原 著

Prenatal exposure to parabens in relation to childhood obesity and the gut microbiome

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Objectives: Parabens, which are common antimicrobial preservatives, are considered to be endocrine-disrupting chemicals. Previous studies regarding maternal exposure to paraben have shown that disturbances in physiological endocrine and metabolic signals during early childhood may lead to the long-term adverse health effects in children. We investigated the effects of maternal exposure to paraben on childhood obesity and gut microbiome diversity. **Methods:** We collected the data on 284 maternalinfant pairs from the central region of Taiwan Maternal-Infant Cohort Study. Liquid chromatography-tandem mass spectrometry was used to detect 4 common parabens, including methyl-paraben, ethyl-paraben, propyl-paraben, and butyl-paraben in maternal urinary samples. In addition, shotgun metagenomics sequencing was used to analyze 98 children's fecal samples. **Results:** Greater maternal exposure to paraben was observed in boys who were significantly shorter and with wider chest circumferences and in girls with higher body mass index. Increased maternal exposure to paraben significantly reduced the abundance of several species, such as *Barnesiella*, *Bacteroides uniformis,* and *Eubacterium rectale*, but increased the abundance of several opportunistic pathogens, which interfered with the regulation of energy consumption. **Conclusions:** Maternal exposure to paraben promoted the development of obesity in girls and disrupted the diversity of gut microbial community. Maternal exposure to paraben may promote obesity in children at preschooler age. In addition, additional studies on the effects of the composition of the gut microbiome after puberty are required. (*Taiwan J Public Health. 2023;**42(1)**:62-74*)

Key Words: parabens, prenatal exposure, childhood obesity, gut microbiome

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INTRODUCTIONS

Childhood obesity is rapidly reaching epidemic levels in developed countries, becoming a crucial public health problem [1]. Lifestyle factors such as processed or fast food intake, genetic predisposition, and urbanization all contribute to childhood overweight [2] but remain inadequate for clarifying the rapid increases in obesity rates worldwide. The additional causal role of environmental factors in the development of overweight is gaining increasing attention [3].

Parabens are a group of esters of parahydroxybenzoic acid. They have been

used for nearly 100 years as antimicrobial preservatives in the food, drug, and cosmetic industries [4]. Biomonitoring has confirmed widespread paraben exposure in newborns, children, adults, and pregnant women [5]. Increasing evidence from epidemiological studies suggests that chronic exposure to parabens may cause endocrine disorders, decreased male fertility, obesity, neurodevelopmental disorders, and carcinogenicity [6,7]. Given the ubiquity of parabens due to extensive use of personal care products worldwide, their adverse effects remain contradictory.

The gut microbiome reaches maturity in the first 3 years of life [8]. Symbiotic microbiota have various functions, such as assisting in the degradation and absorption of nutrients and indigestible carbohydrates, maintaining the intestinal mucosal barrier, blocking pathogens, regulating the immune system, contributing to intestinal health, and producing vitamins and short-chain fatty acids [9]. However, dysbiosis may disrupt these mechanisms. For instance, an increased *Firmicutes*/*Bacteroidetes* ratio (F/B ratio) is commonly observed alongside obesity. In recent years, sophisticated analytical methods have increasingly highlighted the role of microbiota in diseases and obesity [10].

Owing to the widespread use of parabens but limited amount of research into this area, the health effects of prenatal exposure to parabens on children require clarification. The present study investigated the effects of prenatal paraben exposure on obesity and gut microbiome distribution in children.

MATERIALS AND METHODS

Study Population

The Taiwan Maternal and Infant Cohort Study (TMICS) is a nationwide prospective birth cohort that has been conducted in northern, central, southern, and eastern Taiwan since October 2012 [11]. This cohort has been approved by the ethics committees of the National Health Research Institutes (NHRI) and nine hospitals. In the present study, 284 mother–child pairs from the TMICS cohort were recruited from three hospitals in central Taiwan. The participants were invited to these partner hospitals again if they agreed to visit them from October 2016 to May 2018. In the second part of the analysis, which included gut microbiota data from 98 children, fecal samples were collected at home and kept frozen during transport to the NHRI (Figure 1).

Measurement and Classification of Obesity in Children

Children tracked by the TMICS were measured for their height, weight, head circumference, and chest circumference by the partner hospital for physical assessment, and each individual's z-score was calculated by subtracting the mean and dividing by the standard deviation from the population [12]. Children's body mass index (BMI) classification referred to the 2013 BMI values for the growth of children and adolescents recommended by Taiwan's Health Promotion Administration, Ministry of Health and Welfare [13].

Measurement of Parabens in Urine

The urinary concentrations of four paraben species were determined in the third trimester by using liquid chromatography–tandem mass spectrometry. To adjust for interindividual variability in the excretory function, paraben concentrations were calibrated per unit mass of creatinine (μg/g cre). Concentrations below the limit of detection (LOD) were replaced with values corresponding to the LOD/2 [14].

