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# Mediating effects of insulin resistance on lipid metabolism with elevated paraben exposure in the general Taiwan population

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**Introduction:** Parabens are commonly used to prevent bacteria from growing in cosmetics and foodstuffs. Parabens have been reported to influence hormone regulation, potentially leading to metabolic anomalies, including insulin resistance and obesity. However, there is a paucity of knowledge regarding the relationship between urinary paraben levels and lipid metabolism in the general Taiwanese population. Therefore, the objective of this study was to determine whether the mediating role of insulin resistance exists between paraben exposure and lipid metabolism.

**Methods:** We selected the data of 264 adult participants from a representative survey in five major Taiwan area in 2013. UPLC tandem mass spectrometry was used to examine four urine parabens: methyl- (MeP), ethyl- (EtP), propyl- (PrP) and butyl- (BuP). Blood samples were analyzed for concentrations of glucose and lipid metabolic indices using the Dxl 800 immunoassay analyzer and immunoradiometric assay kit. The relationship between urinary paraben levels and metabolism indices were evaluated through a multiple linear regression analysis. Finally, a mediation analysis was employed to understand the underlying mechanism by which paraben exposure influences lipid metabolism through insulin resistance.

**Results:** The significant positive association between MeP exposure and Castelli risk index I (CRI-I;  $\beta = 0.05$ ,  $p = 0.049$ ) was found, and also exhibited the similar associations between EtP exposure and low-density lipoprotein cholesterol ( $\beta = 0.10$ ,  $p = 0.001$ ), total cholesterol ( $\beta = 0.06$ ,  $p = 0.003$ ), and non-HDL cholesterol (NHC;  $\beta = 0.08$ ,  $p = 0.005$ ). EtP exhibited a significant positive association with triglyceride BMI (TyG-BMI;  $\beta = 0.02$ ,  $p = 0.040$ ). Additionally, TyG-BMI was positively associated with CRI-I ( $\beta = 0.98$ ,  $p < 0.001$ ), CRI-II ( $\beta = 1.03$ ,  $p < 0.001$ ) and NHC ( $\beta = 0.63$ ,  $p < 0.001$ ). Moreover, insulin resistance served as mediators for the effects of EtP exposure on lipid metabolism indices.

**Discussion:** The results indicate that changes in insulin resistance mediated the relationship between urinary paraben and lipid metabolism. Large-scale epidemiological and animal studies are warranted to identify biological mechanisms underlying validate these relationships.

## KEYWORDS

parabens, endocrine disruptors, lipid metabolism, insulin resistance, mediation analysis

## 1 Introduction

Obesity has reached epidemic proportions globally, imposing a considerable public health burden in both developed and developing countries (1). According to the Nutrition and Health Survey in Taiwan (NAHSIT), the prevalence of general and abdominal obesity has been increasing from 16–20% and 27–47% from 1993–2016, respectively (55), and it increases the risk of chronic diseases such as cardiovascular disease, and type 2 diabetes (2). In Taiwan, the average body mass index (BMI) of adults is 24.5 kg/m<sup>2</sup>, which exceeds the standard for overweight set by Taiwan's Health Promotion Administration (BMI ≥ 24 kg/m<sup>2</sup>). The prevalence of overweight and obesity in adults was reported to be 50.7%, indicating that approximately half of the adult population has obesity (56). Factors such as genetic predisposition and lifestyle choices, including diet and physical activity, contribute to the complex etiology of obesity (3, 4). There is more evidence that certain endocrine disruptors, such as parabens, could play a role in the development of obesity and diabetes (5–7).

Parabens are extensively used as artificial preservatives in cosmetics and foodstuffs (8, 9) due to their chemical stability, low cost, and broad-spectrum antimicrobial properties (10). The chemical structure of parabens comprises a benzene ring, with a hydroxyl group and an ester group on the para position (11). Parabens differ in the alkyl chain length on the ester group and can be categorized into two types, including short alkyl-chain parabens (e.g., methylparaben, MeP) and long alkyl-chain parabens (e.g., butylparaben, BuP) (9). In addition, methyl paraben (MeP), ethyl paraben (EtP), propyl paraben (PrP), and butyl paraben (BuP) are the most commonly used parabens in commercial products (12), with the maximum usage level of 0.4% for a single compound and 0.8% for mixtures (13). Moreover, benzylparaben (BzP) and heptyl paraben (HeP) were not always incorporated into exposure assessments and statistical analyses due to their low frequency of detection in previous studies, unless stated otherwise (14).

Typical exposure routes for parabens include inhalation, ingestion, and dermal absorption; the latter is the primary exposure route for the general population, primarily owing to the widespread use of parabens in Personal care products (PCPs) (10). In recent years, the potential of parabens to cause endocrine disruption has elevated concerns about exposure to these chemicals.

*In vitro* studies have found that parabens have abilities in activating the glucocorticoid receptor and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) in 3 T3-L1 preadipocytes. Parabens could promote the differentiation of 3 T3-L1 adipocytes and increase their adipogenic potency, such as by increasing the synthesis and accumulation of triglycerides (15). Furthermore, animal studies have indicated that parabens can stimulate adipocyte differentiation and lipogenesis in white adipose tissue and liver fat cells in female rats,

which includes the processes of fatty acid synthesis and subsequent triglyceride synthesis (16).

In epidemiology, studies have also evaluated associations between paraben exposure and human lipid-related traits. Parabens can cause a range of adverse health effects, particularly in the endocrine system. A growing body of evidence from epidemiological and toxicological studies indicates that paraben exposure may be associated with metabolic disorders, including obesity and diabetes mellitus (DM). A longitudinal study conducted on a sub-sample of the Granada EPIC-Spain cohort ( $n = 670$ ) revealed that individuals with elevated levels of PrP exhibited an elevated risk of developing type 2 diabetes after a 23-year follow-up period (57). Furthermore, exposure to MeP and EtP has been linked to an increased risk of DM, with EtP exhibiting a positive association with a higher risk of obesity (17). Blood plasma samples were collected from 27 healthy women at various points throughout their menstrual cycles in order to examine the potential correlation between paraben exposure and obesity (58). The plasma levels of methylparaben, as well as the sum of parabens, were found to be positively associated with plasma adipon levels. Conversely, a negative correlation was observed between methylparaben levels and glucagon, leptin, and PAI-1.

Some critical indices for assessing lipid metabolism include Triglyceride (TG), Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL). Additionally, other indices such as Castelli risk index (CRI-I and CRI-II), non-HDL (NHC), and the atherogenic coefficient (AC) have been used to assess cardiovascular disease status and coronary artery disease risk (18–20). Disruptions in glucose homeostasis could also affect lipid metabolism. Moreover, insulin resistance can alter systemic lipid metabolism, leading to dyslipidemia. It can lead to elevated TG and LDL levels and reduced HDL levels (21, 22).

