excretion of methylparaben in urine.[56] Due to efficient paraben excretion, it is possible that methylparaben was only distributed to the meconium of individuals with the highest paraben exposure. In addition, while urinary measurements may reflect maternal exposure, they cannot account for differential placental transfer across individuals and therefore misclassification of exposure to the fetus may result. Meconium, however, captures cumulative fetal exposure in the second and third trimesters.[29–32]

These results should be considered in the context of four potential limitations. First, owing to a limited number of individuals with thyroid hormone measurements, we were unable to formally assess mediation by endocrine pathways. Second, the high genetic and sociodemographic homogeneity in the GESTE cohort may lower the generalizability of results. However, such homogeneity may also be interpreted as a benefit that limits the likelihood of confounding by genetic or sociodemographic factors. Third, it is difficult to determine the exposure window represented by meconium measurements. Meconium starts to form between the 12^{th} and 16^{th} weeks of gestation, and continues to accumulate until birth.[32] While meconium measurements may be beneficial for modeling the effects of cumulative exposures throughout the second and third trimester, they cannot be used to assess the effects of exposure during more specific windows of gestation. Finally, our analysis of thyroid hormones as outcomes assumes that meconium methylparaben is a proxy for maternal methylparaben exposure. However, meconium methylparaben likely

underestimates maternal exposure based on the higher methylparaben detection rates in maternal urine. Rather than serving as a highly correlated proxy, meconium methylparaben detection may instead indicate mothers with the highest exposure.

Conclusions

Prenatal methylparaben exposure was associated with preterm birth, decreased birthweight, dysregulated maternal thyroid hormones, and child ADHD. Previously, only null associations between maternal paraben exposures and neurodevelopment have been reported, possibly because typical measurements of parabens in urine do not reflect the fetal environment. Future studies should attempt to measure realized fetal exposure to environmental chemicals, either by measuring sample types more relevant to fetal life such as meconium, or by incorporating variation that may influence metabolism, for instance in cytochrome p450 or glutathione s-transferases. Due to their ubiquity, parabens should be treated as a substantial public health concern if they are causally related to these adverse health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

This work was supported by the National Institute of Environmental Health Sciences (R21ES024841, R01ES027845, P30ES009089, K23ES022242) and the Canadian Institutes of Health Research (MOP-84551). This work was also supported by a Canadian Research Chair (CRC-950-230570) Grant from the Natural Sciences and Engineering Research Council of Canada.

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Highlights

- Methylparaben was associated with altered maternal thyroid hormones during pregnancy.
- Methylparaben was adversely associated with birthweight, gestational age and preterm birth.
- Methylparaben was associated with increased odds of ADHD in children aged 6–7 years.
- Adverse birth outcomes partially mediated the association of methylparaben with ADHD.

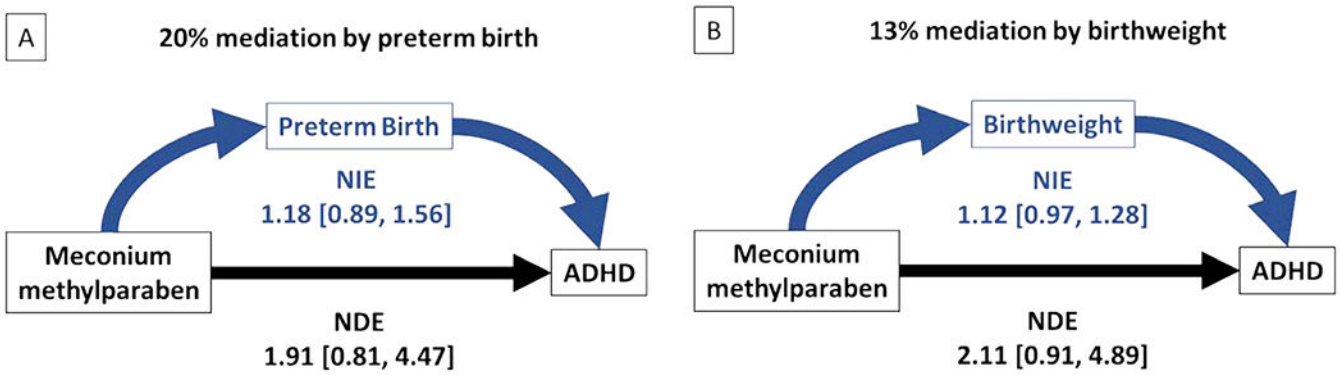

Figure 1:

Mediation of the association between meconium methylparaben and ADHD by (A) preterm birth and (B) birthweight. Odds ratios and 95% confidence intervals shown for natural indirect effect (NIE) and natural direct effect (NDE). Percent mediation calculated as NIE divided by total effect×100%.

Table 1:

Characteristics of study population stratified by methylparaben exposure in the GESTation and the Environment (GESTE) cohort

	No Methylparaben (N=280)	Methylparaben (N=65)	Total (N=345)	*P* value
Child sex				0.81
Female (n (%))	136 (49.3)	30 (47.6)	166 (49.0)	
Male (n (%))	140 (50.7)	33 (52.4)	173 (51.0)	
Missing (n (%))			6 (1.7)	
Maternal age				0.23
Mean (SD)	29.2 (4.7)	28.4 (5.6)	29.0 (4.9)	
Missing (n (%))			1 (0.2)	
Maternal BMI				0.08
Mean (SD)	26.4 (7.8)	24.6 (4.1)	26.0 (7.3)	
Missing (n (%))			15 (4.3)	
Family income (Canadian dollars)				0.87
< 60,000/year (n (%))	129 (51.4)	31 (52.5)	160 (51.6)	
> 60,000/year (n (%))	122 (48.6)	28 (47.5)	150 (48.4)	
Missing (n (%))			35 (10.1)	
Maternal education				0.86
No College or University (n (%))	124 (44.3)	28 (43.1)	152 (44.1)	
College or University (n (%))	156 (55.7)	37 (56.9)	193 (55.9)	
Missing (n (%))			0 (0.0)	
Smoked during pregnancy				0.38
No smoking (n (%))	233 (84.7)	57 (89.1)	290 (85.5)	
Smoking (n (%))	42 (15.3)	7 (10.9)	49 (14.5)	
Missing (n (%))			6 (1.7)	
Alcohol during pregnancy				0.69
No alcohol (n (%))	213 (77.5)	51 (79.7)	264 (77.9)	
Alcohol (n (%))	62 (22.5)	13 (20.3)	75 (22.1)	
Missing (n (%))			6 (1.7)	