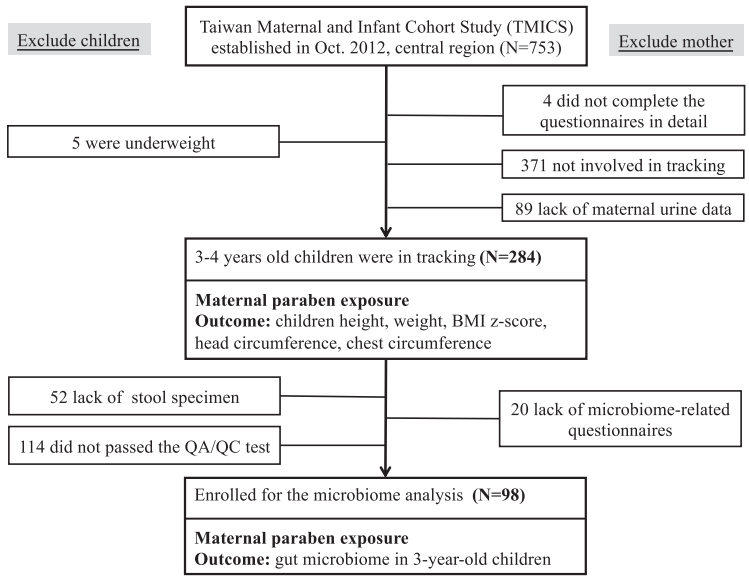

Figure 1. Flow chart for participant's enrollment in the study

Processing of Microbial Samples

Because collecting stool samples at the hospital was inconvenient, we explained the procedure using the stool collection package to mothers so that they could collect a sample at home and keep it frozen during transport to the NHRI. DNA was extracted using the QIAamp Fast DNA Stool Mini Kit (QIAGEN). Indexed adapters were added to the DNA fragments using the Illumina Nextera XT DNA Library Prep Kit. After library construction, samples were sequenced in paired-end 2 × 150 bp format (150PE) using the NovaSeq 6000 system (Illumina, San Diego, CA, USA). Quality trimmed and dehosted reads were classified using Kraken2 against a database containing NCBI RefSeq Complete Genomes. Classified reads were redistributed to the species level using Bracken.

Statistical Analysis

TMICS study data were evaluated using RStudio Server version 3.5 and IBM SPSS version 22.0. We compared demographic characteristics by using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Covariates were mainly considered based on maternal factors (i.e., maternal age, annual family income, prepregnancy BMI, and gestational weeks). Moreover, log-transformed quantities owing to the skewed distribution of the maternal paraben concentrations were calculated and incorporated into the linear regression to identify the correlation of children's outcomes. Logistic regression models with overweight development were applied to compare differences between low- (reference), medium-, and high-tertile paraben exposure groups. A fractional regression model was used to analyze the correlation between paraben exposure and gut bacteria and further modulate the correlation between sex and antibiotics used in children. Microbial datasets were analyzed in GraphPad PRISM 9 for Windows, and $p < .05$ was considered statistically significant.

RESULTS

Participant Characteristics

The mean age of the 284 mother–child pairs was 32.9 years, and the mean prepregnant BMI was 20.94 kg/m^2. Most of the mothers (88.7%) had a bachelor's degree or higher, and 51.6% had an annual household income of more than USD30,000. None of them were habitual smokers, but 17.3% were exposed to secondhand smoke at home. At 3 years of age, 14% (n = 41) of the children were overweight or obese; most of the children (95.8%) had been breastfed, and 26.1% and 57.4% had been given antibiotics and probiotics within 6 months of birth, respectively. The mothers of overweight or obese children tended to have higher weight and prepregnancy BMI than those of children within the healthy BMI range (Table 1).

Table 2 summarizes the concentrations of parabens among the mothers. The detection rates of MeP, EtP, PrP, and BuP were 96.5%, 68.0%, 87.3%, and 68.7%, respectively, and MeP showed the highest geometric mean, namely 27.12 μg/g-cre; no significant differences in prenatal exposure were noted between boys and girls (Table 2).

Association Between Maternal Parabens and Childhood Obesity

Multiple regression models estimating maternal paraben exposure and childhood obesity among the 284 mother–child pairs revealed that per 10-fold increase in prenatal MeP and ΣPB concentration, the height of the children decreased significantly by 0.18 cm and 0.21 cm, respectively ($p = .03$ and $p < .01$, respectively), and that per 10-fold increase in prenatal BuP, the chest circumference increased significantly by 0.17 cm ($p = .02$), with boys more likely to be affected. In addition, maternal PrP and ΣPB were significantly associated with BMI in girls ($p = .03$ and $p = .02$, respectively) (Figure 2).