The above studies suggest that endocrine disruptors may affect human lipid metabolism. Moreover, the literature also reveals that the Taiwanese is commonly exposed to parabens (23, 24). However, the knowledge gap that exists between paraben exposure and lipid metabolism in the general Taiwanese population. Furthermore, fewer studies have investigated the mechanism through which insulin resistance mediates the relationship between urinary paraben levels and lipid metabolism.

To address the aforementioned research gaps, we aimed to investigate the relationship between urinary paraben levels, insulin resistance, and lipid metabolism in Taiwanese adults. Additionally, we explored whether insulin resistance served as mediators for the effects of paraben exposure on lipid metabolism indices. It is hypothesized that parabens may contribute to the development of obesity and cardiovascular disease through the promotion of insulin resistance and dyslipidaemia.

## 2 Methods

### 2.1 Characteristics of participants

Participants for this study were selected from the Taiwan Environmental Survey for Toxicants (TEST) 2013. A number of studies have previously detailed the participant recruitment, selection methods and approval from the Institutional Review Board of National Yang Ming Chiao Tung University in Taiwan (23–25).

Abbreviations: AC, atherogenic coefficient; BuP, butylparaben; CRI-I, Castelli risk index I; CRI-II, Castelli risk index II; EDCs, endocrine-disrupting chemicals; EtP, ethylparaben; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein cholesterol; LOD, limit of detection; LLOQ, lower limit of quantification; NHC, non-HDL cholesterol; PrP, propylparaben; PPAR $\gamma$ , peroxisome proliferator-activated receptor gamma; TC, total cholesterol; TG, triglyceride; TyG-BMI, triglyceride body mass index.

For the present study, participants aged  $\geq 18$  years were included and selected from 11 counties and cities from 5 regions in Taiwan: Northern, Central, Southern, Eastern, and one remote island. The sampling period spanned from May to December 2013. A total of 394 individuals were included through events held at elementary schools and community centers, yielding a response rate of approximately 78%. Before enrollment, all individuals provided informed consent and volunteered to participate in the NAHSIT. After the participants provided informed consent, their first-morning urine samples and fasting blood samples were collected; The concentration of parabens in the urine of an individual may fluctuate considerably over time due to a number of factors, including age, sex, lifestyle, diet, medical history, and environmental exposures. The precise impact of these variables on urinary paraben exposure among study participants remains unclear. Each participant was requested to complete a retrospective questionnaire encompassing demographic information (age and sex), BMI (body mass index) categories (i.e.,  $<24 \text{ kg/m}^2$ ,  $24 \leq$  &  $<27 \text{ kg/m}^2$ , and  $\geq 27 \text{ kg/m}^2$ ), geographical location (northern, central, southern, eastern, and remote islands), and educational attainment ( $\leq$  elementary school, junior high school, senior high school, and  $\geq$  college/graduates), annual family income ( $<15,625$ ,  $15,625$ – $31,250$ ,  $>31,250$  USD), lifestyle factors (cigarette smoking and alcohol consumption) and PCP uses. Participants were categorized into different groups for the purpose of comparison, including different age groups (18–40, 40–65, and 65 and older). In addition, the term “cigarette smoking” is defined as the act of consuming at least one cigarette per day, as reported by the subjects. The subjects were self-reported lifelong non-smokers (never-smokers) who had involuntarily inhaled smoke from cigarettes or other tobacco products. The term “alcohol consumption” is defined as the ingestion of at least one bottle of alcohol per week. Subject who self-reported using at least one kind of PCPs (personal care products), including body wash, lotion, perfume, and nail polishes. The BMI standard for adults was divided into three groups: weight standard ( $\text{BMI} < 24 \text{ kg/m}^2$ ), overweight ( $24 \leq \text{BMI} < 27 \text{ kg/m}^2$ ) and obesity ( $\text{BMI} \geq 27 \text{ kg/m}^2$ ) (59).

Anthropometric variables, including height, body weight, percentage body fat, and body mass index (BMI), were measured in accordance with standardized procedures outlined by Lohman et al. (60). Body height was measured with a portable stadiometer (model AD-6227R, manufactured by A&D Co., Ltd., Tokyo, Japan) to the nearest 0.1 cm. Body mass (0.1 kg) was evaluated by a bioelectrical impedance analyzer (model BC-418, manufactured by Tanita, Japan). BMI was calculated by dividing body weight (kg) by body height squared (m).

Of the original 394 subjects, a total of 28 were excluded from the study due to an insufficient number of urine samples and 27 were excluded due to an insufficient number of biochemical indicators. Additionally, 75 minors were excluded from the study. Our study included 264 TEST participants aged  $>18$  years. Of these participants, 55 were excluded owing to inadequate urine or blood samples. Accordingly, a total of 264 participants were recruited in this study, comprising 125 men and 139 women. Participants aged between 40 and 65 years constituted the largest proportion of our study population (47.7%) (Table 1; Supplementary Figure S1). Moreover, 50.0% of the participants were of standard body weight, and 24.1 and 26.3% were overweight and obese, respectively. Regarding education level, 29.2%

of the participants held a college degree or above. Furthermore, 58.1% of the participants reported having an annual household income of  $<\text{NT\$}500,000$ . Approximately 75% of the participants were nonsmokers; however, nearly half of the participants were exposed to secondhand smoke. In addition, 74.6% of the participants reported using PCPs.

