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# Parabens exposure in early pregnancy and gestational diabetes mellitus

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ABSTRACT

*Background:* Widespread exposure to parabens has been a concern, especially among pregnant women. Only one study reported that parabens are associated with glucose levels among pregnant women. However, studies on parabens exposure and gestational diabetes mellitus (GDM) are lacking.
*Objectives:* This study investigated whether exposure to parabens in early pregnancy is related to GDM.
*Methods:* We conducted a prospective study of 1087 pregnant women from a single tertiary medical center between 2014 and 2015 in Wuhan, China. Parabens [methyl paraben (MeP), ethylparaben (EtP), propylparaben (PrP), butylparaben (BuP), and benzylparaben (BzP)] concentrations were measured in spot urine samples collected between 8 and 16 gestational weeks. GDM was diagnosed according to the International Association of Diabetes and Pregnancy Study Groups Consensus Panel (IADPSG) recommendations. We used the Poisson regression with a robust error variance with generalized estimating equations (GEE) estimation analyses to evaluate associations between parabens exposure and GDM risk.
*Results:* A total of 103 (9.5%) women were diagnosed with GDM. We evaluated the associations of GDM risk with urinary MeP, EtP, and PrP (detection rate: > 90%), but not with BuP and BzP due to the relatively low detection rate (< 50%). After adjustment for potential confounders, urinary EtP was associated with GDM. The risk ratios (RRs) = 1.12 (95% CI: 0.63, 2.01) for the second quartile, RRs = 1.11 (95% CI: 0.64, 1.93) for the third quartile, and RRs = 1.70 (95% CI: 1.02, 2.82) for the highest quartile, compared with the lowest quartile. There was no evidence of associations between urinary MeP or PrP and GDM.
*Conclusions:* To the best of our knowledge, this is the first report of an association between urinary paraben levels in early pregnancy and GDM. Our findings suggest that exposure to EtP may increase the risk of GDM.

## 1. Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that is first recognized during pregnancy (American Diabetes, 2011). Studies have reported an increased prevalence of GDM in China (Zhang et al., 2011) and other countries such as the US (Albrecht et al., 2010; Lavery et al., 2017) and Australia (Anna et al., 2008) in recent decades. GDM may lead to serious adverse maternal and detrimental infant outcomes, for example, high caesarean section rate, pre-eclampsia, macrosomia, infant respiratory distress syndrome, and neonatal hypoglycemia (Poel et al., 2012; Wendland et al., 2012). Known risk factors for GDM include behaviors and dietary habits. However, increasing evidence suggests that exposure to environmental chemicals may be partly responsible for the development of GDM (Ehrlich et al., 2016; Liu et al., 2018; Shapiro et al., 2018; Shapiro et al., 2015). Some epidemiological studies have found associations between environmental chemicals and GDM, such as cadmium (Liu et al., 2018), triclosan (Shapiro et al., 2018), and arsenic (Shapiro et al., 2015), but there have not been enough studies on this issue to draw definitive conclusions.

Parabens are suspected endocrine disruptors (Boberg et al., 2010). As wide spectrum antimicrobial agents, parabens are extensively used in personal care products (PCPs), pharmaceuticals, and foods (Haman et al., 2015; Pycke et al., 2015). Humans are widely exposed to

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parabens through ingestion, inhalation, and dermal absorption (Smith et al., 2013). Beta cell fragmentations were observed when zebrafish embryos were treated daily with 250 nM BuP (Brown et al., 2018), suggesting that parabens may cause beta cell damage. An epidemiological study showed that first-trimester urinary butylparaben (BuP) concentrations were positively associated with glucose levels from the 50 g glucose loading test (GLT) and propylparaben (PrP) concentrations were negatively associated with glucose levels among pregnant women (Bellavia et al., 2018), but did not focus on GDM due to the low number of GDM cases. Limited data were available on the association between parabens and GDM.

In the present study, we collected one spot urine samples during early pregnancy from 1087 pregnant women. We conducted a prospective cohort study to evaluate the association between urinary paraben levels and the risk of GDM.

## 2. Methods

### 2.1. Study population

There were 1265 pregnant women recruited between 2014 and 2015 at Wuhan Women and Children Medical Care Center, a major tertiary medical center in Wuhan, China. The recruitment criteria were reported in our previous work (Liu et al., 2018). The participants were enrolled before 16 weeks of pregnancy. Also, they were willing to have prenatal care and give birth at the participating hospital. This study excluded pregnant women with family histories of diabetes and women with diabetes before pregnancy (n = 1). Meanwhile, pregnant women who did not donate urine samples (n = 35) or did not take the oral glucose tolerance test (OGTT) (n = 142) were excluded. We only included the first delivery records for women who had two separate deliveries. Finally, 1087 pregnant women were included in this study (Supplemental material Fig. S1). All of the participants provided written informed consent at enrollment. The research protocol was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology (No. (2012)07), and Wuhan Women and Children Medical Care Center (No. 2012003).

### 2.2. Urine sample collection and parabens measurements

The random spot urine samples were collected when the pregnant women visited the hospital between 8 and 16 weeks of gestation (on average 13 weeks, standard deviation (SD) = 1.12) and stored in polypropylene tubes at −20° Celsius (°C) for further analysis.

