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The effects of phthalate on physical growth of children

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Abstract

The effects of phthalate on physical growth of children

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Phthalates, a group of well-known endocrine-disrupting chemicals, are widely and globally used as a plasticizer for plastic products. Although detrimental health effects of phthalates have been studied, their associations with disturbances in physical growth in children have been reported inconsistently. This study was aimed to clarify whether prenatal and postnatal exposure to phthalates is associated with physical growth disturbances in children. A systematic review and meta-analysis, and a mother-cohort study were performed to investigate the association between phthalates and the physical growth of children.

The systematic review was performed to understand associations between

prenatal and postnatal exposure to di(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP) and body composition indices of children. Next, 726 mother-child pairs in the Environment and Development of Children cohort were used to investigate the association between prenatal and postnatal phthalate exposure and the physical growth of children. The linear associations between phthalate metabolites including mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxo-hexyl) phthalate (MEOHP), mono(5-carboxy-2-ethylpentyl) phthalate (MECPP), mono-n-butyl phthalate (MnBP), and monobenzyl phthalate (MBzP) in prenatal maternal urine and children's urine, and body composition indices of children (body mass index [BMI] z-score, BMI, fat mass index [FMI], and the skeletal muscle index [SMI]) measured at 6 and 8 years were investigated. Latent growth class modeling was used to classify groups of longitudinal patterns of growth patterns (BMI z-score and weight z-score), and differences in phthalate exposure levels by the groups were tested. Finally, multiple informant models were used to investigate the association of body composition indices with phthalate exposure levels at different time windows.

In the systematic review and meta-analysis, 29 studies that met our inclusion criteria, including 17 longitudinal and 12 cross-sectional studies were reviewed. A significant negative association between prenatal exposure to DEHP and BMI z-score of the offspring was observed, while no significant association between prenatal exposure to DEHP and DBP and body fat percentage of the offspring was observed. The studies on the association between phthalates exposure in childhood and obesity were inconsistent. In the mother-child cohort study, it was found that the significant association between a two-fold increase of ∑DEHP in prenatal maternal urine and decreased SMI at 6 years (-0.05 kg/m^2 per two-fold increase;

95% CI: -0.09, -0.01), and the significant associations between a two-fold increase of MEHHP in prenatal maternal urine and decreased SMI at 6 years (-0.04 kg/m^2; 95% CI: -0.07, -0.01) and 8 years (-0.06 kg/m^2; 95% CI: -0.11, -0.002). In the multiple informant models, negative associations of prenatal exposure to ∑DEHP with SMI at 6- and 8-years were significant, and the significance and size of associations between phthalate exposure and SMI at 6 and 8 years differed by the timing of exposure.

Additionally, the current status of phthalate management in South Korea was reviewed. I reviewed current management and regulation of manufacturing products containing phthalates and human biomonitoring, and suggested stricter regulation and management policies regarding the manufacturing of phthalate-containing products and setting a *standard* (a reference value and/or a guidance value) for phthalate biomonitoring.

Prenatal exposure to phthalates was found to be associated with decreased normal growth of children. Phthalates exposure in childhood and obesity may be associated, but it is still not clear and inconsistent. The results highlight the necessity of improved regulation policies for products containing phthalates, and the implementation of improved phthalates biomonitoring.

Keywords: phthalate, children, pregnancy, growth, skeletal muscle, cohort study

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1. Introduction

1.1. Background

Phthalates, a class of chemicals synthesized by the esterification of phthalic acid, are widely used as plasticizers (to promote flexibility and softness of plastics) and in various personal care products. As its low price and usefulness, the amount of phthalates used stands at around 5.5 million tonnes per year (1). Phthalates can be classified into two groups, high-molecular-weight phthalates (HMWPs) and low-molecular-weight phthalates (LMWPs). HMWPs are used in manufacturing flexible plastics for a variety of products including building materials, medical devices, and paints. Di-(2-ethylhexyl) phthalate (DEHP) is the most widely used HMWP (65.2% of the total consumption of phthalates), and worldwide production was estimated to be 2 million tons per year (2, 3). LMWPs are usually used in cosmetics such as shampoos, cosmetics, lotions, nail care products, and other personal hygiene products, dibutyl phthalate (DBP) being one of the most widely used LMWPs (4). As phthalates can be exposed in the daily living environments, urinary phthalate metabolites were detected in over 75% of Americans in 1999-2000 in the United States (5).

Phthalate is a well-known endocrine-disrupting chemical (EDC) that has anti-androgenic effects. It can induce the decrease of expression of nuclear receptors related to steroidogenic factors and testosterone levels, rather than bind the human androgen receptors (6, 7). As its anti-androgenic properties, it has been focused on the health effects of phthalates including abnormal sexual development such as hypospadias and anogenital distance, adverse birth outcomes, precocious puberty, and hormonal disturbances of testosterone and thyroid hormone (8-12).

Furthermore, recent studies suggest that it is associated with impaired neurodevelopment in children (13-15).

In addition to their characteristics as EDCs, it has been studied that phthalates can interfere with growth and metabolism, which can lead to obesity or changes in body composition indices (16, 17). However, the relationship between phthalates and obesity is still unclear and inconclusive. Studies that investigated the relationship between human body composition and phthalates reported inconsistent results (18-20). A systematic review and meta-analysis study for human studies concluded that there are no significant associations between phthalate exposure and obesity (21).

Recently, the negative association between perinatal exposure to phthalates and body weight was reported in a systematic review and meta-analysis for animal studies (22). In addition, a rodent study reported that prenatal exposure to DEHP could induce decreased muscle mass (23). However, there is a lacking epidemiologic study for this association, although a cross-sectional study reported the association of decreased muscle mass and increased phthalates metabolites (24).

Considering the magnitude of the population that could be affected by phthalate exposure and its widespread usage in products for daily use, the inconsistent results for the association between phthalates and obesity and skeletal muscle in children, further investigation is required to understand the effect of phthalates on physical growth in children.

1.2. Objectives

The study aimed to clarify whether prenatal and postnatal exposures to phthalates are associated with physical growth measured by body composition indices in children. First, a systematic literature review and meta-analysis were performed for the association of phthalates with body composition indices among children. Next, an epidemiologic study using a mother-child cohort was conducted to investigate the association between prenatal exposure of phthalates with BMI z-score and skeletal muscle of children, with the hypothesis as following: prenatal exposure of DEHP is associated with BMI z-score and skeletal muscle of children at 6 and 8 years. Additionally, associations of prenatal and postnatal exposure to phthalates and body composition indices in children were explored. Finally, laws and regulations related to phthalates and children's health in South Korea were reviewed and suggestions for children to protect from phthalates were derived.

2. Materials and Methods

2.1. A systematic review and meta-analysis

Search strategy and selection methods

This study was registered in PROSPERO, an international prospective register of systematic reviews (CRD42021235007). A review question was defined as follows: "Does the prenatal and postnatal exposure of phthalates affect the physical growth of children?"

MEDLINE, EMBASE, and Cochrane Library databases were searched for research articles that reported associations between DEHP and DBP levels and physical growth of children between January 1, 1980, and December 31, 2020. The search string is shown in **Table 1**.

Inclusion criteria were: (1) cohort, case-control, or cross-sectional design; (2) reported effect estimates, such as beta estimates (β) with 95% CIs, or outcome values that allowed for effects to be estimated by calculations in a 2 × 2 cell table.

Exclusion criteria were (1) reported irrelevant outcomes; (2) absence of effect estimates or inability to calculate the size of the association; (3) letter, commentary, or review articles; (4) study population identical to that of a later study (only the latest publication after a review of the full text was included); (5) studies published in languages other than English; and (6) studies involving non-human subjects.

Table 1. Comprehensive search strategies for PubMed and EMBASE

PubMed	
Component 1: exposure	"phthalate" [tw] OR "phthalates" [tw] OR “diethylhexyl phthalate” [MeSH] OR “diethylhexyl phthalate” [tiab] OR di-2-ethylhexylphthalate [tiab] OR DEHP [tiab] OR "dibutyl phthalate" [MeSH] OR "dibutyl phthalate"[tiab] OR DBP [tiab]
Component 2: health problem	Growth [MeSH] OR “Body Mass Index” [MeSH] OR BMI [tiab] OR obesity [MeSH] OR obesity [tiab] OR "body composition" [MeSH] OR “body fat distribution” [MeSH] OR adiposity [MeSH] OR adiposity [tiab] OR overweight [MeSH] OR overweight [tiab] OR “quetelet index” [tiab] OR “weight gain” [MeSH] OR “weight gain” [tiab] OR adipogenesis [MeSH] OR adipogenesis [tiab]ORr "fat mass index" [tiab] OR “body weight” [MeSH] OR ("body weight" [tiab] NOT "kg body weight" [tiab] NOT "body weight/day" [tiab]) OR obesogenic [tiab] OR "Muscle, Skeletal" [MeSH] OR "skeletal muscle index" [tiab] OR "body Height" [Mesh] OR "height" [tiab]
Component 3: human studies	NOT (animals [MeSH Terms] NOT humans [MeSH Terms])
EMBASE	
Component 1: exposure	"phthalate"/exp OR "phthalates"/exp OR “diethylhexyl phthalate”:ab,ti OR di-2-ethylhexylphthalate:ab,ti OR DEHP:ab,ti OR "dibutyl phthalate":ab,ti OR DBP:ab,ti
Component 2: health problem	Growth:ab,ti OR “Body Mass Index”:ab,ti OR BMI:ab,ti OR obesity:ab,ti OR obesity:ab,ti OR "Body Composition":ab,ti OR “body fat distribution”:ab,ti OR adiposity:ab,ti OR adiposity:ab,ti OR overweight:ab,ti OR overweight:ab,ti OR “quetelet index”:ab,ti OR “weight gain”:ab,ti OR “weight gain”:ab,ti OR adipogenesis:ab,ti OR adipogenesis:ab,ti OR "fat mass index":ab,ti OR “body weight”:ab,ti OR obesogenic:ab,ti OR "Muscle, Skeletal":ab,ti OR "skeletal muscle index":ab,ti OR "height":ab, ti
Component 3: human studies	NOT animals/ NOT humans.sh.

Data extraction

The following data were extracted from all articles using a data-extraction sheet: first author, year, country, type of study, sample size, the timing of exposure assessment, measured metabolites and range, statistical analysis, adjustment variables, the timing of outcome assessment, outcome variables, findings, estimates type, estimates, and 95% confidence intervals (CIs) of the association between prenatal phthalate exposure and outcome variables.

The measured DEHP metabolites varied across studies, and results of analyses were presented separately according to the DEHP metabolite measured in each of the included studies, with or without the sum of DEHP metabolites (∑DEHP). ∑DEHP was preferentially selected as an exposure indicator. Among secondary metabolites, the available metabolites were selected in the following order: MECCP, MEHHP, and MEOHP considering the molar fraction of excretion to absorbed DEHP in the human body (25). Considering metabolites of DBP, MnBP was preferentially selected, followed by MiBP (26). When any of the secondary metabolites of DEHP were not available, mono-(2-ethylhexyl) phthalate was used as an indicator of exposure. When beta estimates with 95% CIs were presented for more than one model, the association calculated with the greatest number of adjustment variables was used for meta-analysis.

Quality assessment

The Newcastle-Ottawa quality assessment scale (NOS) was used (27). The NOS for cohort and cross-sectional studies consists of items for selection, comparability, and outcome assessment. Using the NOS, cohort studies were scored in the range 0–9 and classified as low-quality (0–3), moderate-quality (4–6), or high-quality (7–9). Cross-sectional studies were scored in the range 0–10 and classified as low-quality (0–3), moderate-quality (4–7), or high-quality (8–10).

