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## Urinary concentrations of parabens mixture and pregnancy glucose levels among women from a fertility clinic

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### Abstract

**Background:** A number of endocrine disrupting chemicals (EDC) have been associated with gestational diabetes (GDM) risk factors. However, no human study has investigated the association between pregnancy exposure to parabens, a class of EDCs, and pregnancy glucose levels, a risk factor for GDM. Furthermore, little is known about this association in subfertile women—a group at high risk of GDM.

**Methods:** A total of 241 women from the Environment and Reproductive Health Study had data available on 1<sup>st</sup> and/or 2<sup>nd</sup> trimester urinary methylparaben, propylparaben, and butylparaben concentrations, and blood glucose levels after the glucose loading test (GLT), a non-fasting 50 gram glucose loading test taken at late 2<sup>nd</sup> trimester. Trimester-specific associations between specific gravity adjusted methylparaben, butylparaben, and propylparaben with adjusted mean of

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**Author contributions:** TJT conceived of the research question. RH designed the research study and RH, JBF, and MK acquired the data; LMA prepared the dataset; YHC conducted preliminary analyses; AB conducted all statistical analyses and drafted the manuscript under the main supervision of TJT; YHC, FMB, LMA, JBF, MK, JP, PLW, XY, AMC, and RH critically revised the article for important intellectual content. All authors approved the final manuscript and take full responsibility for the content of the manuscript.

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pregnancy glucose levels were evaluated in linear regression models, using quartiles of each paraben's distribution, and as a paraben mixture, using mutual adjustment and Bayesian kernel machine regression (BKMR), a recently proposed method for investigating chemical mixtures that flexibly models the joint effect of chemicals.

**Results:** Investigating parabens one at the time did not provide any significant results. When investigating parabens as a chemical mixture with both multiple regression and BKMR, we observed positive associations of butylparaben (e.g comparing the 4<sup>th</sup> and 1<sup>st</sup> quartiles) with glucose levels, for both the 1<sup>st</sup> trimester (adjusted difference=12.5 mg/dL; 95% CI: 0.9, 24.2) and 2<sup>nd</sup> trimester (adjusted difference=11.2 mg/dL; 95% CI: 0.2, 22.3), and a negative association between 1<sup>st</sup> trimester propylparaben and glucose (adjusted difference=-22.3 mg/dL; 95% CI: -43.2, -1.4).

**Conclusions:** We found 1<sup>st</sup> trimester butylparaben and propylparaben urinary concentrations to be associated with glucose levels in a pregnancy cohort of women at high risk of GDM, even after adjusting for potential confounders. Because exposure to parabens is widespread, these findings may suggest further investigating the effects of this chemical class on pregnancy health.

### Keywords

gestational diabetes; glucose; endocrine disruptors, environmental epidemiology; pregnancy, parabens

## Introduction

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications, affecting over 9% of all pregnancies in the United States.(1) Some population subgroups, including women with subfertility, are at particularly high-risk of GDM, with an up to 2-fold increased risk of this pregnancy complication.(2) Elevated pregnancy glucose levels, typically assessed in the late second trimester, are the first step in GDM diagnosis, when using a two-step screening method for this pregnancy complication.(3) Studies have suggested that even elevated pregnancy glucose levels that do not cross the clinical threshold for GDM diagnosis may also confer an increased risk of adverse pregnancy and delivery outcomes such as high birth weight,(4) preeclampsia,(5) and perinatal depression.(6) Higher glucose levels in pregnancy are associated with a linear increase in adverse pregnancy and neonatal outcomes including preeclampsia, need for cesarean delivery, large for gestational age infant, neonatal hypoglycemia, and >90<sup>th</sup> percentile for neonatal skin-fold thickness. (4,7) Furthermore, prenatal depression is more common in women with abnormal glucose levels from glucose loading tests (GLT), even if they don't develop GDM.(6) Finally, GDM is associated with long-term health risks in mothers and their offspring, including obesity, type 2 diabetes, and atherosclerosis.(8-10)

The rate of GDM has increased over the last decades, suggesting lifestyle and environmental exposures may contribute to the development of this condition.(11,12) In particular, a growing body of literature suggests that environmental chemicals with endocrine disrupting properties may act as metabolic disruptors, with impact on glucose metabolism and risk of diabetes and cardiovascular disease.(13) In the context of pregnancy, these metabolic

disruptors may have an impact on risk of GDM.(13) Parabens, chemicals widely used as preservatives in personal care products, pharmaceuticals, and foods, may also operate as endocrine disrupting chemicals (EDCs).(14–16) While phthalates and bisphenol A have been more extensively examined as metabolic disruptors as it relates to pregnancy complications,(17,18) parabens have been relatively understudied. A recent study in a representative sample of the U.S. population in the 2011–2012 National Health and Nutrition Examination Survey (NHANES) detected common parabens such as methylparaben and propylparaben in over 90% of the participants, and butylparaben in over 50%.(19) Parabens are weakly estrogenic, with the ability to bind to both estrogen receptors (ER) $\alpha$  and (ER) $\beta$ .(17–21) Similar to bisphenol A, parabens may be able to impact glucose metabolism through estrogen-dependent signaling that could alter normal beta cell functioning.(22) As such, exposure to parabens during pregnancy—an increasing insulin resistant state—could impact pregnancy glucose levels and subsequent GDM risk. Yet, no human study has evaluated the association between parabens and pregnancy glucose levels.

