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The sex-specific association between maternal paraben exposure and size at birth

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ABSTRACT

Parabens are a group of esters of parahydroxybenzoic acid and are utilized as antimicrobial preservatives in the majority of personal care products (PCPs). Epidemiological studies regarding the adverse effects of parabens on fetuses are still limited. The aim of this study was to determine the association between maternal paraben exposure and birth outcomes.

One hundred and ninety-nine pregnant women were enrolled, and maternal urine was collected in the third trimester. The urine concentrations of four parabens (methyl (MP), ethyl (EP), propyl (PP), and butyl (BP)) were determined by ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry. Generalized additive model-penalized regression splines and a multivariable regression model were employed to determine the association between paraben exposure levels and birth outcomes. A causal mediation analysis was conducted to determine the mediation effect of oxidative stress on birth outcomes.

The geometric means of urinary MP, EP, PP, and BP were 51.79, 1.26, 4.21, and 1.25 μg/g cre., respectively. In the penalized regression splines, sex-specific associations between maternal MP levels and birth outcomes were observed; a downward curvature was observed between the MP level and birth weight, length, head circumference, and thoracic circumference among female newborns. Pregnant women in the group with MP levels above the third quartile had neonates with significantly lower body weight ($\beta = -215.98$ g, p value = 0.02) compared to those in the group with MP levels lower than the third quartile. No significant mediation of oxidative stress was observed between maternal MP exposure and female birth weight. The estimated proportion mediated ranged from −6% to 15%. The negative association between maternal paraben exposure and female birth outcomes in relation to child development should be carefully considered.

1. Introduction

Parabens, a group of esters of parahydroxybenzoic acid that are used as antifungal and antibacterial agents, are widely used in personal care products (PCPs), foodstuffs, and pharmaceuticals (Myridakis et al., 2015). Parabens are used in over 10,000 formulations in nearly all types of cosmetics and a wide range of PCPs (Elder, 1984; Guo and Kannan, 2013; Johnsson et al., 2011). The permitted amounts of parabens in PCPs are regulated in Europe through the Cosmetic Regulation. The maximum concentrations of two preservatives (propyl paraben (PP) and butyl paraben (BP)) were revised up to 0.14% when used individually or mixed with other esters (Commission, 2014). In China, methyl paraben (MP) accounted for the largest proportion and PP accounted for the second largest proportion of parabens, which are found in all categories of PCPs, including creams, lotions, and face cleansers (Guo et al., 2014). In the US, parabens were detected in approximately 40% of rinse-off products and 60% of leave-on products, and the parabens with the highest concentrations in the analysis were MP, ethyl paraben (EP), PP, and BP (Guo and Kannan, 2013). Given the ubiquity of parabens in numerous consumer products, humans can

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List of acronyms

8-iso-$PGF_{2\alpha}$	8-iso-prostaglandin $F_{2\alpha}$
8-NO_2Gua	8-nitroguanine
8-OHdG	8-hydroxy-2-deoxyguanosine
BP	Butyl paraben
EP	Ethyl paraben
HNE-MA	N-acetyl-S-(tetrahydro-5-hydroxy-2-pentyl-3-furanyl)-L-cysteine
MP	Methyl paraben
PP	Propyl paraben

easily be exposed to parabens through continuous dermal exposure and absorption by using PCPs. Moreover, biological monitoring has also verified the ubiquitous exposure of parabens among neonates, children, pubertal students, pregnant women, adults, and elderly individuals (Frederiksen et al., 2013; Kang et al., 2013a; Wang et al., 2015a; Wolff et al., 2010).

Safety concerns regarding parabens were raised during the last decade (Prusakiewicz et al., 2007b; Tavares et al., 2009). Parabens exert proven estrogenic/antiandrogenic effects by interfering with the function of the endocrine system and disrupting normal signaling pathways (Oishi, 2002; Prusakiewicz et al., 2006). The estrogenic activities of parabens are directly mediated via binding to estrogen receptors (ERs) or indirectly lead to elevations in free estradiol levels (Boberg et al., 2010; Prusakiewicz et al., 2007a). Xenoestrogen exposure, especially in susceptible and vulnerable pregnant women, may have adverse consequences on fetuses (Chang et al., 2013; Huang et al., 2017). Increasing evidence has proven the ability of endocrine disruptors to cross the human placenta and transfer into the maternal-fetal placental circulation (Miller et al., 2004). A biomonitoring study also revealed a significant and positive correlation between the urinary paraben concentrations of pregnant women and their newborn infants (Kang et al., 2013a). Despite the widespread exposure to parabens due to the intensive use of PCPs, epidemiological studies regarding the adverse effects of parabens are still conflicting.

Parabens can obstruct redox homeostasis and cause oxidative stress by elevating lipid peroxidation and the generation of intracellular reactive oxygen species (ROS) (Dubey et al., 2017; Kopalli et al., 2013). In an epidemiological study, maternal urinary paraben levels were found to be associated with several biomarkers of oxidative stress, such as 8-hydroxy-2-deoxyguanosine (8-OHdG), malondialdehyde, and isoprostane (Kang et al., 2013b; Watkins et al., 2015). Although oxidative stress is a common characteristic during pregnancy, the excessive production of ROS caused by maternal xenoestrogen exposure may decrease the placental antioxidant capacity (Al-Gubory, 2014; Casanueva and Viteri, 2003). Evidence has indicated that free radical damage is correlated with gestational hypertension, preeclampsia, and diabetes, leading to preterm birth and low birth weight (Bharadwaj et al., 2017; Kim et al., 2005; Negi et al., 2012; Turpin et al., 2015). However, the association between parabens and birth outcomes related to oxidative stress requires further investigation.

Due to the intensive use of PCPs and limited epidemiological studies, the health effects of parabens on vulnerable pregnant women and their fetuses need to be addressed. This study would test the hypothesis that a host's paraben exposure profile influences redox regulation and leads to the adverse birth outcomes. The purpose of the present study was to determine the association between maternal paraben exposure and birth outcomes and effects related to oxidative stress.

2. Materials and methods

2.1. Study population

Recruitment was conducted at an obstetrics clinic in northern Taiwan from May 2014 to August 2015. The research protocol was approved by the Ethics Committee of Taipei City Hospital, Taipei. Pregnant women with a gestational age of 27–38 weeks (third trimester) were recruited. Of the 274 pregnant women enrolled in this study, 31 were lost to follow-up, and 3 withdrew due to inconvenience. Multiple births and cases of fetal demise were excluded. Pregnant women who had abnormal urinary creatinine levels (less than 0.3 g/L or greater than 3.0 g/L) were also excluded. In total, there were 199 pregnant women who were followed until delivery.

