Journal of Exposure Science & Environmental Epidemiology (2020) 30:845–855
https://doi.org/10.1038/s41370-020-0205-7

ARTICLE

Association between urinary paraben concentrations and gestational weight gain during pregnancy

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Received: 27 June 2019 / Revised: 22 November 2019 / Accepted: 17 December 2019 / Published online: 10 February 2020

Abstract

Parabens, a group of endocrine-disrupting chemicals, have been associated with obesity in previous studies. However, there is a paucity of literature regarding the effects of paraben exposures on gestational weight gain (GWG), a considerable predictor of obesity risk in both mothers and offspring later in life. The aim of the present study was to evaluate the associations between urinary paraben concentrations and GWG during the three trimesters of pregnancy. We collected urine samples from 613 pregnant women during the first, second, and third trimesters of their pregnancies between 2014 and 2015 in Wuhan, China. The urine concentrations of five parabens, including methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP), butylparaben, and benzylparaben, were measured. Gestational weight in each trimester and prepregnancy weight were used to calculate trimester GWG. Linear mixed models were used to evaluate the trimester-specific and overall associations between paraben exposures and GWG rate (trimester GWG divided by the gestational week of the weight measurement, kg/week). We performed stratified analysis to further explore the potential effect modification by prepregnancy BMI. In the trimester-specific association analyses, the first-trimester concentrations MeP, EtP, PrP, and ∑parabens (sum of all five parabens's molar concentrations) were associated with an increased first-trimester GWG rate, and these associations were stronger than those of the second or third trimesters. The overall association analysis showed that increased trimester GWG rates were associated with the combined effects of exposure to MeP, PrP, or ∑parabens during all three trimesters. Stratified analysis showed that higher paraben exposures were associated with higher trimester GWG rates among overweight/obese women that among normal-weight or underweight women. Our results showed that paraben exposures were positively associated with trimester GWG rate during pregnancy, especially during the first trimester. Replicated research in populations exposed to higher paraben levels is needed in the future.

Keywords Paraben · Gestational weight gain · Exposure during pregnancy · Prepregnancy BMI

Introduction

Parabens are a group of synthetic organic chemicals that are commonly applied in industrial manufacturing [1]. Parabens extensively serve as preservatives in personal care products (including cosmetics, sunscreens, and hair care products), food, and pharmaceutical products, which are the main sources of human exposure [2]. Parabens were generally

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Supplementary information The online version of this article (https://doi.org/10.1038/s41370-020-0205-7) contains supplementary material, which is available to authorized users.

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regarded as "safe", with a low degree of systemic toxicity, and were approved for use in food by the US Food and Drug Administration [3] and European Union regulations [4] because of their broad-spectrum antibacterial activity and low production cost. However, accumulative evidence has demonstrated that these compounds have endocrine-disrupting effects [5, 6].

Exposure to parabens is associated with an elevated risk of some diseases related to the endocrine system, including gestational diabetes [7], infertility [8], and breast cancer [9]. In vitro studies have shown that parabens may promote adipocyte differentiation and increase adiposity by activating glucocorticoid receptors or peroxisome proliferator-activated receptor gamma (PPARγ) [10–13]. Parabens are also classified as "obesogens", which may potentially predispose individuals to weight gain despite efforts to decrease energy intake and increase activities [14]. Pregnancy is a unique period that is characterized by rapid weight gain in female adults, and gestational weight gain (GWG) is a considerable predictor of obesity risk and adverse health outcomes for both the mother and her offspring later in life. Elevated GWG, even that not exceeding medical recommendations, can pose an increased risk for postpartum weight retention [15], high blood pressure during pregnancy [16] or the postpartum period [17], obesity in the offspring over the short and long term [18, 19], and adverse cardio-metabolic outcomes for adolescent offspring [20]. Due to the physiological changes that occur during pregnancy, pregnant women are susceptible to the potentially adverse impacts of environmental pollutants [21]. However, the impacts of prenatal paraben exposures on GWG have not yet been studied.

Previous studies examining the effects of environmental pollutants on GWG were primarily focused on total GWG as an outcome [22–25]; however, GWG during different trimesters may produce different susceptibilities to environmental exposures. Ambient fine particulate exposure was reported to exert a stronger effect on first-trimester GWG than on second- and third-trimester GWG [26]. To explore the effects of paraben exposures on GWG in different trimesters and to better elucidate the window of sensitivity, we conducted a trimester-specific analysis instead of focusing only on total GWG. Since the reproducibility of urinary paraben concentrations among trimesters is low [intraclass correlation coefficients (ICCs) range from 0.36 to 0.48] [27], paraben exposures and trimester GWG should be measured repeatedly during pregnancy to avoid exposure misclassification.

Our study aimed to explore the associations between prenatal paraben exposures and trimester GWG in a cohort of pregnant Chinese women. We longitudinally followed participants in their first (1st) trimester, second (2nd) trimester, and third (3rd) trimester and evaluated the associations between urinary concentrations of parabens and GWG during each trimester. Given the possible impact of prepregnancy weight on GWG [15, 28, 29], we further examined the associations stratified by prepregnancy BMI (PP-BMI).