Statistical analysis

Standardized regression coefficient effect size and its standard error were used for meta-analyses for the association between phthalates and body composition (28). The heterogeneity of results across studies was examined by Q test. *P*-value < 0.10 implied substantial heterogeneity. The overall estimate was calculated using a random-effects model. In the final round of analysis, I evaluated the included studies for publication bias using a Begg funnel plot and the Egger test. If the funnel plot was asymmetric or *p*-value from the Egger test was less than 0.05, the existence of publication bias was assumed. Statistical analyses were conducted using R software, “metafor” package, version 2.13.2 (Wolfgang Viechtbauer, Maastricht, the Netherlands).

2.2. A mother-child cohort study in South Korea

Study Participants

This prospective birth cohort study was based on the Environment and Development of Children cohort (EDC cohort), an ongoing cohort study to observe the effects of environmental exposure to EDCs on the development of children. A total of 726 mother-child pairs were enrolled, and follow-ups of all children and parents were conducted every 2 years. During the follow-up examination, parents took a survey on demographic factors, medical history, recent illness of their children, and environmental factors. Urine and blood samples of the children were collected. More details are described in the published cohort profile paper (29).

Phthalate measurement

Maternal phthalate metabolites were measured in maternal urine samples collected at the second trimester of pregnancy (a mean of 20.3 weeks of gestation with standard deviations [SDs] of 4.5, ranging from 6.9 to 29.6 weeks). Maternal spot urine was collected from each participant between 9 am and 11 am and stored at -20°C. Childhood phthalate metabolites were measured in the first-morning urine sample of the offspring at 6 years of age. The first-morning urine of children was collected in a urine collection cup (pre-screened for phthalate metabolites) by their mothers. Mono-(2-ethyl-5-hydroxy-hexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP), and mono(5-carboxy-2-ethylpentyl) phthalate (MECPP) for DEHP metabolites, mono-n-butyl phthalate (MnBP) for DBP metabolites, and monobenzyl phthalate (MBzP) for butyl benzyl phthalate (BBP) were measured. A molar sum of MEHHP, MEOHP, and MECPP was

calculated for the sum of DEHP metabolite (∑DEHP) by dividing the concentrations of MEHHP, MEOHP, and MECPP by their molecular weights (294.34 g/mol, 292.33 g/mol, and 308.33 g/mol, respectively) (30).

All laboratory analyses were conducted at Green Cross Laboratories, certified by the Korean Society for Laboratory Medicine. First, for measuring urinary concentrations of MEHHP, MEOHP, MECCP, MnBP, and MBzP thawed and vortexed urine samples were treated with 2 M sodium acetate buffer solution (1.0 mL) and β-glucuronidase (20 μL) and were hydrolyzed at 37°C for 16 h. After hydrolysis, 50 μL of internal standards and 4 mL of ethyl acetate were added. After 1 h of shaking and 5 min of centrifugation, the solution layers were removed, and the extract was dried with a nitrogen evaporator. The dried extract was treated with 300 μL of 60% acetonitrile and analyzed using high-performance liquid chromatography-tandem mass spectrometry (TQ4500; AB Sciex, USA). The limits of detection (LOD) for MEHHP, MEOHP, MECCP, MnBP, and MBzP were 0.208, 0.487, 0.724, 0.270, and 0.356 μg/mL, respectively. The values below the limits of detection were substituted as LOD/$\sqrt{2}$. Creatinine-adjusted phthalate metabolites (μg/g Cr) and urinary creatinine levels were used as covariates in statistical models for controlling measurement error bias caused by the difference in urine dilutions (31). Creatinine was measured using a kinetic colorimetric assay with a Hitachi 7600 machine (Hitachi®, Tokyo, Japan) and CREA reagent (Roche®, Indianapolis, IN, USA).

Body composition

Weight (kg) and height (cm) of children were measured at 2, 4, 6, and 8 years of age. Body composition at 6 and 8 years was assessed using an InBody® 770 body composition analyzer (Inbody®, Seoul, Korea), which uses the 4-electrode method. Bioelectrical impedance analysis (BIA) is a method to assess total fat mass and skeletal muscle mass in the body (32). InBody® 770 body composition analyzer, which measures body composition using BIA, has reasonable accuracy compared to dual X-ray absorptiometry measurements, a gold-standard method for measuring body composition (33). Children were required to fast overnight and each child was given the same instructions while measuring body composition. BMI z-score was calculated based on the reference data of Korean adolescents developed by the Korean Pediatric Society (34). Fat mass index (FMI) was calculated as body fat mass divided by height squared (kg/m^2) (35). Skeletal muscle index (SMI) was suggested by Baumgartner to quantitate muscle objectively relative to the height and was calculated as skeletal muscle mass divided by height squared (kg/m^2) (36). It was used two definitions for low-SMI, as a) $<25^{th}$ percentile among each gender, and b) $<50^{th}$ percentile among each gender. Previously published cut-offs for skeletal muscle mass and/or SMI were not well-established and used for healthy adults (37).

Covariates

The hospital delivery records of participating mothers were acquired, including maternal age at birth, maternal pre-pregnancy BMI, birth weight of their offspring, and gestational age at delivery. Data on demographic, socioeconomic status and health-related issues were collected from participating mothers through self-assessed questionnaires and were reviewed by trained interviewers. Collected data included household income per month (< 4,000,000 KRW [≒ 3,333 US$], 4,000,000 KRW – 6,000,000 KRW [≒ 5,000 US$], and ≥ 6,000,000 KRW) and maternal education level (≤ high school graduate, college graduate, and above college). The frequency of strength exercise among children was obtained by the following question: "How often do your children do muscle-strengthening exercises per week?" Energy intake per day was assessed using the Computer-Aided Nutritional Analysis Program 4.0 for Professionals (Korean Society of Nutrition, Seoul, Republic of Korea) with food frequency questionnaires completed by the mothers.

Statistical analysis

Demographic characteristics of the study participants were collected, and differences in SMI according to the characteristics were tested using Student's t-test or analysis of variance. Next, mean values of body composition indices of the study participants, including height, weight, BMI z-score, BMI, FMI, and SMI were assessed. Geometric means (GMs) and SDs of metabolites of phthalates were also assessed. In statistical models for evaluating the association between phthalate metabolites and body composition, potential confounders were selected a priori

using directed acyclic graphs (38). For the association between phthalate exposure in children and their body composition, maternal education, household income, energy intake per day, and sex were selected a priori using directed acyclic graphs (**Figure 1** and **Figure 2**). First, nonparametric associations between phthalate metabolites and body composition parameters (BMI z-score, FMI, and SMI) were explored by using a generalized additive model. Next, the association between prenatal exposure to DEHP and BMI z-score and SMI was investigated by using multivariate linear regression models to test the hypothesis. To control the overall testing error rate, the false discovery rate (FDR) using Benjamini-Hochberg correction, and calculated the corrected *p*-values as $p\text{-}_{FDR}$ (39). The analysis was also performed after stratifying for sex. Additionally, multivariate linear regressions were performed to explore associations between all measured phthalate metabolites (MEHHP, MEOHP, MECCP, MnBP, and MBzP) and body composition parameters, which were not used in the hypothesis testing. Log_2-transformed values of phthalate metabolites were used for analyses as the values of these parameters were not normally distributed. The assumption of normality of the residuals was violated among few linear regression models for log_2-transformed phthalates metabolites and body composition indices, but, the number of observations was considered sufficient ($n \geq 100$) to overcome moderate non-normality (40). The estimates of the linear regression model were interpreted as differences in the body composition by a two-fold increase in phthalate metabolites. Multivariate logistic regression for the association between quartiled phthalate metabolites in prenatal maternal urine and low-SMI was also analyzed.

Next, latent growth class models were constructed. Latent growth curve models can classify repeatedly measured data into trajectory patterns groups

according to the variables measured at various time points. Latent growth class models estimate the possibility of trajectory patterns grouping using individual variability of the selected variables and their effect sizes (41). After grouping the trajectory patterns of body composition indices, the differences of prenatal exposure to phthalates were tested according to the trajectory patterns using multivariate linear regression models. The number of subgroups was chosen using model selection with Bayesian Information Criteria.

Multiple informant models were constructed to investigate the association of body composition indices with different time windows of phthalate exposure (42). Multiple informant models can test whether the exposure coefficients are equal across different time windows.

The models were based on generalized estimating equations, and estimate the exposure associations, β_{1k} at each time window k=1, 2, …, K (where Z_i are covariates), from the regressions as following:

$$Y_i=\beta_{0k}+\beta_{1k}X_{ki}+\beta_{2k}Z_i+\epsilon k_i$$

FDR with Benjamini-Hochberg correction was used to calculated p for interaction ($p_{\text{int-FDR}}$) to consider the multiple testing issue.

All analyses were performed for all the participants before and after stratification according to sex. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-tailed p-values < 0.05 were considered statistically significant.

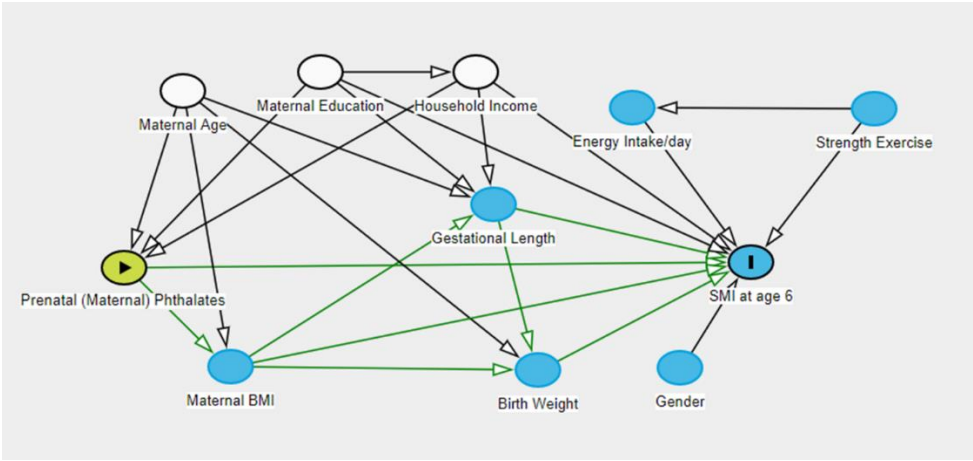

Figure 1. Directed acyclic graphs showing the relationship of prenatal phthalate exposure, body composition, and covariates

Note: Directed acyclic graphs (DAGs) show the hypothesized causal relationship among postnatal (in children) phthalate exposure (yellow circle), body composition ('I' in a blue circle), and covariates. The proposed adjustment variable using the DAGitty is indicated by white circles. Ancestors of the outcome, which are not proposed adjustment variables in the model are indicated by blue circles.

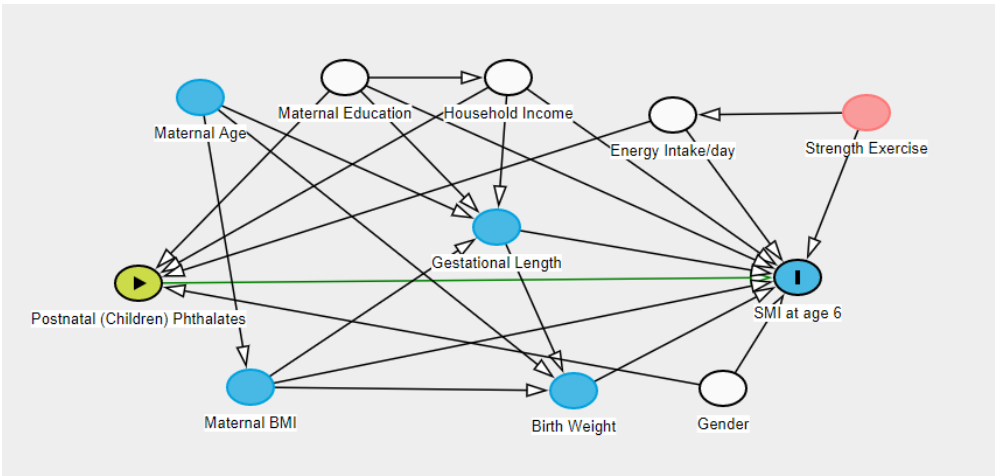

Figure 2. Directed acyclic graphs showing the relationship of postnatal (children) phthalate exposure, body composition, and covariates

Note: Directed acyclic graphs (DAGs) show the hypothesized causal relationship among postnatal (in children) phthalate exposure (yellow circle), body composition ('I' in a blue circle), and covariates. The proposed adjustment variable using the DAGitty is indicated by white circles. Ancestors of the outcome, which are not proposed adjustment variables in the model are indicated by blue circles.