The urine samples were analyzed for total concentrations (free plus conjugated) of methyl paraben (MeP), ethylparaben (EtP), PrP, BuP, and benzylparaben (BzP) at the Key Laboratory of Environmental and Biological Analysis, Hong Kong Baptist University. The method of urinary parabens analysis was previously described (Zhao et al., 2017). Briefly, the urine samples were glucuronidated by β-glucuronidase/sulfatase, separated via high-performance liquid chromatography, and detected using tandem mass spectrometry. Quality control (QC) samples were prepared by spiking the standards and internal standards (20 ng/mL in final concentration) to the mixed urine to check for instrumental drift. QC samples were incorporated every 10 samples. Intra- and inter-day precision for parabens were lower than 7.4% and 6.7%, respectively. The ranges for the instrumental calibration curve were 0.5 to 50 ng/mL for MeP, EtP, and BzP, and 1.00 to 100 ng/mL for PrP and BuP. The regression coefficients (r) were 0.991–0.998. The limits of detection (LODs) for EtP and BzP were 0.01 μg/L. LODs were 0.05 μg/L for MeP, PrP, and BuP.

The concentrations of parabens were adjusted for variation in dilution by urinary specific gravity (SG) according to the following formula: $P_c = P_i[(SG_m - 1)/(SG_i - 1)]$, where $P_c$ = SG-adjusted metabolite concentration (μg/L or nmol/L), $P_i$ = observed metabolite concentration, $SG_i$ = specific gravity of the urine sample, and $SG_m$ = median SG of the cohort ($SG_m$ = 1.014) (Just et al., 2010). SG was measured using a pocket refractometer (Atago PAL-10S, Atago, Tokyo, Japan).

### 2.3. Data collection

Standard face-to-face interviews were conducted by trained nurses to collect retrospective information about sociodemographic characteristics (maternal age and education) and lifestyle habits during pregnancy (smoking, passive smoking, and alcohol consumption) when the pregnant women came to the hospital for delivery. Information on the hypertensive disorders in pregnancy was obtained from medical records. Gestational age was calculated based on ultrasound estimates. Maternal height was measured using a stadiometer and self-reported pre-pregnancy body weights were collected at the first prenatal visit to the hospital. Pre-pregnancy body mass index (BMI) was calculated by pre-pregnancy body weight and height. Passive smoking was defined as the exposure of nonsmoking women to tobacco smoke during pregnancy (her family members or other people smoke in the household or workplace) (Vardavas et al., 2016). Smoking in this study was defined as women who smoked at least one cigarette during pregnancy.

### 2.4. GDM diagnosis

GDM was assessed by 75 g OGTT. The mean (SD) of gestational age was 26.4 (2.44) at the time of the test in the study population. Women were diagnosed with GDM according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations (American Diabetes, 2011): fasting plasma glucose (FPG) ≥ 5.1 mmol/L (≥92 mg/dL), or 1-hour plasma glucose (1 h-PG) ≥ 10.0 mmol/L (≥180 mg/dL), or 2-hour plasma glucose (2 h-PG) ≥ 8.5 mmol/L (≥153 mg/dL).

### 2.5. Statistical analysis

Descriptive statistics were conducted for the study population characteristics (women with GDM or not). Paraben levels below LODs were replaced with a value of 1/2 LOD. The total concentrations of parabens (Σparabens) (nmol/L) were denoted as the sum of the parabens weighted by the individual relative estrogenic potential of the parabens:

$$\Sigma\text{parabens} = [1 \times \text{MeP} + 16.7 \times \text{EtP} + 83.3 \times \text{PrP} + 250 \times \text{BuP}],$$

where MeP, EtP, PrP, and BuP were the SG-adjusted molar concentrations (Shirai et al., 2013). BzP were excluded for the calculations due to the low detection rate. The median and interquartile ranges (IQR) were calculated to describe the distributions of urinary parabens and the SG-adjusted paraben concentrations.

Differences in the distributions of the paraben concentrations between women with and without GDM were examined using the Wilcoxon rank test. The paraben concentrations were right-skewed and transformed by natural logarithm (Ln) to satisfy statistical normality. The correlations of SG-adjusted Ln-parabens were evaluated by Pearson correlation coefficients.

The SG-adjusted paraben concentrations were analyzed in both continuous (Ln-parabens) and categorical indicators (quartile-coded data) to explore the linear and non-linear relationships, respectively. Poisson regression with a robust error variance with generalized estimating equations (GEE) estimation (Spiegelman and Hertzmark, 2005) were used to test the associations of paraben concentrations with the risk of GDM by calculating the risk ratios (RRs) and 95% confidence intervals (CIs). We conducted trend tests using the median value within each quartile of urinary parabens as the score variable (He et al., 2013) and assessed the statistical significance of this predictor using the Wald test (Alderman et al., 2006).

To examine if there was a dose-response relationship between the paraben levels and risk of GDM, we conducted a 3-knot, restricted cubic

spline analysis (Desquilbet and Mariotti, 2010). The Ln-transformed concentrations of parabens were regarded as a continuous variable, the referent value was set to the median, and 3 knots were set at the fifth, fiftieth, and ninety-fifth.

We further examined the associations between Ln-transformed, SG-adjusted concentrations of paraben levels and continuous plasma glucose (PG) concentrations (mmol/L) using multiple linear regressions. The glucose level had approximately normal distribution, thus we did not transform it.