Upon enrollment, each woman filled out a structured questionnaire that was used to collect relevant information on sociodemographic characteristics (age, weight, height, and education level), smoking habits, alcohol and coffee consumption, frequency of PCP use, consumption of foods, and medical conditions. Dietary information was acquired through the semi-quantitative method of collecting information on the frequency (times per day/week/month) and portions (small/medium/large) ingested. Prenatal and perinatal information (height, pre-pregnancy weight, weight at delivery, and adverse pregnancy outcomes) were obtained from the hospital information system. A pediatrician measured neonatal body weight, body length, and head and thoracic circumference after delivery. Birth weight was obtained on an electronic scale that was calibrated properly. The infant was weighed without a diaper and to the nearest 0.01 kg. Birth length was measured in the recumbent position with the baby being supine, knees fully extended and soles of feet held firmly. The head circumference was measured at the maximum diameter through the glabella and occiput with a non-elastic tape to the nearest 0.1 cm. Thoracic circumference was measured at the level of nipple with a non-elastic tape. To eliminate the influence of gestational age on birth outcomes (weight, length, and head circumference), an individual's z-score was calculated using the mean and standard deviation from the population (Hsieh et al., 2006). Apgar scores were obtained at 1 min and at 5 min after delivery. The Rohrer's ponderal index (PI) of the newborns was calculated as follows:

$$\text{Ponderal index} = \frac{100^{*}\text{body weight (g)}}{\text{body length (cm)}3}$$

2.2. Urine collection and measurement of paraben

Prior to urinary collection, each glass collection jar was soaked in 10% hydrochloric acid overnight, soaked in an ultrasonic bath for 30 min, rinsed with DI water, and then dried in an oven to prevent contamination. Maternal urine was collected in a 30-mL brown glass vessel during a routine prenatal visit in the third trimester, and four parabens—namely, methyl (MP), ethyl (EP), propyl (PP), and butyl (BP)—were measured. The pretreatment method was modified from a study by Lee et al. (2013) (Lee et al., 2013). One milliliter of urine sample was spiked with 25 µL of internal standard ($^{13}C_6$-MP, $^{13}C_6$-EP, $^{13}C_6$-PP, and $^{13}C_6$-BP) and centrifuged at 4000 rpm for 5 min. A total of 0.5 mL of 1 M ammonium acetate solution was added to the urine sample supernatants followed by 20 µL of β-glucuronidase, and the samples were incubated for 15 h at 37 °C in a shaker bath. All samples were adjusted to a pH of 3 by adding 0.3 mL of 1 N HCl. Deconjugated samples were cleaned with PH solid phase extraction (SPE) cartridges (Agilent, USA), which were preconditioned with 2 mL of methanol followed by 1 mL of deionized water that had been acidified with HCl. After sample application, each cartridge was washed with 1 mL of deionized water immediately. Lastly, analytes were eluted with 1 mL of methanol. All samples were filtered through a 0.25-µm

polytetrafluoroethylene (PTFE) membrane filter, and paraben levels were determined by using ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UPLC–QTOF MS). A concentration lower than the limit of detection (LOD) was replaced with values corresponding to the LOD/2 (Hornung and Reed, 1990).

2.3. Measurement of oxidative stress

The analytical method was identical to that described in previous studies (Wang et al., 2015b, c; Wu et al., 2016). Briefly, each urine sample was centrifuged, and the supernatant was diluted with deionized water containing 1 mM ammonium acetate. After each SPE cartridge was preconditioned (Oasis HLB cartridge, Waters, USA) and the urine sample was applied, analytes were eluted with 1 mL of methanol, evaporated to dryness with a vacuum centrifuge, and redissolved in 200 μL of 5% methanol containing 1 mM ammonium acetate. Urinary 8-hydroxy-2-deoxyguanosine (8-OHdG), 8-nitroguanine (8-NO_2Gua), 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$), and N-acetyl-S-(tetrahydro-5-hydroxy-2-pentyl-3-furanyl)-L-cysteine (HNE-MA) were simultaneously measured by high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (HPLC-ESI-MS/MS).

8-OHdG and 8-NO_2Gua are the biomarkers of oxidative DNA damage and nitrative DNA damage, respectively, that have been recognized as indicators of health risk due to their mutagenic potential (Kawanishi et al., 2006; Ogino and Wang, 2007; Silva et al., 2014). 8-isoPF2α is an intermediate product of peroxidized polyunsaturated fatty acids (PUFAs), which are formed when ROS react with the double bonds of PUFAs to induce formation of lipid hydroperoxides (Hendrickse et al., 1994). Another lipid peroxidation biomarker, HNE (4-hydroxy-2-nonenal), was further metabolized to form HNE-mercapturic acid (HNE-MA) (Ayala et al., 2014).

2.4. Measurement of creatinine

The creatinine concentration in urine was measured using a commercial kit (Eagle Diagnostics, Desoto, Texas, USA). Briefly, 3 mL of picric acid (3.3 mM) was added to 0.1 mL of each urine sample, and the mixture was incubated at 37 °C for 15 min in a shaker bath. The concentration was quantified using a spectrophotometer at a wavelength of 510 nm. Urinary paraben and oxidative stress biomarkers concentrations were adjusted to the level of creatinine.

2.5. Statistical analysis

R software version 3.4.4 (The R Foundation for Statistical Computing; Vienna, Austria) was employed for statistical analysis. Covariates were selected according to at least one of the following criteria: (1) associated with outcomes or exposure interest (Szklo and Nieto, 2014); and (2) based on the literature. Covariates were considered mainly on the basis of maternal factors (age, height, and pre-pregnancy body mass index (BMI)) and pregnancy condition (gestational age, maternal weight gain, parity, and adverse pregnancy outcomes). Adverse pregnancy outcomes mainly included gestational diabetes mellitus, pregnancy-induced hypertension, and placenta previa and were adjusted as a composite variable due to the small number of pregnant women. In addition, due to the skewed distribution of the urinary paraben concentrations, a log-transformed quantity was used and incorporated into the generalized additive model (GAM)-penalized regression splines to determine the non-linear association of birth outcomes. The number of knots that were chosen mainly depended on the improvement in the generalized cross-validation (GCV) statistics in the model to avoid under- or over-fitting the data (Cai and Betensky, 2003; Cao et al., 2010). The smoothing parameter estimation was performed by iterative solution to fit the minimization of the equation (Wood, 2017). The equation is described as follows:

$$\frac{nD}{(n- DoF)2}$$

where D is the deviance, n is the number of pregnant women, and DoF is the effective degrees of freedom of the model. A multivariable regression model was applied to determine whether birth outcomes were affected by maternal paraben exposure. To avoid the influence of intrauterine growth restriction on the fetus, sensitivity analysis was also applied to examine the impact of maternal paraben exposure on the birth outcomes of the model for pregnant women who did not have