2.3. Research ethics

The systematic review and meta-analysis study were not reviewed by the Institutional Review Board as it is not a human subject study or a human material study. For the mother-child cohort study, informed consent was obtained from all parents, and the study protocol was approved by the Institutional Review Board at the College of Medicine, Seoul National University (IRB No. 1201-010-392).

3. Results

3.1. A systematic review and meta-analysis

Figure 3 shows the process used to identify relevant studies. Of the 1,115 records screened, 878 studies were excluded based on their titles. After the abstracts were assessed, 184 irrelevant studies were excluded. After assessing the full texts of 53 studies, 29 studies met our inclusion criteria. Finally, I checked reference lists of the included studies, and no additional existent studies which were not already included in the final step were found.

Table 2 summarizes 29 observational, 17 longitudinal, and 12 cross-sectional studies. The study size varied between 72 and 2,884 participants. Studies were conducted in the U.S. (n=9), South Korea (n=3), China (n=3), Taiwan (n=3), Spain (n=2), Australia (n=1), France (n=1), Greece (n=1), Italy (n=1), Netherland (n=1), Sweden (n=1), Thailand (n=1), Iran (n=1), and in multiple countries of Europe (n=1). The quality of the studies as assessed by the NOS is presented in **Table 3** and **Table 4**. The scores of the included longitudinal studies (n=17) ranged from 8 to 9, and all longitudinal studies were classified as good quality. Cross-sectional studies (n=12) ranged from 5 to 8 and included 6 high-quality studies and 5 moderate-quality studies.

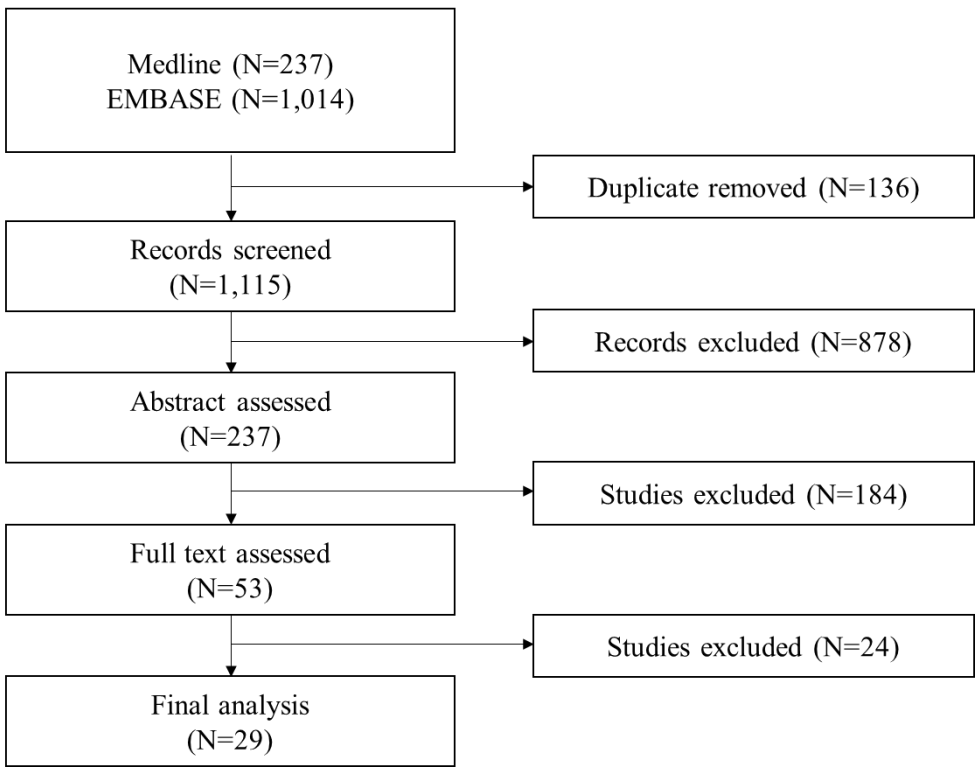

Figure 3. Flow diagram of the study selection process

Table 2. Summary of studies included in the systematic review

ID	First author	Year	Study design	Country	Sample Size	Study	Exposure assessment	Measured metabolites and range	Timing of outcome assessment	Outcome variables
1	K. Agay-Shay (43)	2015	Cohort study	Spain	470	INMA Spanish Birth cohort	Maternal urine in the 1st and 3rd trimester of pregnancy	GM of MECPP, MEHHP, MEOHP, and MEHP (40.8 µg/g Cr, 28.6 µg/g Cr, 27.8 µg/g Cr, and 14.6 µg/g Cr, respectively) 'GM of MnBP and MiBP (32.4 µg/g Cr, 32.6 µg/g Cr, respectively)	7 y	BMI z-scores
2	Y. E. Berman (44)	2020	Cohort study	Australia	410		Maternal urine in the 2nd and 3rd trimester of pregnancy	Median of ∑DEHP metabolites, and ∑DBP metabolites (9.34 µg/L, 4.10 µg/L, respectively)	1, 2, 3, 5, 8, 10, 14, 17 and 20 y	Height, BMI, DXA (total fat %, total fat mass [g], total lean mass [g])
3	J. Botton (45)	2016	Cohort study	France	520	EDEN mother-child cohort	Maternal urine in the 2nd trimester	Median of molar ∑DEHP metabolites, MnBP and MiBP (0.32 µM/L, 43 µg/L, and 39 µg/L, respectively)	5 y	BMI
4	J. P. Buckley (46)	2016	Cohort study	U.S.	707	MSSM + CCCEH + HOME Study	Prenatal maternal urine	GM of molar ∑DEHP metabolites, MnBP and MiBP (0.277 µM/L, 30.6 µg/L, and 6.45 µg/L, respectively)	4–9 y	BMI z-score and overweight/obese (BMI ≥ 85th percentile)
5	J. P. Buckley (18)	2016	Cohort study	U.S.	180	MSSM Study	Prenatal maternal urine	GM of molar ∑DEHP metabolites, MnBP and MiBP (0.284 µM/L, 32.9 µg/L, and 5.83 µg/L, respectively)	4 and 9 y	Body composition (total fat %)
6	M. C. Buser (47)	2014	Cross-sectional study	U.S.	not described	NHANES 2007–2010	Urine of the participants	(children and adolescents aged 6-19) GM of molar ∑DEHP metabolites, MnBP and MiBP (0.24 µM/L, 23.0 µg/L, and 10.43 µg/L,	children and adolescent	(children and adolescent) obese 95th percentile ≥

ID	First author	Year	Study design	Country	Sample Size	Study	Exposure assessment	Measured metabolites and range	Timing of outcome assessment	Outcome variables
								respectively) (adults ≥ 20 y) GM of ∑DEHP metabolites, MnBP and MiBP (0.18 μM/L, 15.21 μg/L, and 6.75 μg/L, respectively)	aged 6-19, adults ≥ 20 y	BMI z-score; overweight, 95th percentile > BMI z-score ≥ 85th percentile (adults) obese, BMI ≥ 30 kg/m^2; overweight, 30 kg/m^2 > BMI ≥ 25 kg/m^2
7	C. H. Chang (48)	2020	Cross-sectional study	Taiwan	152	RAPIT program	Urine of the participants	GM of ∑DEHP metabolites, MnBP and MiBP (59.29 μg/g Cr, 49.44 μg/g Cr, and 28.85 μg/g Cr, respectively)	5 y	BMI, total fat (%)
8	A. L. Deierlein (49)	2016	Cohort study	U.S.	1,239	The Breast Cancer and Environment Research Program	Urine of the participants at the baseline (6–8 y)	GM of ∑DEHP metabolites (182 μg/g Cr [6 y], 152 μg/g Cr [7 y], and 152 μg/g Cr [8 y]) and LMWH (184 μg/g Cr [6 y], 136 μg/g Cr [7 y], and 163 μg/g Cr [8 y])	3 times until the last visit when girls were on average 14 y old (11–16 y)	BMI
9	B. C. Heggeseth (50)	2019	Cohort Study	U.S.	335	CHAMACOS cohort study	Prenatal maternal urine	Median of MECPP, MEHHP, MEOHP, MnBP, and MiBP (24.05 μg/L, 14.8 μg/L, 10.75 μg/L, 20.7 μg/L, and 2.8 μg/L, respectively)	11 follow-up visits between ages 2 and 14 y	BMI
10	J. W. Hou (51)	2015	Cross-sectional study	Taiwan	308	270 normal adolescents (6.5–15 y)	Urine of the participants	GM of ∑DEHP, MnBP, and MiBP (193.73 μg/L, 75.42 μg/L, and 47.06 μg/L, respectively)	When assessing phthalate	Obese (BMI), waist-to-hip ratio,

ID	First author	Year	Study design	Country	Sample Size	Study	Exposure assessment	Measured metabolites and range	Timing of outcome assessment	Outcome variables
						and 38 complainants (6.5–8.5 y)			exposure (6.5–8.5 y)	Subcutaneous fat thickness
11	J. H. Kim (52)	2016	Cohort Study	South Korea	128	128 healthy pregnant women and their infants in 2012	Umbilical cord blood, newborns' first urine	GM of MEHHP in maternal blood, maternal urine, cord blood, placenta, and newborns' urine (0.31 μg/L, 18.23 μg/L, 0.,33 μg/L, 0.10 μg/L, and 5.83 μg/L, respectively), GM of MEOHP in maternal urine and newborns' urine (15.88 μg/L, and 3.02 μg/L, respectively)	Perinatal	BMI z-score change during 3 months (Evaluation criterion for relative body mass increase was BMI z-score change over the 50th percentile)
12	S. H. Kim (53)	2018	Cross-sectional study	South Korea	137	65 overweight children (6–13 y) and 72 controls	Urine of the participants	GM OF MECPP, MEOHP, and MEHHP (87.3 μg/g Cr, 29.5 μg/g Cr, and 36.8 μg/g Cr, respectively)	When assessing phthalates exposure (6–13 y)	BMI percentile
13	D. W. Lee (54)	2020	Cohort study	South Korea	481	EDC cohort	Prenatal maternal urine and urine of the participants	GM of molar ∑DEHP in prenatal maternal urine and children's urine at 6 years of age (0.11 μM/L, and 0.33 μM/L, respectively) GM of ∑MnBP in prenatal maternal urine and children's urine at 6 years of age (39.68 μg/L, and 70.00 μg/L, respectively)	6 y	BMI z-score, percentage of fat mass, fat mass index, percentage of skeletal muscle mass, skeletal muscle index