Bivariate analyses were conducted between maternal age, pre-pregnancy BMI, maternal education, parity, passive smoking, and hypertensive disorders in pregnancy with GDM. The covariates included in the final multivariable models were those that were associated with GDM in bivariate analyses ($P \leq 0.1$) and previous studies. Maternal age (< 30, 30–35, ≥35), maternal education (more than high school, high school, and less than high school), parity (primiparous and multiparous), and pre-pregnancy BMI categorized based on the Chinese standard (Zhou and Cooperative Meta-Analysis Group of China Obesity Task, 2002) (< 18.5, 18.5–23.9, and ≥24.0 kg/m$^2$) were included in final models. Our previous study suggested that cadmium exposure is associated with the risk of GDM (Liu et al., 2018), thus we included SG-adjusted cadmium levels (< 0.74 and ≥0.74 μg/L) in the final models.

Maternal age and pre-pregnancy BMI were related to the risk of GDM in previous studies (Chu et al., 2007; Solomon et al., 1997). A priori study of age or BMI found differences in the relationships of paraben levels and the risk of GDM (Bellavia et al., 2018), but no significant effect modifications by age or BMI were found. We also evaluated the potential effect modifications of maternal age and pre-pregnancy BMI. The median age of the pregnant women at delivery (28 years old) was used as the cut-point for these stratified analyses. We also included an interaction term between parabens and maternal age or pre-pregnancy BMI in the models.

All of the statistical analyses were performed using SAS (version 9.4; SAS Institute Inc.). Two-sided $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. General characteristics

Among the 1087 participants, 103 (9.5%) were diagnosed with GDM. Overall, 51, 45, and 59 women were diagnosed with GDM based on their fasting glucose, 1 h-glucose, and 2 h-glucose, respectively. The means (SD) of the plasma glucose concentrations on fasting, 1 h, and 2 h were 4.36 ± 0.51, 5.99 ± 1.63, and 6.30 ± 1.33 mmol/L, respectively. The pregnant women with GDM were older (30.4 ± 4.3 vs. 28.4 ± 3.2 years), had greater pre-pregnancy BMI (22.6 ± 2.9 vs. 20.8 ± 2.8 kg/m$^2$), and had lower educational attainment compared with the non-GDM women (Table 1). No women reported alcohol consumption during pregnancy, and only one woman smoked during pregnancy in this study. The study population characteristics were similar to those of all of the participants recruited (Supplemental material Table S1).

### 3.2. Urinary paraben levels

The distributions of urinary paraben concentrations are shown in Table 2. The detection rates of parabens were approximately 95% for MeP, EtP, and PrP. The detection rates of BuP and BzP were 43.1% and 27.4%, respectively (Table 2). The Pearson correlation coefficients of Ln-parabens ranged from 0.001 to 0.727 (Table S2). The median EtP concentration of the pregnant women with GDM was higher than that of the women without GDM (0.66 μg/L vs. 0.43 μg/L, $P$ value = 0.01), but the difference was not significant after adjusting for SG. Urinary MeP and PrP levels were not significantly different between the women with and without GDM, whether SG-adjusted or not.

**Table 1**
Characteristics of the study population [n (%)].

| Characteristic | Total (N = 1087) | Non-GDM (N = 984) | GDM (N = 103) | $P$ value[a] |
|---|---|---|---|---|
| Age (years) | | | | < 0.01 |
| < 25 | 81 (7.45) | 78 (7.93) | 3 (2.91) | |
| 25–29 | 656 (60.35) | 604 (61.38) | 52 (50.49) | |
| 30–34 | 283 (26.04) | 253 (25.71) | 30 (29.13) | |
| ≥35 | 67 (6.16) | 49 (4.98) | 18 (17.47) | |
| Pre-BMI (kg/m$^2$) | | | | < 0.01 |
| < 18.5 | 198 (18.21) | 191 (19.41) | 7 (6.80) | |
| 18.5–23.9 | 735 (67.62) | 672 (68.29) | 63 (61.17) | |
| ≥24 | 154 (14.17) | 121 (12.30) | 33 (32.03) | |
| Parity | | | | 0.05 |
| 1 | 951 (87.49) | 868 (88.21) | 83 (80.58) | |
| ≥2 | 136 (12.51) | 116 (11.79) | 20 (19.42) | |
| Education | | | | < 0.01 |
| More than high school | 869 (79.95) | 803 (81.61) | 66 (64.08) | |
| High school | 161 (14.81) | 133 (13.52) | 28 (27.18) | |
| Less than high school | 57 (5.24) | 48 (4.87) | 9 (8.74) | |
| Passive smoking during pregnancy | | | | 0.52 |
| No | 734 (67.53) | 667 (67.78) | 67 (65.05) | |
| Yes | 353 (32.47) | 317 (32.22) | 36 (34.95) | |
| Hypertensive disorders in pregnancy | | | | 0.32 |
| No | 1053 (96.87) | 955 (97.05) | 98 (95.15) | |
| Yes | 34 (3.13) | 29 (2.95) | 5 (4.85) | |

Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; SG, specific gravity.
[a] $P$ value for the difference according to the chi-square test.

### 3.3. Paraben levels and GDM

The associations between urinary paraben concentrations in early pregnancy and the risk of GDM are displayed in Table 3. We evaluated the associations between the urinary paraben concentrations and the risk of GDM, except BuP and BzP, due to the low detection rates of these compounds. After adjusting for a range of potential confounders (maternal age, maternal education, parity, pre-pregnancy BMI, and cadmium levels), there was a significant increase in the risk of GDM across increasing quartiles of SG-adjusted EtP in the GEE models [adjusted RR (95% CI): first quartile = 1; second quartile = 1.12 (0.63, 2.01); third quartile = 1.11 (0.64, 1.93); and fourth quartile = 1.70 (1.02, 2.82); $P$ for trend = 0.015]. Compared with the first quartile, the RRs of GDM for the second, third, and fourth quartiles of the urinary MeP quartile were 0.53 (0.31, 0.89), 0.75 (0.46, 1.21), and 0.82 (0.52, 1.29), respectively. The $P$ trend was not significant for MeP-GDM ($P$ trend = 0.726). The associations of the Σparabens and PrP levels with the risk of GDM were not significant (Table 3). Moreover, no significant dose-response relationship was detected between parabens and GDM in the restricted cubic spline model (Fig. S2).