Materials and methods

Study participants

We recruited pregnant women when they attended their first antenatal care visits at Wuhan women and children's health care center in Hubei province, China, between 2014 and 2015. Pregnant women were invited to take part in the study if they met the following criteria: (1) less than 16 weeks of pregnancy; (2) singleton pregnancy; (3) Wuhan resident; (4) intention to have antenatal care and deliver at this study hospital; and (5) able to provide biospecimens repeatedly during pregnancy. We initially recruited 856 pregnant women. For this study, we included the participants who provided urine samples in all three trimesters (mean ± SD and range: 1st, 12.9 ± 1.0 weeks, 1–13 weeks; 2nd, 23.8 ± 3.3 weeks, 14–27 weeks; 3rd, 36.2 ± 3.2 weeks, 28–40 weeks) and had gestational weight records for two or more trimesters. A total of 613 pregnant women were thus included in the present study. All women were informed for the details of this study and signed informed consent forms to take part in the present study. This research has been approved by the ethics committees of the Wuhan women and children's health care center and Tongji Medical College.

Outcomes and covariates

Because not all participants were weighed on the exact same gestational day, we calculated trimester GWG and the trimester GWG rate as the major outcome of this study. Trimester GWG was computed as the difference between the body weight of the pregnant woman recorded at the 1st, 2nd, or 3rd trimester and her prepregnancy body weight. The body weights of the women were measured at the times of urine collection (1st: 11–13 weeks; 2nd: 25–27 weeks; 3rd: 36–38 weeks). All of the participants ($n = 613$) had 1st-trimester GWG, 71.1% ($n = 436$) had 2nd-trimester GWG, and 54.8% ($n = 336$) had 3rd-trimester GWG. The participants without GWG in the 2nd or 3rd trimester were excluded when we evaluated the associations between trimester paraben exposures and 2nd- or 3rd-trimester GWG. The trimester GWG rate (kg/week) was calculated as the raw trimester GWG value divided by the gestational week of the weight measurement [22]. We calculated total GWG (the sum of three

trimester GWGs) as the secondary outcome for the sensitivity analysis.

Questionnaire information regarding maternal sociodemographic factors (marital status, education level, nutritional status, etc.) and lifestyle factors (physical activity, alcohol consumption, active smoking, sleep quality, etc.) was collected in a face-to-face interview by specifically trained medical personnel in the study hospital. Information on history of parity, maternal height, age, last menstrual period, delivery date, and disease history of pregnancy-induced hypertension syndrome (PIH) and gestational diabetes was obtained from the medical records of the participants. Gestational age (weeks) was estimated according to the 1st-trimester ultrasonographic examination. The PP-BMI (kg/m^2) was the ratio of the self-reported weight (kg) of the woman before pregnancy to her height squared (m^2). The body weights of the pregnant women were scaled by a standard digital scale at the study hospital, and the pregnant women were requested to take off their shoes and coats prior to the measurements.

Measurement of urinary paraben concentrations

Urine samples were collected at each trimester when the participants came for antenatal care at the study hospital, and samples were divided into aliquots and stored in 5-mL polypropylene cryovials at −20 °C. An Ultimate 3000 ultra-high-performance liquid chromatography system (Dionex, Sunnyvale, CA, USA) connected to a Thermo Scientific™ TSQ Quantiva™ Triple Quadrupole mass spectrometer (Thermo Scientific, San Jose, CA) (UPLC-MS/MS) was used to measure the concentrations of methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP), butylparaben (BuP), and benzylparaben (BzP). The urine sample preparation procedure and UPLC-MS/MS parameters have been reported in a previous study [30]. Briefly, 1 mL of the thawed urine sample was mixed with ammonium acetate (pH = 5.0) and β-glucuronidase and then incubated overnight in a 37 °C water bath. After the enzymatic hydrolysis, the mixture was extracted three times with 3 mL of solvent (methyl tert-butyl ether/ethyl acetate [5/1, v/v]) each time. The supernatants were evaporated under a flow of nitrogen gas, reconstituted in 200 μL of acetonitrile/water (6/4, v/v) and centrifuged at 13,000 rpm for 10 min at 4 °C. Their separation took place in a binary gradient mobile phase with water and acetonitrile and was achieved on a Thermo Scientific Betasil C18 column (2.1 × 100 mm, 3 μm). The detection was conducted in heated-electrospray ionization negative ion mode and multiple reaction monitoring mode. In each batch of samples, we incorporated the procedural blanks to correct contamination during preparation, the quality control samples to correct the instrumental drift, and the pure blank solution to monitor instrument background. The limits of detection (LOD) for MeP, PrP, and BuP were 0.05 ng/mL, and those for EtP and BzP were 0.01 ng/mL. The levels for concentrations of all parabens below the LODs were considered LOD/$\sqrt{2}$ [31].