ID	First author	Year	Study design	Country	Sample Size	Study	Exposure assessment	Measured metabolites and range	Timing of outcome assessment	Outcome variables
14	M. M. Maresca (55)	2016	Cohort study	U.S.	424	CCCEH cohort	Prenatal maternal urine	GM of molar ∑DEHP metabolites, MiBP, and MnBP (0.29 μM/L, 8.81 μg/L, 37.58 μg/L)	5 y and 7 y	BMI z-score at 5 y and 7 y, percent of fat mass at 7 y, FMI at 7 y, WC at 7 y
15	K.G. Harley (56)	2017	Cohort study	U.S.	219	CHAMACOS cohort study	Prenatal maternal urine, two times	GM of ∑DEHP, MECPP, MEHHP, MEOHP, MnBP, and MiBP in each measurement (0.2 and 0.2 nmol/mL, 25.9 and 32.4 μg/L, 15.1 and 18.8 μg/L, 11.2 and 13.8 μg/L, 22.8 and 28.5 μg/L, and 2.7 and 3.4 μg/L, respectively)	12 y	BMI z-score, WC
16	T. Saengkaew (57)	2017	Cross-sectional study	Thailand	155	Children aged 7–18 y	Urine of the participants	Median of MBP (216.47 μg/g Cr), detection rate 82.58%	When assessing phthalate exposure	BMI z-score, WC
17	J. Shoaff (58)	2017	Cohort study	U.S.	219	HOME study	up to two times prenatally and six times from 1 to 8 y	GM of ∑DEHP, MiBP, and MnBP for children (86 μg/L, 4.8 μg/L, and 25 μg/L, respectively)	8 y	BMI z-score, WC, body fat percent
18	A. Smerieri (59)	2015	Cross-sectional study	Italy	72	41 obese children and 31 controls (mean age 12 y)	Urine of the participants	Detection rates of MECPP, MEOHP, and MEHHP were 80.5%, 87.8%, and 80.5% among obese group, and 38.7%, 74.2%, and 8.39% among control group, respectively.	When assessing phthalate exposure	WC

ID	First author	Year	Study design	Country	Sample Size	Study	Exposure assessment	Measured metabolites and range	Timing of outcome assessment	Outcome variables
19	L. Trasande (16)	2013	Cross-sectional study	U.S.	2,884	NHANES 2003–2008 (children 6–19 y)	Urine of the participants	GM of ∑DEHP metabolite (0.358 μM/L among males and 0.360 among females) and ∑LMW metabolite (0.593 μM/L among males and 0.680 μM/L among females)	When assessing phthalate exposure	BMI z-score, overweight (BMI z-score ≥ 85th percentile), and obesity (BMI z-score ≥ 95th percentile)
20	Y. A. Tsai (60)	2016	Cohort study	Taiwan	88	RAPIT program (6.0–10.5 y)	Estimated the total daily intake of DEHP, and urine of the participants	Mean of ∑DEHP metabolite 106.19 μg/g Cr	When participants were examined	Weight percentile and height percentile above 50th percentile (based on the standards provided by the Ministry of Health and Welfare)
21	M. Vafeiadi (61)	2018	Cohort Study	Greece	500	Rhea Study	Prenatal maternal urine and urine of the participants	GM of molar ∑DEHP, MiBP, and MnBP in prenatal maternal urine (0.1 μM/g Cr, 33.5 μg/g Cr, and 37.1 μg/g Cr, respectively) GM of molar ∑DEHP, MiBP, and MnBP in children's urine (0.3 μM/gCr, 41.1 μg/g Cr, and 21.7 μg/g Cr, respectively)	4–6 y	BMI z-score
22	D. Valvi (62)	2015	Cohort study	Spain	391	INMA Spanish birth cohort	Prenatal maternal urine at 1st and 3rd trimester.	GM of ∑DEHP metabolites, MnBP and MiBP (99.6 μg/gCr, 32.7 μg/gCr, and 33.0 μg/gCr, respectively)	Birth to 6 mos., 1, 4, and 7 y of age	BMI z-score, weight gain z-score (0–6 months)
23	M. Vrijheid (63)	2020	Cohort study	Europe	1,031	HELIX study (BiB	77 prenatal exposure and	Not described	BMI z-score (age-and-sex	BMI z-score

ID	First author	Year	Study design	Country	Sample Size	Study	Exposure assessment	Measured metabolites and range	Timing of outcome assessment	Outcome variables
						in the U.K., EDEN in France, INMA in Spain, KANC in Lithuania, MoBa and Rhea in Greece)	96 childhood exposure including air pollutants, built environments, and biomarkers of chemical pollutants.		standardized z-scores)	
24	B. Wu (64)	2020	Cross-sectional study	U.S.	2,372	NHANES 2005-2010 (6–19 y)	Urine of the participants	GM of MiBP, 9.98 μg/L	When assessing phthalate exposure	BMI z-score
25	B. Xia (65)	2018	Cross-sectional study	China	159	PTHEC study, 69 overweight /obese children and 80 normal weight children	Urine of the participants	Median of MEOHP, MEHHP, and MnBP among normal participants (2.97 μg/L, 7.57 μg/L, and 13.68 μg/L, respectively) and overweight/obese participants (2.6 μg/L, 6.5 μg/L, and 18.68 μg/L, respectively)	When assessing phthalate exposure	Overweight/obese

ID	First author	Year	Study design	Country	Sample Size	Study	Exposure assessment	Measured metabolites and range	Timing of outcome assessment	Outcome variables
26	C. Xie (66)	2015	Case-control study	China	167	57 boys with constitutional delay for growth and puberty and 110 controls (11 y)	Urine of the participants	Median of ∑DEHP metabolites and MnBP among cases (20.06 μg/L and 37.43 μg/L, respectively), and controls (12.85 μg/L and 15.56 μg/L, respectively)	When assessing phthalate exposure	Constitutional delay of growth and puberty
27	A. Zettergren (67)	2021	Cohort study	Sweden	100	BAMSE birth cohort	Urine of the participants at 4 years of age	GM of ∑DEHP metabolites and MnBP (331 μg/L, 296 μg/L)	24 y	BMI, WC, Body fat %, trunk fat % (BIA)
28	Y. Zhang (19)	2014	Cross-sectional study	China	497	PTHEC study (8–13 y)	Urine of the participants	GM of ∑DEHP metabolites and MnBP; boys (8–10 y), 29.6 μg/L; boys (11–13 y), 21.9 μg/L; girls (8–10 y), 32.5 μg/L; girls (11–13 y), 16.5 μg/L	When assessing phthalate exposure	BMI z-score, body fat % (Yao's formula)
29	M.M. Amin (68)	2017	Cross-sectional study	Iran	242		Urine of participants	Mean of MEOHP, MEHHP, MEHP, MBzP, MBP, and MMP were 257.98 μg/L, 149.44 μg/L, 104.46 μg/L, 233.01 μg/L, 218.17 μg/L, and 59.82 μg/L	6–18 y	BMI z-score, WC

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MnBP, mono-n-butyl phthalate (MnBP); MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; MBzP, Monobenzyl phthalatete; BMI, body mass index; WC, waist circumference.

Table 3. Newcastle-Ottawa Quality Assessment Scale for included longitudinal Studies

ID	First author	Study Design	Newcastle-Ottawa Scale								
			S1	S2	S3	S4	C	O1	O2	O3	Sum
1	K. Agay-Shay	Cohort study	*	*	*	*	**	*	*	*	9
2	Y. E. Berman	Cohort study	*	*	*	*	**	*	*	*	9
3	J. Botton	Cohort study	*	*	*	*	**	*	*	*	9
4	J. P. Buckley	Cohort study	*	*	*	*	**	*	*	*	9
4	J. P. Buckley	Cohort study	*	*	*	*	**	*	*	*	9
8	A. L. Deierlein	Cohort study	*	*	*	*	*	*	*	*	8
9	B. C. Heggeseth	Cohort Study	*	*	*	**	*	*	*	*	9
11	J. H. Kim	Cohort Study	*	*	*	*	**	*	*	*	9
13	D. W. Lee	Cohort study	*	*	*	*	**	*	*	*	9
14	M. M. Maresca	Cohort study	*	*	*	*	**	*	*	*	9
15	K. G. Harley	Cohort study	*	*	*	*	**	*	*	*	9
17	J. Shoaff	Cohort study	*	*	*	*	**	*	*	*	9
20	Y. A. Tsai	Cohort study	*	*	*		**	*	*	*	8
21	M. Vafeiadi	Cohort Study	*	*	*	*	**	*	*	*	9
22	D. Valvi	Cohort study	*	*	*	*	**	*	*	*	9
23	M. Vrijheid	Cohort study	*	*	*	*	**	*	*	*	9
27	A. Zettergren	Cohort study	*	*	*	*	**	*	*	*	9

Table 4. Newcastle-Ottawa Quality Assessment Scale for included cross-sectional studies

ID	First author	Study Design	Newcastle-Ottawa Scale							
			S1	S2	S3	S4	C	O1	O2	Sum
6	M. C. Buser	Cross-sectional study	*			**	**	**	*	8
7	C. H. Chang	Cross-sectional study	*			**	**	**	*	8
10	J. W. Hou	Cross-sectional study			*	**	**	*	*	7
12	S. H. Kim	Cross-sectional study			*	**	*	*	*	6
16	T. Saengkaew	Cross-sectional study			*	**		**		5
18	A. Smerieri	Cross-sectional study			*	**		**		5
19	L. Trasande	Cross-sectional study	*			**	**	**	*	8
24	B. Wu	Cross-sectional study	*			**	**	**	*	8
25	B. Xia	Cross-sectional study	*			**		**	*	6
26	C. Xie	Case-control study	*	*			**	*		5
28	Y. Zhang	Cross-sectional study	*			**	**	**	*	8
29	M. M. Amin	Cross-sectional study	*			**	**	**	*	8

Prenatal exposure to phthalates and BMI in children

Table 5 describes studies that investigate the association between prenatal exposure to phthalates and BMI. Among a total of 29 studies, 14 studies investigated the association between prenatal exposure to phthalates and BMI. The results for this association were inconsistent, and a limited number of studies reported statistical significance. Kim et al. studied 128 healthy pregnant women and their infants and investigated the association between phthalate levels in umbilical cord blood and newborns' first urine and BMI z-score change during 3 months. The BMI z-score changes by one-unit log of ∑DEHP in newborns' urine, maternal blood, maternal urine, and cord blood were 0.882 (95% CI: 0.587, 1.176), -0.924 (95% CI: -3.672, 1.825), -0.200 (95% CI: -0.842, 0.442), and 0.110 (95% CI: -3.053, 3.273), respectively. Thus, the authors concluded that body mass increase could be accelerated in newborn infants exposed to DEHP (52). Maresca et al. studied 424 mother-child pairs in the CCCEH cohort in the U.S. and reported the association between phthalates in prenatal maternal urine and BMI z-score at 5 and 7 years of age. They performed principal component analyses, and β of prenatal non-DEHP component score among boys (-0.30 [95% CI: -0.54, -0.06]) was statistically significant; they noted that contrary to their expectation, prenatal non-DEHP phthalate exposure was associated with a lower BMI z-score (55). A study performed in Spain by Valvi et al. reported that β of one unit increase in ∑DEHP metabolites was significant in boys (-0.32, [95% CI: -0.64, -0.02]), but not in girls (0.21, [95% CI: -0.11, 0.53]). Statistical significance of associations between phthalate metabolites and BMI of children was summarized in **Table 6**.

Figure 4 shows the results of a meta-analysis on the association between prenatal DEHP exposure and BMI z-score in children. Eight studies presented the

eligible results for the meta-analysis, which were selected for meta-analysis. Data from Agay-Shay et al. was not included because it was derived from the same study population (INMA cohort) with data from Shoaff et al. Heterogeneity among these studies was not significant (p = 0.380). In the random effect model, there was a significant and negative association between prenatal DEHP exposure and BMI z-score index (β=-0.057; 95% CI: -0.106, -0.008). Visual inspection of the funnel plot revealed no asymmetry (**Figure 5**), and the Egger test showed no publication bias (p=0.797).

Figure 6 shows the results of a meta-analysis on the association between prenatal DBP exposure and BMI z-scores in children. Six studies presented data on BMI z-scores, and these articles were selected for the meta-analysis. Heterogeneity among these studies was found, but it was not statistically significant (p = 0.0505). In the random-effects model, there was no significant association between prenatal DBP exposure and BMI z-score (β=-0.022; 95% CI: -0.100, 0.056). Visual inspection of the funnel plot revealed no asymmetry (**Figure 7**), and the Egger test showed no publication bias (p=0.538).