On the basis of the significant associations of maternal paraben exposure with height and chest circumference in boys and with BMI in girls, we stratified the correlation by sex, and mothers were classified by tertile urinary paraben concentration. After adjustment for covariates, compared with mothers with low MeP and ΣPB exposure, those with high MeP and ΣPB exposure had male children with significantly shorter height (β = 0.367 cm, 95% confidence interval [CI]: -8.690, -2.594; β = 0.391 cm, 95% CI: -9.087, -3.159) and wider chest circumference (β = 0.204 cm, 95% CI: 0.014, 2.800). By contrast, a maternal MeP and ΣPB exposure–related BMI increase was more evident in girls, and significant correlations existed between increased MeP and ΣPB levels and higher BMI (β = 0.378 cm, 95% CI: 1.811, 7.813; β = 0.310 cm, 95% CI: 0.939, 7.046) compared with mothers with low MeP and ΣPB exposure (Table 3).

Distribution of the Gut Microbiome in Children

This study analyzed gut microbiota data from 98 children. The average relative abundance at the phylum level included 62% for Bacteroidetes and 20% for Firmicutes, followed by Proteobacteria, Actinobacteria, and Verrucomicrobia. The average relative abundance at the genus level included 38% for Bacteroides, 16% for *Phocaeicola*, and 9% for *Faecalibacterium* (Figure 3a, 3b). The F/B ratio (0.046) of the BMI z-score level above the third tertile was marginally higher than that in the second and first tertile groups (0.038 and 0.041, respectively) (Figure 3c).

Table 1. The demographic characteristics of pregnant women and children

Characteristic		Mean (SD)/ n (%)			
		Normal (n=243)	Ow/Ob (n=41)	p-value[a]	Total (n=284)
Mother					
Maternal age (years)		33.04 (4.18)	32.51 (4.56)	0.647	32.96 (4.23)
Maternal height (cm)		160.10 (5.02)	160.52 (5.57)	0.794	160.16 (5.09)
Maternal weight (kg)		53.01 (8.02)	57.97(10.38)	0.004**	53.72 (8.55)
Pre-pregnancy BMI (kg/m^2)[b]		20.68 (2.81)	22.48 (3.15)	<0.001**	20.94 (2.93)
Maternal GWG		9.12 (4.51)	8.81 (3.68)	0.990	9.08 (4.40)
Maternal education	≤ 12	26 (10.7)	6 (14.6)	0.619	32 (11.3)
(years)	13–16	176 (72.4)	30 (73.2)		206 (72.5)
	> 16	41 (16.9)	5 (12.2)		46 (16.2)
Household income	< 30 K	101 (41.6)	20 (48.8)	0.446	121 (42.6)
(USD/year)	30-50 K	65 (26.7)	12 (29.3)		77 (27.1)
	> 50 K	63 (25.9)	7 (17.1)		70 (24.5)
Pre-pregnancy BMI	Underweight	42 (17.3)	1 (2.4)	0.016*	43 (15.1)
	Normal	166 (68.3)	30 (73.2)		196 (69.0)
	Overweight	16 (6.6)	6 (14.6)		22 (7.7)
Caesarean	Yes	66 (27.2)	14 (34.1)	0.366	80 (28.2)
Maternal allergy	Yes	99 (40.7)	12 (29.3)	0.172	111 (39.1)
Children					
Age (years)		3.86 (0.55)	3.97 (0.58)	0.257	3.90 (0.57)
Gender	Boy	151 (62.1)	24 (58.5)	0.661	175 (61.6)
	Girl	92 (37.9)	17 (41.5)		109 (38.4)
Height (cm)		101.36 (5.37)	103.59 (6.30)	0.024*	101.68 (5.56)
Weight (kg)		15.64 (1.79)	19.26 (3.02)	<0.001**	16.17 (2.38)
BMI (kg/m^2)		15.21 (0.91)	17.87 (1.35)	<0.001**	15.60 (1.36)
Head circumference (cm)		50.22 (1.40)	51.40 (1.70)	<0.001**	50.39 (1.50)
Chest Circumference (cm)		52.73 (2.75)	57.01 (3.70)	<0.001**	53.34 (3.26)
Gestational age (week)		38.66 (1.67)	38.53 (1.49)	0.797	38.64 (1.64)
Parity	1	116 (47.7)	23 (56.1)	0.322	139 (48.9)
	2	127 (52.3)	18 (43.9)		145 (51.1)
Breastfeeding	Yes	232 (95.5)	40 (97.6)	0.273	272 (95.8)
Passive smoking	Yes	43 (17.7)	6 (14.6)	0.653	49 (17.3)
Antibiotics[c]	Yes	64 (26.3)	10 (24.4)	0.526	74 (26.1)
Probiotics[c]	Yes	143 (58.8)	20 (48.8)	0.271	163 (57.4)
Lactics[c]	Yes	136 (56.0)	24 (58.5)	0.401	160 (56.3)
Asthma	Yes	11 (4.5)	4 (9.8)	0.171	15 (5.3)
Allergic rhinitis	Yes	53 (21.8)	10 (24.4)	0.733	63 (22.2)
Atopic dermatitis/ eczema	Yes	71 (29.2)	12 (29.3)	0.955	83 (29.2)