Therefore, we evaluated the association between urinary paraben concentrations and blood glucose levels assessed at the standard glucose tolerance test taken at the 2<sup>nd</sup> trimester of pregnancy utilizing data from a prospective pregnancy cohort of women seeking treatment at a fertility clinic. We assessed whether both 1<sup>st</sup> and 2<sup>nd</sup> trimester concentrations of parabens, individually and as a mixture of parabens, were related to this GDM risk factor. To our knowledge, this is the first human study to investigate the association between urinary concentration of parabens and glucose levels during pregnancy among subfertile women, a group of women at high risk of developing GDM.

## Methods

### Study population

Study participants were women enrolled in the Environment and Reproductive Health (EARTH) Study, an ongoing prospective cohort established in 2004 to evaluate environmental and dietary determinants of fertility. EARTH enrolls women between 18 and 45 years from the Massachusetts General Hospital (MGH) Fertility Center (Boston, MA). For this study, we used data on women enrolled between 2005 and 2015 who had completed at least one in vitro fertilization (IVF) cycle, and had contributed at least one urinary sample during first or/and second trimester. We a priori excluded IVF cycles for which women used an egg donor (n=18) and cryo-thaw cycles (n=34). In total, 241 women with pregnancies that resulted in live births and had data on parabens were included in this study. Only the first pregnancy was evaluated if participating women had more pregnancies during the time study. The study was approved by the Human Studies Institutional Review Boards of the MGH, Harvard T.H. Chan School of Public Health, and the Centers for Disease Control and Prevention (CDC).

### Outcome assessment

The main outcome of the study was blood glucose levels assessed at MGH during the 2<sup>nd</sup> trimester of pregnancy (median: 27 weeks gestation) through a 1-hour non-fasting, 50-gram GLT used as the first step in screening for GDM.(23) We evaluated glucose levels as a

continuous outcome, without any transformation because the distribution was not skewed. In sensitivity analyses we also evaluated blood glucose as a binary outcome. For this, we compared women with glucose levels  $\geq 140$ mg/dL from the GLT to women with glucose levels  $<140$ mg/dL; women with results above 140mg/dL are referred for additional GDM screening as a part of the two-step Carpenter-Coustan criteria employed by MGH throughout the entire study.(21) As such, we denote women with glucose levels  $\geq 140$ mg/dL as having abnormal GLT

### Urine sample collection and quantification of paraben concentrations

Urine samples were collected during the 1<sup>st</sup> and 2<sup>nd</sup> trimesters of pregnancy (median: 7 and 21 gestation weeks, respectively), with up to two spot urine samples for each time point. Urine was collected in sterile polypropylene cups at the MGH. Specific gravity (SG) was measured within one hour of urine collection, at room temperature, and using a handheld refractometer (National Instrument Company, Inc., Baltimore, MD, USA) calibrated with deionized water before each measurement. Samples were stored at  $-80^{\circ}\text{C}$  and shipped to the CDC for analysis. Urinary concentrations of total (free + conjugated) methylparaben, propylparaben, and butylparaben were quantified as described in detail elsewhere.(24) In brief, 100  $\mu\text{L}$  of urine were treated with  $\beta$ -glucuronidase/sulfatase (*Helix pomatia*, H1; Sigma Chemical Co, St. Louis, MO, USA) to hydrolyze the paraben-conjugated species. Each paraben was retained and concentrated by online solid phase extraction, separated from each other and other urine matrix components by high-performance liquid chromatography, and detected by isotope dilution negative ion-atmospheric pressure chemical ionization tandem mass spectrometry. The limits of detection (LODs) were 1.0  $\mu\text{g/L}$  for methylparaben, and 0.2  $\mu\text{g/L}$  for propylparaben and butylparaben. All paraben concentrations were adjusted for SG using the formula  $P_c = P [(1.014 - 1)/(SG - 1)]$ , where  $P_c$  is the SG-corrected paraben concentration ( $\mu\text{g/L}$ ),  $P$  is the measured paraben concentration ( $\mu\text{g/L}$ ), and 1.014 is the mean SG concentration in the study population included in the analysis. When two urine samples were available (about 80% of measurements), we used the geometric mean of the SG-adjusted concentrations as a measure of trimester-specific urinary paraben concentration. For concentrations below LOD, we assigned a value equal to the LOD divided by the square root of 2, prior to SG adjustment. (25)

### Covariate assessment

Information on sociodemographic factors, family medical history, and lifestyle factors, were obtained from a brief questionnaire administered by the study staff at enrollment and from a detailed take-home questionnaire. Pre-pregnancy body mass index (BMI) was calculated as weight (in kilograms) over height (in meters) squared, using anthropometric information measured by the nurse at enrollment. Clinical information was abstracted from the patient's electronic medical record. Infertility diagnosis by a physician was assigned to each patient based on the Society for Assisted Reproductive Technology. All statistical models were adjusted for the following *a priori* identified potential confounders based on the literature: maternal age (continuous, years), pre-pregnancy BMI (continuous,  $\text{kg/m}^2$ ), total physical activity (continuous, h/week), race (binary, white/non-white), self-reported smoking status (binary, ever/never), education levels (binary, some college degree or lesser vs college

graduate or higher), infertility diagnosis (female factor, male factor, or unexplained), number of fetuses (binary, one/more), previous IVF, previous intrauterine insemination (IUI). Since missing data proportion was negligible (<15%), all adjusted models were conducted as complete-case analyses.