In addition, we computed the sum of paraben concentration (∑parabens, μmol/L) as the sum of molar concentrations of all five parabens together (∑parabens = MeP/152.149 + EtP/166.174 + PrP/180.203 + BuP/194.227 + BzP/228.247).

Urinary paraben concentrations were corrected by urinary specific gravity (SG) to control for variations associated with urine dilution. SG was immediately measured using a refractometer (Atago PAL-10S, Atago, Tokyo, Japan) after the urine samples were thawed. SG-adjusted concentrations of urinary parabens were calculated with the formula $P_S = P_i \times [(SG_T\text{-}1)\ /SG_i\text{-}1]$, where P_i is the measured urinary paraben concentration (μg/L) of an individual sample; SG_i is the measured SG of the individual urinary sample; and SG_T is the median urinary SG for the 1st, 2nd, and 3rd trimester, namely, 1.013, 1.011, and 1.011, respectively.

Statistical analysis

We summarized the characteristics of the excluded and included participants and compared them using Student's *t* tests for continuous variables and chi-square tests for categorical variables. The distributions of all five paraben metabolites, as well as ∑parabens, were skewed to the right, and thus, we used log2-transformation of the concentrations to approach normal distributions. Geometric means and medians at each trimester and over the entire pregnancy, including unadjusted and SG-adjusted concentrations, were computed to describe the exposure distribution of parabens. We also computed ICCs by a random intercept linear mixed model to assess the variability in urinary paraben concentrations across the three trimesters.

Because the purpose of this study was to assess the associations between multiple exposures and multiple outcomes, we used linear mixed models with a random intercept, wherein the within-individual effects could be controlled at the same time, to analyse the associations. We put the paraben concentrations of the three trimesters and GWG rates of the three trimesters into one model and added a product term of additive effect (paraben concentration × trimester) so that we could estimate the effect of trimester-specific paraben exposure on the corresponding trimester GWG rate. Then, we estimated the overall associations between trimester paraben exposures and GWG rates using linear mixed models to estimate the combined exposure effects of the three trimesters. When we examined the overall associations, we also put the three trimester paraben concentrations and three trimester GWG rates into one model while keeping only the main effects (paraben

concentrations) in the models and removing the product term (paraben concentration × trimester).

The stratified analysis was conducted to explore the associations between urinary paraben concentrations and trimester GWG rate categorized by PP-BMI (underweight <18.5 kg/m^2, normal 18.5−22.9 kg/m^2, overweight ≥23 kg/m^2) according to the cutoff points for Asians [32–35]. The trimester-specific and overall associations in the stratified analysis were analysed by means of the abovementioned statistical methods. In addition, we also calculated p values for the interaction (paraben × PP-BMI) in the linear mixed models for the stratified analysis to test whether the effects of parabens on GWG rate were influenced by PP-BMI.

Furthermore, to examine the potential relationships between trimester paraben exposures and the subsequent trimester GWG, we also analysed the associations between the 1st-trimester paraben exposures and the 2nd- or 3rd-trimester GWG and between the 2nd-trimester paraben exposures and the 3rd-trimester GWG using a generalized estimating equation, respectively.

Considering the possible associations between GWG and PIH and gestational diabetes [36, 37], we also performed a sensitivity analysis that excluded the participants with PIH and/or gestational diabetes using linear mixed models. Thus, in the sensitivity analysis, we ultimately included 559 participants in the 1st trimester, 402 in the 2nd trimester, and 309 in the 3rd trimester.

To guarantee the robustness of the results, we performed the following sensitivity analyses by replacing exposure or outcomes calculated by other methods. (1) We used multiple imputation based on the Markov Chain Monte Carlo method to impute the exposure values below LOD [38, 39]. Then, we evaluated the trimester-specific and overall associations between paraben exposures and trimester GWG rates by using the data after imputation with linear mixed models. (2) We calculated the average paraben exposures through three trimesters (geometric means), and the generalized estimating equation was used to analyse the relationships between the average paraben exposures and the total GWG. A total of 336 pregnant women who had complete sets of GWG measurements for the three trimesters were analysed.

The covariates included in the final models were considered based on their biological and statistical associations with exposures or outcomes. If a covariate was statistically associated with paraben exposures and/or GWG by bivariate analysis ($p < 0.1$) or related to GWG biologically [40–44], it was considered a potential confounder; these covariates included maternal age (<25, 25−29, 30−34, ≥35), gestational age (weeks), PP-BMI (<18.5, 18.5−22.9, ≥23; except in models stratified by PP-BMI), parity (primiparous and multiparous), nutritional status (good, normal, poor), sleep quality (good, normal, poor), passive smoking (yes or no), physical activities (never, 1–4 days/weeks, ≥5 days/weeks), educational levels (no more than 9 years, 10–12 years, more than 12 years), PIH (yes or no), and gestational diabetes (yes or no). Considering the effect of measurement time on gestational weight, we also added the gestational week of the weight measurement (continuous variable) into the model as a covariate to control for its potential effect. Since the data showed that just one participant was an active smoker and that no participant consumed alcohol during pregnancy in our study, we did not include tobacco or alcohol consumption as covariates in the adjusted models.