We found significant associations between the EtP concentrations and 2 h-PG [adjusted β (95% CI): first quartile = reference, fourth quartile = 0.24 (0.02, 0.45), $P$ trend = 0.060]. No significant associations were observed between Ln-EtP and FPG or 1 h-PG (Table S3). Associations of MeP and PrP with PG concentrations were not found at any time points.

### 3.4. Exploratory analysis

As an exploratory analysis, we evaluated the association between paraben concentrations and GDM stratified by maternal age as shown in Table 4. The risk of GDM increased with increasing quartiles of EtP [adjusted RR (95% CI) for the fourth quartile vs. the first quartile = 2.06 (1.08, 3.96); $P$ trend = 0.036] among the older women

**Table 2**
First trimester urinary parabens of the women according to GDM status (N = 1087).

| Contaminants (μg/L) | Detection rate (%) | Non-GDM (N = 984) | GDM (N = 103) | *P* value[a] |
|---|---|---|---|---|
| | | Median (IQR) | Median (IQR) | |
| MeP | 98.16 | 13.97 (3.79, 78.31) | 17.96 (3.57, 76.34) | 0.82 |
| EtP | 94.85 | 0.43 (0.19, 1.47) | 0.66 (0.30, 3.55) | 0.01 |
| PrP | 98.25 | 0.88 (0.18, 8.95) | 0.94 (0.25, 7.39) | 0.51 |
| BuP | 43.05 | < LOD (< LOD, 0.021) | < LOD (< LOD, 0.021) | 0.84 |
| BzP | 27.41 | < LOD (< LOD, 0.004) | < LOD (< LOD, 0.001) | 0.25 |
| Σparabens (nmol/L) | | 1047.68 (224.28, 6893.60) | 1451.62 (249.82, 7736.16) | 0.58 |
| SG-adjusted | | | | |
| MeP | – | 18.97 (4.44, 101.94) | 22.87 (3.78, 117.91) | 0.85 |
| EtP | – | 0.53 (0.24, 1.77) | 0.83 (0.27, 3.91) | 0.06 |
| PrP | – | 1.15 (0.23, 12.44) | 1.26 (0.28, 10.41) | 0.66 |
| BuP | – | 0.011 (0.005, 0.031) | 0.010 (0.005, 0.028) | 0.54 |
| BzP | – | 0.001 (0.001, 0.007) | 0.001 (0.001, 0.004) | 0.18 |
| Σparabens (nmol/L) | – | 1569.44 (273.88, 8470.48) | 2069.33 (281.90, 8378.45) | 0.78 |

Abbreviations: GDM, gestational diabetes mellitus; IQR, interquartile range; SG, specific gravity; MeP, methyl paraben; EtP, ethyl paraben; PrP, propyl paraben; Σparabens, the sum of parabens weighted by individual relative estrogenic potential; LOD, limit of detection.
[a] *P* values from Wilcoxon test.

**Table 3**
Associations of first trimester urinary SG-adjusted paraben levels with GDM.

| Paraben concentrations (μg/L) | GDM/total | Crude RR (95% CI)[a] | Adjusted RR (95% CI)[b] |
|---|---|---|---|
| MeP | | | |
| Per unit | 103/1087 | 0.98 (0.90, 1.08) | 0.97 (0.89, 1.07) |
| Q1 (< 4.35) | 32/271 | 1.00 | 1.00 |
| Q2 (4.35–19.25) | 18/273 | 0.56 (0.32, 0.97) | 0.53 (0.31, 0.89) |
| Q3 (19.25–102.41) | 25/271 | 0.78 (0.48, 1.28) | 0.75 (0.46, 1.21) |
| Q4 (≥102.41) | 28/272 | 0.87 (0.54, 1.41) | 0.82 (0.52, 1.29) |
| *P* trend[c] | | 0.634 | 0.726 |
| EtP | | | |
| Per unit | 103/1087 | 1.04 (0.96, 1.12) | 1.02 (0.95, 1.11) |
| Q1 (< 0.24) | 20/272 | 1.00 | 1.00 |
| Q2 (0.24–0.54) | 22/272 | 1.10 (0.61, 1.97) | 1.12 (0.63, 2.01) |
| Q3 (0.54–1.93) | 24/271 | 1.20 (0.68, 2.13) | 1.11 (0.64, 1.93) |
| Q4 (≥1.93) | 37/272 | 1.85 (1.10, 3.10) | 1.70 (1.02, 2.82) |
| *P* trend[c] | | 0.007 | 0.015 |
| PrP | | | |
| Per unit | 103/1087 | 1.01 (0.93, 1.09) | 0.99 (0.92, 1.07) |
| Q1 (< 0.23) | 21/271 | 1.00 | 1.00 |
| Q2 (0.23–1.18) | 28/272 | 1.33 (0.77, 2.28) | 1.19 (0.69, 2.05) |
| Q3 (1.18–12.09) | 31/272 | 1.47 (0.87, 2.49) | 1.33 (0.79, 2.25) |
| Q4 (≥12.09) | 23/272 | 1.09 (0.62, 1.92) | 0.97 (0.55, 1.68) |
| *P* trend[c] | | 0.594 | 0.405 |
| Σparabens | | | |
| Per unit | 103/1087 | 1.01 (0.93, 1.10) | 1.00 (0.92, 1.09) |
| Q1 (< 274.95) | 25/272 | 1.00 | 1.00 |
| Q2 (274.95–1637.00) | 24/272 | 0.81 (0.47, 1.40) | 0.88 (0.52, 1.50) |
| Q3 (1637.00–8414.95) | 30/271 | 1.08 (0.65, 1.79) | 1.14 (0.69, 1.87) |
| Q4 (≥8414.95) | 24/272 | 1.08 (0.65, 1.79) | 0.87 (0.52, 1.45) |
| *P* trend[c] | | 0.796 | 0.608 |