### Statistical analysis

We present descriptive characteristics in the overall population and by categories of glucose levels from the GLT. For both 1<sup>st</sup> and 2<sup>nd</sup> trimesters, we calculated SG-adjusted geometric means, 5<sup>th</sup>, 25<sup>th</sup>, 75<sup>th</sup> and 95<sup>th</sup> percentiles, as well as the minimum and maximum parabens concentrations.

To relax the assumption of linearity in the dose-response associations, we categorized all paraben biomarkers concentrations into quartiles of their distribution and presented statistical associations by using the lowest quartile as referent category. Information on urinary paraben concentrations at the 1<sup>st</sup> and 2<sup>n</sup> medical visits were independently used as two separate exposures. A set of sensitivity analyses was also conducted: i) since the proportion of butylparaben measurements below the LOD was about one third, we replicated the analysis for the single butylparaben by using tertiles of the distribution, so to have all values below the LOD in the referent group; ii) we further excluded all women with a diagnosis of Polycystic Ovary Syndrome (PCOS, n=22); iii) we further excluded women under anti-diabetic medications at baseline (n=7); iv) we evaluated BMI (<25 vs ≥25 kg/m<sup>2</sup>), age (<37, ≥37 years) as potential effect modifier by means of stratified analysis; v) we replicated the main analysis by evaluating glucose as a binary outcome, evaluating the odds of abnormal GLT with multivariable-adjusted logistic regression models; and vi) we further adjusted for calendar year, to evaluate whether eventual changes in paraben levels over the 10 years of recruitment could have influenced the results.

In this first set of analyses, methylparaben, butylparaben, and propylparaben were evaluated as three separated categorical predictors, and linear regression models were used to estimate differences in mean glucose level. Next, we evaluated the simultaneous exposure to the three parabens as a chemical mixture. For this, we first ran a multiple regression mutually-adjusting for all parabens. Next, we used Bayesian kernel machine regression (BKMR), a recently proposed method for investigating chemical mixtures that flexibly models the joint effect of chemicals using a kernel function.<sup>(26)</sup> BKMR allows the visualization of the exposure-response association for each component of a mixture, while taking into account the correlation between the mixture components. In addition, possible synergistic and non-linear effects can be evaluated. We presented results from this analysis by displaying: i) the paraben-specific dose-response curves; and ii) the difference in pregnancy glucose levels for a change in paraben concentration between the 10<sup>th</sup> and 90<sup>th</sup> percentile. For both analyses we set the other components of the mixture at their median values. For all BKMR models, measurements of SG-adjusted parabens concentrations were treated as continuous predictors and *log*-transformed due to their pronounced right-skewedness.

All analyses were performed in Stata, version 15 (StataCorp, College Station, Texas), with exception of the BKMR models that were conducted using the specific R package *bkmr*.

Statistical tests were two-tailed and all p-values < 0.05 were conventionally regarded to as statistically significant.

## Results

Descriptive statistics of the study population are shown in Table 1. Women with abnormal GLT had higher BMI, had lower levels of physical activity, were more likely to be Asian, and more likely to have a diagnosis of infertility due to female factor. Other baseline characteristics were similar among women regardless of blood glucose levels. We detected frequently methylparaben and propylparaben (100% and ~98%, respectively), while butylparaben was detected in 64.2% and 64.7% of the urinary samples of the 1<sup>st</sup> and 2<sup>nd</sup> trimester, respectively (Table 2). Median differences in the time between exposure and outcome measurements were 20 and 6 weeks (respectively for 1<sup>st</sup> trimester urinary parabens concentrations and 2<sup>nd</sup> trimester glucose levels, as well as 2<sup>nd</sup> trimester urinary parabens concentrations and 2<sup>nd</sup> trimester glucose levels). Correlations between the two measurements of the same metabolites (between-trimester correlations) were moderate for both butylparaben ( $r=0.64$ ), propylparaben ( $r=0.45$ ), and methylparaben ( $r=0.33$ ).

Table 3 presents unadjusted and adjusted differences in late 2<sup>nd</sup> trimester glucose levels across quartiles of 1<sup>st</sup> and 2<sup>nd</sup> trimester urinary parabens concentrations, evaluating parabens in separate statistical models. Positive associations were seen between butylparaben and pregnancy glucose levels in both the 1<sup>st</sup> trimester (comparing the 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> quartiles with the 1<sup>st</sup> quartile of butylparaben, respectively: adj.  $\beta=7.5$  mg/dL, 95% CI: -3.4, 18.9; adj.  $\beta=7.7$  mg/dL, 95% CI: -3.0, 18.4; adj.  $\beta=8.1$  mg/dL; 95% CI: -2.6, 18.9) and 2<sup>nd</sup> trimester (adj.  $\beta=13.6$  mg/dL, 95% CI: 3.5, 23.7; adj.  $\beta=11.8$  mg/dL, 95% CI: 1.7, 22; adj.  $\beta=10.1$  mg/dL; 95% CI: 0.7, 20.2, respectively). No evidence of an association between methylparaben and glucose was observed. On the other hand, 1<sup>st</sup> trimester urinary propylparaben concentrations had a suggestive inverse association with glucose levels; however, this finding had wide confidence intervals and did not reach statistical significance.