All statistical analyses were two-sided and regarded as significant at p values < 0.05. Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform these analyses.

Results

The characteristics of the study population (those of the included, $n = 613$; and excluded pregnant women, n = 243), are presented in Table 1. Most of these characteristics, except parity and education, were not statistically different between the two groups. The average maternal age of the study population was 28.6 (range, 21−41) years, and 13 women were at a gestational age of less than 37 weeks. Sixty-one percent of the participants had a normal PP-BMI (18.5−22.9 kg/m^2). The average trimester GWGs in the 1st, 2nd, and 3rd trimesters were 1.6, 6.6, and 8.0 kg, respectively. The average trimester GWG rates in the 1st, 2nd, and 3rd trimesters were 0.13 kg/week, 0.52 kg/week, and 0.62 kg/week, respectively. A moderate proportion of women had poor sleep quality during their gestation (30.0%) and were exposed to passive smoking during pregnancy (33.3%). Most of the pregnant women were primiparous (87.6%), participated in physical activities ≥5 days per week (75.0%), had an educational level of more than 12 years (80.8%), and had a good nutritional status (90.9%). The detection rate and urinary concentrations of parabens (including original concentrations and SG-adjusted concentrations) for the participants during the three trimesters are presented in Table 2. MeP, EtP, and PrP were detected in more than 93% of the samples tested. BuP and BzP were detected in far fewer samples (<40%) and were thus excluded from further statistical analyses. The ICC values were low (<0.4; 0.34 for EtP and 0.35 for ∑parabens) to moderate (0.4–0.6; 0.42 for MeP and 0.46 for PrP).

The unadjusted and adjusted regression coefficients (β [95% CI]) for the trimester-specific and overall associations between paraben concentrations and GWG rate are shown in Table 3. After adjustments by the covariates, each doubling in the concentration of MeP, EtP, PrP, or ∑parabens in the 1st trimester was positively associated with small-

Table 1 General characteristics of the pregnant women included and excluded in the present study (mean ± SD or *n* [%]).

Characteristics	Included $n = 613$	Excluded $n = 243$	*P*
Age of mothers (years)	28.6 ± 3.2	28.7 ± 3.7	0.69
<25	45 (7.3)	17 (7)	0.58
25–29	365 (59.5)	148 (60.9)	
30–34	168 (27.4)	59 (24.3)	
≥35	35 (5.7)	19 (7.8)	
Gestational age (weeks)	39.0 ± 1.1	38.9 ± 1.4	0.54
<37 weeks	13 (2.1)	8 (2.1)	0.33
≥37 weeks	600 (97.9)	235 (97.9)	
Prepregnancy BMI (kg/m2)	20.9 ± 2.8	21.7 ± 2.9	0.38
Normal (18.5–22.9)	375 (61.2)	153 (62.9)	0.67
Underweight (<18.5)	117 (19.1)	40 (16.5)	
Overweight (≥23)	121 (19.7)	50 (20.6)	
Education			
>12 years	495 (80.8)	176 (72.4)	**0.00**
10–12 years	93 (15.2)	41 (16.9)	
≤9 years	25 (4.1)	26 (10.7)	
Passive smoking during pregnancy			
No	409 (66.7)	161 (66.3)	0.94
Yes	204 (33.3)	82 (33.7)	
Parity			
Primiparous	537 (87.6)	199 (81.9)	**0.04**
Multiparous	76 (12.4)	44 (18.1)	
Nutritional status			
Good	557 (90.9)	215 (88.5)	0.33
Normal	54 (8.8)	28 (11.5)	
Bad	2 (0.3)	0 (0)	
Sleep quality			
Good	174 (28.4)	65 (27)	0.91
Normal	255 (41.6)	101 (41.9)	
Bad	184 (30)	75 (31.1)	
Physical activities during pregnancy			
Never	52 (8.5)	19 (7.8)	0.60
1–4 days/weeks	95 (15.5)	32 (13.2)	
≥5 days/weeks	460 (75)	191 (78.6)	
Miss	6 (1)	1 (0.4)	
Gestational diabetes			
No	571 (93.1)	219 (90.1)	0.15
Yes	42 (6.9)	24 (9.9)	
Pregnancy-induced hypertension syndrome			
No	600 (97.9)	238 (97.9)	0.95
Yes	13 (2.1)	5 (2.1)	
Gestational weight gain (kg)			
First trimester	1.6 ± 3.1 ($n = 613$)	–	
Second trimester	6.6 ± 3.0 ($n = 436$)	–	
Third trimester	8.0 ± 3.0 ($n = 336$)	–	
Total gestational weight gain	16.5 ± 4.2 ($n = 336$)	–	
Rate of gestational weight gain (kg/week)			
First trimester	0.13 ± 0.26 ($n = 613$)	–	
Second trimester	0.52 ± 0.24 ($n = 436$)	–	
Third trimester	0.62 ± 0.23 ($n = 336$)	–	