Abbreviations: GDM, gestational diabetes mellitus; SG, specific gravity; RR, risk ratio; CI, confidence interval; MeP, methyl paraben; EtP, ethyl paraben; PrP, propyl paraben; Σparabens, the sum of parabens weighted by individual relative estrogenic potential.
[a] Unadjusted risk ratio.
[b] Adjusted for maternal age, education, maternal pre-pregnancy BMI, parity, and cadmium levels.
[c] *P* values for trend were derived using a continuous variable with the median value of each quartile.

(≥28 years old) (Table 4). No significant interactions between parabens and age were found in the parabens-GDM association. Additionally, no significant associations were found in the glucose levels and Ln-EtP levels in the younger and older women (Table S4).

Table 5 shows the associations of parabens with GDM stratified by pre-pregnancy BMI. Among the women with high pre-pregnancy BMI (≥24.0 kg/m$^2$), the adjusted RRs increased with the increasing EtP quartile, and the adjusted RR (95% CI) for the fourth quartile vs. the first quartile was 2.83 (1.05, 7.63), *P* trend = 0.004 (Table 5). Among the normal pre-pregnancy BMI women, the RRs were not significant [fourth quartile vs. first quartile adjusted RR = 1.38 (0.74, 2.56), *P* trend = 0.260]. We did not observe significant interactions between parabens and pre-pregnancy BMI in the parabens-GDM association. Meanwhile, significant associations between the Ln-EtP concentration and FPG, 1 h-PG, and 2 h-PG were found (Table S5) [adjusted β (95% CI): first quartile = reference, FPG fourth quartile = 0.41 (0.05, 0.78), *P* trend = 0.018, 1 h-PG fourth quartile = 0.94 (0.07, 1.82), *P* trend = 0.121, 2 h-PG fourth quartile = 0.93 (0.15, 1.72), *P* trend = 0.033].

**Table 4**
Associations of first trimester urinary SG-adjusted paraben levels with GDM stratified by age.

| Paraben concentrations (μg/L) | Age < 28 (N = 462) | | | Age ≥ 28 (N = 625) | | | *P* for interaction[c] |
|---|---|---|---|---|---|---|---|
| | GDM/total | Crude RR (95% CI)[a] | Adjusted RR (95% CI)[b] | GDM/total | Crude RR (95% CI)[a] | Adjusted RR (95% CI)[b] | |
| MeP | | | | | | | 0.308 |
| Per unit | | 0.86 (0.74, 1.01) | 0.85 (0.72, 1.00) | | 1.04 (0.94, 1.16) | 1.04 (0.94, 1.16) | |
| Q1 (< 4.33) | 13/116 | 1.00 | 1.00 | 19/155 | 1.00 | 1.00 | |
| Q2 (4.33–18.57) | 2/115 | 0.16 (0.04, 0.67) | 0.16 (0.04, 0.71) | 16/157 | 0.83 (0.44, 1.55) | 0.78 (0.42, 1.44) | |
| Q3 (18.57–101.90) | 5/114 | 0.39 (0.14, 1.06) | 0.39 (0.15, 1.02) | 20/158 | 1.04 (0.58, 1.87) | 1.03 (0.58, 1.83) | |
| Q4 (≥101.90) | 6/117 | 0.46 (0.18, 1.16) | 0.47 (0.19, 1.17) | 22/155 | 1.16 (0.65, 2.05) | 1.11 (0.63, 1.96) | |
| *P* trend[d] | | 0.638 | 0.645 | | 0.371 | 0.394 | |
| EtP | | | | | | | 0.813 |
| Per unit | | 0.93 (0.76, 1.14) | 0.91 (0.72, 1.14) | | 1.06 (0.98, 1.14) | 1.06 (0.98, 1.14) | |
| Q1 (< 0.24) | 9/134 | 1.00 | 1.00 | 11/139 | 1.00 | 1.00 | |
| Q2 (0.24–0.54) | 7/123 | 0.83 (0.32, 2.17) | 0.92 (0.36, 2.37) | 15/148 | 1.28 (0.61, 2.69) | 1.32 (0.62, 2.80) | |
| Q3 (0.54–1.89) | 3/119 | 0.37 (0.10, 1.34) | 0.35 (0.09, 1.31) | 21/153 | 1.75 (0.87, 3.49) | 1.66 (0.83, 3.32) | |
| Q4 (≥1.89) | 7/86 | 1.20 (0.47, 3.11) | 1.22 (0.49, 3.01) | 30/186 | 2.04 (1.06, 3.92) | 2.06 (1.08, 3.96) | |
| *P* trend[d] | | 0.313 | 0.293 | | 0.048 | 0.036 | |
| PrP | | | | | | | 0.230 |
| Per unit | | 0.89 (0.75, 1.05) | 0.90 (0.77, 1.06) | | 1.05 (0.97, 1.14) | 1.04 (0.95, 1.13) | |
| Q1 (< 0.23) | 8/121 | 1.00 | 1.00 | 12/149 | 1.00 | 1.00 | |
| Q2 (0.23–1.14) | 7/107 | 0.77 (0.28, 2.09) | 0.90 (0.31, 2.61) | 22/166 | 1.65 (0.84, 3.21) | 1.40 (0.71, 2.78) | |
| Q3 (1.14–11.78) | 9/117 | 1.04 (0.43, 2.54) | 1.22 (0.51, 2.93) | 22/155 | 1.76 (0.91, 3.43) | 1.53 (0.79, 2.97) | |
| Q4 (≥11.78) | 2/117 | 0.23 (0.05, 1.05) | 0.26 (0.06, 1.15) | 21/155 | 1.68 (0.86, 3.30) | 1.45 (0.73, 2.86) | |
| *P* trend[d] | | 0.046 | 0.048 | | 0.500 | 0.659 | |
| Σparabens (nmol/L) | | | | | | | 0.397 |
| Per unit | | 0.90 (0.74, 1.09) | 0.92 (0.76, 1.10) | | 1.05 (0.95, 1.15) | 1.04 (0.94, 1.14) | |
| Q1 (< 274.95) | 8/122 | 1.00 | 1.00 | 17/150 | 1.00 | 1.00 | |
| Q2 (274.95–1637.00) | 5/114 | 0.67 (0.23, 1.98) | 0.75 (0.27, 2.12) | 19/158 | 1.06 (0.57, 1.96) | 0.93 (0.50, 1.73) | |
| Q3 (1637.00–8414.95) | 11/108 | 1.55 (0.65, 3.72) | 1.55 (0.67, 3.57) | 19/163 | 1.03 (0.56, 1.90) | 1.02 (0.56, 1.88) | |
| Q4 (≥8414.95) | 2/118 | 0.26 (0.06, 1.19) | 0.29 (0.07, 1.25) | 22/154 | 1.26 (0.70, 2.28) | 1.12 (0.62, 2.03) | |
| *P* trend[d] | | 0.271 | 0.049 | | 0.484 | 0.530 | |