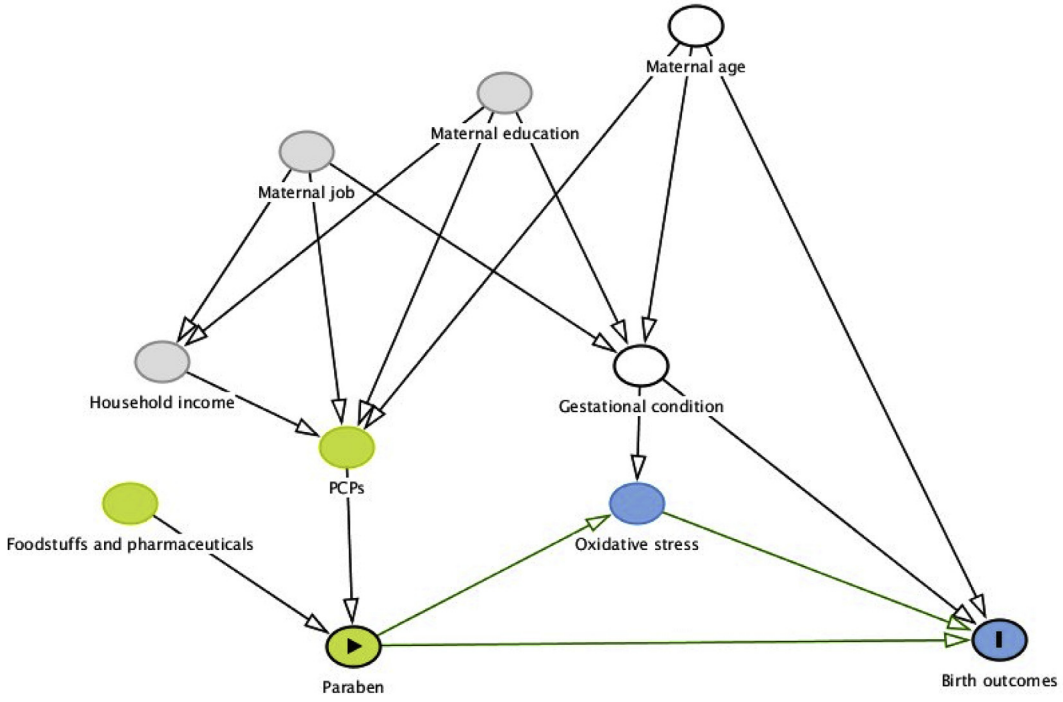

Fig. 1. Directed acyclic graph of the association among maternal paraben exposure, oxidative stress level, and birth outcomes.

adverse pregnancy outcomes, low birth weight infants, or preterm birth. Both the GAM and linear regression model were used to determine the relationship between maternal paraben exposure and birth outcomes after adjusting for identical covariates. The rationale for the selection of these two models was mainly based on the Akaike information criterion (AIC). To clarify the mediation effects of oxidative stress due to maternal paraben exposure on birth outcomes, a causal mediation analysis was conducted. Fig. 1 shows an example of a mediation effect of oxidative stress on birth outcomes by using DAG (directed acyclic graph) (Fig. 1). Estimation of the causal mediation effects was based on the method developed by Imai et al. (2010). The first step was to fit the outcome model using paraben (X) and oxidative stress (M) to predict birth outcomes. $E(Y) = \beta_0 + \beta_1$*paraben + β_2*M + β*C

Then conduct the mediator model using parabens to predict oxidative stress. $E(M) = \theta_0 + \theta_1$*paraben + θ*C

The identical covariates (C) were adjusted in both models. The control direct effect was evaluated by estimating β_1 and the indirect effect was calculated by estimating the cross-product of β_2 and θ_1. The corresponding 95% confidence intervals (CIs) were calculated using a non-parametric bootstrapping method (Hayes and Scharkow, 2013). Bootstrap samples were created by randomly sampling observations from the original data with replacement. Estimate of the direct/indirect was generated for each random sampling and the process repeated 1,000 times to obtain a bootstrap distribution and CIs. To isolate the effect of oxidative stress in the mediation analysis, each biomarker of oxidative stress was independently selected in the model. The implemented R codes were developed by Imai et al. (2017). The direct effect was the effect of maternal paraben exposure on birth outcomes, which was unexplained by oxidative stress. The indirect effect was the effect of paraben exposure that was due to the influence of paraben exposure on oxidative stress. The total effect is the sum of the direct and indirect effect. The proportion of mediation was calculated as the ratio of indirect effect to the total effect.

3. Results

Among the 199 pregnant women in this study, the average age was 33.2 years, and the average BMI before gestation was 21.7 kg/m^2. More than 15% (N = 35) of the women were classified as overweight or obese, and 25.8% were primiparous. Most of the women (84.9%) had a bachelor's degree or higher. None were habitual smokers, but 46 were exposed to environmental tobacco smoke in the workplace or at home. Of the 199 singleton live births including 99 male and 100 female neonates, the average body weight and height were 3103.9 ± 342.1 g and 49.4 ± 1.8 cm, respectively. The Apgar scores of all newborns were greater than 7 at 1 min and 5 min after delivery (Table 1).

Table 2 summarizes the concentrations of the parabens and oxidative stress biomarkers among the pregnant women (Table 2). The detection rates of MP, EP, PP, and BP were 100%, 81.4%, 87.9%, and 67.8%, respectively, and MP exhibited the highest geometric mean (GM) of 51.79 μg/g creatinine. The GM concentrations of the four oxidative stress biomarkers 8-OHdG, 8-NO_2Gua, 8-iso-$PGF_{2\alpha}$, and HNE-MA were 4.52, 8.81, 17.21, and 83.44 μg/g cre., respectively. There were significant positive correlations among MP, EP, PP, and BP levels (r = 0.19–0.60, p value < 0.05). Urinary parabens were positively associated with 8-NO_2Gua (r = 0.14–0.20) but negatively associated with 8-iso-$PGF_{2\alpha}$ (r = −0.04–0.18) (Fig. 2).