## 2.2 Paraben analysis

Parabens and their metabolites do not accumulate in the body, and are eliminated within a few hours of exposure (26, 27). Serum paraben concentrations, even after intravenous injection, decline quickly and remain low in the blood (28). Given the short half-life of parabens in blood, the parent compounds and their metabolites are conjugated and excreted in urine. Therefore, urinary measurements in humans can be used to estimate paraben uptake (29). Urinary levels of parent parabens can be used as biomarkers of recent human monitoring (30–33). Significant positive correlations between urinary and blood levels were also observed in a Chinese study, suggesting that urinary concentrations are good predictors of human exposure to parabens and metabolites (34). In the present study, the reagents and chemical standards as well as the measurement procedures for the four parabens used in our study are comprehensively described elsewhere (35). Briefly, spot urine samples were kept and stored at  $-80^\circ\text{C}$  until analysis. For analysis, the collected urine samples were thawed at  $4^\circ\text{C}$  for 24 h. Each sample was extracted through a supported liquid extraction (SLE) column, and the extract was then eluted twice with 0.9 mL of dichloromethane. Finally, the extract was dried under vacuum conditions, followed by the addition of MeOH and Milli-Q water (both 100  $\mu\text{L}$ ) were added to reconstitute the extract for injection. Paraben concentrations were measured using a Waters Acquity UPLC system equipped with a Thermo Scientific™ Hypersil Gold™ column ( $50 \times 2.1 \text{ mm}$ ,  $1.9 \mu\text{m}$ ) (35). The coefficient of determination for parabens ( $r^2$ ) was higher than 0.9952. We observed that the average recovery rates of the parabens at low, medium, and high concentrations were 91.6–100.9% (5.4–10.5%), 84.4–99.5% (1.9–7.1%), and 86.8–98.4% (1.7–13.7%), respectively. Furthermore, the within-run and between-run accuracy ( $>85\%$ ) and precision ( $<14.2\%$ ) of our measurements were noted to meet the standards set by the European Medicines Agency (36). In instances where the paraben concentrations fell below the LOD, the measured concentrations were substituted with half the LOD. The LOD and LLOQ of each paraben were evaluated by SLE using paraben-spiked artificial urine and were 0.1 and 0.3 ng/mL, respectively (23, 24, 35). The present study has revealed that parabens Urinary creatinine levels were measured by spectrophotometry using a picric acid reagent with a wavelength of 520 nm (DXC 800 Synchron; Coulter, Brea, CA, United States).

## 2.3 Measurement of concentrations of metabolism indices

The UniCel DxI 800 Access Immunoassay System analyzer and an immunoradiometric assay kit (DIAsource, Louvain-la-Neuve, Belgium) were used to measure the concentrations of insulin resistance indices (e.g., glucose and insulin) and lipid

TABLE 1 Demographic characteristics of the study participants ( $N = 264$ ).

Variables	Item	$N$	%	Mean $\pm$ SD
Gender	Male	125	47.3	
	Female	139	52.7	
Age (years, mean $\pm$ SD)	All	264		53.5 $\pm$ 17.1
	18–40	62	23.5	
	40–65	126	47.7	
	65 and older	76	28.8	
BMI <sup>a</sup> (kg/m <sup>2</sup> ) (mean $\pm$ SD)	All	264		24.7 $\pm$ 4.38
	Normal	132	50.0	
	Overweight	64	24.2	
	Obese	68	25.8	
Region	Northern Taiwan	83	31.4	
	Central Taiwan	36	13.6	
	Southern Taiwan	73	27.7	
	Eastern Taiwan	45	17.0	
	Remote island	27	10.2	
Marriage status	Single	44	16.7	
	Married	193	73.1	
	Divorce/widowed	27	10.2	
Education	$\leq$ Elementary school	73	27.7	
	Junior high school	38	14.4	
	Senior high school	76	28.8	
	$\geq$ College/graduates	77	29.2	
Annual family income <sup>b</sup> (NTD)	<15,625	147	58.1	
	15,625–31,250	69	27.3	
	>31,250	37	14.6	
Cigarette smoking <sup>c</sup>	Yes/No	64/200	24.2/75.8	
Passive smoker <sup>d</sup>	Yes/No	132/132	50.0/50.0	
Alcohol consumption <sup>e</sup>	Yes/No	34/226	13.1/86.9	
PCPs usage <sup>f</sup>	Yes/No	197/67	74.6/25.4	

<sup>a</sup>BMI standard for adults: weight standard (BMI < 24 kg/m<sup>2</sup>), overweight (24  $\leq$  BMI < 27 kg/m<sup>2</sup>) and obesity (BMI  $\geq$  27 kg/m<sup>2</sup>) (59).

<sup>b</sup>The currency exchange rate of converting USD to new Taiwan dollar (NTD) is 1:32.

<sup>c</sup>Subjects who self-reported consuming at least one cigarette per day.

<sup>d</sup>Subject who self-reported as lifelong nonsmokers (never-smokers) but involuntary inhalation of smoke from cigarettes or other tobacco.

<sup>e</sup>Subject consuming at least one bottle of alcohol drink per week.

<sup>f</sup>Subject who self-reported using at least one kind of PCPs (personal care products), including body wash, lotion, perfume, and nail polishes.

metabolism indices (e.g., TG, HDLC, LDLC, and TC). The measurements were conducted randomly by technicians who were not aware of the metabolic status in Taiwan accredited laboratories (37, 38). Among our participants, 17.4 and 26.4% exhibited fasting blood glucose and insulin concentrations outside the reference range, respectively, and 13.6, 9.5, 29.9, and 37.9% exhibited TG, HDLC, LDLC, and TC levels outside the reference range, respectively. Furthermore, metabolic status was calculated using metabolism indices used in previous studies, including TG glucose-body mass index (TyG-BMI), CRI-I, CRI-II, NHC, and atherogenic coefficient (AC). TyG-BMI is an effective indicator for assessing insulin resistance Equation 1. TG metabolites affect the insulin sensitivity of adipose and muscle tissues and have been extensively studied for predicting diabetes. CRI-I, also known as

the cardiac hazard ratio, reflects coronary plaque formation Equation 2. Moreover, CRI-II and AC are effective predictors of coronary artery disease risk Equations 3, 5. NHC is an indicator for predicting cardiovascular disease Equation 4. These indices can be calculated as follows (18–20, 39):

$$\text{TyG} - \text{BMI} = \text{Ln} \left( \frac{\text{TG} \times \text{glucose}}{2} \right) \times \text{BMI} \quad (1)$$

where glucose represents fasting glucose (mg/dL), and TG (mg/dL) and BMI (kg/m<sup>2</sup>) are already defined earlier (39).

$$\text{CRI} - \text{I} = \frac{\text{TC}}{\text{HDL}} \quad (2)$$



$$\text{CRI-II} = \frac{\text{LDLC}}{\text{HDL}} \quad (3)$$

where TC (mg/dL), LDLC (mg/dL) and HDLC (mg/dL) are already defined earlier (20).

$$\text{NHC} = \text{TC} - \text{HDL} \quad (4)$$

where TC (mg/dL) and HDLC (mg/dL) are already defined earlier (19).

$$\text{AC} = \frac{(\text{TC} - \text{HDL})}{\text{HDL}} \quad (5)$$

where TC (mg/dL) and HDLC (mg/dL) are already defined earlier (18).

## 2.4 Statistical methods

The medians and geometric means (GMs) of the concentrations of urinary parabens and lipid metabolism indices are first calculated. Subsequently, we used the Mann–Whitney U test to assess differences in the concentrations of parabens and lipid metabolism indices between the genders. The correlation between parabens and lipid metabolism indices was evaluated through a Spearman correlation analysis.