Abbreviations: GDM, gestational diabetes mellitus; SG, specific gravity; RR, risk ratio; CI, confidence interval; MeP, methyl paraben; EtP, ethyl paraben; PrP, propyl paraben; Σparabens, the sum of parabens weighted by individual relative estrogenic potential.

[a] Unadjusted risk ratio.

[b] Adjusted for maternal age, education, maternal pre-pregnancy BMI, parity, and cadmium levels.

[c] *P* values for the interaction term between maternal urinary parabens and age.

[d] *P* values for trend were derived using a continuous variable with the median value of each quartile.

## 4. Discussion

To the best of our knowledge, this is the first study to assess early pregnancy parabens exposure in relation to GDM. Several parabens exposures were highly prevalent among the pregnant women. Positive associations were found between EtP exposure and the risk of GDM. The associations of higher urinary EtP with increased GDM risk were stronger among the women who were older or overweight/obese before pregnancy.

Approximately 95% of the women in this study had detectable urinary concentrations of MeP, EtP, and PrP. Urinary paraben concentrations were lower than those reported in pregnant women in the US (Smith et al., 2012), Denmark (de Renzy-Martin et al., 2014), Puerto Rico (Meeker et al., 2013), Greece (Myridakis et al., 2015), and Japan (Shirai et al., 2013) (Table 6). The paraben levels of the pregnant women in this study were also lower than those recorded in the National Report on Human Exposure to Environmental Chemicals (NHANES) during 2013–2014 (NHANES, 2018) (Table 6). The lower urinary paraben levels in the present study may be due to the differences in the sample collection periods, analyses methods, lifestyles (Lin et al., 2015), and PCP use patterns (Guo et al., 2014).

To the best of our knowledge, one epidemiological study from Boston revealed the association of paraben levels with glucose levels among pregnant women by detecting the urinary MeP, PrP, and BuP levels of 241 women in the first and second trimesters. They found that BuP levels in first or second trimesters were associated with higher GLT glucose levels (first trimester: adjusted β = 12.5 mg/dL; 95% CI: 0.9, 24.2; second trimester: adjusted β = 11.2 mg/dL; 95% CI: 0.2, 22.3) and first trimester PrP concentrations were associated with lower glucose (adjusted β = −22.3 mg/dL; 95% CI: −43.2, −1.4) (Bellavia et al., 2018). We found that just EtP exposure increased the risk of GDM, and the RR in the fourth quartile vs. the first quartile was 1.70 (95% CI: 1.02, 2.82). We did not find that increasing PrP concentrations were associated with lower glucose levels or a lower risk of GDM. These inconsistent results may be due to the exposure levels, populations, and diagnosis criteria. Boston pregnant women had higher exposure to parabens than our participants (median: MeP: 113 vs. 14.38, PrP: 20 vs. 0.89, and BuP: 0.5 vs. < LOD). Additionally, the previous study chose women who had completed at least one in vitro fertilization cycle and thus the results may not be generalizable to women with natural conception. Finally, the previous study used 50 g GLT, which cannot be used for the diagnosis of GDM, while we chose the 75 g OGTT test, which can be used to diagnose GDM. This enabled us to accurately evaluate the associations of paraben levels with GDM. In our study, we further examined the associations of paraben levels with continuous PG concentrations. Among the three glucose measures (FPG, 1 h-PG, and 2 h-PG), only 2 h-PG had a significant association with EtP levels, which was similar to the association of EtP with GDM. Higher 2 h-PG may be associated with impaired insulin action (Retnakaran et al., 2008).