[a] p-values were estimated using Mann-Whitney U test and Chi-square test between normal weight and Ow/Ob group.
[b] Pre-pregnancy BMI classified by Underweight: BMI <18.5; Normal: 18.5 ≤BMI <24; Overweight: BMI ≥24
[c] Antibiotics, probiotics and lactics use within six months.
Ow/Ob, Overweight/ Obese; BMI, body mass index; GWG, gestational weight gain, K, thousand.
*p value<0.05, **p value<0.01

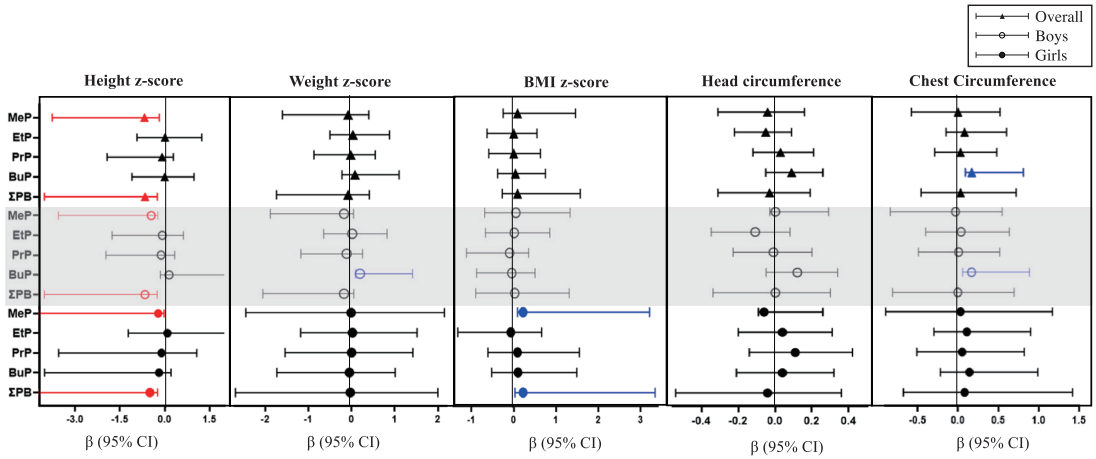

Figure 2. Associations between maternal urinary paraben concentrations and childhood obesity

Note: Model adjusted for annual family income, maternal age, breastfeeding, BMI before pregnancy, gestational age. Red line: significantly negative association; blue line: significantly positive association.

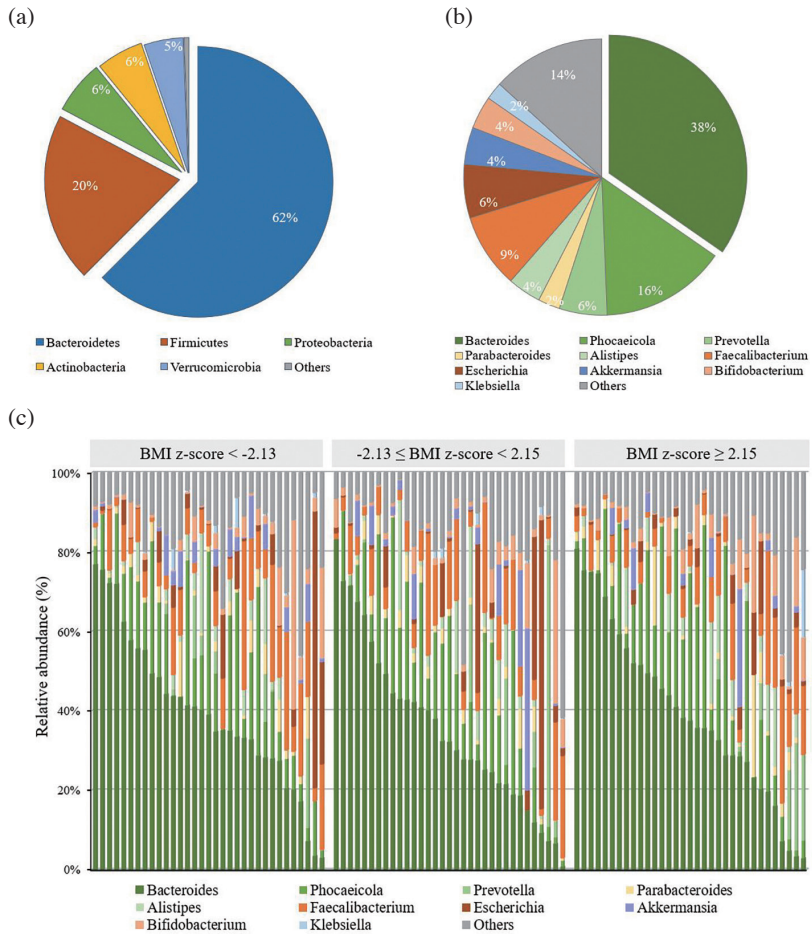

Figure 3. (a) Phylum level and (b) Genus level of relative abundance of gut microbiota in children (c) Genus level of gut microbiota in children classified by tertiles of BMI z-score