Notes: Study sample data before imputation and inverse probability weighting shown. *P* values from chi-square goodness of fit tests for binary variables and two-sample t-tests for continuous variables.

Table 2:

Associations between meconium methylparaben and child ADHD (whole study sample, N = 345)

	Number (%)		Odds Ratios			
Meconium methylparaben exposure	**ADHD+**	**ADHD−**	**Crude**	***P* value**	**Weighted [a]**	***P* value**
No methylparaben	23 (6.7)	257 (74.5)	-	-	-	-
Methylparaben	10 (2.9)	55 (15.9)	2.03 [0.92, 4.51]	0.082	2.33 [1.45, 3.76]	<0.01

[a]Inverse probability weighted for maternal age at birth, maternal BMI, maternal smoking and alcohol during pregnancy, maternal education, family income, and child sex

Table 3:

Associations between meconium methylparaben and potential mediators

Thyroid hormones (<20 weeks gestation, N = 123)	Number (%)		Estimate or Odds Ratio [a]			
	Methylparaben	No methylparaben	Crude	*P* value	Weighted [b]	*P* value
Log_2(TSH)	-	-	0.93 [0.60, 1.41]	0.72	0.76 [0.58, 0.99]	0.05
Log_2(Total T3)	-	-	0.93 [0.84, 1.02]	0.13	0.84 [0.75, 0.96]	<0.01
Log_2(Free T3)	-	-	0.97 [0.95, 1.01]	0.12	0.97 [0.94, 1.00]	0.07
Log_2(Total T4)	-	-	1.06 [0.98, 1.14]	0.17	1.10 [1.01, 1.19]	0.02
Log_2(Free T4)	-	-	0.99 [0.94, 1.05]	0.85	1.00 [0.95, 1.05]	0.99
Normal Free T4 (ref)	19 (15.4)	93 (75.6)	-	-	-	-
Low Free T4	3 (2.4)	8 (6.5)	1.78 [0.43, 7.33]	0.43	2.50 [1.01, 6.22]	0.05
Birth outcomes (N = 345)						
Term (ref)	59 (17.1)	273 (79.1)	-	-	-	-
Preterm	6 (1.7)	7 (2.0)	3.97 [1.29, 12.27]	0.02	4.81 [2.29, 10.10]	<0.01
Gestational age (wk)	-	-	−0.52 [−0.90, −0.15]	<0.01	−0.61 [−0.93, −0.29]	<0.01
Birthweight (kg)	-	-	−0.13 [−0.25, −0.01]	0.04	−0.12 [−0.21, −0.03]	0.01

[a] Odds ratios from logistic regression shown for low free T4 and preterm birth. Estimates from linear models shown for gestational age and birthweight. Relative concentrations shown for log_2 transformed thyroid hormones (see methods).

[b] Inverse probability weighted for maternal age at birth, maternal BMI, maternal smoking and alcohol during pregnancy, maternal education, family income, and child sex. Hormone models additionally adjusted for TPO and other thyroid hormones.

Table 4:

Associations between potential mediators and child ADHD

Thyroid hormones (<20 weeks gestation, N = 123)	Number (%)		Odds Ratios			
	ADHD+	ADHD-	Crude	*P* value	Weighted [a]	*P* value
Log_2(TSH)	-	-	1.26 [0.65, 2.43]	0.49	1.59 [0.64, 3.96]	0.32
Log_2(Total T3)	-	-	6.11 [1.21, 30.84]	0.03	16.78 [2.23, 126.32]	<0.01
Log_2(Free T3)	-	-	0.21 [0.002, 24.85]	0.52	0.07 [0.0003, 15.48]	0.33
Log_2(Total T4)	-	-	0.33 [0.04, 2.99]	0.33	0.18 [0.02, 1.44]	0.11
Log_2(Free T4)	-	-	0.21 [0.002, 24.85]	0.52	0.30 [0.004, 21.39]	0.58
Normal Free T4 (ref)	6 (4.9)	106 (86.2)	-	-	-	-
Low Free T4	3 (2.4)	8 (6.5)	6.42 [1.35, 30.63]	0.02	8.33 [3.28, 21.18]	<0.01
Birth outcomes (N = 345)						
Gestational age (wk)	-	-	0.90 [0.71, 1.15]	0.41	0.91 [0.71, 1.16]	0.45
Birthweight (kg)	-	-	0.55 [0.24, 1.23]	0.14	0.44 [0.20, 0.97]	0.04
Term birth (ref)	29 (8.4)	303 (87.5)	-	-	-	-
Preterm birth	4 (1.2)	9 (2.3)	4.66 [1.35, 16.10]	0.01	3.39 [2.27, 5.06]	<0.01

[a]Inverse probability weighted for maternal age at birth, maternal BMI, maternal smoking and alcohol during pregnancy, maternal education, family income, and child sex. Hormone models additionally adjusted for TPO and other thyroid hormones.