In this study, a multiple linear regression analysis was conducted; for this analysis, the measured concentrations of parabens and metabolism indices were subjected to a natural logarithm transformation to satisfy the normality assumptions via the Kolmogorov–Smirnov test. Moreover, age (continuous), sex (categorical), BMI (categorical), education (categorical), income (categorical) and use of PCPs (categorical) were selected as covariates; this selection was based on the findings of relevant studies (17, 40) and on whether the inclusion of any of these covariates would engender a > 10% change in the estimated coefficient. Additionally, we adjusted for endocrine disease status to minimize potential interference effects of endocrine diseases on our analysis results. We also adjusted for the metabolite di(2-ethylhexyl) phthalate, considering its association with lipid metabolism, as indicated in previous research (23–25). Directed Acyclic Graphs (DAGs) were utilised to investigate the potential role of confounding variables in the association between urinary paraben levels and lipid metabolism indicator (see [Supplementary Figure S2](#)). The minimum sufficient adjustment sets for estimating the total effect of urinary paraben levels on lipid metabolism indicator were determined to be age, sex, BMI, education, income and use of personal care products (PCPs). The directed acyclic graph (DAG) was constructed using a web-based tool (DAGitty® version 3.1; 61). A mediation analysis was conducted using PROCESS v4.2 to explore the effect of insulin resistance on the relationship between parabens and lipid metabolism. In the mediation analysis, both indirect and direct effects were assessed, and the proportion of insulin resistance mediated the relationship between parabens and lipid metabolism was estimated (62). All data analyses were performed using SPSS software (version 24.0), and a *p*-value below 0.05 was considered statistically significant.

## 3 Results

### 3.1 Urinary concentrations of parabens and blood lipid metabolism indices

[Table 2](#) presents the detection rate for the parabens as well as the medians and GMs of the concentrations of the parabens. The detection rate for the parabens was 100%. The parabens could be ordered as follows (in descending order) in terms of the GMs of their concentrations: MeP (383 µg/L), PrP (109 µg/L), EtP (39.5 µg/L), and BuP (6.35 µg/L). After stratifying our participants by gender, we observed that the GM of the concentrations of the parabens was higher in men than in women (MeP: 411 vs. 360 µg/L; EtP: 40.8 vs. 38.4 µg/L; PrP: 115 vs. 104 µg/L; BuP: 6.65 vs. 6.10 µg/L). However, the Mann–Whitney U test revealed no significant difference in urinary paraben concentrations between the genders.

We also observed that the detection rate for all lipid metabolism indices was 100% ([Table 3](#)). The GMs of the concentrations of TG, LDLC, HDLC, and TC were 109, 110, 56.4, and 190 mg/dL, respectively. After stratifying our participants by gender, we observed that the GM of the concentration of TG was significantly higher in men than in women (125 vs. 96.0 mg/dL, *p* < 0.001). The GM of the concentration of LDLC was also higher in men than in women (112 vs. 107 mg/dL, *p* = 0.299). By contrast, the concentration of HDLC was significantly higher in women than in men (62.5 vs. 50.1 mg/dL, *p* < 0.001), and the concentration of TC was higher in women than in men (192 vs. 188 mg/dL, *p* = 0.334).

### 3.2 Associations of urinary parabens with lipid metabolism and insulin resistance indices

As indicated in [Table 4](#) and [Figure 1](#), our Spearman correlation analysis revealed a significant positive association between urinary parabens and lipid metabolism indices (*p* < 0.01). EtP was significantly positively correlated with LDLC (*r* = 0.139, *p* = 0.024) and TC (*r* = 0.123, *p* = 0.047).

The multiple linear regression model was also used to explore the association of urinary parabens with lipid metabolism indices and insulin resistance indices ([Table 5](#)). After controlling for confounders, we observed that MeP exhibited a significant positive association with CRI-I (*β* = 0.05, *p* = 0.049). EtP also exhibited significant positive associations with LDLC (*β* = 0.10, *p* = 0.001), TC (*β* = 0.06, *p* = 0.003), and NHC (*β* = 0.08, *p* = 0.005). Furthermore, regarding the associations between urinary parabens and insulin resistance indices, EtP was positively associated with TyG-BMI (*β* = 0.02, *p* = 0.040).

### 3.3 Associations between lipid metabolism and insulin resistance indices

Concerning the association between lipid metabolism and insulin resistance indices, TyG-BMI exhibited positive associations with TG (*β* = 3.02, *p* < 0.001), CRI-I (*β* = 0.98, *p* < 0.001), CRI-II (*β* = 1.03, *p* < 0.001), NHC (*β* = 0.63, *p* < 0.001), and AC (*β* = 1.07, *p* < 0.001). However, a negative association was observed between TyG-BMI and HDLC ([Supplementary Table S1](#)).

TABLE 2 Distribution of parabens concentration ( $\mu\text{g/L}$ ) in the general Taiwanese adult population by sex ( $N = 264$ ).

Parabens	Group	DR (%) <sup>a</sup>	N	GM (95%CI)	Min	25th (95%CI)	50th (95%CI)	75th (95%CI)	95th (95%CI)	Max	<i>p</i> -value <sup>b</sup>
MeP	Adults	100	264	383 (356–412)	64.2	257 (225–277)	399 (360–456)	622 (542–690)	1,025 (936–1,103)	1,188	
	Men	100	125	411 (369–457)	90.4	266 (239–310)	419 (368–471)	654 (548–767)	1,059 (972–1,116)	1,134	0.152
	Women	100	139	360 (323–404)	64.2	234 (209–273)	376 (321–456)	615 (499–697)	1,015 (909–1,094)	1,188	
EtP	Adults	100	264	39.5 (36.7–42.6)	6.86	25.9 (23.8–28.0)	38.8 (35.1–43.5)	64.3 (56.9–76.7)	107 (99.3–112)	130	
	Men	100	125	40.8 (36.1–45.3)	6.86	25.9 (22.6–31.1)	40.5 (34.5–44.2)	74.6 (54.5–85.5)	110 (100–120)	130	0.484
	Women	100	139	38.4 (34.6–42.5)	7.16	25.5 (21.7–28.1)	37.9 (32.7–45.3)	60.7 (54.3–71.7)	107 (90.2–111)	112	
PrP	Adults	100	264	109 (102–116)	26.5	77.7 (67.4–82.1)	117 (105–124)	165 (149–180)	226 (217–239)	258	
	Men	100	125	115 (104–124)	26.5	80.5 (72.1–92.2)	115 (97.1–139)	179 (153–195)	228 (216–238)	253	0.134
	Women	100	139	104 (96–114)	31.2	65.6 (57.0–79.7)	117 (101–125)	156 (139–170)	225 (205–243)	258	
BuP	Adults	100	264	6.35 (5.98–6.77)	1.39	4.46 (4.18–4.92)	6.60 (6.00–7.36)	9.47 (8.93–10.0)	14.2 (13.4–15.0)	16.7	
	Men	100	125	6.65 (6.08–7.20)	1.40	4.84 (4.21–5.42)	6.84 (5.81–8.02)	9.60 (8.65–10.9)	14.8 (13.9–15.7)	15.8	0.305
	Women	100	139	6.10 (5.61–6.74)	1.39	4.34 (3.91–4.84)	6.54 (5.55–7.45)	9.47 (8.36–9.99)	13.4 (12.3–14.7)	16.7	

GM = Geometric mean.