Evaluating butylparabens in tertiles provided smaller estimates but did not change the direction of the associations. Results were similar when excluding women with a diagnosis of PCOS or taking medication at baseline (data not shown). No evidence of effect modification by age, BMI was documented (data not shown). Finally, results were similar when investigating glucose levels as a binary outcome (<140 vs. 140mg/dL), and when further adjusting for calendar year (data not shown).

In Table 4, we present the association between pregnancy glucose levels and the parabens mixture evaluated with multiple regression, adjusting for potential confounders and for each paraben in the same model (mutually-adjusted). Methylparaben and propylparaben were highly correlated in both 1<sup>st</sup> and 2<sup>nd</sup> trimester samples ( $r=0.89$  and  $r=0.79$ , for each trimester respectively), while lower and moderate correlations ( $r<0.50$ ) were observed between butylparaben and the other two parabens at both time points. We observed positive associations between both 1<sup>st</sup> and early 2<sup>nd</sup> trimester butylparaben concentrations and late 2<sup>nd</sup> trimester pregnancy glucose levels. For example, when comparing the lowest and highest quartiles of 1<sup>st</sup> and 2<sup>nd</sup> trimester butylparaben, respectively: adj.  $\beta$  for 1<sup>st</sup> trimester = 12.5

mg/dL, 95% CI:0.9, 24.2; adj.  $\beta$  for 2<sup>nd</sup> trimester=11.2 mg/dL, 95% CI:0.2,22.3). In addition, a pronounced negative dose-response was observed between 1<sup>st</sup> trimester propylparaben and glucose levels, with a 22.3 mg/dL lower glucose level when comparing the lowest and highest quartiles ( $\beta$  for 1<sup>st</sup> trimester=-22.3 mg/dL, 95% CI:-43.2,-1.4).

Results from BKMR were in line with findings from multiple regression, with a positive association between 1<sup>st</sup> trimester butylparaben and glucose levels, and suggestive inverse association with 1<sup>st</sup> trimester propylparaben (Figure 1A). Specifically, the difference in glucose between the 10<sup>th</sup> and 90<sup>th</sup> percentile of each paraben evaluated at the 1<sup>st</sup> trimester was -13.9 mg/dL for propylparaben (95% CI: -30.4, 2.6), and 10.2 mg/dL for butylparaben (95% CI:0,20.4) (Figure 2). With BKMR, no clear evidence of associations was seen for 2<sup>nd</sup> trimester paraben concentrations and later 2<sup>nd</sup> trimester pregnancy glucose levels (Figure 1B). Also, no evidence of synergistic effects between the three parabens were detected (data not shown).

## Discussion

In the present study from a prospective cohort of women from a fertility clinic, we found urinary concentrations of butylparaben to be positively associated with blood glucose levels, when assessed individually and as a mixture with two other parabens. We also found inverse associations between urinary propylparaben concentrations and glucose levels. These associations were more pronounced when assessing parabens as a chemical mixture. Given the ubiquitous nature of parabens exposure, these findings suggest further evaluation of paraben exposures as possibly modifiable risk factors of pregnancy glucose levels in higher-risk women.

Recent studies have suggested that exposure to EDCs, such as phthalates and bisphenol A, may be possible risk factors for GDM.(13,27–29) This is of particular concern in women conceiving with medically assisted reproduction, and women with underlying causes of infertility, who represent a high risk group with an increased risk of not only GDM, but also elevated glucose levels in pregnancy.(30,31) Moreover, such women could be particularly affected by exposure to EDCs that alter glucose metabolism.(32) Parabens are a group of alkyl esters of p-hydroxybenzoic acid commonly used as preservatives in cosmetics, personal care products, pharmaceuticals and food.(33) Methyl, propyl, and butyl parabens have been detected in a large proportion of the U.S. population,(19) thus suggesting widespread exposure to these compounds. Several in vitro and in vivo studies have demonstrated the endocrine disrupting properties of parabens, including their weak estrogenicity; however the estrogenic properties of these chemicals varies by chain length, with butylparaben being the most estrogenic.(34–37)

While a handful of population-based studies have investigated parabens as they relate to pregnancy outcomes,(38–40) limited information exist about the association between paraben concentrations and glucose levels during pregnancy. Such associations may be valid and could operate through a number of pathways. First, parabens can activate glucocorticoid receptors,(41,42) thus interfering with normal glucose regulation. Second, parabens could also act as a thyroid hormone receptor and could alter normal thyroid functioning.

Specifically, one study showed inverse associations between parabens and thyroid hormones known to be involved in glucose metabolism.(43) Third, parabens are agonist of peroxisome proliferator-activated receptor, which could alter glucose metabolism through alterations to adipocyte production and insulin resistance.(44) Potentially harmful effects of parabens have also been confirmed by recent human studies.(43,45,46) Interestingly and relevant to the current findings, in vitro studies have suggested that parabens, especially butylparaben, may contribute to obesity,(34,36) a risk factor for GDM.

In this study we observed a positive association between butylparaben and glucose levels. This finding is line with previous studies reporting stronger estrogenic effect and higher glucocorticoid-like activity for butylparaben.(38,41) On the other hand, we also reported a negative association between propylparaben and glucose levels. Of note, parabens may also differ by other properties, with respect to endocrine disruption. For example one study showed that butylparaben was able to increase plasma leptin.(47) Another study showed propylparaben had the ability to perturb mitochondrial function.(48,49) These potential differences could possibly explain differences in the associations between butylparaben and glucose levels and propylparaben and glucose levels. However, reasons for the associations between these parabens and glucose levels, along with the differing results, remain unclear and further work is needed to explain how parabens might be able to perturb glucose metabolism during pregnancy.