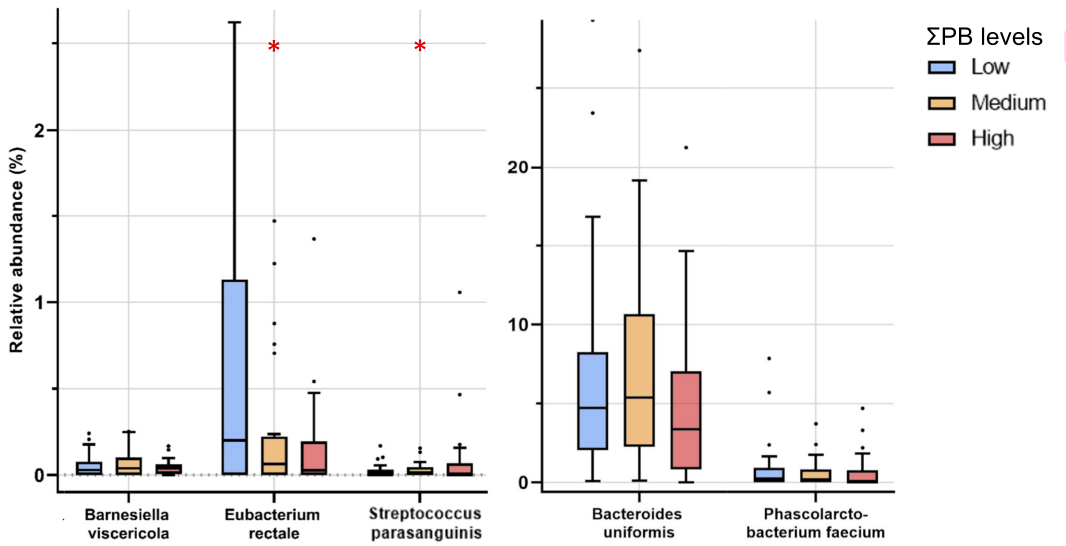

Figure 4. Distributions species level of gut microbiota classified by the tertiles of urinary total paraben

Note: Low: ΣPB <0.21 molar sum; Medium: 0.21 ≤ ΣPB < 0.75 molar sum; High: ΣPB >0.75 molar sum.
*p-values were estimated using ANOVA trend test.

Table 2. Summarized statistics for urinary paraben concentrations among pregnant women (n=284)

	>DF (%)	LOD (ng/mL)[a]	Mean (SD)	GM (95% CI)	Min	Percentile			Max
						25th	50th	75th	
Paraben (μg/g-cre)									
MeP	96.5	0.020	137.78 (562.78)	27.12 (21.13, 34.82)	< LOD	10.70	32.68	96.76	1,339.13
EtP	68.0	0.020	14.42 (62.22)	0.78 (0.56, 1.10)	< LOD	0.04	1.36	6.48	856.04
PrP	87.3	0.024	56.06 (173.94)	4.86 (3.54, 6.69)	< LOD	1.35	6.65	32.09	1,369.94
BuP	68.7	0.024	21.27 (96.33)	0.97 (0.70, 1.37)	< LOD	0.05	1.80	7.88	938.62
ΣPB[b]	-	-	1.41 (4.10)	0.35 (0.28, 0.44)	-	0.13	0.38	1.13	50.94

[a] When concentration below LOD, the value was recalculated as (LOD/2)
[b] ΣPB = (MeP/152.15+EtP/166.17+PrP/180.2+BuP/194.23), unit: molar sum
MeP, methyl-paraben; EtP, ethyl-paraben; PrP, propyl-paraben; BuP, butyl-paraben; DF, detection frequency; LOD, limit of detection; GM, geometric mean; Min, minimum; Max, maximum; cre, creatinine.

Association Between Maternal Parabens and Gut Microbiota in Children

In the fractional regression model adjusted for annual family income, child sex, BMI, antibiotic and probiotic use, and maternal MeP were negatively associated with *Eubacterium rectale* (β = -0.366, p < .01) and *Phascolarcto-bacterium faecium* (β = -0.246, p = .01); maternal PrP was negatively associated with *Bacteroides uniformis* (β = -0.333, p < .01); and maternal MeP was positively associated with *Streptococcus parasanguinis* (β = 0.212, p = .05) (Table 4).