Table 5. Description of papers accessing the association between prenatal exposure to phthalates and BMI

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
1	K. Agay-Shay	2015	Maternal urine in the 1st and 3rd trimesters of pregnancy	7 y	Multiple linear regression	β and 95% CI	(BMI z-scores) MECPP highest tertile (vs. lowest tertile), -0.26 (95% CI: -0.55, 0.04); MnBP highest tertile (vs. lowest tertile), -0.08, (95% CI: -0.37, 0.22)	sex, gestational age at birth, birth weight, age, maternal country of origin, maternal age at delivery, maternal pre-pregnancy BMI, maternal weight gain during pregnancy, maternal social class, breastfeeding duration, and maternal smoking during pregnancy
2	Y. E. Berman	2020	Maternal urine in the 2nd and 3rd trimesters of pregnancy	1, 2, 3, 5, 8, 10, 14, 17, and 20 y	Linear mixed effect model	β and 95% CI or tertial and 95% CI	(BMI Z-score) Marginal mean z-score of 2nd tertile for MiBP in 2–11 y [0.46 (95% CI: 0.28, 0.64)] and in 11–20 y [0.43 (95% CI: 0.24, 0.63)]. Marginal mean z-score of 2nd tertile for ∑low molecular phthalates metabolites in 2–11 y [0.44 (95% CI: 0.26, 0.62)]	age, gestational age at birth, birthweight, and maternal pre-pregnancy BMI
3	J. Botton	2016	Maternal urine in the 2nd trimester	5 y	Multiple linear regression	β and 95% CI	(BMI) IQR increase of MEP 0.17 kg/m^2 (0.04, 0.30); ∑DEHP metabolites and DBP metabolites in maternal urine were not significantly associated with BMI at 5 years of age (data was not shown)	recruitment center, maternal height, BMI using self-reported pre-pregnancy weight, smoking during pregnancy, education level, age, weight gain during pregnancy, and parity.
4	J. P. Buckley	2016	Prenatal maternal urine	4–9 y	Linear mixed effect model	β and 95% CI or OR and 95% CI	**(BMI z-score) β for natural log ∑DEHP metabolites (-0.04 [95% CI: -0.15, 0.07]), β for natural log MnBP (0.03 [95% CI: -0.12, 0.18])**	cohort, maternal race/ethnicity, maternal age at delivery, maternal education, maternal work status during pregnancy, maternal pre-

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
							(Overweight/obese) OR for standard deviation increase in natural log ∑DEHP metabolites, MnBP and MiBP (0.87 [0.53, 1.4], 1.0 [0.51, 2.0], and 0.84 [0.44, 1.6], respectively)	pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, the calendar date of urine collection, and parity.
8	A. L. Deierlein	2016	Urine of the participants at the baseline (6–8 y)	3 times until the last visit when girls were on average 14 y old (11–16 y)	Linear mixed effect model	β and 95% CI	(BMI) β of ∑DEHP high vs. low, 0.63 (-0.17, 1.4); LMWH high versus low, 1.2 (0.28, 2.1)	age, age^2, race/ethnicity, age×phthalate categories, age^2×phthalate categories, and race/ethnicity×age.
12	B. C. Heggeseth	2019	Prenatal maternal urine	11 follow-up visits between the ages of 2 and 14 y	GAM, Growth Mixture Models, FPCA, Regression Trees, Random Forest	β and 95% CI	(β for Principal component 1 for BMI trajectories, boy) MECPP 0.2 (-2.18, 2.58), MnBP 1.18 (-0.63, 3.00), and MiBP 0.04 (-1.57, 1.65); (β for Principal component 1 for BMI trajectories, girls) MECPP 1.46 (-0.63, 3.56), MnBP 0.57 (-1.38, 2.52), and MiBP 0.22 (-1.45, 1.90)	maternal pre-pregnancy BMI, gestational weight gain, diet quality index during pregnancy, smoking during pregnancy, education, marital status, age, and number of years in the U.S.
14	J. H. Kim	2016	Umbilical cord blood, newborns' first urine	Perinatal	Generalized linear models	β and 95% CI	**(BMI z-score) β of natural log of ∑DEHP in each medium in maternal urine, -0.200 (-0.842, 0.442)**; β of natural log of ∑DEHP in cord blood, 0.110 (-3.053, 3.273); 0.114, (-2.197, 2.424)	maternal age, maternal BMI, gestational period, caesarean section, delivery experience, urinary creatinine levels, newborns' sex, common log of

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
								ponderal index, and common log of triglyceride
15	K. G. Harley	2017	Prenatal maternal urine, two times	5, 7, 9, 10.5, and 12 y	Generalized estimating equations	β and 95% CI	**(BMI z-score) β of log_2 ∑DEHP for BMI z-score at 5 year (0.05 [95% CI: -0.05, 0.16]).** β of log_2 ∑DEHP for BMI z-score at 7 (0.08 [95% CI: -0.02, 0.18]), 9 (0.09 [95% CI: -0.01, 0.20]), 10.5 (0.09 [95% CI: -0.02, 0.19]) and 12 years (0.08 [95% CI: -0.03, 0.19]). **β of log_2 MnBP for BMI z-score at 5 year (0.09 [95% CI: 0.00, 0.19]).** β of log_2 MnBP for BMI z-score at 7 (0.07 [95% CI: -0.01, 0.17]), 9 (0.06 [95% CI: -0.02, 0.14]), 10.5 (0.06 [95% CI: -0.03, 0.14]) and 12 years (0.06 [95% CI: -0.03, 0.15]).	maternal age, maternal education, marital status, years in United States prior to delivery, smoking during pregnancy, poverty status during pregnancy, child's food insecurity at each time point, child's fast food consumption at each time point, and prenatal bisphenol A exposure level
17	D. W. Lee	2020	Prenatal maternal urine and urine of the participants	6 y	Multivariate linear regression	β and 95% CI	**(BMI z-score) β of log_2 ∑DEHP in prenatal maternal urine (-0.07 [-0.16, 0.02])**, and β of log_2 ∑DEHP in children's urine (-0.03 [-0.09, 0.14]); **β of log_2 MnBP in prenatal maternal urine (-0.07 [95% CI: -0.17, 0.03])** and β of log_2 MnBP in children's urine -0.03 (95% CI: -0.15, 0.1)	maternal age, maternal education, and household income for the association between maternal phthalates, body composition indices of their children and urinary creatinine, and adjusted for maternal education, household income, energy intake per day, sex of the children, and urinary creatinine

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
20	M. M. Maresca	2016	Prenatal maternal urine	5 y and 7 y	Generalized Estimating Equation and principal component analysis	β and 95% CI	**(BMI z-score) β of natural log ∑DEHP were -0.09 (95% CI: -0.28, 0.11) among boys and -0.08 (95% CI: -0.25, 0.09) among girls**; **β of natural log MnBP were -0.22 (95% CI: -0.44, 0.00) among boys and 0.11 (95% CI: -0.12, 0.34) among girls**; β of prenatal DEHP component score among boys (-0.00 [-0.24, 0.24]) and girls (-0.12 [-0.31, 0.08]); β of prenatal non-DEHP component score among boys (-0.30 [-0.54, -0.06]) and girls (0.13 [-0.14, 0.41]);	age, maternal pre-pregnancy obesity, birth weight, maternal race/ethnicity, maternal receipt of public assistance during pregnancy, urinary specific gravity, and urinary metabolite concentration component scores of children aged 3 and 5 y
28	J. Shoaff	2017	up to two times prenatally and six times from 1 to 8 years of age	8 y	Multiple informant model (Generalized estimating equation)	β and 95% CI	**(BMI z-score) β of log_{10} ∑DEHP at prenatal (-0.1 [95% CI: -0.4, 0.2])**; β of log_{10} ∑DEHP at 1 y, 2 y, 3 y, 4 y, 5 y, and 8 y (-0.4 [-0.8, 0.0], -0.2 [-0.6, 0.2], 0.1 [-0.3, 0.5], 0.1 [-0.3, 0.6], 0.4 [0.0, 0.9], and -0.1 [-0.4, 0.3], respectively); **β of log_{10} MnBP at prenatal (-0.1 [95% CI: -0.5, 0.4])**;	maternal age at delivery, race, marital status, insurance, income, education, parity, cotinine, depressive symptoms, mid pregnancy BMI, food security, fruit/vegetable and fish consumption, prenatal vitamin use, child's sex, and child's age at the visit
32	M. Vafeiadi	2018	Prenatal maternal urine and urine of the participants	4–6 y	Generalized estimating equations	β and 95% CI	**(BMI z-score) β of log_{10} ∑DEHP in prenatal maternal urine (-0.21 [95% CI: -0.45, 0.03])** and children's urine (-0.02 [95% CI: -0.27, 0.22])**; β of log_{10} sum of MnBP metabolites in maternal urine (-0.18 [95% CI: -0.41, 0.05])** and in children's urine (0.15 [95% CI: -0.03, 0.34])	sex, age, maternal age at delivery, parity, education, pre-pregnancy BMI, and smoking in pregnancy

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
33	D. Valvi	2015	Prenatal maternal urine at 1st and 3rd trimesters.	Birth to 6 mo., 1, 4, and 7 y	Generalized estimating equations	β and 95% CI	**(BMI z-score) β of log_2 ∑DEHP (boys, -0.32 [95% CI: -0.64, -0.02]; girls, (0.21, [95% CI: -0.11, 0.53])**	sex, age, maternal country of origin, maternal age at delivery, maternal parity, maternal education, maternal social class, pre-pregnancy BMI, and smoking in pregnancy
34	M. Vrijheid	2020	77 cases of prenatal exposure and 96 cases of childhood exposure	BMI z-score	Multivariate linear regression	β and 95% CI	(BMI z-score) β of IQR increase in ∑DEHP metabolites in maternal urine (-0.03 [-0.11, 0.05]; IQR 116.5 μg/g Cr) and in children's urine (-0.04 [-0.13, 0.04]; IQR 75.3 μg/g Cr)	Enrolled cohort, sex, maternal BMI, maternal education, maternal age at conception, parity, parental country of origin, breastfeeding, and birth weight

BMI, body mass index; CI, confidence interval; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate; IQR, interquartile range

Beta estimates used in the meta-analysis in bold

Table 6. Statistical significance of associations between prenatal phthalates exposure and BMI in children

No	Author	∑phthalate	∑DEHP	MECCP	MEHHP	MEOHP	MnBP	MiBP	Remarks
1	K. Agay-Shay	n.s.							BMI z-score at 7 years
2	Y. E. Berman	n.s.	n.s.	n.s.			n.s.	(+)	BMI z-score at 2-11 years
3	J. Botton		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	BMI at 5 years
4	J. P. Buckley		n.s.				n.s.	n.s.	BMI z-score at 4-7 years
8	A. L. Deierlein		n.s.				n.s.	n.s.	BMI at 6-8 years
12	B. C. Heggeseth			n.s.	n.s.	n.s.	n.s.	n.s.	BMI Trajectory Group
14	J. H. Kim		(+)		(+)	(+)			△BMI z-score form birth to 3 months
15	K. G. Harley		n.s.				n.s.	(+)	BMI z-score at 5 years
17	D. W. Lee		n.s.		n.s.	n.s.	n.s.		BMI z-score at 6 years
20	M. M. Maresca		n.s.						BMI z-score at ages 5 and 7 years
28	J. Shoaff		n.s.				n.s.	n.s.	BMI at 8 years
32	M. Vafeiadi		n.s.				n.s.	n.s.	BMI z-score at 4-6 years. Significant findings in girls
33	D. Valvi		n.s.						BMI z-score at 1, 4, and 7 years. Significant findings in boys
34	M. Vrijheid		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	BMI z-score at 6-11 years

n.s., not statistically significant; (+), a statistically significant and positive association; (-), a statistically significant and negative association; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; MnBP, mono-n-butyl phthalate (MnBP); MiBP, Monoisobutyl phthalate