This study is subject to several limitations. First, due to the relatively low number of GDM cases we could not focus on clinically-diagnosed GDM and only evaluated continuous glucose levels from the 50-gram GLT that is standardly given to all women as a part of the GDM screening test in late 2<sup>nd</sup> trimester. Second, our analysis did not include other chemicals such as phthalates and BPA; exposure to these chemicals may correlate with exposure to parabens and be associated with glucose levels. Future studies should evaluate exposure to mixtures of several chemical classes as this relates to GDM. Nevertheless, this is one of the first studies to evaluate paraben mixtures as it relates to pregnancy glucose levels. Third, we evaluated results from the non-fasting GDM screening test that could be influenced by the timing or content of the last meal, information that was unavailable in our dataset. In addition, all our results are based on a population of women seeking care at a fertility clinic, and results may not be generalizable to women who conceived naturally or to subgroups of the population under-represented in our sample (e.g. non-white). Finally, despite having up to two exposure assessments, 1<sup>st</sup> and 2<sup>nd</sup> trimester urinary concentrations of parabens were treated separately because previous studies have suggested trimester-specific associations for GDM risk factors. Future studies with larger sample sizes should investigate the trajectory of exposure and take into account changes in the urinary concentrations of parabens occurring during pregnancy. It is also important to mention that parabens are non-persistent chemicals with low to moderate variability, and exposure misclassification may exist. In this study the correlation between paraben concentrations in the first and second trimesters was moderate. That said, we evaluated multiple time periods finding differing associations, which may be suggestive, in agreement with previous studies, (27,29) that second trimester may be a particularly sensitive time window of exposure with respect to the association between parabens and glucose levels in pregnancy. Future studies



should focus on known sources of parabens such as personal care products, evaluating whether these change over pregnancies or not.

Our study also has several strengths. First, to our knowledge, this was the first study investigating pregnancy exposure to parabens as it relates to glucose levels in the 2<sup>nd</sup> trimester of pregnancy, a clinically-relevant indicator of future risk of GDM. Moreover, the prospective design of the study, with two exposure assessments in the 1<sup>st</sup> and 2<sup>nd</sup> trimesters, allowed us to evaluate a larger and potentially sensitive time window of pregnancy. The prospective nature of the study also strengthens the interpretation of our results by reducing the risk of reverse causation. Third, in addition to evaluating the independent contribution of three parabens, we investigated parabens as a chemical mixture.(50) In particular, by using the recently proposed BKMR, we were able to flexibly evaluate the simultaneous contribution of multiple and highly-correlated exposures, while also taking into account potential non-linear dose-responses and interactions.(26)

In conclusion, we observed a positive association between pregnancy butylparaben urinary concentrations and glucose levels from a late 2<sup>nd</sup> trimester GDM screening test. We also found a suggestive negative association between propylparaben concentrations during the first trimester and pregnancy glucose levels. These findings suggest that certain parabens may have the ability to affect glucose regulation, with potential downstream impacts on GDM risk and associated sequelae. Subfertile women, given their higher risk of glucose intolerance in pregnancy, may be particularly vulnerable to the effects of these EDCs. Given the widespread use of parabens in consumer products and the increasing prevalence of GDM in U.S. women, future studies would benefit from further investigations of the association between parabens and pregnancy outcomes.

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## Abbreviations:

<b>BKMR</b>	Bayesian kernel machine regression
<b>EDC</b>	endocrine disrupting chemicals
<b>GDM</b>	gestational diabetes mellitus
<b>GLT</b>	glucose loading test
<b>IVF</b>	in-vitro fertilization