*The bold values were the significant results (*P*-values >0.05).

magnitude changes in the 1st-trimester GWG rate: 0.008 kg/week (95% CI: 0.002, 0.015), 0.006 kg/week (95% CI: 0, 0.011), 0.010 kg/week (95% CI: 0.004, 0.016), and 0.013 kg/week (95% CI: 0.006, 0.020), respectively. In the 2nd and 3rd trimesters, the associations between the concentration of MeP, EtP, PrP, or ∑parabens and GWG rate in the 2nd or 3rd trimester showed a similar positive tendency, although these relationships were all nonsignificant. In the overall association analysis that was performed to investigate the combined effects of paraben exposures during pregnancy on GWG rates (Table 3), a doubling in the trimester concentration of MeP, PrP, or ∑parabens was associated with a slight increase of 0.004 kg/week (95% CI: 0, 0.009), 0.006 kg/week (95% CI: 0.002, 0.009) or 0.007 kg/week (95% CI: 0.002, 0.012) in the trimester GWG rate, respectively.

After stratification according to PP-BMI, we found the associations between paraben exposures and GWG rate to be more prominent in the overweight/obese group in the 1st trimester and in the overall association analysis (Table 4). For the 1st-trimester GWG rate, each doubling in the 1st-trimester PrP concentration was associated with an increase of 0.022 kg/week (95% CI: 0.006, 0.038) in the overweight/obese group; however, the increase was only 0.007 kg/week (95% CI: 0, 0.014) in the normal-weight group and 0.005 kg/week (95% CI: −0.009, 0.018) in the underweight group. For overall associations, a doubling in the PrP concentration was associated with an increase in the trimester GWG rate of 0.012 kg/week (95% CI: 0.001, 0.024) in the overweight/obese group, 0.003 kg/week (95% CI: −0.001, 0.008) in the normal-weight group, and 0.005 kg/week (95% CI: −0.004, 0.014) in the underweight group.

In the analysis of the potential relationships between trimester paraben exposures and subsequent trimester GWG, we did not observe any significant associations (Table 5).

Excluding pregnant women with PIH and/or gestational diabetes resulted in a subgroup of 559 pregnant women in the analysis, and the direction of the estimates between paraben exposures and the GWG rate remained unchanged, with slightly decreased estimates compared with the estimates for the entire population (Supplementary Material Table S1). In the analysis using the exposure data after multiple imputation (Table S2), the estimations remained in the same direction. Although the magnitudes of MeP, EtP, and PrP associated with trimester GWG rate showed slight increases compared with the results in Table 3, the results for ∑parabens remained stable. In the analysis of the estimated associations between average paraben exposures over the course of pregnancy and total GWG (Table S3), we also observed a positive tendency, although the associations in this analysis were not significant.

Discussion

To our knowledge, this is the first study to report the associations between prenatal paraben exposures and GWG.

Table 2 Concentrations of parabens measured in urine samples collected at each pregnancy trimester.

Analytes	LOD	1st trimester			2nd trimester			3rd trimester			Over entire pregnancy			ICC
		Detection rate (%)	GM	Median	Detection rate (%)	GM	Median	Detection rate (%)	GM	Median	Detection rate (%)	GM	Median	
MeP (μg/L)	0.05	97.88			96.25			96.60			97.01			
Unadjusted			16.10	16.89		12.00	12.87		9.51	8.90		13.68	12.10	0.37
SG adjusted			19.17	20.74		13.96	17.55		11.71	12.33		14.72	15.42	0.42
EtP (μg/L)	0.01	93.80			93.31			94.13			93.75			
Unadjusted			0.59	0.47		0.51	0.43		0.42	0.36		0.37	0.42	0.34
SG adjusted			0.71	0.54		0.59	0.48		0.51	0.43		0.40	0.49	0.34
PrP (μg/L)	0.05	98.21			96.90			93.96			96.36			
Unadjusted			0.96	0.70		0.76	0.55		0.48	0.31		0.38	0.49	0.43
SG adjusted			1.14	0.90		0.88	0.75		0.59	0.41		0.41	0.62	0.46
BuP (μg/L)	0.05	40.13			37.19			37.36			38.23			
Unadjusted			NA	<LOD		NA	<LOD		NA	<LOD		NA	<LOD	0.47
SG adjusted			NA	<LOD		NA	<LOD		NA	<LOD		NA	<LOD	0.42
BzP (μg/L)	0.01	25.29			24.96			22.19			24.14			
Unadjusted			NA	<LOD		NA	<LOD		NA	<LOD		NA	<LOD	0.51
SG adjusted			NA	<LOD		NA	<LOD		NA	<LOD		NA	<LOD	0.56
∑Parabens (μmol/L)	–	–			–			–			–			
Unadjusted			0.15	0.16		0.12	0.14		0.09	0.09		0.11	0.12	0.34
SG adjusted			0.18	0.20		0.14	0.18		0.11	0.11		0.12	0.16	0.35

MeP methylparaben, *EtP* ethylparaben, *PrP* propylparaben, *BuP* butylparaben, *BzP* benzylparaben, *∑Parabens* sum parabens, *SG* specific gravity, *GM* geometric mean, *NA* not available, *LOD* limit of detection, *ICC* intraclass correlation coefficient.