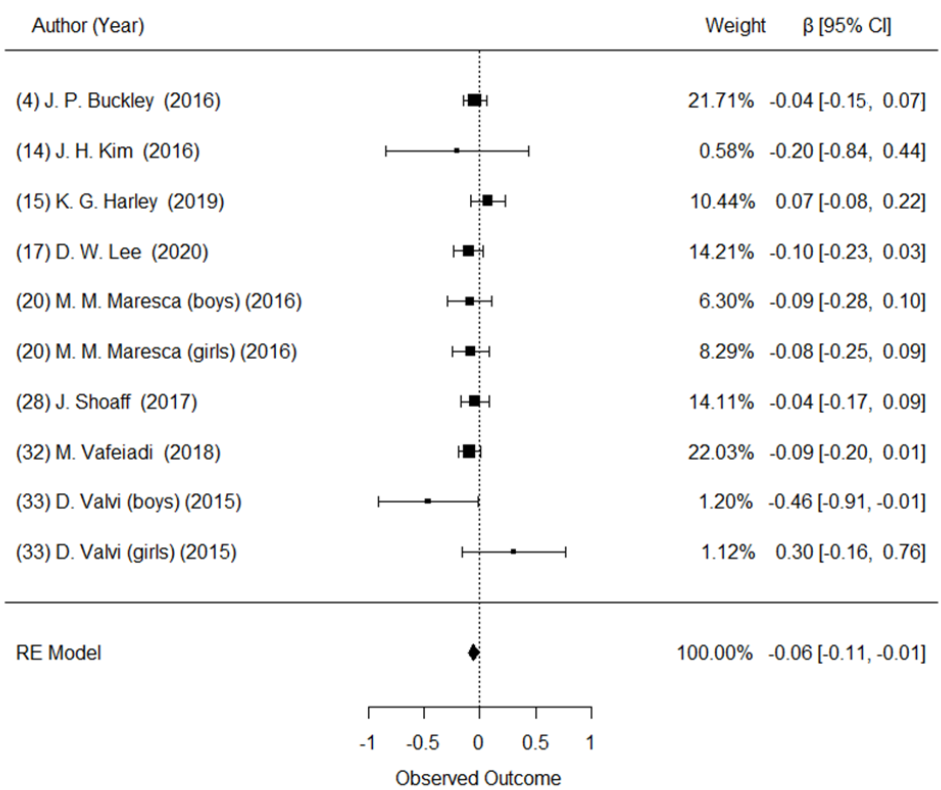

Figure 4. Forest plot of studies on the association of DEHP exposure with BMI z-scores: longitudinal studies

Estimates were standardized as β and 95% confidence intervals as one unit increase of natural log of DEHP metabolites

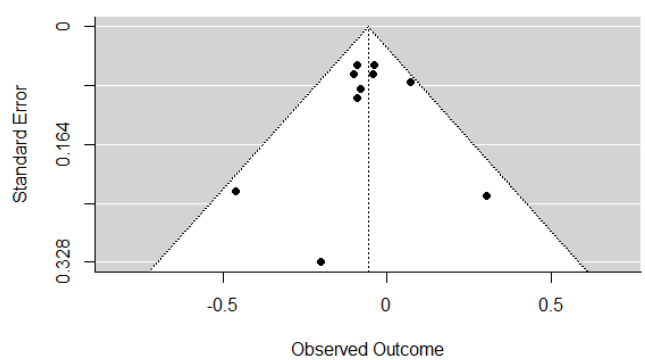

Figure 5. Funnel plot of studies on the association of DEHP exposure with BMI z-scores: longitudinal studies

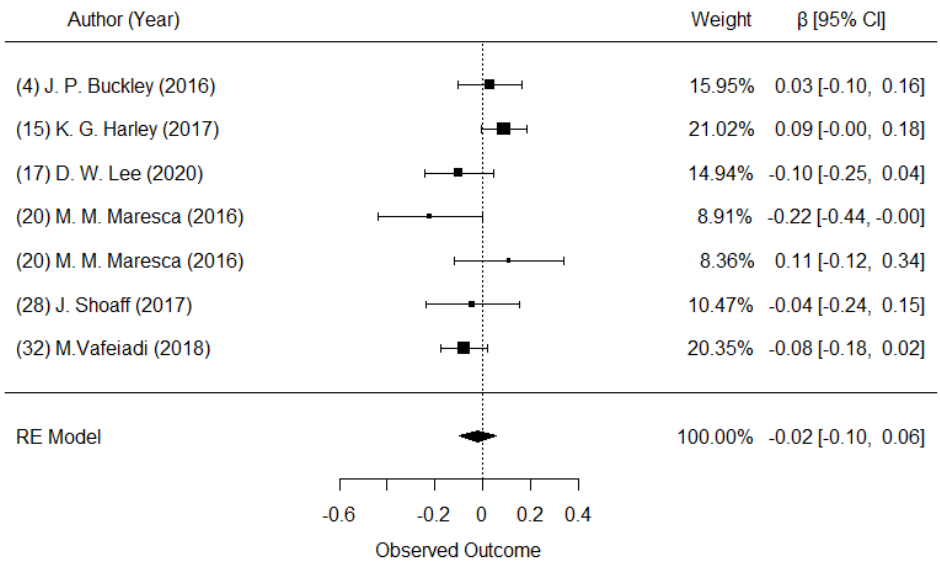

Figure 6. Forest plot of studies on the association of DBP exposure with BMI z-scores: longitudinal studies

Estimates were standardized as β and 95% confidence intervals as one unit increase of natural log of DBP metabolites

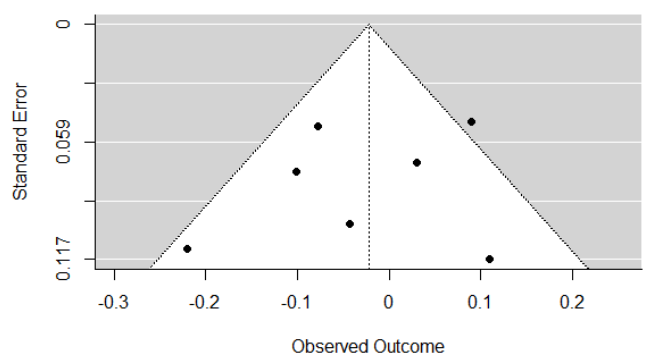

Figure 7. Funnel plot of studies on the association of DBP exposure with BMI z-scores: longitudinal studies

Prenatal exposure to phthalates and body fat percentage

Table 7 describes studies that investigate the association between prenatal exposure to phthalates and body fat percentage. From a total of 29 studies, 7 were included. The results for this association were inconsistent, and only a limited number of studies reported statistical significance. Statistical significance of associations between phthalate metabolites and body fat percentage of children was summarized in **Table 8**.

Figure 8 shows the results of a meta-analysis for the association between prenatal DEHP exposure and body fat percentage. Six studies presented data regarding body fat percentage, and these articles were chosen to perform the meta-analysis. Heterogeneity among these studies was not found (p = 0.358). In the random-effect model, no significant associations between prenatal DEHP exposure and body fat percentage were found (β=0.01; 95% CI: -0.41, 0.44). Visual inspection of the funnel plot revealed no asymmetry (**Figure 9**), and the Egger test showed no publication bias (p=0.287).

Figure 10 shows the results of a meta-analysis on the association between prenatal DBP exposure and body fat percentage. Five studies presented data regarding body fat percentage, and these articles were selected for the meta-analysis. Heterogeneity among these studies was not found (p = 0.184). There were no significant associations between prenatal DBP exposure and body fat percentage (β=-0.42; 95% CI: -1.04, 0.19). Visual inspection of the funnel plot revealed no asymmetry (**Figure 11**), and the Egger test showed no publication bias (p=0.601).

Table 7. Description of studies on the association between prenatal exposure to phthalates and body fat percentage

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
2	Y. E. Berman	2020	Maternal urine in the 2nd and 3rd trimester of pregnancy	1, 2, 3, 5, 8, 10, 14, 17, and 20 y	Linear mixed effect model	β and 95% CI or OR and 95% CI	(body fat percentage) ∑DEHP metabolites highest tertile (vs. lowest tertile), β 0.97 (0.84, 1.12); ∑DBP metabolites highest tertile (vs. lowest tertile), β 1.05 (0.91, 1.21)	age, gestational age at birth, birthweight, and maternal pre-pregnancy BMI
5	J. P. Buckley	2016	Prenatal maternal urine	4 and 9 y	Linear mixed effect model	β and 95% CI	**(body fat percentage) β of natural log ∑DEHP (-0.89 [95% CI: -2.24, 0.47]) and β of natural log MnBP (-0.86 [95% CI: -0.37, 1.36])**	urine dilution and collection date, maternal race/ethnicity, age, education, work status, and smoking during pregnancy; maternal height and pre-pregnancy, BMI, adequacy of gestational weight gain, breastfeeding, child's age in mos. and physical activity at follow-up, and child's sex.
13	D. W. Lee	2020	Prenatal maternal urine and urine of the participants	6 y	Multivariate linear regression	β and 95% CI	(body fat percentage) **β of log_2 ∑DEHP at prenatal (-0.05 [95% CI:-0.09, -0.02])** and **β of log_2 MnBP at prenatal (0.01 [95% CI: -0.31, 0.33])**	maternal age, maternal education, and household income for the association between maternal phthalates, body composition indices, and urinary creatinine of the children. Parameters were adjusted for maternal education, household income, energy intake

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
								per day, sex of the children, and urinary creatinine
14	M. M. Maresca	2016	Prenatal maternal urine	5 and 7 y	Generalized Estimating Equation	β and 95% CI	(body fat percentage) **β of natural log ∑DEHP among boys (-0.39 [95% CI: -1.57, 0.79]) and girls (-0.13 [95% CI: -1.09, 0.84]); β of natural log MnBP among boys (-1.05 [95% CI: -2.26, 0.15]), and girls (-0.52 [95% CI: -0.72, 1.76])**	age, maternal pre-pregnancy obesity, birth weight, maternal race/ethnicity, maternal receipt of public assistance during pregnancy, urinary specific gravity, and urinary metabolite concentration component scores of children at 3 and 5 years of age
15	K. G. Harley	2017	Prenatal maternal urine, two times	5, 7, 9, 10.5, and 12 y	Generalized estimating equations	β and 95% CI	(body fat percentage) **β of log_2 ∑DEHP at 9 (1.0 [95% CI: -0.2, 2.2])**, 10.5 (1.0 [95% CI: -0.2, 2.2]), and 12 year (1.1 [95% CI: -0.2, 2.4]); **β of log_2 MnBP at 9 (0.9 [95% CI: -0.1, 1.9])**, 10.5 (1.0 [95% CI: 0.0, 1.9]), and 12 year (0.7 [95% CI: -0.4, 1.8])	maternal age, maternal education, marital status, years in United States prior to delivery, smoking during pregnancy, poverty status during pregnancy, child's food insecurity at each time point, child's fast food consumption at each time point, and prenatal bisphenol A
17	J. Shoaff	2017	up to two times prenatally and six times	8 y	Multiple informant model (Generalized	β and 95% CI	(body fat percentage) **β of log_{10} ∑DEHP at prenatal (0.5 [95% CI: -1.4, 2.3])**	maternal age at delivery, race, marital status, insurance, income, education, parity, urinary cotinine levels, depressive symptoms, mid-pregnancy BMI, food security,

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
			from 1 to 8 years of age		estimating equation)			fruit/vegetable and fish consumption, prenatal vitamin use, child's sex, and child's age in months at the visit
27	A. Zettergren	2021	Urine of the participants at 4 years of age	24 y	Generalized estimating equations and multivariate linear regression	β and 95% CI	(body fat percentage) **β of natural log ∑DEHP (1.62 [95% CI: -0.97, 4.20]) and β of natural log MnBP (-0.77, [95% CI: -3.47, 1.94])**	sex, maternal smoking during pregnancy, socioeconomic status, breastfeeding duration, physical activity, smoking, and urinary cotinine levels.