Another case-control study addressed the associations between parabens exposure and risk of type 2 diabetes (Li et al., 2018). They found that high urinary concentrations of MeP, EtP, and PrP were associated with type 2 diabetes [MeP: 9.21 (95% CI: 1.60, 53.2); EtP: 104 (95% CI: 10.6, 10e3); PrP: 9.48 (95% CI: 1.37, 65.5)]. However, we did not find a significant association of MeP and PrP exposure with increased risk of GDM. The different results may be attributed to varying study designs or different types of diseases.

Potential mechanisms for associations between parabens exposure

**Table 5**
Associations of first trimester urinary SG-adjusted paraben levels with GDM stratified by pre-pregnancy BMI.

| Paraben concentrations (μg/L) | BMI < 24.0 (N = 933) | | | BMI ≥ 24.0 (N = 154) | | | *P* for interaction[c] |
|---|---|---|---|---|---|---|---|
| | GDM/total | Crude RR (95% CI)[a] | Adjusted RR (95% CI)[b] | GDM/total | Crude RR (95% CI)[a] | Adjusted RR (95% CI)[b] | |
| MeP | | | | | | | 0.588 |
| Per unit | | 0.98 (0.87, 1.10) | 0.97 (0.87, 1.09) | | 1.00 (0.87, 1.14) | 0.98 (0.86, 1.12) | |
| Q1 (< 4.33) | 21/232 | 1.00 | 1.00 | 11/39 | 1.00 | 1.00 | |
| Q2 (4.33–18.57) | 13/237 | 0.61 (0.31, 1.18) | 0.60 (0.31, 1.14) | 5/36 | 0.49 (0.19, 1.28) | 0.45 (0.18, 1.12) | |
| Q3 (18.57–101.90) | 15/227 | 0.73 (0.39, 1.38) | 0.73 (0.39, 1.37) | 10/44 | 0.81 (0.38, 1.69) | 0.79 (0.37, 1.69) | |
| Q4 (≥101.90) | 21/237 | 0.98 (0.55, 1.74) | 0.93 (0.53, 1.64) | 7/35 | 0.71 (0.31, 1.63) | 0.63 (0.29, 1.39) | |
| *P* trend[d] | | 0.424 | 0.500 | | 0.824 | 0.655 | |
| EtP | | | | | | | 0.163 |
| Per unit | | 0.98 (0.89, 1.09) | 0.98 (0.89, 1.08) | | 1.16 (1.04, 1.30) | 1.15 (1.02, 1.29) | |
| Q1 (< 0.24) | 16/237 | 1.00 | 1.00 | 4/35 | 1.00 | 1.00 | |
| Q2 (0.24–0.54) | 17/233 | 1.08 (0.56, 2.09) | 1.11 (0.58, 2.12) | 5/39 | 1.12 (0.33, 3.85) | 1.09 (0.30, 3.92) | |
| Q3 (0.54–1.89) | 16/234 | 1.01 (0.52, 1.98) | 1.02 (0.53, 1.97) | 8/37 | 1.89 (0.62, 5.73) | 1.50 (0.50, 4.51) | |
| Q4 (≥1.89) | 21/229 | 1.36 (0.73, 2.54) | 1.38 (0.74, 2.56) | 16/43 | 3.26 (1.20, 8.86) | 2.83 (1.05, 7.63) | |
| *P* trend[d] | | 0.271 | 0.260 | | 0.002 | 0.004 | |
| PrP | | | | | | | 0.966 |
| Per unit | | 1.00 (0.91, 1.09) | 0.99 (0.91, 1.09) | | 1.03 (0.89, 1.18) | 1.00 (0.86, 1.15) | |
| Q1 (< 0.23) | 15/236 | 1.00 | 1.00 | 6/36 | 1.00 | 1.00 | |
| Q2 (0.23–1.14) | 20/236 | 1.33 (0.70, 2.54) | 1.26 (0.66, 2.42) | 8/36 | 1.30 (0.50, 3.35) | 1.08 (0.39, 3.01) | |
| Q3 (1.14–11.78) | 20/228 | 1.38 (0.72, 2.63) | 1.40 (0.74, 2.64) | 11/44 | 1.46 (0.60, 3.55) | 1.25 (0.49, 3.22) | |
| Q4 (≥11.78) | 15/233 | 1.01 (0.51, 2.02) | 0.96 (0.49, 1.91) | 8/39 | 1.20 (0.46, 3.11) | 0.94 (0.35, 2.56) | |
| *P* trend[d] | | 0.527 | 0.437 | | 0.937 | 0.644 | |
| Σparabens | | | | | | | 0.769 |
| Per unit | | 1.01 (0.91, 1.12) | 1.00 (0.90, 1.10) | | 1.02 (0.87, 1.20) | 1.00 (0.85, 1.16) | |
| Q1 (< 274.95) | 17/236 | 1.00 | 1.00 | 8/36 | 1.00 | 1.00 | |
| Q2 (274.95–1637.00) | 18/233 | 1.07 (0.57, 2.03) | 1.08 (0.57, 2.04) | 6/39 | 0.69 (0.27, 1.80) | 0.64 (0.24, 1.70) | |
| Q3 (1637.00–8414.95) | 20/233 | 1.19 (0.64, 2.22) | 1.24 (0.67, 2.30) | 10/38 | 1.18 (0.53, 2.66) | 1.05 (0.47, 2.37) | |
| Q4 (≥8414.95) | 15/231 | 0.90 (0.46, 1.76) | 0.85 (0.45, 1.62) | 9/41 | 0.99 (0.43, 2.29) | 0.90 (0.39, 2.05) | |
| *P* trend[d] | | 0.869 | 0.390 | | 0.728 | 0.900 | |

Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; SG, specific gravity; RR, risk ratio; CI, confidence interval; MeP, methyl paraben; EtP, ethyl paraben; PrP, propyl paraben; Σparabens, the sum of parabens weighted by individual relative estrogenic potential.