In the penalized regression splines, a downward curvature was observed between the MP level and female birth outcomes, but an upward curvature was observed in male birth outcomes (Fig. 3). For EP, PP, and BP, no consistent directionality in terms of birth outcomes was observed between male and female neonates (Fig. S1). In the multivariable linear regression model, maternal MP level was significantly associated with male head circumference (β = 0.27 cm, p < 0.01) and PI (β = 0.03 g/cm^3, p = 0.04) (Table S1). Due to an inverted U distribution between maternal MP levels and female birth outcomes and the limitation of the beta estimate in the GAM, pregnant women were further classified by the cutoff point for the median or 3rd-quartile urinary paraben concentration in accordance with breakpoint analysis. After adjusting for other covariates, pregnant women exposed to MP levels above the 3rd quartile had female newborns with significantly lower birth weight (β = −215.98 g, p value = 0.02), shorter head (β = −0.56 cm, p value = 0.05) and thoracic (β = −0.87 cm, p value = 0.02) circumference relative to those women with low MP exposure (below 3rd-quartile concentration). A marginally significant association existed between high maternal MP levels and a short birth length (β = −0.82 cm, p value = 0.09). Significant associations also existed between EP and head circumference in female newborns. Among male newborns, a positive association between high MP levels and Ponderal index existed (β = 0.11 g/cm^3, p value = 0.04). This study further examined the interactions between sex and maternal MP exposure level on birth outcomes. The result indicated a significant interaction in head circumference (β = −0.84 cm, p = 0.02) and Ponderal index (β = -0.14 g/cm^3, p value = 0.04) (Table 3). In the sensitivity analysis, the negative association between high maternal MP levels and female birth weight still existed among pregnant women who did not have adverse pregnancy outcomes (β = −203.74 g, p value = 0.03) or preterm and low birth weight neonates (β = −205.76 g, p value = 0.02) (Table 4). Based on the statistically significant associations of maternal MP exposure with female birth weight and oxidative stress, the present study further determined whether oxidative stress mediated the association between MP exposure and female birth weight. After adjusting for other covariates, the coefficient of indirect effect for oxidative stress ranged from −31.44–12.19 g, and the estimated proportion mediated ranged from −6% to 15%. Compared to pregnant women who were exposed to MP levels below the 3rd quartile, pregnant women with high MP exposure had female newborns with lower body weight. However, the

Table 1
Sociodemographic characteristics of the pregnant women and neonatal outcomes.

	N (%)	Mean ± SD
Total	199	
Age, years		33.2 ± 3.6
< 30	30 (15.1)	
30-34	100 (50.3)	
> 34	69 (34.6)	
Pre-pregnancy BMI, kg/m^2		21.7 ± 3.4
< 18.5	31 (15.7)	
18.5–24	132 (66.7)	
≥24	35 (17.6)	
Weight gain, kg		11.8 ± 4.2
Parity		
Primiparas	51 (25.8)	
Multiparas	147 (74.2)	
Having a bachelor's degree or above	169 (84.9%)	
Smoking habits	0 (0)	
Environmental tobacco smoke	46 (23.1)	
Gestational diabetes mellitus	6 (3.02)	
Pregnancy-induced hypertension	5 (2.51)	
Placenta previa	1 (0.50)	
Neonatal outcomes		
Birth sex		
Male	99 (49.8)	
Female	100 (50.2)	
Low birth weight	10 (5.03)	
Preterm birth	8 (4.02)	
Gestational age (weeks)		38.6 ± 1.3
Birth weight (g)		3103.9 ± 342.1
Birth length (cm)		49.4 ± 1.8
Head circumference (cm)		34.2 ± 1.1
Thoracic circumference (cm)		32.5 ± 1.3
Ponderal index (g/cm^3)		2.6 ± 0.2

SD: standard deviation.
Information on the pre-pregnancy BMI and parity of one pregnant woman was lost.

Table 2
The concentrations of parabens and oxidative stress among pregnant women.

	Detection rate (%)	LOD (ng/ml)	GM (GSD) [a]	GM (GSD) [b]	Min[b]	Percentile[b]			Max[b]
						25th	50th	75th	
MP	100	0.10	40.91 (5.41)	51.79 (5.21)	0.87	16.09	57.50	154.46	90281.75
EP	81.4	0.10	0.94 (10.00)	1.19 (9.64)	0.02	0.21	1.11	6.05	170.05
PP	87.9	0.10	3.19 (13.14)	4.04 (12.53)	0.03	0.71	4.25	22.79	2025.76
BP	67.8	0.10	0.88 (17.57)	1.12 (18.61)	0.02	0.07	0.85	10.42	4098.50
8-OHdG	99.5	0.10	3.58 (2.43)	4.52 (2.47)	0.13	2.85	4.81	8.24	62.66
8-NO_2Gua	79.9	0.40	6.97 (8.53)	8.81 (8.77)	0.09	1.40	16.97	45.00	415.69
8-iso-$PGF_{2\alpha}$	99.5	0.20	13.59 (2.67)	17.21 (2.45)	0.27	10.25	17.15	28.94	171.82
HNE-MA	100	0.20	65.94 (3.50)	83.44 (3.32)	1.86	44.58	94.31	185.45	1455.14

MP: methyl paraben; EP: ethyl paraben; PP: propyl paraben; BP: butyl paraben.
[a] Ng/ml.
[b] μg/g cre.; GM: geometric mean; GSD: geometric standard deviation.

present study did not observe evidence of mediation by oxidative stress in the relationship between female birth weight and maternal exposure to MP (Table 5).

4. Discussion

This study presents the exposure profile of parabens among pregnant women. In general, MP was the predominant paraben in maternal urine, and the concentration in the present study was lower than that in the US, Greece, Japan, and South Korea (Geer et al., 2016; Kang et al., 2013a; Myridakis et al., 2015; Shirai et al., 2013). The possible explanation for the differences in paraben concentrations might be attributable to weather conditions, economic status, or culture, leading to usage habits and product preferences (Kessler, 2015). According to an investigation of the amount of PCPs consumed, women tended to use skincare products, especially emulsions, cream, and make-up base, more frequently and in larger amounts in winter compared with summer. The large temperature difference might also account for the variation in exposure to parabens (Yamaguchi et al., 2017). In this study, most pregnant women seldom or never used nail polish or perfume but used lotion almost every day. The high frequency of lotion application may be the main exposure source of parabens.