<sup>a</sup>DR = Detection rate: number of urine sample with level of each paraben above detection limit/all analyzed urine samples.<sup>b</sup>Comparison of urinary paraben levels between men and women using Mann–Whitney U test; \*\*\*  $p < 0.001$ .TABLE 3 Distribution of lipid metabolism indicators in the general Taiwanese adult population by sex ( $N = 264$ ).

	Group	DR (%) <sup>b</sup>	N	GM (95%CI)	Min	25th (95%CI)	50th (95%CI)	75th (95%CI)	95th (95%CI)	Max	<i>p</i> -value <sup>c</sup>
TG (mg/dL) <sup>a</sup>	Adults	100	264	109 (101–117)	35.0	72.0 (66.0–76.5)	102 (94.0–111)	147 (132–164)	284 (258–361)	3,821	
	Men	100	125	125 (112–139)	35.0	79.5 (74.0–92.5)	119 (103–133)	184 (157–224)	383 (280–582)	1,512	<0.001***
	Women	100	139	96.0 (88.5–107)	35.0	66.8 (60.0–72.5)	93.5 (85.0–104)	126 (116–137)	221 (175–274)	3,821	
HDL-C (mg/dL) <sup>a</sup>	Adults	100	264	56.4 (54.6–58.5)	23.2	46.5 (45.6–48.9)	56.3 (54.4–58.3)	68.7 (64.3–70.8)	85.1 (81.0–96.0)	118	
	Men	100	125	50.1 (47.7–52.6)	23.2	42.7 (40.8–45.2)	48.9 (46.3–53.3)	58.2 (55.8–62.2)	73.5 (69.9–105)	117	<0.001***
	Women	100	139	62.5 (60.2–65.2)	30.7	52.8 (50.7–55.9)	62.2 (59.8–64.4)	73.0 (70.7–77.1)	89.5 (83.1–110)	118	
LDLC (mg/dL) <sup>a</sup>	Adults	100	264	110 (105–113)	30.0	90.0 (85.5–95.0)	112 (109–116)	139 (128–145)	174 (166–189)	271	
	Men	100	125	112 (106–118)	40.0	94.0 (83.0–101)	112 (109–121)	144 (129–149)	175 (161–199)	271	0.299
	Women	100	139	107 (101–113)	30.0	88.8 (83.0–94.0)	112 (98.0–118)	134 (124–144)	173 (166–190)	199	
TC (mg/dL) <sup>a</sup>	Adults	100	264	190 (186–195)	92.0	168 (163–173)	190 (184–195)	220 (211–229)	263 (252–276)	493	
	Men	100	125	188 (181–195)	120	166 (155–174)	185 (180–195)	220 (205–230)	263 (246–284)	365	0.334
	Women	100	139	192 (185–200)	92.0	168 (162–178)	192 (185–198)	222 (209–234)	267 (248–286)	493	

GM = Geometric mean TG = Triglycerides, HDLC = High Density Lipoprotein Cholesterol, LDLC = Low Density Lipoprotein Cholesterol, and TC = Total cholesterol.

<sup>a</sup>The laboratory reference ranges of adults for TG, HDL-C, LDL-C, and TC were < 150 mg/dL, > 40 mg/dL, < 130 mg/dL, and < 200 mg/dL, respectively.<sup>b</sup>DR = Detection rate: number of urine sample with each lipid metabolism indicators concentration above detection limit/all analyzed urine samples.<sup>c</sup>Comparison of lipid metabolism indicators concentration between men and women using Mann–Whitney U test; \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\*  $p < 0.001$ .

TABLE 4 Spearman’s correlation coefficients between urinary paraben concentrations in adults and lipid metabolism indicators (N = 264).

	MeP	EtP	PrP	BuP	TG (mg/dL)	HDLC (mg/dL)	LDLC (mg/dL)	TC (mg/dL)	BMI (kg/m²)
MeP (µg/L)	1.000	<b>0.414**</b>	<b>0.613**</b>	<b>0.577**</b>	0.068	−0.044	0.074	0.087	−0.062
EtP (µg/L)		1.000	<b>0.649**</b>	<b>0.548**</b>	0.090	0.027	<b>0.139*</b>	<b>0.123*</b>	−0.025
PrP (µg/L)			1.000	<b>0.719**</b>	0.062	0.027	0.074	0.075	−0.037
BuP (µg/L)				1.000	0.028	0.025	0.056	0.070	−0.052
TG (mg/dL)					1.000	<b>−0.482**</b>	<b>0.260**</b>	<b>0.225**</b>	<b>0.443**</b>
HDLC (mg/dL)						1.000	0.066	<b>0.344**</b>	<b>−0.314**</b>
LDLC (mg/dL)							1.000	<b>0.849**</b>	0.097
TC (mg/dL)								1.000	−0.023
BMI (kg/m²)									1.000

TG = Triglycerides, HDLC = High Density Lipoprotein Cholesterol, LDLC = Low Density Lipoprotein Cholesterol, and TC = Total cholesterol. \**p* < 0.05; \*\**p* < 0.01; \*\*\* *p* < 0.001 Bold: *p* < 0.05.