We analyzed the distribution of gut microbiota classified by the tertiles of maternal total urinary parabens. Mothers exposed to ΣPB levels above the third tertile had a

Table 3. Adjusted changes of maternal exposure to maternal parabens classified by tertiles of **ΣiPB** concentration related to childhood obesity

Variables[a]	Boys (n=175)								Girls (n=109)			
	Height z-score				Chest circumference (cm)				BMI z-score			
	Crude		Adjusted[b]		Crude		Adjusted[b]		Crude		Adjusted[b]	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
MeP												
T1	Ref		Ref		Ref		Ref		Ref		Ref	
T2	-0.298 (0.11)	<0.001**	-0.313 (0.10)	0.003**	-0.063 (0.08)	0.475	-0.099 (0.07)	0.362	-0.075 (0.05)	0.490	-0.056 (0.04)	0.632
T3	-0.377 (0.09)	<0.001**	-0.367 (0.11)	<0.001**	-0.049 (0.05)	0.577	-0.032 (0.05)	0.764	0.259 (0.07)	0.019*	0.378 (0.12)	0.002**
EtP												
T1	Ref		Ref		Ref		Ref		Ref		Ref	
T2	-0.084 (0.05)	0.343	-0.073 (0.02)	0.503	-0.038 (0.06)	0.671	-0.080 (0.04)	0.466	0.017 (0.03)	0.875	0.001 (0.02)	0.994
T3	-0.097 (0.04)	0.276	-0.144 (0.04)	0.186	-0.006 (0.02)	0.943	0.056 (0.04)	0.612	-0.121 (0.06)	0.271	-0.105 (0.03)	0.403
PrP												
T1	Ref		Ref		Ref		Ref		Ref		Ref	
T2	-0.034 (0.02)	0.695	-0.006 (0.01)	0.953	0.049 (0.01)	0.582	0.099 (0.05)	0.364	0.153 (0.03)	0.165	0.017 (0.06)	0.896
T3	-0.218 (0.02)	0.013*	-0.183 (0.06)	0.082	0.008 (0.03)	0.928	0.017 (0.03)	0.872	0.225 (0.06)	0.042*	0.121 (0.05)	0.317
BuP												
T1	Ref		Ref		Ref		Ref		Ref		Ref	
T2	0.174 (0.03)	0.048*	0.180 (0.05)	0.086	0.080 (0.02)	0.365	0.108 (0.02)	0.304	-0.127 (0.04)	0.258	-0.096 (0.06)	0.464
T3	0.074 (0.01)	0.397	0.148 (0.07)	0.148	0.193 (0.04)	0.029*	0.204 (0.09)	0.048*	0.021 (0.02)	0.851	0.111 (0.08)	0.401
ΣPB												
T1	Ref		Ref		Ref		Ref		Ref		Ref	
T2	-0.434 (0.04)	<0.001**	-0.451 (0.12)	<0.001**	-0.032 (0.03)	0.716	-0.057 (0.06)	0.598	-0.054 (0.03)	0.620	-0.019 (0.06)	0.866
T3	-0.437 (0.02)	<0.001**	-0.391 (0.11)	<0.001**	-0.014 (0.03)	0.878	-0.020 (0.03)	0.852	0.215 (0.10)	0.050*	0.310 (0.11)	0.011*

[a] Parabens were adjusted for log10-creatinine concentrations.

[b] Adjusted model was control for annual family income, maternal age, breastfeeding, BMI before pregnancy, gestational age and birth weight.

MeP, methyl-paraben; EtP, ethyl-paraben; PrP, propyl-paraben; BuP, butyl-paraben; T, tertile; BMI, body mass index

*p value<0.05, **p value<0.01

higher relative abundance of *Streptococcus parasanguinis*, whereas those with low ΣPB exposure were more likely to have children with a significantly higher relative abundance of *Eubacterium rectale* (Figure 4).

DISCUSSIONS

This paper describes the exposure profile of parabens among pregnant women in central Taiwan. This study was divided into two parts to investigate the effects of maternal paraben exposure on childhood obesity and the resultant changes in gut microbiome distribution among preschool children. MeP was generally the primary paraben in maternal urine, and the urinary concentrations in this study were lower than those reported in Iran, Greece, and another Taiwanese cohort study in 2014 [15-17]. The urinary concentrations of EtP (0.78 μg/g-cre) and PrP (4.86 μg/g-cre) in our pregnant women were higher than those in Iranian pregnant women (0.23 and 2.2 μg/g-cre, respectively) [15]. In addition, the urinary concentrations of MeP, EtP, and PrP in our pregnant women were significantly lower than those in Greek

Table 4. The association between maternal urinary paraben levels and the relative abundance of gut microbiota in children (n=98)