BMI, body mass index; CI, confidence interval; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate; IQR, interquartile range
Beta estimates used in the meta-analysis in bold

Table 8. Statistical significance of associations between prenatal phthalates exposure and percent fat mass in children

No	Author	∑phthalate	∑DEHP	MECCP	MEHHP	MEOHP	MnBP	MiBP	Remarks
2	Y. E. Berman	n.s.	n.s.	(+)			n.s.	n.s.	Percent fat mass at 2-11 years
5	J. P. Buckley		n.s.	n.s.			n.s.		Percent fat mass at 4-7 years
13	D. W. Lee		n.s.		n.s.	n.s.	n.s.		Percent fat mass at 6 years
14	M. M. Maresca		n.s.						Percent fat mass at 5 and 7 years
15	K. G. Harley		(+)				n.s.	n.s.	Percent fat mass at 5 years
17	J. Shoaff		n.s.				n.s.	n.s.	Percent fat mass at 8 years
27	A. Zettergren		n.s.	n.s.	n.s.	n.s.	n.s.		Percent fat mass at 24 years

n.s., not statistically significant; (+), a statistically significant and positive association; (-), a statistically significant and negative association; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; MnBP, mono-n-butyl phthalate (MnBP); MiBP, Monoisobutyl phthalate

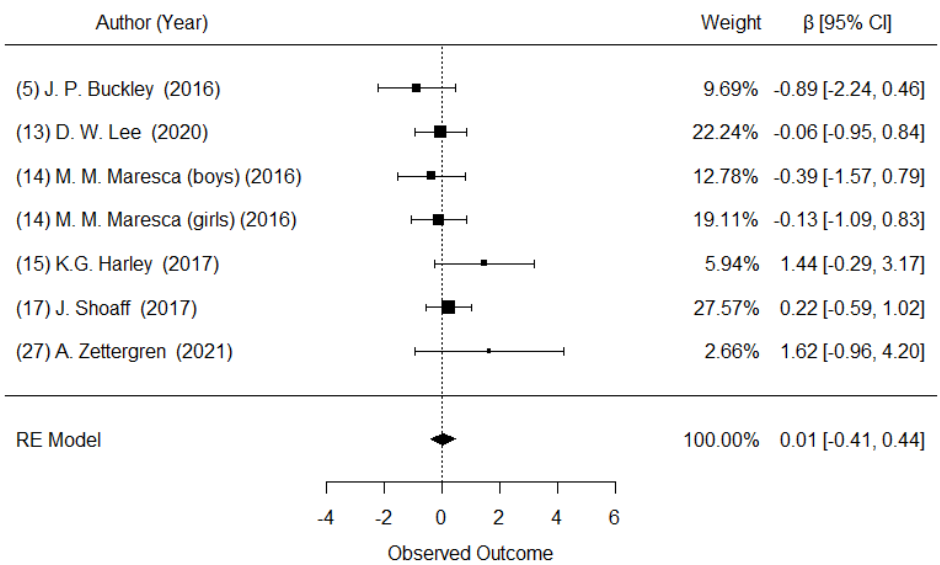

Figure 8. Forest plot of studies on the association of DEHP exposure with body fat percentage: longitudinal studies
Estimates were standardized as β and 95% confidence intervals as one unit increase of natural log of DEHP metabolites

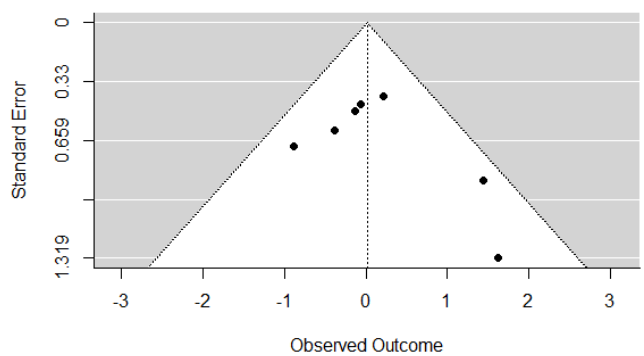

Figure 9. Funnel plot of studies on the association of DEHP exposure with body fat percentage: longitudinal studies

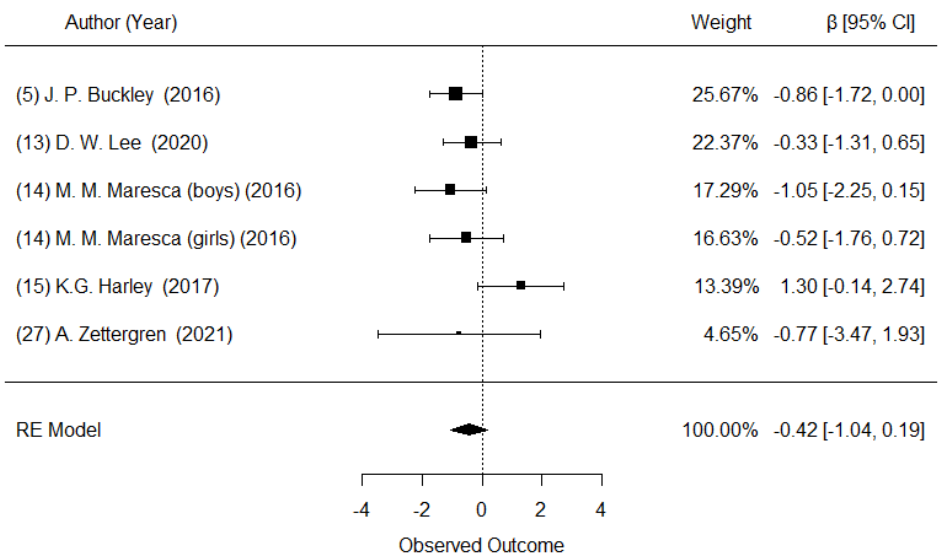

Figure 10. Forest plot of studies on the association of DBP exposure with body fat percentage: longitudinal studies
Estimates were standardized as β and 95% confidence intervals as one unit increase of natural log of DEHP metabolites

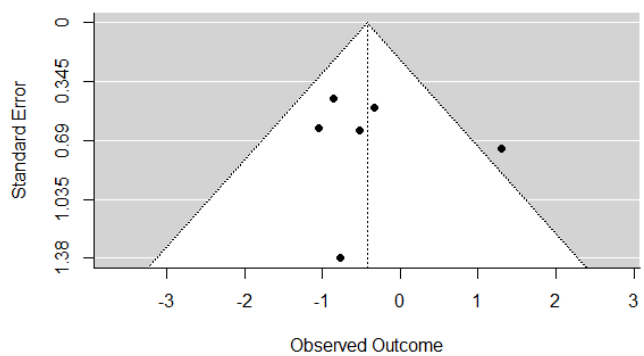

Figure 11. Funnel plot of studies on the association of DEHP exposure with body fat percentage: longitudinal studies

Prenatal exposure to phthalates and other body composition indices

Table 9 describes papers accessing the association between prenatal exposure to phthalates and body composition indices other than BMI or body fat percentage. Berman et al. assessed height, BMI, and body composition measured by DXA (total fat percentage, total fat mass, and total lean mass) and reported MiNP and MEHP were associated with decreased total lean mass (44). Buckley et al. used overweight/obesity defined by BMI z-score as the outcome variable (46). Lee et al. reported the association between phthalate metabolites and BMI z-score, percentage of fat mass, fat mass index, percentage of skeletal muscle mass, and skeletal muscle index and reported that high levels of prenatal exposure to phthalates were significantly associated with decreased SMI among girls (54). The study performed by Maresca et al. used BMI z-score, body fat mass, FMI, and waist circumference (WC) as outcome variables, and reported that prenatal non-DEHP phthalate exposure was associated with lower BMI z-score, WC, and fat mass in boys during early childhood contrary to their hypothesis (55). Valvi et al. reported that weight gain Z-score was significantly associated with prenatal exposure to DEHP among boys (62).

Table 9. Description of studies on the association between prenatal exposure to phthalates and other body composition indices

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Outcome variables	Estimates	Adjustment variables
2	Y. E. Berman	2020	Maternal urine in the 2nd and 3rd trimester of pregnancy	1, 2, 3, 5, 8, 10, 14, 17 and 20 y	Linear mixed effect model	β and 95% CI or OR and 95% CI	Height, BMI, DXA (total fat %, total fat mass [g], total lean mass [g])	(Deviation from mid-parental height at 20 y z-score) ∑DEHP metabolites highest tertile (vs. lowest tertile), β 0.08 (95% CI: -0.21, 0.37); ∑DBP metabolites highest tertile (vs. lowest tertile), β 0.10 (95% CI: -0.19, 0.40) (total fat %) ∑DEHP metabolites highest tertile (vs. lowest tertile), OR 0.97 (95% CI: 0.84, 1.12); ∑DBP metabolites highest tertile (vs. lowest tertile), OR 1.05 (95% CI: 0.91, 1.21)	age, gestational age at birth, birthweight, and maternal pre-pregnancy BMI
4	J. P. Buckley	2016	Prenatal maternal urine	4–9 y	Linear mixed effect model	β and 95% CI or OR and 95% CI	BMI z-score and overweight/obesity (BMI ≥ 85th percentile)	(Overweight/obese) OR for standard deviation increase in natural log ∑DEHP metabolites, MnBP and MiBP (0.87 [95% CI: 0.53, 1.4], 1.0 [95% CI: 0.51, 2.0], and 0.84 [95% CI: 0.44, 1.6], respectively)	cohort, maternal race/ethnicity, maternal age at delivery, maternal education, maternal work status during pregnancy, maternal pre-pregnancy BMI, gestational weight gain, maternal smoking during pregnancy, calendar date of urine collection, and parity.

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Outcome variables	Estimates	Adjustment variables
13	D. W. Lee	2020	Prenatal maternal urine and urine of the participants	6 y	Multivariate linear regression	β and 95% CI	BMI z-score, percentage of fat mass, fat mass index, percentage of skeletal muscle mass, skeletal muscle index	(Skeletal muscle index) β of two-fold increase of ∑DEHP in prenatal maternal urine and in children's urine (-0.05, [95% CI: -0.09, -0.02], and 0.003 [95% CI: -0.05, 0.053], respectively); MnBP in prenatal maternal urine and in children's urine (-0.05 [95% CI: -0.09, -0.005], and -0.04 [95% CI: -0.10, 0.01], respectively)	maternal age, maternal education, and household income for the association between maternal phthalates, body composition indices of their children and urinary creatinine, and adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine
14	M. M. Maresca	2016	Prenatal maternal urine	5 y and 7 y	Generalized Estimating Equation	β and 95% CI	BMI z-score at 5 y and 7 y, percent of fat mass at 7 y, FMI at 7 y, WC at 7 y	(FMI) β of ln-transformed ∑DEHP, and MnBP among girls (-0.13 [95% CI: -0.19, 0.84], and -0.52 [95% CI: -0.72, 1.76], respectively), among boys (-0.39 [95% CI: -1.57, 0.79]), and -1.05 [95% CI: -2.26, 0.15]), respectively) (WC) β of ln-transformed ∑DEHP, and MnBP among girls (-0.13 [95% CI: -1.37, 1.12], and 0.85 [95% CI: -0.76, 2.47], respectively), among boys (-0.65 [95% CI: -2.16, 0.87]), and -1.34 [95% CI: -2.91, 0.23]), respectively)	age, maternal pre-pregnancy obesity, birth weight, maternal race/ethnicity, maternal receipt of public assistance during pregnancy, urinary specific gravity, and urinary metabolite concentration component scores of children aged 3 and 5 y