[a] Unadjusted risk ratio.

[b] Adjusted for maternal age, education, maternal pre-pregnancy BMI, parity, and cadmium levels.

[c] *P* values for the interaction term between maternal urinary paraben and pre-pregnancy BMI.

[d] *P* values for trend were derived using a continuous variable with the median value of each quartile.

and GDM are not clear. Previous studies showed that islets have relatively low concentrations of anti-oxidative hydroxide and oxygen free radicals (Mahadevan et al., 2013), which means beta cells were sensitive to oxidative stress (Bast et al., 2002). Furthermore, an in vitro study indicated that beta-cell destruction may appear as higher MDA levels in islets (Rabinovitch et al., 1996). Meanwhile, several epidemiological studies suggested that increased MDA levels may contribute to disease processes in GDM (Chaudhari et al., 2003; Karacay et al., 2010) (Aydemir et al., 2016). An epidemiological study detected pregnant women's urinary MeP, EtP, and PrP levels and found positive associations between EtP levels and maternal urinary malondialdehyde (MDA) (Kang et al., 2013). This result suggested that EtP may cause oxidative stress, but MeP or PrP does not. We speculate that EtP exposure during pregnancy may cause islet beta-cell dysfunction by inducing oxygen free radicals, then resulting in GDM. The exact mechanisms need to be further investigated.

Bellavia et al. suggested that there was no significant effect modification on the parabens-GDM association by age and pre-pregnancy BMI (Bellavia et al., 2018). We found that the associations of higher urinary EtP with increased GDM risk were stronger among the women who were older or overweight/obese before pregnancy. One possible mechanism is that the baseline risk of GDM is higher in obese/older women compared to normal weight/younger women. Also, these stronger associations might be due to a potential confounder (for example, diet, which is a source of parabens). Future studies are needed to clarify the underlying mechanisms.

The large sample size (1087) of the present prospective study helped us find the associations between parabens exposures and GDM with more precision. The prospective study also strengthens the interpretation of our results by reducing the risk of reverse causation. The interviews and medical records provided extensive data on potential confounders, which could adjust the confounder interference. Our study

**Table 6**
Comparison of medians of uncorrected urinary parabens from the present report and previous studies (μg/L).

| Reference | Location | Sampling years | n | Population | MeP | EtP | PrP |
|---|---|---|---|---|---|---|---|
| Present study | Wuhan, China | 2013–2015 | 1087 | Pregnant women | 14.38 | 0.44 | 0.89 |
| National Report on Human Exposure to Environmental Chemicals 2018 | USA | 2013–2014 | 1401 | Female | 73.9 | 1.6 | 13.5 |
| de Renzy-Martin et al., 2014 | Denmark | 2010–2012 | 200 | Pregnant women | 20.70 | 1.01 | 4.17 |
| Meeker et al., 2013 | Puerto Rico | 2010–2012 | 105 | Pregnant women | 381 | – | 130 |
| Shirai et al., 2013 | Japan | 2007–2010 | 111 | Pregnant women | 75.8 | 7.53 | 20.2 |
| Myridakis et al., 2015 | Greece | 2007–2008 | 239 | Pregnant women | 98.3 | 2.6 | < LOD |
| Smith et al., 2012 | Boston, MA, USA | 2004–2010 | 129 | Pregnant women | 135 | – | 22.8 |

Abbreviations: MeP, methyl paraben; EtP, ethyl paraben; PrP, propyl paraben; LOD, limits of detection.

has some limitations. First, the interviews were conducted at delivery, which was after the diagnosis of GDM. This may lead to recall bias in the confounders. Second, although we excluded pregnant women with a family history of diabetes and type 2 diabetes, the information on the family history of diabetes was self-reported, which may not be totally accurate (Hariri et al., 2006). We did not obtain information on polycystic ovary syndrome, impaired glucose tolerance, history of GDM, and weight gain during the second trimester, which are classic GDM risk factors. Information on food consumption was not collected, which may be related to GDM risk or paraben levels. Third, the paraben concentrations measured at one spot time may not accurately reflect paraben exposure because the biological half-life of parabens is short (within 24 h) (Soni et al., 2005) and the intraclass correlation coefficients representing the degree of within-person variability for parabens were not high according to previous studies (MeP: 0.35–0.78, EtP: 0.34–0.48, PrP: 0.32–0.63, and BuP: 0.29–0.56) among pregnant women from different countries (Guidry et al., 2015; Meeker et al., 2013; Philippat et al., 2013; Vernet et al., 2018). Further studies with repeated paraben measurements are needed. Additionally, the lack of determination of conjugated and free parabens hindered a more effective estimation of the active species in the participants.

## 5. Conclusion

This report's findings suggest that EtP exposure in early pregnancy may be a potential risk factor for GDM. However, additional studies are needed to confirm these findings in other study populations.

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## Conflicts of interest statement

The authors have no conflicts of interest to declare.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.02.040.

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