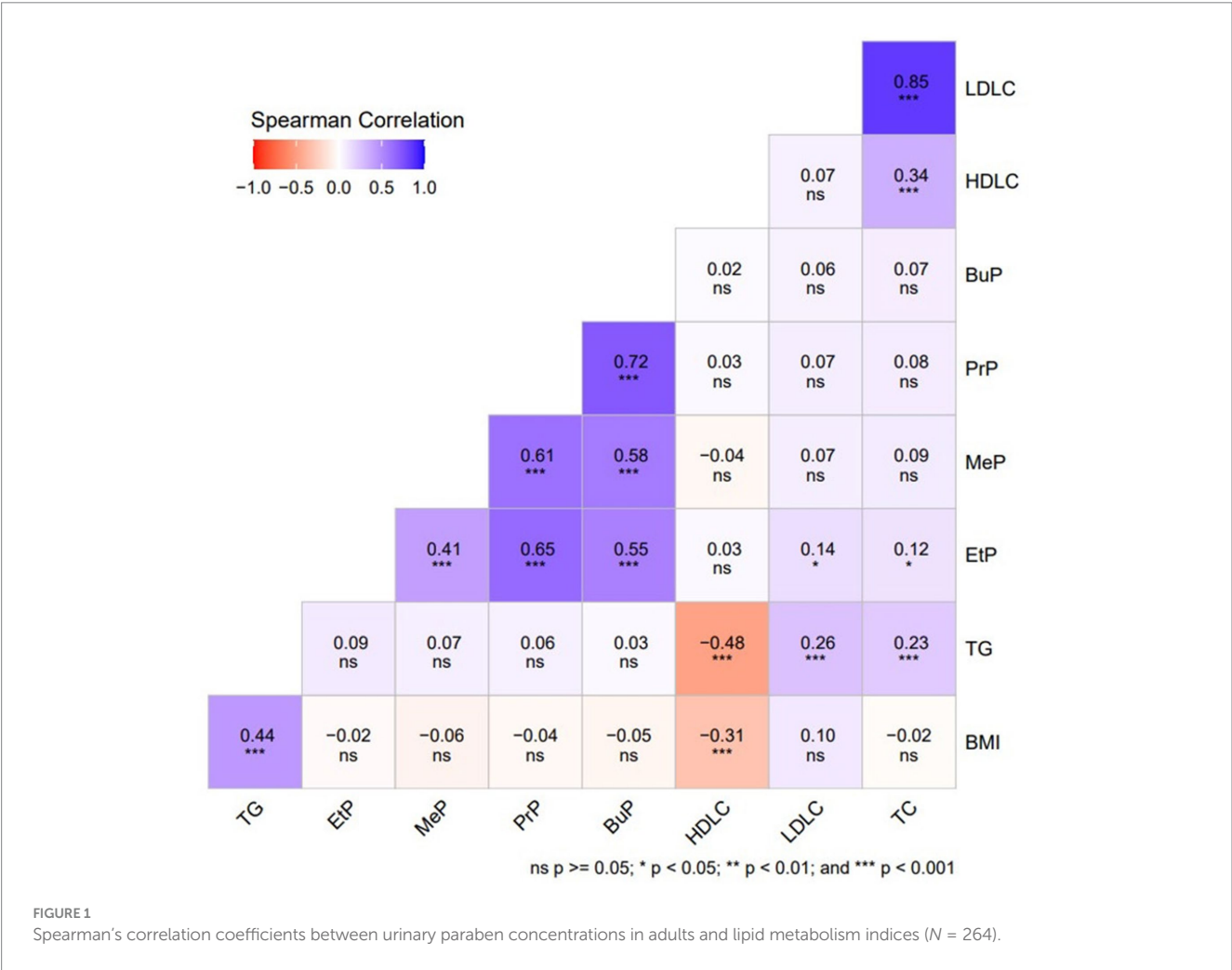


FIGURE 1 Spearman’s correlation coefficients between urinary paraben concentrations in adults and lipid metabolism indices (N = 264).

3.4 Mediating role of insulin resistance in the association between urinary paraben levels and lipid metabolism

We selected parabens that, upon exposure, were significantly associated with lipid metabolism and insulin resistance indices to conduct a mediation analysis; in this analysis, we identified that insulin resistance could serve as mediators for the effects of paraben exposure on lipid metabolism indices. In mediation analysis, TyG-BMI mediated

17.2% of the association between EtP and NHC (indirect effect = 0.014, 95% confidence interval [CI] = 0.003–0.029); the mediation effect was significant (shown in [Supplementary Table S2](#) and [Figure 2](#)).

4 Discussion

Our study revealed that MeP was positively associated with CRI-I and that EtP was positively associated with LDLC, TC, and NHC. The

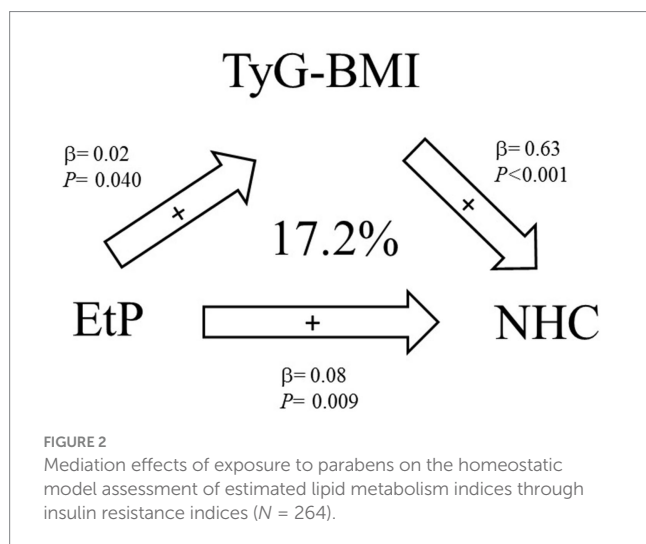
TABLE 5 Adjusted regression coefficients ( $\beta$ ), 95% confidence intervals (CI), and  $p$ -values ( $p$ ) for change in lipid and glucose metabolism indicators in relation to unit-increased in Ln-parabens ( $\mu\text{g/L}$ ) in Taiwanese adults ( $N = 264$ ).