Epidemiological studies have indicated inconclusive associations between paraben exposure in pregnant women and their neonates. A

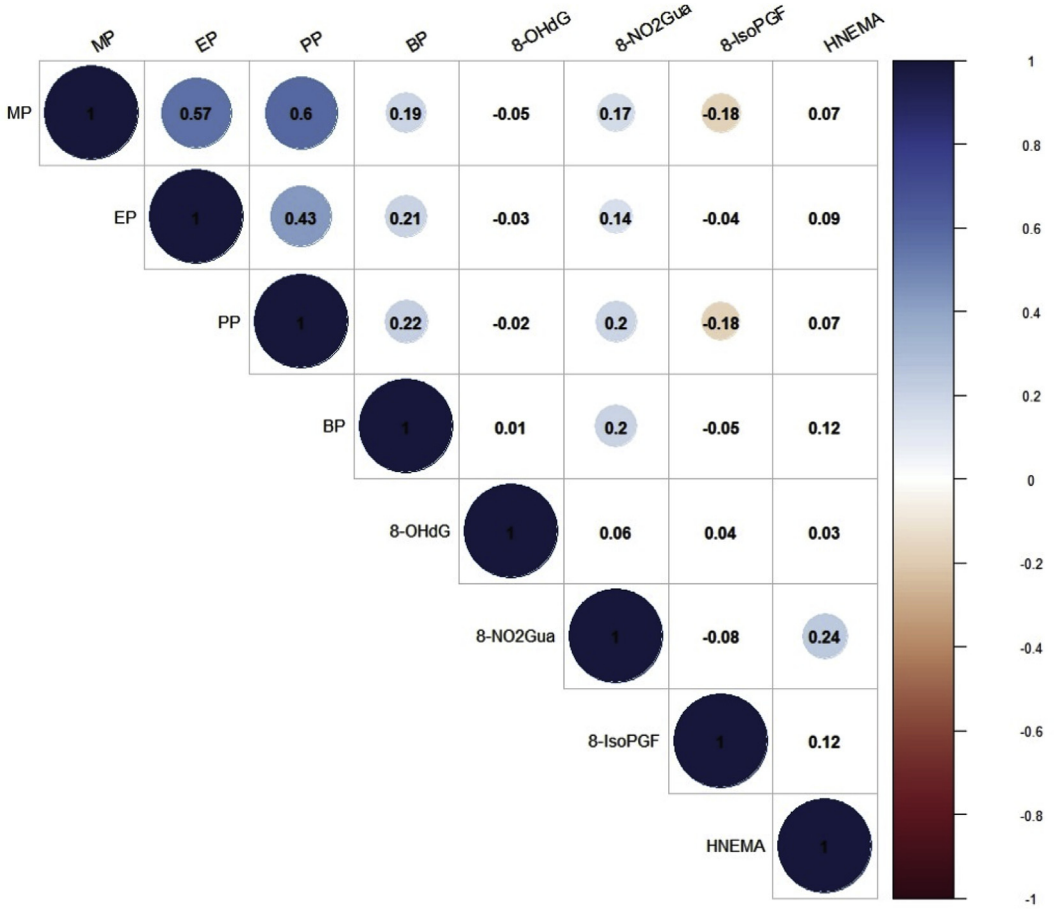

Fig. 2. Spearman's correlation coefficient between maternal creatinine-corrected parabens and oxidative stress levels. The size of the circle is a measure of the strength of the correlation. The blue/red circle indicated a significant positive/negative correlation (p value < 0.05). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