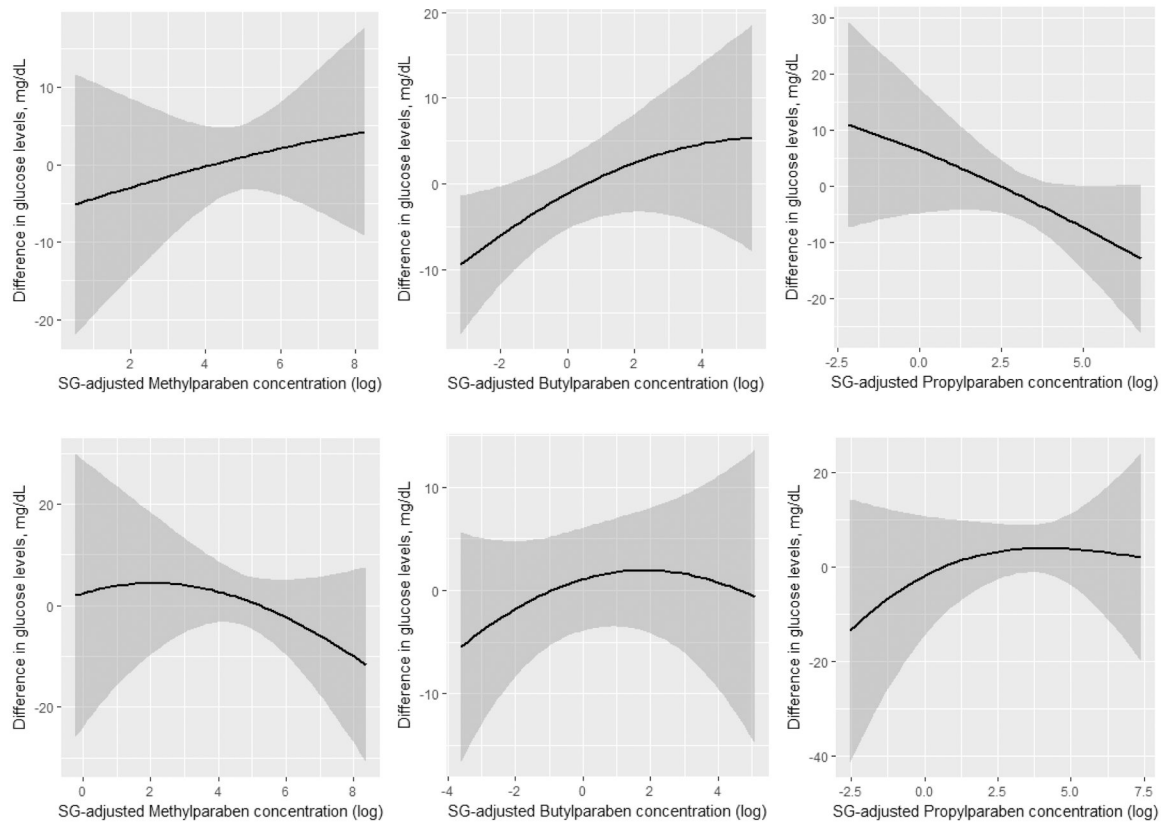
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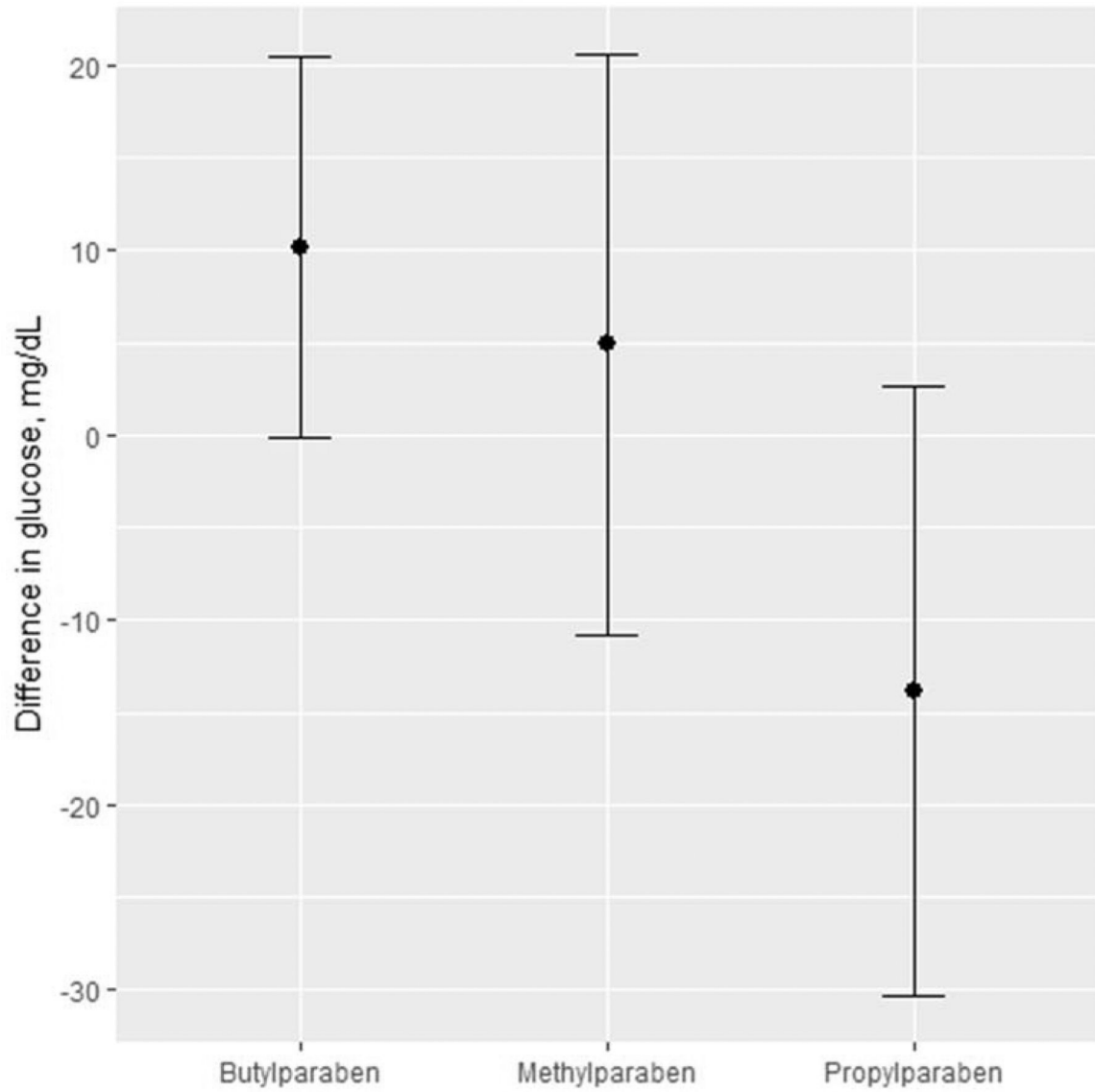
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**Figure 1.**

Dose-response associations between urinary parabens concentration (log-transformed and SG adjusted) at 1<sup>st</sup> (panel A) and 2<sup>nd</sup> (panel B) trimester, and later 2<sup>nd</sup> trimester glucose levels. Results obtained by running Bayesian Kernel Machine Regression (BKMR) for the mixture of parabens further adjusting for physical activity (continuous), maternal age (continuous), BMI (continuous), smoking, race, education, infertility diagnosis, number of fetuses.