Variable	MeP ( $\mu\text{g/L}$ )			EtP ( $\mu\text{g/L}$ )			PrP ( $\mu\text{g/L}$ )			BuP ( $\mu\text{g/L}$ )		
	$\beta$	95% CI	$p$ value	$\beta$	95% CI	$P$ value	$\beta$	95% CI	$P$ value	$\beta$	95% CI	$P$ value
Model 1 <sup>a</sup>												
TG (mg/dL)	0.08	(−0.03, 0.18)	0.147	0.06	(−0.05, 0.17)	0.300	0.03	(−0.11, 0.16)	0.711	0.06	(−0.06, 0.19)	0.318
HDLC (mg/dL)	−0.03	(−0.07, 0.02)	0.250	0.03	(−0.02, 0.08)	0.192	0.03	(−0.03, 0.09)	0.306	0.01	(−0.04, 0.07)	0.684
LDLC (mg/dL)	0.03	(−0.03, 0.09)	0.340	<b>0.10</b>	<b>(0.04, 0.16)</b>	<b>0.001</b>	0.07	(−0.01, 0.15)	0.083	0.07	( $<0.01$ , 0.14)	0.050
TC (mg/dL)	0.02	(−0.02, 0.06)	0.261	<b>0.06</b>	<b>(0.02, 0.10)</b>	<b>0.003</b>	0.04	(−0.01, 0.09)	0.134	0.04	(−0.01, 0.09)	0.086
CRI-I	<b>0.05</b>	<b>(<math>&lt;0.01</math>, 0.10)</b>	<b>0.049</b>	0.03	(−0.02, 0.08)	0.229	0.01	(−0.06, 0.07)	0.788	0.03	(−0.03, 0.09)	0.312
CRI-II	0.06	(−0.01, 0.13)	0.115	0.07	( $> -0.01$ , 0.14)	0.059	0.04	(−0.05, 0.13)	0.410	0.06	(−0.02, 0.14)	0.155
NHC	0.04	(−0.01, 0.10)	0.123	<b>0.08</b>	<b>(0.02, 0.13)</b>	<b>0.005</b>	0.04	(−0.03, 0.11)	0.230	0.06	(−0.01, 0.12)	0.096
AC	0.07	( $> -0.01$ , 0.14)	0.057	0.05	(−0.03, 0.12)	0.205	0.01	(−0.08, 0.11)	0.793	0.04	(−0.04, 0.13)	0.316
TyG-BMI	0.01	(−0.01, 0.03)	0.271	<b>0.02</b>	<b>(<math>&lt;0.01</math>, 0.05)</b>	<b>0.040</b>	0.01	(−0.02, 0.04)	0.648	0.01	(−0.02, 0.03)	0.705
Model 2 <sup>b</sup>												
TG (mg/dL)	0.07	(−0.05, 0.18)	0.250	0.06	(−0.05, 0.17)	0.282	0.02	(−0.12, 0.16)	0.798	0.07	(−0.06, 0.20)	0.269
HDLC (mg/dL)	−0.02	(−0.06, 0.03)	0.479	0.03	(−0.02, 0.08)	0.189	0.03	(−0.03, 0.10)	0.258	0.02	(−0.04, 0.07)	0.546
LDLC (mg/dL)	0.03	(−0.03, 0.09)	0.347	<b>0.11</b>	<b>(0.05, 0.17)</b>	<b>0.001</b>	0.07	(−0.01, 0.15)	0.075	<b>0.08</b>	<b>(<math>&lt;0.01</math>, 0.15)</b>	<b>0.048</b>
TC (mg/dL)	0.02	(−0.02, 0.07)	0.259	<b>0.07</b>	<b>(0.02, 0.11)</b>	<b>0.002</b>	0.04	(−0.02, 0.09)	0.157	0.04	( $> -0.01$ , 0.09)	0.075
CRI-I	0.04	(−0.01, 0.09)	0.119	0.03	(−0.02, 0.09)	0.209	$<0.01$	(−0.06, 0.07)	0.906	0.03	(−0.03, 0.09)	0.374
CRI-II	0.05	(−0.03, 0.12)	0.202	<b>0.08</b>	<b>(0.01, 0.15)</b>	<b>0.034</b>	0.04	(−0.05, 0.13)	0.417	0.06	(−0.03, 0.14)	0.187
NHC	0.04	(−0.02, 0.10)	0.175	<b>0.08</b>	<b>(0.03, 0.14)</b>	<b>0.004</b>	0.04	(−0.03, 0.11)	0.273	0.06	(−0.01, 0.13)	0.094
AC	0.06	(−0.02, 0.13)	0.139	0.05	(−0.02, 0.13)	0.178	0.01	(−0.09, 0.10)	0.899	0.04	(−0.05, 0.13)	0.369
TyG-BMI	0.01	(−0.01, 0.03)	0.361	<b>0.03</b>	<b>(<math>&lt;0.01</math>, 0.05)</b>	<b>0.018</b>	0.01	(−0.02, 0.04)	0.438	0.01	(−0.02, 0.04)	0.546

<sup>a</sup>Model 1: adjustment for age, sex, BMI, urinary creatinine levels, endocrine disease status, and Ln  $\Sigma\text{DEHPm}$ . Bold:  $p < 0.05$ .

<sup>b</sup>Model 2: adjustment for age, sex, education, income, PCPs use, BMI, urinary creatinine, endocrine disease status, and Ln  $\Sigma\text{DEHPm}$ . Bold:  $p < 0.05$ .





findings of this study indicate that exposure to parabens may be associated with obesity and indicators of lipid metabolism, as well as adverse health outcomes, in adults. These findings are consistent with those reported in previous epidemiological studies. In an ongoing three-year cycle cross-sectional biomonitoring programme [KoNEHS Cycle 3 (2015–2017)], an adult population (aged 19 years or older) was investigated to ascertain the current level of exposure to major environmental chemicals among the general Korean population. The KoNEHS study also revealed a positive association between urinary EtP levels in adults and obesity [ $\beta = 0.03$ ,  $p = 0.038$ ; (17)]. A total of 1,454 children, 891 adolescents, and 3,758 adults (for BMI) and 3,424 adults (for TG/HDL) from the Korean National Environmental Health Survey (2015 to 2017) were included in this cross-sectional study. The findings of Kim's study suggest that exposure to EDC mixtures is associated with elevated BMI and TG/HDL levels in both adolescents and adults. The association is more pronounced in adults than in adolescents. Moreover, adolescence may signify a critical period for EDC mixtures in terms of outcomes (41).

In a related study, blood plasma samples were collected from 27 healthy women at various points throughout their menstrual cycles in order to examine the potential correlation between paraben exposure and obesity (58). The plasma levels of methylparaben, as well as the sum of parabens, were found to be positively associated with plasma adipon levels. Conversely, a negative correlation was observed between methylparaben levels and glucagon, leptin, and PAI-1. These inconsistencies in the impact of urinary paraben concentrations on lipid metabolism indices could be attributed to differences in study design or participant characteristics, including sex, age, or ethnicity.