Paraben exposures were more strongly associated with GWG rate in the 1st trimester than in the other two trimesters. In addition, we observed that women who were overweight/obese had greater increases in their GWG rates associated with exposure to parabens than normal-weight women or underweight women.

The high detection rates (93–98%) of MeP, EtP, and PrP indicated that the population in our study was widely exposed to these parabens. The urinary MeP, EtP, and PrP concentrations (medians, 15.42, 0.49, and 0.62 μg/L) during the entire pregnancy in this study were similar to those of pregnant women in a study from Denmark (medians, 20.7, 1.01, and 4.17 μg/L) [45] but lower than those of pregnant women in studies from other developed countries, including France (medians, 97.8, 4.1, and 12.5 μg/L) [46], Japan (medians, 108, 7.26, and 33.3 μg/L) [47], and the United States (medians, 279, 1.44, and 75.3 μg/L) [48]. Women from the developed countries used larger amounts of cosmetics than individuals from the developing countries [49]. Factors pertaining to the different regions, economic statuses, lifestyles, and sample collection conditions may also have contributed to the differences in exposure levels. However, endocrine-disrupting chemicals (EDCs) at low doses can have an impact on personal health [50]. Although the exposure levels were relatively low in the present study, the underlying adverse health impact induced by parabens should not be ignored.

No study has reported the associations between prenatal paraben exposures and GWG, but accumulative studies have reported that prenatal exposure to other EDCs, such as perfluoroalkyl substances and phthalates, is positively associated with GWG or an increased risk for excessive GWG [22, 23, 51]. Several epidemiological studies have investigated the associations between paraben exposures and adiposity measures, with inconsistent findings. One study reported that Czech women aged 26–33 years with BMIs of 25–34.9 (kg/m^2) had higher urinary MeP and PrP concentrations than those with BMIs of 18.5–24.9 (kg/m^2) [52]. Another study of Korean adults aged 19–69 years also found that higher urinary concentrations of MeP and PrP were associated with increased BMI [53]. However, BMI was reported to be inversely associated with urinary concentrations of BuP and MeP among black women aged 23–34 years residing in Michigan [54]. A cross-sectional study in the US also found an inverse associations between BMI or waist circumference and urinary concentrations of parabens (MeP, EtP, PrP, and BuP) among adults [55]. Paraben exposures appear to activate PPARγ or glucocorticoid receptors and then promote adipocyte differentiation [10, 12, 13], which may contribute to increases in GWG. Although the magnitudes of the increases in GWG rate values (0.006–0.013 kg/week) associated with paraben exposures were small in our study, we cannot discount the potential physiologic hazards.

In our analysis, we reported an increased tendency in the association between trimester paraben exposures and trimester GWG rate. Nevertheless, we observed significant associations only in the 1st trimester, wherein the

Table 3 The unadjusted and adjusted regression coefficients (β [95% CI]) for the trimester-specific and overall associations between paraben concentrations and GWG rate (kg/week).

Analytes	Unadjusted β (95% CI)	Adjusted[a] β (95% CI)
MeP (μg/L)		
1st GWG rate	**0.008 (0.001, 0.014)**	**0.008 (0.002, 0.015)**
2nd GWG rate	0 (−0.007, 0.008)	0.001 (−0.006, 0.008)
3rd GWG rate	0.003 (−0.007, 0.012)	0.002 (−0.008, 0.011)
Overall	**0.004 (0, 0.008)**	**0.004 (0, 0.009)**
EtP (μg/L)		
1st GWG rate	**0.005 (0, 0.011)**	**0.006 (0, 0.011)**
2nd GWG rate	0.003 (−0.004, 0.010)	0.003 (−0.004, 0.010)
3rd GWG rate	−0.007 (−0.015, 0.002)	−0.007 (−0.016, 0.002)
Overall	0.002 (−0.002, 0.006)	0.002 (−0.002, 0.006)
PrP (μg/L)		
1st GWG rate	**0.009 (0.003, 0.015)**	**0.010 (0.004, 0.016)**
2nd GWG rate	0 (−0.006, 0.007)	0.001 (−0.006, 0.007)
3rd GWG rate	0.005 (−0.003, 0.013)	0.004 (−0.004, 0.012)
Overall	**0.005 (0.001, 0.009)**	**0.006 (0.002, 0.009)**
ΣParabens (μmol/L)		
1st GWG rate	**0.012 (0.005, 0.019)**	**0.013 (0.006, 0.020)**
2nd GWG rate	0.001 (−0.008, 0.009)	0.001 (−0.007, 0.010)
3rd GWG rate	0.003 (−0.007, 0.013)	0.002 (−0.009, 0.012)
Overall	**0.007 (0.002, 0.011)**	**0.007 (0.002, 0.012)**

[a]Adjusted for age, prepregnancy BMI, parity, nutritional status, sleep quality, maternal education, passive smoke, gestational age, pregnancy-induced hypertension syndrome, gestational diabetes, physical activities during pregnancy, measurement time of gestational weight.