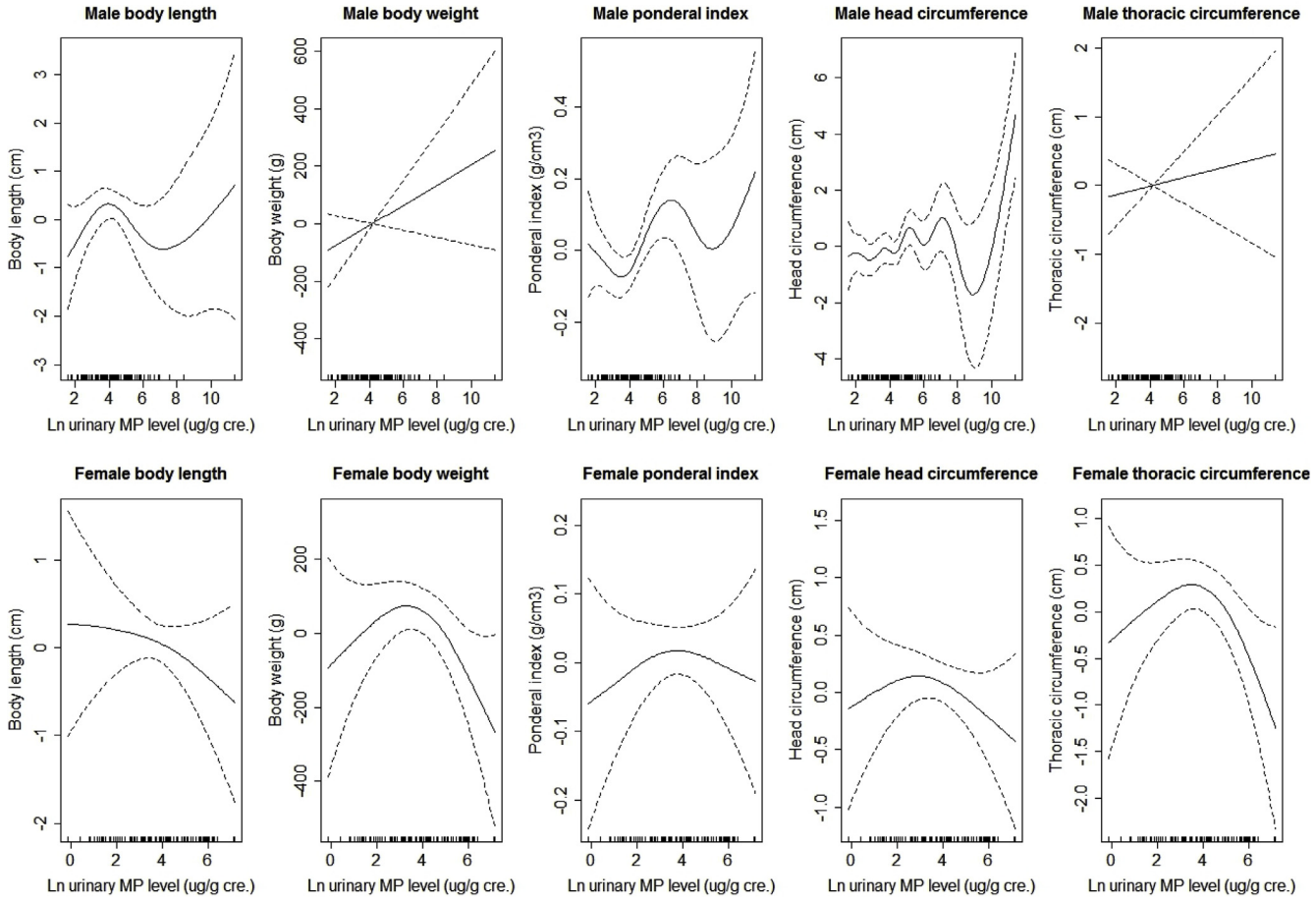

Fig. 3. Relationship between maternal paraben levels and neonatal outcomes in penalized regression splines. The fitted line (solid line) and the 95% confidence interval (dotted lines). Adjusted covariates included age, height, pre-pregnancy BMI, gestational age, weight gain, parity, and adverse pregnancy outcomes.

mother-child cohort study in France found no statistically significant linear association between paraben concentrations and birth outcomes (Philippat et al., 2012). In a Chinese birth cohort conducted by Wu et al., maternal urinary levels of MP were positively associated with length at birth in boys (Wu et al., 2017). Another study indicated associations between maternal urinary BP and decreased gestational age among 34 paired singleton neonates (Geer et al., 2017). In a prospective pre-conception cohort of subfertile couples, a significant decrease in neonatal head circumference related to maternal preconception MP level was observed (Messerlian et al., 2018). A prospective birth cohort study utilized repeated measures of fetal growth by ultrasonic scan and indicated that maternal paraben exposure was associated with lower abdominal circumference among male fetuses (Ferguson et al., 2018). This study demonstrated the non-linear and sex-specific association of parabens; a downward curvature and negative association were observed between the MP level and birth weight among female newborns. Similar to most cohort studies exhibiting negative associations between maternal paraben exposure and birth outcomes, the present study shared some common features including the period of urine collection (Geer et al., 2017), relatively high paraben exposure levels and maternal age (Ferguson et al., 2018; Messerlian et al., 2018). A positive association was found for pregnant women exposed to low paraben levels (Wu et al., 2017). In the present study, a significant association existed only for pregnant women exposed to MP above the 3rd quartile (154.46 μg/g cre.). Although the level of MP was similar to the geometric mean or median in those cohort studies, the similar direction in association between parabens and birth outcomes revealed comparable significant associations. Possible explanations for the inconsistent associations may be attributed to the different ranges of paraben exposure level, period of urine collection, population, co-exposure assessment, and covariate selection based on socioeconomic status in the regression model. In addition, the GAM also demonstrated the goodness of fit for the lower AIC in comparison with the linear regression model in the present study. An inverted U-shaped distribution between maternal MP levels and most birth outcomes indicated that either positive or negative directions were exhibited when pregnant women were exposed to low or high levels of MP, respectively. The present study further standardized the birth outcomes by calculating z-scores from the population mean and its deviation in different gestational age strata and stratified pregnant women by the sex of their newborns (Fig. S2) (Hsieh et al., 2006). The result showed a consistent pattern with Fig. 3, and a downward trend in birth outcomes was also observed in female neonates.

Hormonal regulation in pregnant women plays an important role in the process of fetal growth and development: estrogen is critical for the initiation and maintenance of pregnancy, promotion of the expression of essential growth factors for placental villous angiogenesis and regulation of fetal adrenal maturation and the onset of parturition (Albrecht and Pepe, 2010; Evain-Brion, 1994; Fujimoto et al., 2005). The estrogenic activities of parabens are mediated via binding to ERs or via inhibition of sulfotransferase, and these effects indirectly lead to elevations in free estradiol levels (Boberg et al., 2010; Prusakiewicz et al., 2007a). *In vitro*, the agonistic interactions with ER depend on the bulkiness of the alkyl group; the activity of parabens is proportional to the carbon number of the alkyl group from MP to BP (Watanabe et al., 2013). However, MP was found to influence the expression of a greater number of genes in MCF7 human breast cancer cells, and the anti-androgenic activity increased with the short length of the linear alkyl

Table 3
Multivariable linear regression model of birth outcomes and maternal urinary paraben concentration.

	Birth weight (g)	Birth length (cm)	Head circumference (cm)	Thoracic circumference (cm)	Ponderal index (g/cm^3)
Overall (N = 199), β (95% CI)					
MP[a]	6.52 (−28.06–41.10)	−0.07 (−0.25–0.11)	0.10 (−0.03–0.23)	−0.02 (−0.16–0.12)	0.02 (−0.01–0.04)
EP[a]	0.18 (−23.25–23.61)	0.07 (−0.05–0.19)	−0.04 (−0.12–0.05)	−0.02 (−0.13–0.07)	−0.01 (−0.03–0.01)
PP[a]	6.98 (−13.78–27.74)	0.05 (−0.06–0.16)	−0.05 (−0.13–0.03)	0.03 (−0.06–0.11)	< -0.01 (−0.02–0.01)
BP[a]	−4.16 (−19.27–10.95)	−0.03 (−0.11–0.05)	−0.01 (−0.07–0.04)	−0.04 (−0.10–0.02)	< 0.01 (−0.01–0.01)
Male neonates (N = 99), β (95% CI)					
MP[b]	17.96 (−160.69-196.62)	−0.71 (−1.64–0.21)	0.64 (−0.12–1.40)	0.16 (−0.64–0.96)	0.11 (0.01–0.22)*
EP[b]	−2.92 (−163.05-157.21)	−0.06 (−0.89–0.76)	−0.20 (−0.86–0.46)	−0.32 (−1.01–0.38)	0.01 (−0.09–0.11)
PP[b]	71.37 (−101.73-244.48)	0.66 (−0.24–1.55)	−0.09 (−0.79–0.62)	0.24 (−0.51–0.98)	−0.04 (−0.15–0.06)
BP[b]	−17.85 (−156.65–120.95)	−0.17 (−0.89–0.55)	−0.03 (−0.61–0.54)	−0.31 (−0.92–0.29)	0.01 (−0.07–0.10)
Female neonates (N = 100), β (95% CI)					
MP[b]	−215.98 (−393.03–38.94)*	−0.82 (−1.78–0.13)#	−0.56 (−1.12–0.01)*	−0.87 (−1.57–0.17)*	−0.04 (−0.17–0.09)
EP[b]	89.76 (−77.13-256.65)	0.37 (−0.54–1.27)	0.63 (0.11–1.15)*	0.18 (−0.49–0.84)	0.02 (−0.10–0.14)
PP[b]	59.36 (−108.80-227.52)	0.34 (−0.57–1.25)	−0.32 (−0.85–0.20)	0.28 (−0.39–0.95)	−0.01 (−0.14–0.11)
BP[b]	−110.08(-260.17–40.02)	−0.63 (−1.44–0.19)	−0.29 (−0.76–0.18)	−0.35 (−0.95–0.25)	< 0.01 (−0.11–0.11)
Overall (N = 199), β (95% CI)					
MP*birth sex[b]	−182.56 (−378.72–13.59)#	−0.02 (−1.06–1.02)	−0.84 (−1.56–0.12)*	−0.70 (−1.51–0.11)	−0.14 (−0.27–0.01)*
p value[c]	0.07	0.97	0.02	0.09	0.04
EP*birth sex[b]	−20.78 (−225.27-183.72)	0.31 (−0.76–1.38)	0.30 (−0.45–1.05)	0.04 (−0.80–0.87)	−0.06 (−0.20–0.07)
p value[c]	0.84	0.57	0.43	0.93	0.35
PP*birth sex[b]	−113.81 (−311.42-83.81)	−0.21 (−1.25–0.83)	−0.52 (−1.25–0.20)	−0.35 (−1.16–0.45)	−0.06 (−0.19–0.07)
p value[c]	0.26	0.69	0.15	0.39	0.35
BP*birth sex[b]	−88.41 (−287.17–110.34)	−0.45 (−1.49–0.59)	−0.27 (−1.00-0.47)	−0.02 (−0.84–0.80)	−0.01 (−0.14–0.13)
p value[c]	0.38	0.40	0.48	0.96	0.94