**Figure 2.** Differences in glucose in mg/dL as a function of 1<sup>st</sup> trimester paraben concentrations. Point estimates for exposure changes between the 10<sup>th</sup> and 90<sup>th</sup> percentile of their distribution.

**Table 1.**

Baseline characteristics of 241 women included in the analysis, overall, and by impaired glucose tolerance status (glucose from GLT  $\geq 140$  mg/dL versus  $<140$  mg/dL)

Characteristics	Total (n=241)	Glucose $<140$ (n=199)	Glucose $\geq 140$ (n=42)
Maternal age, years (sd)	35.3 (3.8)	35.3 (3.8)	35.7 (3.7)
BMI, kg/m <sup>2</sup> (sd)	24.2 (4.8)	24.0 (4.6)	25.1 (5.7)
Total physical activity, h/week (sd)	6.7 (6.9)	6.9 (7.2)	5.6 (5.0)
Smoking, n (%)			
Never	180 (75)	151 (76)	29 (69)
Former	54 (22)	43 (22)	11 (26)
Current	7 (3)	5 (3)	2 (5)
Race, n (%)			
White	209 (87)	176 (88)	33 (79)
Black/African American	5 (2)	4 (2)	1 (2)
Asian	17 (7)	10 (5)	7 (17)
Other	10 (4)	9 (5)	1 (2)
Education, n (%)			
High school graduate or less	23 (10)	18 (9)	5 (12)
Some college	6 (2)	6 (3)	0 (0)
College graduate or higher	212 (88)	175 (88)	37 (88)
Infertility diagnosis, n (%)			
Male factor	77 (32)	64 (32)	13 (31)
Female factor	68 (28)	49 (25)	19 (45)
Unexplained	96 (40)	86 (43)	10 (24)
Previous IVF, n(%)	135 (56)	111 (56)	24 (57)
Previous IUI, n(%)	54 (22)	44 (22)	10 (24)
Currently under medication, n (%)	7 (3)	5 (3)	2 (5)
More than one fetus, n (%)	46 (19)	36 (18)	10 (24)

IVF=in vitro fertilization, IUI=intra uterine insemination, GLT=glucose load test, BMI=body mass index.

Table 2.

Distribution of trimester-specific urinary paraben concentrations ( $\mu\text{g/L}$ )

Paraben type	Geometric mean ( $\mu\text{g/L}$ )	Detection frequency	Distribution percentiles ( $\mu\text{g/L}$ )						
			Min	5th	25th	50th	75th	95th	Max
<b>1<sup>st</sup> trimester (n=204)</b>									
Methylparaben (MP)	102.9	100%	1.4	5.8	27	113	406.2	1549.8	4770.7
Sg-adjusted MP	124.1	100%	1.7	11.3	39.5	122.7	425.6	1443.8	3850
Propylparaben (PP)	19.3	98.5%	<LOD*	<LOD	5	20	93.1	344.1	621
SG-adjusted PP	23.2	98.5%	<LOD	<LOD	7.3	25.7	110.1	331.9	855
Butylparaben (BP)	0.8	64.2%	<LOD	<LOD	<LOD	0.5	3.6	41.5	242
SG-adjusted BP	0.94	64.2%	<LOD	<LOD	<LOD	0.7	3.9	34.6	239.6
<b>2<sup>nd</sup> trimester (n=207)</b>									
Methylparaben (MP)	89.8	100%	1.1	5	36.4	91	290	949	6098
Sg-adjusted MP	120.2	100%	0.9	9.9	51	137.1	364	1092.9	4573.6
Propylparaben (PP)	19	98.1%	<LOD	<LOD	4.4	25.7	79.4	367	2291
SG-adjusted PP	25.3	98.1%	<LOD	<LOD	8.6	33.9	114.7	347	1718.4
Butylparaben (BP)	0.8	64.7%	<LOD	<LOD	<LOD	0.5	3.1	36.9	282
SG-adjusted BP	1	64.7%	<LOD	<LOD	<LOD	0.8	4.9	43	171.4

\* The limits of detection (LODs) were 1.0  $\mu\text{g/L}$  for methylparaben and 0.20  $\mu\text{g/L}$  for propylparaben and butylparaben. All concentrations below LOD were assigned a value equal to the LOD divided by square root of 2.



**Table 3.**

Multivariable-adjusted differences in pregnancy glucose levels in mg/dL from 50-gram GLT across categories of 1<sup>st</sup> and 2<sup>nd</sup> trimester urinary paraben concentrations\*, evaluated in separate statistical models.