[*]The bold values were the significant results (*P*-values >0.05).

associations were much stronger than those in either the 2nd or 3rd trimester. These results suggested that physiologic processes associated with the 1st trimester may be more sensitive to paraben exposure. However, our findings may have been due to the higher urinary paraben concentrations present in the 1st trimester than in the 2nd and/or 3rd trimester, as biochemical and physiologic changes in pregnancy may influence the physiologic responses to environmental pollutants [56]. The other possible reason for the higher concentrations observed in the 1st trimester is that pregnant women may reduce their usage of personal care products, especially cosmetics, in middle and late pregnancy. In addition, the nonsignificant associations observed in the 2nd and 3rd trimesters might be because fewer pregnant women were included in the analyses of the second- and third-trimester GWG rates.

Our stratified analysis indicated that overweight/obese pregnant women had greater associations between GWG rate and paraben exposures. As we noted above, paraben exposures might increase weight by activating PPARγ, which is mostly present in adipose tissue and plays an essential role in promoting adipogenesis [57, 58]. As parabens may be deposited in adipose tissue [59], overweight/obese populations may be more sensitive to paraben exposure than normal-weight or underweight individuals. In addition, to stimulating PPARγ signaling pathways, parabens can promote adipogenesis by altering the levels of thyroid hormones [60]. Urinary EtP and PrP concentrations have been found to be associated with decreased total thyroxine, free thyroxine, and triiodothyronine in serum samples from American women [61]. Obese individuals have been reported to have subclinical alterations in thyroid function and thyroid hormone resistance, which is reflected in elevated plasma total thyroxine and triiodothyronine concentrations [62, 63]. Paraben exposures combined with overweight/obesity may thus contribute to a higher GWG rate via dysregulation of the thyroidal axis.

Our study had several strengths. First, we collected three urine samples per person during each of the three trimesters to represent paraben exposures during pregnancy and assessed the trimester-specific relationship between paraben exposures and GWG. Moreover, we obtained a large amount of information from face-to-face interviews and medical records. Such information assisted us in controlling for confounders such as varying socioeconomic, perinatal, and environmental factors.

The present study also had several limitations. First, although we adjusted for covariates, we could not guarantee

Table 4 The adjusted regression coefficients (β [95% CI]) for the trimester-specific and overall associations between paraben concentrations and GWG rate (kg/week), categorized by prepregnancy BMI.

Analytes	Underweight β (95% CI)[a]	Normal weight β (95% CI)[a]	Overweight/Obese β (95% CI)[a]	P^a for interaction
MeP (μg/L)				
1st GWG rate	0.006 (−0.008, 0.020)	0.007 (−0.001, 0.015)	0.016 (−0.002, 0.033)	0.211
2nd GWG rate	0.015 (−0.001, 0.031)	−0.002 (−0.011, 0.007)	−0.005 (−0.025, 0.016)	
3rd GWG rate	−0.010 (−0.039, 0.019)	0.001 (−0.011, 0.012)	0.007 (−0.015, 0.029)	
Overall	0.007 (−0.003, 0.017)	0.003 (−0.003, 0.008)	0.007 (−0.005, 0.018)	0.224
EtP (μg/L)				
1st GWG rate	0.002 (−0.011, 0.016)	0.006 (−0.001, 0.013)	0.008 (−0.007, 0.023)	0.283
2nd GWG rate	−0.002 (−0.019, 0.016)	0.005 (−0.003, 0.013)	0 (−0.020, 0.020)	
3rd GWG rate	−0.002 (−0.024, 0.020)	−0.004 (−0.014, 0.007)	−0.025 (−0.049, −0.001)	
Overall	0 (−0.009, 0.010)	0.004 (−0.001, 0.009)	0 (−0.012, 0.011)	0.182
PrP (μg/L)				
1st GWG rate	0.005 (−0.009, 0.018)	**0.007 (0, 0.014)**	**0.022 (0.006, 0.038)**	**0.006**
2nd GWG rate	0.013 (−0.004, 0.029)	−0.001 (−0.009, 0.007)	−0.004 (−0.024, 0.016)	
3rd GWG rate	−0.004 (−0.023, 0.015)	0.003 (−0.007, 0.012)	0.014 (−0.010, 0.037)	
Overall	0.005 (−0.004, 0.014)	0.003 (−0.001, 0.008)	**0.012 (0.001, 0.024)**	**0.002**
ΣParabens (μmol/L)				
1st GWG rate	0.009 (−0.008, 0.025)	**0.011 (0.003, 0.020)**	**0.025 (0.005, 0.044)**	**0.006**
2nd GWG rate	0.013 (−0.007, 0.033)	−0.001 (−0.011, 0.010)	−0.004 (−0.029, 0.022)	
3rd GWG rate	−0.013 (−0.041, 0.016)	0.002 (−0.011, 0.015)	0.005 (−0.020, 0.031)	
Overall	0.007 (−0.005, 0.018)	0.006 (0, 0.011)	0.012 (−0.002, 0.025)	0.324

[a]Adjusted for age, parity, nutritional status, sleep quality, maternal education, passive smoke, gestational age, pregnancy-induced hypertension syndrome, gestational diabetes, physical activities during pregnancy, measurement time of gestational weight.