MP: methyl paraben; EP: ethyl paraben; PP: propyl paraben; BP: butyl paraben.
Adjusted covariates: age, height, pre-pregnancy BMI, gestational age, weight gain, parity, adverse pregnancy outcomes, oxidative stress, and birth sex.
*: p value < 0.05; #: p value < 0.10.
[a] Concentration of the natural-log transformation.
[b] Pregnant women were classified by the cutoff point for 3rd quartile urinary paraben concentration. Pregnant women with a paraben level below the 3rd quartile level were used as the reference group.
[c] p value for interaction.

chain of the paraben (Ding et al., 2017; Pugazhendhi et al., 2007). Consistent results have also been observed *in vivo*. Parabens caused uterotrophic effects in immature or ovariectomized female mice and decreased sperm counts and testosterone levels in male mice (Lemini et al., 2003; Oishi, 2002). In addition, some evidence has revealed that parabens can modulate the osteogenic and chondrogenic differentiation of multipotent stem cells (C3H10T1/2) and decrease serum markers of bone formation in mice, suggesting that the suppression of osteoblast differentiation via paraben exposure may influence fetal development during pregnancy (Hu et al., 2016, 2017). Even though the critical time window for fetal bone and muscle development is thought to be the 2nd trimester, a spot urine sample can fairly represent a person's internal concentration of parabens during pregnancy based on stable dietary intake and PCP usage (Fisher et al., 2017; Watkins et al., 2014). The moderate reliability (intraclass coefficient correlations: 0.55–0.65) within short-term (1 week) and long-term (4 months) exposure levels also revealed that the spot urinary sample was a good predictor of exposure to parabens (Dewalque et al., 2015). The negative association between maternal parabens exposure and abdominal circumference was also exhibited across repeated measures throughout the whole trimester (Ferguson et al., 2018).

The non-monotonic dose-response effect of endocrine-disrupting chemicals acting as estrogens and antiandrogens has been proposed for receptor selectivity and competition and for responses at specific dose ranges (Vandenberg et al., 2012). For example, BPA can bind to ERs at low doses but also binds weakly to androgen receptors and thyroid hormone receptors, which leads to non-monotonic dose-response curves in molecular mechanistic analyses (Villar-Pazos et al., 2017; Zhang et al., 2016). Thus, different ranges of exposure levels may account for the inconsistent results in epidemiological studies. The present study employed the GAM to describe the inverted U-shaped curve for maternal MP exposure and female birth outcomes and to allow for

Table 4
Sensitivity analysis of association between MP and birth outcomes.

	Birth weight (g)	Birth length (cm)	Head circumference (cm)	Thoracic circumference (cm)	Ponderal index (g/cm^3)
Male neonates, β (95% CI)					
Model 1 (N = 100)	17.96 (−160.69-196.62)	−0.71 (−1.64–0.21)	0.64 (−0.12–1.40)	0.16 (−0.64–0.96)	0.11 (0.01–0.22)*
Model 2 (N = 94)	16.30 (−164.54–197.14)	−0.77 (−1.70–0.17)	0.49 (−0.27–1.26)	0.16 (−0.64–0.97)	0.12 (0.01–0.23)*
Model 3 (N = 86)	71.40 (−107.21–250.01)	−0.54 (−1.44–0.35)	0.42 (−0.32–1.16)	0.21 (−0.56–0.98)	0.14 (0.03–0.26)*
Female neonates, β (95% CI)					
Model 1 (N = 99)	−215.98 (−393.03–38.94)*	−0.82 (−1.78–0.13)#	−0.56 (−1.12–0.01)*	−0.87 (−1.57–0.17)*	−0.04 (−0.17–0.09)
Model 2 (N = 93)	−203.74 (−364.20–21.30)*	−0.81 (−1.77–0.16)#	−0.56 (−1.13–0.01)#	−0.83 (−1.54–0.12)*	−0.03 (−0.16–0.09)
Model 3 (N = 88)	−205.76 (−383.27–28.26)*	−0.91 (−1.87–0.05)#	−0.54 (−1.13–0.04)#	−0.91 (−1.60–0.22)*	−0.02 (−0.14–0.11)

Pregnant women were classified by the cutoff point for 3rd quartile urinary parabens concentration.
Adjusted covariates: age, height, pre-pregnancy BMI, gestational age, weight gain, parity, and adverse pregnancy outcomes.
Model 1: A total of 199 pregnant women.
Model 2: The model excluded pregnant women who had gestational diabetes, preeclampsia, and placenta previa.
Model 3: The model excluded pregnant women who had adverse pregnancy outcomes or preterm and low birth weight neonates.
*: p value < 0.05; #: p value < 0.10.