	1st trimester (n=204)				2nd trimester (n=207)			
	Unadjusted		Adjusted <sup>†</sup>		Unadjusted		Adjusted <sup>†</sup>	
	Glucose levels (mg/dL) (95% CI)				Glucose levels (mg/dL) (95% CI)			
	Beta (mg/dL)	95% CI	Beta (mg/dL)	95% CI	Beta (mg/dL)	95% CI	Beta (mg/dL)	95% CI
Methylparaben								
Q1	0	Ref	0	Ref	0	Ref	0	Ref
Q2	-5.1	(-15.7, 5.4)	-4.4	(-15.3, 6.5)	-2.8	(-13.0, 7.4)	-1.6	(-12.1, 8.8)
Q3	-4.1	(-14.6, 6.5)	-3.8	(-14.8, 7.2)	-2.4	(-12.5, 7.8)	-1.5	(-11.9, 8.9)
Q4	0.3	(-10.2, 10.9)	-1.1	(-11.8, 9.6)	2.2	(-8.1, 12.4)	0	(-10.8, 10.8)
Propylparaben								
Q1	0	Ref	0	Ref	0	Ref	0	Ref
Q2	-6.9	(-17.5, 3.6)	-8.2	(-19.2, 2.7)	-5.9	(-16.0, 4.2)	-5.7	(-16.0, 4.6)
Q3	-7.0	(-17.5, 3.6)	-7.3	(-18.3, 3.8)	1.8	(-8.3, 12.0)	2.5	(-7.9, 12.9)
Q4	-4.4	(-14.9, 6.2)	-6.6	(-17.3, 4.2)	2.5	(-7.7, 12.7)	1.0	(-9.8, 11.7)
Butylparaben								
Q1	0	Ref	0	Ref	0	Ref	0	Ref
Q2	8.8	(-1.7, 19.3)	7.5	(-3.4, 18.9)	12.7	(2.8, 22.6)	13.6	(3.5, 23.7)
Q3	7.4	(-3.2, 17.9)	7.7	(-3.0, 18.4)	12.0	(1.9, 22.1)	11.8	(1.7, 22.0)
Q4	6.7	(-3.9, 17.2)	8.1	(-2.6, 18.9)	8.7	(-1.4, 18.8)	10.1	(0.7, 20.2)
Butylparaben <sup>‡</sup>								
T1	0	Ref	0	Ref	0	Ref	0	Ref
T2	4.7	(-4.4, 13.8)	4.1	(-5.2, 13.4)	3.8	(-5.1, 12.6)	2.2	(-6.8, 11.2)
T3	5.8	(-3.3, 14.9)	7.1	(-2.2, 16.4)	3.0	(-5.7, 11.7)	3.5	(-5.2, 12.2)

\*Parabens concentrations log-transformed and SG-adjusted

<sup>†</sup>Models adjusted for physical activity (continuous), maternal age (continuous), BMI (continuous), smoking, race, education, infertility diagnosis, number of fetuses.

<sup>‡</sup>Tertiles of Butylparaben

Multivariable-adjusted differences in glucose levels across categories of 1<sup>st</sup> and 2<sup>nd</sup> trimester parabens mixture, evaluated with multiple regression\*

**Table 4.**

		1 <sup>st</sup> trimester (n=204)			2 <sup>nd</sup> trimester (n=207)			
		Unadjusted	Adjusted <sup>†</sup>	Unadjusted	Adjusted <sup>†</sup>			
		Glucose levels (mg/dL) (95% CI)						
	Beta	95% CI	Beta	95% CI	Beta	95% CI	Beta	
<b>Methylparaben</b>								
Q1	0	Ref	0	Ref	0	Ref	0	
Q2	-2.3	(-14.2, 9.6)	-1.6	(-13.1, 12.4)	-4.5	(-16.1, 7.0)	-3.7	(-15.4, 8.0)
Q3	5.9	(-10.9, 22.8)	5.9	(-10.6, 24.9)	-5.1	(-17.8, 7.6)	-4.4	(-17.1, 8.4)
Q4	14.3	(-5.8, 34.6)	13.1	(-7.9, 34.0)	-2.1	(-16.9, 12.7)	-4.8	(-19.8, 10.3)
<b>Propylparaben</b>								
Q1	0	Ref	0	Ref	0	Ref	0	
Q2	-9.8	(-21.4, 1.9)	-11.2	(-23.4, 1.0)	-5.2	(-16.4, 6.0)	-5.7	(-17.1, 6.6)
Q3	-17.0	(-33.6, -0.4)	-17.7	(-35.1, -0.3)	1.8	(-10.7, 14.4)	2.2	(-10.5, 14.8)
Q4	-20.8	(-40.9, -0.7)	-22.3	(-43.2, -1.4)	1.7	(-12.9, 16.3)	1.2	(-13.6, 16.0)
<b>Butylparaben</b>								
Q1	0	Ref	0	Ref	0	Ref	0	
Q2	11.0	(0.3, 21.6)	10.0	(-1.0, 21.0)	12.3	(2.2, 22.4)	13.3	(3.0, 23.6)
Q3	9.9	(-1.0, 20.9)	10.5	(-0.6, 21.6)	12.6	(2.1, 23.0)	12.3	(1.8, 22.9)
Q4	10.7	(-0.7, 22.2)	12.5	(0.9, 24.2)	9.4	(-1.5, 20.3)	11.2	(0.2, 22.3)

\* Parabens concentrations are log-transformed, SG-adjusted, and mutually adjusted in the same statistical models

<sup>†</sup> Models further adjusted for physical activity (continuous), maternal age (continuous), BMI (continuous), smoking, race, education, infertility diagnosis, number of fetuses.