Variables (μg/g-cre)	Bacteroides uniformis	p value	*Streptococcus parasanguinis*	p value	Barnesiella viscericola	p value	*Eubacterium rectale*	p value	*Phascolarcto-bacterium faecium*	p value
	β (SE)		β (SE)		β (SE)		β (SE)		β (SE)	
Crude model [a]										
MeP	-0.035 (0.012)	0.807	-0.019 (0.001)	0.775	0.013 (0.001)	0.897	-0.336 (0.007)	0.005**	-0.285 (0.002)	0.004**
EtP	0.112 (0.008)	0.272	0.096 (0.006)	0.346	0.042 (0.002)	0.682	-0.089 (0.004)	0.468	-0.191 (0.001)	0.059
PrP	-0.155 (0.008)	0.127	0.057 (0.001)	0.576	-0.196 (0.001)	0.051*	-0.244 (0.004)	0.055	-0.020 (0.007)	0.849
BuP	0.087 (0.008)	0.392	0.169 (0.003)	0.096	-0.128 (0.006)	0.245	0.010 (0.004)	0.935	-0.111 (0.001)	0.276
ΣPB	0.066 (0.013)	0.520	-0.037 (0.001)	0.718	-0.051 (0.001)	0.617	-0.335 (0.007)	0.005	-0.200 (0.002)	0.048*
Model 1 [a]										
MeP	0.001 (0.013)	0.997	0.007 (0.003)	0.951	-0.003 (0.001)	0.977	-0.375 (0.008)	0.004**	-0.275 (0.002)	0.008**
EtP	0.118 (0.009)	0.271	0.109 (0.001)	0.312	0.063 (0.006)	0.566	-0.115 (0.005)	0.341	-0.155 (0.003)	0.140
PrP	-0.163 (0.008)	0.137	0.093 (0.002)	0.394	-0.235 (0.001)	0.038*	-0.217 (0.005)	0.105	0.005 (0.004)	0.960
BuP	0.079 (0.008)	0.467	0.192 (0.001)	0.072	-0.141 (0.008)	0.192	-0.016 (0.004)	0.901	-0.126 (0.001)	0.231
ΣPB	0.107 (0.014)	0.323	-0.005 (0.003)	0.965	-0.067 (0.001)	0.537	-0.372 (0.008)	0.004	-0.191 (0.002)	0.068
Model 2 [b]										
MeP	0.088 (0.012)	0.438	0.046 (0.001)	0.684	0.020 (0.001)	0.865	-0.366 (0.007)	0.003**	-0.246 (0.002)	0.010*
EtP	0.062 (0.008)	0.588	0.136 (0.005)	0.235	0.104 (0.001)	0.368	-0.120 (0.005)	0.351	-0.192 (0.001)	0.090
PrP	-0.333 (0.008)	0.004**	0.151 (0.001)	0.198	-0.218 (0.004)	0.065	-0.172 (0.005)	0.198	-0.009 (0.005)	0.938
BuP	-0.017 (0.008)	0.880	0.212 (0.001)	0.050*	-0.104 (0.006)	0.369	0.047 (0.004)	0.717	-0.126 (0.001)	0.267
ΣPB	0.021 (0.013)	0.858	0.075 (0.001)	0.513	-0.264 (0.001)	0.792	-0.364 (0.007)	0.004	-0.216 (0.002)	0.056

[a] All models were adjusted for log10-creatinine paraben concentrations and for model 1 was control for annual family income and child's gender.

[b] Model 2 was control for annual family income, child's gender, BMI, antibiotic and probiotic use.

MeP, methyl-paraben; EtP, ethyl-paraben; PrP, propyl-paraben; BuP, butyl-paraben.

*p value<0.05, **p value<0.01

pregnant women (103.2, 3.2, and 11.3 μg/g-cre, respectively) [16]. These discrepancies have resulted from product preferences and usage habits due to economic status, climatic conditions, or culture [18]. Women tend to use skin care products, especially cosmetic products, more frequently in winter; this phenomenon could also lead to variations in paraben exposure [19].

We observed that maternal MeP and ΣPB were negatively associated with height in boys, whereas maternal PrP and ΣPB were positively associated with BMI in girls. A longitudinal cohort of children in California revealed that PrP was consistently correlated with an increased BMI z-score and overweight status for 5-year-olds (MeP, β = 0.08, 95% CI: 0.01, 0.16; PrP, β = 0.06, 95% CI: 0.02, 0.10) [20]. Philippat et al. found that higher maternal exposure to MeP and EtP was correlated with a significant increase in BMI in male children aged 2–3 years (β = 1.38, 95% CI: 0.25, 2.5; β = 1.27, 95% CI: 0.05, 2.49) [21]. A German cohort study reported a positive relationship between maternal BuP exposure and childhood overweight during the first 8 years of life (β = 0.26 kg/m^2, 95% CI: 0.02, 0.05), with a stronger trend in girls. That study proved this relationship by exposing pregnant mice to BuP, which resulted in higher weight gain and food intake in female offspring. This effect was accompanied by an epigenetic modification,

leading to reduced hypothalamic POMC expression. Maternal exposure to parabens may promote the development of childhood overweight by altering the POMC-mediated regulation of neuronal appetite [6].