Table 5
Estimation of natural indirect and direct effects of methyl paraben on oxidative stress and female birth weight.

Oxidative stress	Indirect effect (ACME, 95% CI)	Direct effect (ADE, 95% CI)	Total effect (95% CI)	Estimated proportion mediated (95% CI)
8-OHdG[a]	12.19 (−16.54–48.57)	−228.17 (−397.69–63.68)*	−215.98 (−386.54–48.65)*	−0.06 (−0.40–0.12)
8-NO_2Gua[a]	−1.73 (−31.66–16.18)	−214.25 (−387.00–38.87)*	−215.98 (−381.00–38.54)*	0.01 (−0.08–0.18)
8-iso-$PGF_{2\alpha a}$	−5.45 (−38.51–18.78)	−210.54 (−381.84–42.36)*	−215.98 (−389.53–55.42)*	0.03 (−0.11–0.25)
HNE-MA[a]	−31.44 (−114.11–48.23)	−184.54 (−337.93–33.73)*	−215.98 (−371.64–58.05)*	0.15 (−0.45–0.63)

Adjusted covariates: age, height, pre-pregnancy BMI, gestational age, weight gain, parity, and adverse pregnancy outcomes.
Pregnant women were classified by the cutoff point for 3rd quartile urinary paraben concentration. Pregnant women with a paraben level below the 3rd quartile level were used as the reference group.
Indirect effect (average causal mediation effects, ACME): The coefficient-linked maternal MP exposure and female birth weight due to the influence of MP exposure on oxidative stress.
Direct effect (average direct effect, ADE): The coefficient-linked maternal MP levels and female birth weight.
Total effect: the sum of the direct and indirect effects.
Proportion mediated: the ratio of indirect effect to the total effect.
[a] Concentration of the natural-log transformation.

more interpretability in the models. To confirm the influence of exposure to MP and to avoid the influence of intrauterine growth restriction on the fetus, this study excluded pregnant women who had adverse pregnancy outcomes and preterm and low birth weight neonates, and the results of the sensitivity analysis were similar. Further study is needed to clarify the impacts of estrogenic and/or anti-androgenic chemicals during gestation.

During pregnancy, women are subjected to a degree of oxidative stress that might be attributed to the production of free radicals in the mitochondria-rich placenta (Casanueva and Viteri, 2003). A growing body of evidence has indicated that free radical damage is correlated with adverse pregnancy outcomes such as gestational hypertension, preeclampsia, and insulin resistance and diabetes, leading to preterm birth and low birth weight (Bharadwaj et al., 2017; Kim et al., 2005; Negi et al., 2012; Turpin et al., 2015). Nonetheless, paraben-induced oxidative stress remains controversial (Dubey et al., 2017; Kopalli et al., 2013). In human keratinocyte cells, MP can enhance lipid peroxidation and intracellular ROS generation (Dubey et al., 2017). However, based on the antioxidant property of MP, at nanomolar concentrations, MP can attenuate hydrogen peroxide-induced cytotoxicity in neuroblastoma cells and suppress lipid peroxidation products in mouse brain tissues (Kopalli et al., 2013). A similar result was also presented in in vivo research, indicating the elevated activity of oxidative stress and reduced levels of lipid peroxidation after exposure to most parabens (Silva et al., 2018). In the present study, parabens were positively associated with 8-NO_2Gua but negatively associated with 8-iso-$PGF_{2\alpha}$ in pregnant women, revealing that exposure to parabens may increase nitrative DNA damage but decrease lipid hydroperoxides (Kawanishi et al., 2006; Ogino and Wang, 2007). The inverse association with 8-iso-$PGF_{2\alpha}$ could also be explained by the non-monotonic dose responses in mitochondrial oxidation or the activity of antioxidant enzymes (Vandenberg et al., 2012).

Food intake is one of the major routes of exposure to parabens. In the US, parabens were detectable in more than 90% of 267 food samples including beverages, dairy products, fats and oils, fish and shellfish, grains, meat, fruits, and vegetables (Liao et al., 2013b). Among 282 food samples in China, 99% contained at least one detectable paraben (Liao et al., 2013a). Parabens can be used as additive antimicrobials in processed food (Soni et al., 2005). According to the Taiwan Food and Drug Administration, the permitted amount of paraben used in food is less than 0.25 g/kg for bean curd sheets and soy sauce, 0.1 g/kg for vinegar and beverages without carbonic acid and 0.012 g/kg for fresh vegetables and fruit. This study also examined the association between maternal paraben exposure and food consumption. The results revealed that only the frequencies of milk ($r = 0.29$, p value < 0.01) and vegetable ($r = 0.16$, p value $= 0.05$) ingestion were significantly associated with PP among pregnant women.

This prospective cohort design provided an informative and longitudinal evaluation of maternal paraben exposure and its influence on neonatal outcomes. Another strength of the present study is that the results could aid in identifying biological implications. The increase in oxidative stress might be enhanced by nitrative DNA damage among pregnant women exposed to parabens. Some limitations of this study should be considered. First, the relatively small sample size due to the challenge of establishing a cohort of pregnant women could be the major limitation of the present study. While we did not find evidence of mediation by oxidative stress on the relation between birth weight and maternal exposure to MP, larger studies are needed to confirm this finding as the non-significant results of the mediation analysis may have resulted due to insufficient power (64.8% by utilizing the Sobel test statistic) in this study. Second, this study population comprised highly educated pregnant women, and thus, the results of this study would be difficult to generalize. Third, the effects of co-exposure to multiple environmental toxicants including bisphenol A, phthalates, and polycyclic aromatic hydrocarbons, on birth outcomes cannot be ignored. Fourth, a single spot urine sample during the third trimester might be criticized for representativeness. However, several studies have reported that a spot urine sample was a good predictor of long-term exposure and provided sufficient sensitivity to classify individual exposure levels in epidemiologic studies (Dewalque et al., 2015; Mahalingaiah et al., 2008)

This study demonstrated the paraben exposure profile of pregnant women in northern Taiwan and revealed a negative association between maternal MP exposure and female birth outcomes. The downward curvature between maternal paraben exposure and neonatal body weight, head circumference and thoracic circumference in relation to child development should be considered. The non-significant mediation by oxidative stress in the relationship between paraben exposure and neonatal body weight should be further confirmed. Further study is needed to clarify the mechanism in relation to the sex-specific association of parabens.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

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