It is hypothesised that paraben exposure may impact insulin sensitivity in human organs, thus providing an underlying mechanism that could explain the observed association. Hu et al. (15) found that parabens promote adipogenesis in 3 T3-L1 cells, contributing to obesity by disrupting lipid synthesis and decomposition via the PPAR $\gamma$  receptor. Their findings showed a significant positive association between EtP and TyG-BMI. Animal studies suggest that paraben exposure can damage pancreatic islet cells. For example, zebrafish embryos exhibited enlarged islet areas, abnormal shapes, and increased aberrant  $\beta$ -cells (42). Pereira-Fernandes et al. (43) demonstrated that parabens strongly bind to and activate PPAR $\gamma$ , a key regulator of insulin sensitivity. Our results showed a significant positive association between EtP and TyG-BMI, suggesting that paraben exposure may disrupt blood glucose

regulation and increase insulin resistance risk. These findings align with the KoNEHS Cycle 3 study (2015–2017) in South Korea, which reported positive associations between MeP (OR = 1.68, 95% CI = 1.08–2.60) and EtP (OR = 2.74, 95% CI = 1.77–4.24) with diabetes (17). Similarly, Bai et al. (44) found a significant positive association between PrP and insulin resistance (OR = 1.72, 95% CI = 1.15–2.57) in NHANES (2009–2016). A case–control study from the Henan Rural Cohort Study, including 1,713 participants (880 with type 2 diabetes and 833 controls), used generalized linear regression models to assess the effects of parabens on T2DM and insulin resistance indicators (63). The study found a linear positive association between MeP or paraben mixtures and T2DM risk, while EtP and BuP showed a non-linear association, with moderate-to-high exposure levels contributing to T2DM development (63). The findings of this study demonstrated that exposure to MeP or paraben mixtures was found to have a linear positive association with the risk of T2DM. EtP and BuP demonstrated a non-linear association with insulin resistance, with moderate-high exposure levels contributing to the development of T2DM (63).

A prospective study of 1,087 pregnant women from a single tertiary medical center also shows that urinary EtP was associated with gestational DM, with risk ratios of 1.12, 1.11 and 1.70 for the second, third and highest quartiles, respectively (64). Furthermore, a case–control study of adults ( $n = 101$ ) in Jeddah, Saudi Arabia during 2015–2016 also found that increased parabens (including MeP, EtP, and PrP) exposure could lead to an over six-fold increase in the risk of diabetes (65).

We found that insulin resistance indices were positively linked to LDLC and lipid metabolism markers but negatively associated with HDLC, suggesting a role in dyslipidemia and obesity. Previous studies indicate that insulin resistance and type 2 diabetes can elevate TG or reduce HDLC levels (45, 46). Insulin resistance may impair VLDL degradation, leading to increased VLDL synthesis (47). VLDL transports fat from the liver to tissues and converts to LDLC after unloading most of its fat (48, 49).

Consequently, insulin resistance may lead to elevated TG levels, resulting in hypertriglyceridemia. Insulin resistance also reduces the activity of lipoprotein lipase, a key mediator of VLDL clearance (50). This reduction in VLDL and LDLC uptake by the liver prolongs the duration of these lipoproteins in the plasma (22, 47). Gencer et al. (51) confirmed that insulin resistance in polycystic ovary syndrome (PCOS) is linked to fasting insulin, HOMA index, BMI, and right ovarian volume. In PCOS with Hashimoto's thyroiditis (PCOS+HT), insulin resistance also correlates with fasting insulin, HOMA index, BMI, SHBG, and left ovarian volume. Among PCOS patients with insulin resistance, 37.5% had increased right ovarian volume, while left ovarian volume was elevated in 35.7% of those without insulin resistance and 68.8% of those with it. PCOS shares clinical similarities with certain thyroid diseases, particularly hypothyroidism and autoimmune thyroid diseases (AITDs) (52). Its coexistence with hyperthyroidism is rare, suggesting thyroid influence on PCOS through metabolism and immunity. Thyroid function affects insulin resistance, a key factor in PCOS, with hypothyroidism exacerbating it more than hyperthyroidism. The rising prevalence of obesity further impacts health, as hypothyroid patients are prone to obesity, and those with both PCOS and hypothyroidism often have a higher BMI and greater metabolic disease risk. Further research is required to confirm these findings and to elucidate the underlying mechanisms. Nevertheless, it is evident that strategies to reduce EDC exposure from early life stages may be necessary to lower the risk of metabolic disease.

Our mediation analysis revealed that TyG-BMI could mediate the association between EtP and NHC. Therefore, TyG-BMI may be a mediator in the association between EtP exposure and NHC. Parabens increase the risk of obesity and cardiovascular disease by fostering the development of insulin resistance and dyslipidemia. Extensive epidemiological and mechanistic studies (both *in vivo* and *in vitro*) are warranted to validate these associations and elucidate the potential corresponding biological mechanisms.

There are four key strengths in this study. First, our current data were obtained from a representative survey including participants aged 7 to 97 years. Therefore, our study can accurately reflect the exposure profile of the general population in Taiwan. Second, few studies have explored the association between paraben exposure and metabolism indices in the general Taiwanese adult. Third, we employed various metabolic indices that are currently used in clinical practice but are rarely used in research, thus enriching the understanding of overall metabolic conditions. Finally, we conducted a mediation analysis to explore the potential mediating role of insulin resistance in the association between paraben exposure and lipid metabolism in the general Taiwanese adult population.

Despite its strengths, our study has some limitations that warrant consideration. First, we applied a cross-sectional design; hence, we could not establish a causal relationship between exposure and health effects. Second, our sample size was relatively small, which could potentially affect the reliability and interpretability of our statistical findings. Future research should consider a larger sample size for improved representativeness and robustness. Third, the measurement of urinary paraben concentrations using morning urine samples may not fully capture long-term exposure; however, this limitation is mitigated by evidence suggesting that daily exposure patterns for parabens could be consistent over time (53, 54).

## 5 Conclusion

The present study has revealed that parabens have the capacity to affect metabolic homeostasis. The potential mediation of the association between paraben exposure and lipid metabolism by insulin resistance is also indicated. The risk of obesity and cardiovascular disease is increased by parabens via the fostering of the development of insulin resistance and dyslipidemia. Whilst the participants in the present study were selected from the general population, the findings are limited to Taiwanese individuals. Therefore, future studies must include a greater number of samples in order to elucidate these underlying mechanisms and increase the generalizability of the results.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Institutional Review Board of National Yang Ming Chiao Tung University in Taiwan. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

P-CH: Conceptualization, Methodology, Resources, Software, Supervision, Writing – original draft. H-CC: Investigation, Methodology, Resources, Writing – review & editing. H-BH: Investigation, Methodology, Writing – review & editing. Y-LL: Investigation, Methodology, Resources, Writing – review & editing. W-TC: Investigation, Writing – review & editing. S-HL: Investigation, Writing – review & editing. HC: Investigation, Writing – review & editing. J-WC: Data curation, Formal analysis, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing, Writing – original draft.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2025.1416264/full#supplementary-material>

**SUPPLEMENTARY FIGURE S1**  
Flow chart of the recruitment for the study.

**SUPPLEMENTARY FIGURE S2**  
Visualized directed acyclic graph (DAG) to apply the minimal sufficient adaptation set as covariates.

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