Our results indicated a significant correlation between paraben exposure and gut microbiota at the species level and consequent effects on human health. Maternal MeP was significantly negatively associated with *Eubacterium rectale* and *Phascolarctobacterium faecium*, and maternal PrP was significantly negatively associated with *Bacteroides uniformis*. In an animal study, Hu et al. exposed female rats to MeP and then nursed their pups after weaning and continued to observe their weight changes. This phenomenon is consistent with the decrease in body weight of adolescent female rats, which suggests that MeP may affect gut microbiota diversity and lead to metabolic changes in rats [22]. In addition, maternal MeP was positively associated with *Streptococcus parasanguinis*, which is one of the major colonizers of dental surfaces [23].

Eubacterium rectale and *Phascolarctobacterium faecium* ferment indigestible carbohydrates into short-chain fatty acids, which are composed mainly of acetate, propionate, and butyrate [24]. Higher concentrations of these species in feces have been associated with gut permeability, markers of metabolic disorders, hypertension, and obesity [9]. Although they prevent diet-induced obesity in the host, excess short-chain fatty acids also provide additional energy, thereby promoting obesity.

The general heritability of the microbiome could be less than 5%, and more than 25% of the variation in the microbiome is caused by dietary, drug, and environmental factors [25]. Gut microbiota depend on the host's diet for survival energy and can be altered by changes in diet. For instance, mice fed a high-fat diet were found to have a decreased abundance of *Bacteroidetes* and an increased abundance of *Firmicutes* and *Proteobacteria*. In summary, diet is the main trigger of obesity, which is progressively characterized by high sugar and fat consumption in developed countries [26].

Limitations

Our study had some limitations. First, parabens have a short half-life in urine and were sampled at different times; our results might have suffered from analytical bias. Second, other endocrine disruptor chemicals with obesogenic effects, such as BPA and phthalates, were not measured in this study. These chemicals are not only prevalent in daily life but also may be interfering factors when people are coexposed. This reality may have prevented us from fully determining the extent to which maternal paraben exposure contributes to obesity in later generations. Next, this study was limited by its underrepresentation of obese children (n = 41), which restricted the generalizability of the results. Finally, because of strain specificity, microorganisms of the same genus may have contrasting effects on obesity, which may have led to contradictory results.

Conclusions and Future Research Directions

In this study, a positive association was observed between urinary paraben concentration and childhood BMI, with a stronger trend in girls. Gut dysbiosis exhibited a strong association with obesity, and maternal parabens were potentially obesogenic to the offspring at preschool age. Because of the complexity of the gut microbiota, data analyses with larger samples are warranted to elucidate the mechanisms underlying the

correlations with obesity, and functional pathway studies are required to identify potential pathogenic species. In addition, future studies are recommended to explore the management of personal care products containing parabens and specific microbiota in obese individuals.

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出生前對羥基苯甲酸酯暴露與兒童肥胖及其腸道菌相組成之相關性探討

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目標：對羥基苯甲酸酯（Parabens, PB）作為常見防腐劑也具有干擾內分泌的特性。過去研究指出產前PB的暴露會干擾人體內分泌和代謝信號並可能會對健康造成長期的影響。本研究欲探討孕婦PB暴露對孩童過重與其腸道菌分布的影響。**方法：**納入台灣婦幼世代研究（TMICS）在中部地區的284組母子。以液相層析串聯式質譜儀（LC-MS/MS）檢測孕婦尿中四種常見的PB，包括對羥基苯甲酸甲酯、對羥基苯甲酸乙酯、對羥基苯甲酸丙酯、對羥基苯甲酸丁酯。將98位兒童的糞便樣本以總基因體定序法（shotgun metagenomics sequencing）獲得腸道菌的組成和相對豐度，再分析產前PB暴露與兒童成長及腸道菌相之相關性。**結果：**產前PB暴露增加，觀察到男童的身高顯著降低，胸圍則較寬，而女童的BMI則較高。在腸道菌部分，顯著減少了分解多醣、纖維等有益物種的豐度，如*Barnesiella spp*、*Bacteroides uniformis*和*Eubacterium rectale*。相反地，伺機性菌種明顯增加，並干擾了能量攝入的調節。**結論：**產前PB對出生至學齡前兒童具潛在的致肥胖性，並影響其腸道菌叢的分布，而對於在青春期後成長情形的影響與腸道菌相組成的變化，待進一步研究做驗證。（台灣衛誌 2023；**42(1)**：62-74）

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