*The bold values were the significant results (*P*-values >0.05).

that all potential confounders, such as maternal stress levels or information regarding the frequency of use of personal care products during pregnancy, had been included in our models. Most questionnaire-based information was self-reported. We collected data from only the self-evaluation of nutritional status and sleep quality but did not evaluate a precise index of these variables. Nutritional status may have a large effect on GWG, but we did not collect detailed dietary information. These factors may lead to residual confounding. Second, the trimester gestational weight of each women of the study population was not measured on the same gestational week, which may predispose the data to misclassification. Thus, we calculated the trimester GWG rate as the primary outcome and additionally adjusted for the gestational week of the weight measurement in our analyses. Future studies should consider the timing of the gestational weight measurement. Third, we did not analyse the associations categorized by the IOM recommendation. The recommended GWG for different PP-BMIs is based on the cutoff values of 18.5/25/30 for the PP-BMI. However, pregnant Asian women have lower PP-BMIs than pregnancy American and European women [35]. Only 8.65% and 0.82% of our population had PP-BMIs higher than 25 and 30, respectively, which prevented us from being able to analyse differences by classifying GWG according to the IOM recommendation. To date, there is no GWG recommendation for Asians, so further investigation is needed. Fourth, although parabens are nonpersistent organic pollutants, we do not know whether paraben exposures during specific trimesters have potential relationships with subsequent trimester GWG. The exposure measurement for several pregnant women was made after their trimester GWG measurement, which may undermine the causal associations. Although we analysed the associations between trimester paraben concentrations and subsequent trimester GWG, the results of these analyses were not significant. Finally, the magnitudes of the GWG rate changes associated with the paraben exposures were small in this study, and this may be a consequence of low paraben exposure levels. Future replicated research, especially in populations with higher paraben exposure levels, is needed to validate these findings and make definitive conclusions.

Conclusion

This present study suggests that paraben exposures during pregnancy have potential to increase the GWG rate,

Table 5 Generalized estimating equation evulating the relationships between trimester paraben exposures and gestational weight gain (GWG, kg).

Analytes	Unadjusted β (95% CI)	Adjusted[a] β (95% CI)
MeP (μg/L)		
1–2[b]	−0.07 (−0.16, 0.03)	−0.06 (−0.15, 0.03)
1–3[b]	−0.05 (−0.16, 0.05)	−0.06 (−0.15, 0.03)
2–3[b]	0 (−0.10, 0.10)	0.02 (−0.08, 0.12)
EtP (μg/L)		
1–2[b]	−0.02 (−0.10, 0.06)	−0.02 (−0.10, 0.05)
1–3[b]	−0.08 (−0.17, 0.01)	−0.04 (−0.14, 0.07)
2–3[b]	−0.03 (−0.13, 0.07)	−0.01 (−0.11, 0.08)
PrP (μg/L)		
1–2[b]	−0.01 (−0.10, 0.08)	0 (−0.09, 0.08)
1–3[b]	−0.06 (−0.16, 0.04)	−0.06 (−0.18, 0.05)
2–3[b]	0.01 (−0.09, 0.10)	0.02 (−0.08, 0.11)
∑Parabens (μmol/L)		
1–2[b]	−0.08 (−0.18, 0.02)	−0.08 (−0.18, 0.02)
1–3[b]	−0.08 (−0.20, 0.03)	−0.05 (−0.15, 0.05)
2–3[b]	0 (−0.13, 0.12)	0.01 (−0.11, 0.13)

[a]Adjusted for age, prepregnancy BMI, parity, nutritional status, sleep quality, maternal education, passive smoke, gestational age, pregnancy-induced hypertension syndrome, gestational diabetes, physical activities during pregnancy, measurement time of gestational weight.

[b]1–2, 1st-trimester exposure vs. 2nd-trimester GWG; 1–3, 1st-trimester exposure vs. 3rd-trimester GWG; 2–3, 2nd-trimester exposure vs. 3rd-trimester GWG.

especially the first-trimester GWG rate. The associations we observed were more prominent among overweight/obese women. Since higher paraben exposure levels are found in developed countries, future studies in populations with higher paraben exposure levels are needed.

Acknowledgements This work was supported by the National Natural Science Foundation of China (91643207, 21437002, and 91743103), the National Key Research and Development Plan of China (2016YFC0206203 and 2016YFC0206700), the Fundamental Research Funds for the Central Universities, Huazhong University of Science and Technology (2015ZDTD047, 2016YXZD043, and 2018KFYXMPT00), and Program for HUST Academic Frontier Youth Team (2018QYTD12, 2018QYTD06).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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