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Outcome variables	Estimates	Adjustment variables
15	K. G. Harley	2017	Prenatal maternal urine, two times	5, 7, 9, 10.5, and 12 y	Generalized estimating equations	β and 95% CI	WC z-score	(WC z-score) β of 2-fold increase in ∑DEHP was associated with WC z-score at 5, 7, 9, 10.5, and 12 year as 0.14 (95% CI: 0.05, 0.23), 0.00 (95% CI: -0.08, 0.09), 0.00 (95% CI: -0.09, 0.09), 0.10 (95% CI: 0.00, 0.19) and 0.09 (95% CI: -0.01, 0.20). β of 2-fold increase in MnBP was associated with WC z-score at 5, 7, 9, 10.5, and 12 year as 0.07 (95% CI: -0.01, 0.14), 0.12 (95% CI: 0.05, 0.19), 0.12 (95% CI: 0.05, 0.19), 0.05 (95% CI: -0.03, 0.12), and 0.04 (95% CI: -0.04, 0.13).	maternal age, maternal education, marital status, years in the U.S. prior to delivery, smoking during pregnancy, poverty status during pregnancy, child's food insecurity at each time point, child's fast food consumption at each time point, and prenatal bisphenol A
17	J. Shoaff	2017	up to two times prenatally and six times from 1 to 8 years of age	8 y	Multiple informant model (Generalized estimating equation)	β and 95% CI	BMI z-score, WC, body fat percent	(body fat percentage) β of ∑DEHP at prenatal, 1 y, 2 y, 3 y, 4 y, 5 y, and 8 y (0.5 [95% CI: -1.4, 2.3], -2.7 [95% CI: -4.8, -0.5], -1.4 [95% CI: -3.9, 1.2], 0.9 [95% CI: -1.5, 3.3], 1.3 [95% CI: -1.2, 3.9], 2.9 [95% CI: 0.3, 5.5], and -0.6 [95% CI: -2.8, 1.6], respectively);	maternal age at delivery, race, marital status, insurance, income, education, parity, cotinine, depressive symptoms, mid pregnancy BMI, food security, fruit/vegetable and fish consumption, prenatal vitamin use, child's sex, and child's age at the 8-year visit

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Outcome variables	Estimates	Adjustment variables
20	Y. A. Tsai	2016	Estimated the total daily intake of DEHP, and urine of the participants	When participants were examined	Logistic regression	OR and 95% CI	Weight percentile and Height percentile above 50th percentile	(Weight) OR of estimated phthalates dietary intake (>median vs. <= median), 0.07 (95% CI: 0.02, 0.19); (Height) OR of estimated dietary intake (>median vs. <= median), 0.30, (95% CI: 0.12, 0.75)	sex, maternal age at pregnancy
22	D. Valvi	2015	Prenatal maternal urine at 1st and 3rd trimester.	Birth to 6 mos., 1, 4, and 7 years of age	Generalized estimating equations	β and 95% CI	BMI z-score, weight gain z-score (0–6 months)	(Weight gain z-score 0–6 months) β of one unit increase in ∑DEHP metabolites in girls (0.26 [95% CI: -0.13, 0.65]) and in boys (-0.36 [95% CI: -0.70, -0.01])	sex, age, maternal country of origin, maternal age at delivery, maternal parity, maternal education, maternal social class, pre-pregnancy BMI, and smoking in pregnancy

BMI, body mass index; CI, confidence interval; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate; WC, waist circumference; DXA, dual-energy X-ray absorptiometry; IQR, interquartile range; OR, odds ratio

Postnatal exposure to phthalates and BMI

Table 5 summarizes the studies assessing the association between postnatal exposure to phthalates and BMI. The results of included studies were inconsistent, and there were a limited number of studies that reported the association of BMI with phthalate metabolites as a continuous variables. Chang et al. studied 152 children in Taiwan and reported non-significant associations of BMI with DEHP metabolites, MnBP, and MiBP (48). Shaoff et al. analyzed the data of 219 children from HOME study and reported that associations between BMI z-score at 8 years and DEHP metabolites at prenatal, 1, 2, 3, 4, 5, and 8 years of age were not statistically significant. The only significant association was between a ten-fold increase in DEHP metabolites at 5 years of age and a 0.04 unit increase in BMI z-score (95% CI: 0.0, 0.9). Trasande et al. reported that one unit increase in the natural log-transformed sum of LMW phthalates was associated with a 0.07 unit increase in BMI z-score (95% CI: 0.02, 0.13) using the data of children surveyed at NHANES 2003–2008 (16). Zettergren et al. investigated the participants' phthalate metabolites at 4 years of age and their BMIs at 24 years of age and found that DiNP was associated with BMI, but DEHP and DBP were not (67). Statistical significance of associations of phthalate metabolites in children and BMI and/or obesity of children was summarized in **Table 11**.

Table 10. Description of studies on the association between postnatal exposure to phthalates and BMI

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Esti-mates Type	Estimates	Adjustment variables
6	M. C. Buser	2014	Urine of the participants	children and adolescents aged 6–19 y, adults ≥ 20 years of age	Multivariate linear regression and logistic regression	β and 95% CI or OR and 95% CI	(BMI z-score) β of One unit increase in natural log-transformed sum of DEHP metabolites and LMW metabolites (-0.01 [95% CI: -0.06, 0.04] and 0.07 [95% CI: 0.02, 0.13]) (Obesity) OR of one unit increase in natural log-transformed sum of DEHP metabolites and LMW metabolites (1.04 [95% CI: 0.89, 1.20], and 1.02 [95% CI: 0.90, 1.17])	urinary creatinine, sex, poverty-income ratio, parental education, serum cotinine, age, race/ethnicity category, caloric intake, and watching television
7	C. H. Chang	2020	Urine of the participants	5 y	Multivariate linear regression	β and 95% CI	(BMI z-score) β of IQR increase in sum of DEHP metabolites in maternal urine (-0.03 [95% CI: -0.11, 0.05]; IQR 116.5 μg/g Cr) and in children's urine (-0.04 [95% CI: -0.13, 0.04]; IQR 75.3 μg/g Cr)	cohort, sex, maternal BMI, maternal education, maternal age at conception, parity, parental country of origin, breastfeeding, and birth weight
8	A. L. Deierlein	2016	Urine of the participants at the baseline (6–8 y)	3 times until the last visit when girls were on average 14 y old (11–16 y)	Multivariate linear regression, WQS	β and 95% CI	(BMI z-score) β of MiBP (highest quartile vs. lowest quartile), 0.10 (95% CI: -0.07, 0.27)	age, sex, race, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine, and log-transformed creatinine
10	J. W. Hou	2015	Urine of the participants	When assessing phthalates exposure (6.5–8.5 y)	Generalized estimating equations and multivariate	β and 95% CI	(BMI) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.24 [95% CI: -0.31, 2.79]) and MnBP (-0.11, [95% CI: -1.75, 1.53]) (WC) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of	Sex, maternal smoking during pregnancy, socioeconomic status, breastfeeding duration, physical activity, smoking, and urinary cotinine.

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Esti-mates Type	Estimates	Adjustment variables
					linear regression		DEHP (3.44 [95% CI: -0.45, 7.33] and MnBP (0.36, [95% CI: -3.77, 4.48]) (Body fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.62 [95% CI: -0.97, 4.20]) and MnBP (-0.77, [95% CI: -3.47, 1.94]) (Trunk fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.61 [95% CI: -1.26, 4.49]) and MnBP (95% CI: -1.05 [-4.05, 1.95])	
12	S. H. Kim	2018	Urine of the participants	When assessing phthalates exposure (6–13 y)	Multivariate linear regression and logistic regression	β and 95% CI or OR and 95% CI	(BMI z-score) β of One unit increase in natural log-transformed sum of DEHP metabolites and LMW metabolites (-0.01 [95% CI: -0.06, 0.04] and 0.07 [95% CI: 0.02, 0.13]) (Obesity OR) OR of One unit increase in natural log-transformed sum of DEHP metabolites and LMW metabolites (1.04 [95% CI: 0.89, 1.20], and 1.02 [95% CI: 0.90, 1.17]), -0.01 [95% CI: -0.06, 0.04] and 0.07 [95% CI: 0.02, 0.13])	urinary creatinine, sex, poverty-income ratio, parental education, serum cotinine, age, race/ethnicity category, caloric intake, and watching television
16	T. Saengkaew	2017	Urine of the participants	When assessing phthalates exposure	Multivariate linear regression	β and 95% CI	(BMI z-score) β of IQR increase in sum of DEHP metabolites in maternal urine (-0.03 [95% CI: -0.11, 0.05]; IQR 116.5 μg/g Cr) and in children's urine (-0.04 [95% CI: -0.13, 0.04]; IQR 75.3 μg/g Cr)	Cohort, sex, maternal BMI, maternal education, maternal age at conception, parity, parental country of origin, breastfeeding, and birth weight
17	J. Shoaff	2017	up to two times prenatally and six times from 1 to 8 years of age	8 y	Multivariate linear regression, WQS	β and 95% CI	(BMI z-score) β of MiBP (Highest quartile vs. lowest quartile), 0.10 (95% CI: -0.07, 0.27)	age, sex, race, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine, and log-transformed creatinine

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Esti-mates Type	Estimates	Adjustment variables
19	L. Trasande	2013	Urine of the participants	When assessing phthalate exposure	Generalized estimating equations and multivariate linear regression	β and 95% CI	(BMI) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.24 [95% CI: -0.31, 2.79]) and MnBP (-0.11, [95% CI: -1.75, 1.53]) (WC) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (3.44 [95% CI: -0.45, 7.33] and MnBP (0.36, [95% CI: -3.77, 4.48]) (Body fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.62 [95% CI: -0.97, 4.20]) and MnBP (-0.77, [95% CI: -3.47, 1.94]) (Trunk fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.61 [95% CI: -1.26, 4.49]) and MnBP (-1.05 [95% CI: -4.05, 1.95])	sex, maternal smoking during pregnancy, socioeconomic status, breastfeeding duration, physical activity, smoking, and urinary cotinine levels.
23	M. Vrijheid	2020	77 cases of prenatal exposure and 96 cases of childhood exposure including exposure to air pollutants, built environments, and biomarkers of chemical pollutants.	BMI z-score (age-and-sex standardized z-scores)	Logistic regression	OR and 95% CI	(Obesity vs normal) OR of MBP (highest quartile vs. lowest quartile) among boys, 5.768 (95% CI: 1.622, 20.515); OR of the sum of DEHP metabolites (highest quartile vs. lowest quartile) among girls, 0.078 (95% CI: 0.008, 0.791)	socioeconomic level, physical activity, dietary nutriment intake and puberty onset, phthalate metabolite concentrations.
24	B. Wu	2020	Urine of the participants	When assessing	Multivariate linear	β and 95% CI	(BMI z-score) β of One unit increase in natural log-transformed sum of DEHP metabolites and	urinary creatinine, sex, poverty-income ratio, parental

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Esti-mates Type	Estimates	Adjustment variables
				phthalate exposure	regression and logistic regression	or OR and 95% CI	LMW metabolites (-0.01 [95% CI: -0.06, 0.04] and 0.07 [95% CI: 0.02, 0.13]) (Obesity OR) OR of One unit increase in natural log ∑DEHP metabolites and LMW metabolites (1.04 [95% CI: 0.89, 1.20], and 1.02 [95% CI: 0.90, 1.17]), -0.01 [95% CI: -0.06, 0.04] and 0.07 [95% CI: 0.02, 0.13])	education, serum cotinine, age, race/ethnicity category, caloric intake, and watching television
27	A. Zettergr en	2021	Urine of the participants at 4 years of age	24 y	Multivariate linear regression	β and 95% CI	(BMI z-score) β of IQR increase in sum of DEHP metabolites in maternal urine (-0.03 [95% CI: -0.11, 0.05]; IQR 116.5 µg/gCr) and in children's urine (-0.04 [95% CI: -0.13, 0.04]; IQR 75.3 µg/g Cr)	cohort, sex, maternal BMI, maternal education, maternal age at conception, parity, parental country of origin, breastfeeding, and birth weight
28	Y. Zhang	2014	Urine of the participants	When assessing phthalates exposure	Multivariate linear regression, WQS	β and 95% CI	(BMI z-score) β of MiBP (highest quartile *vs.* lowest quartile), 0.10 (95% CI: -0.07, 0.27)	age, sex, race, educational levels, family income-to-poverty ratio, caloric intake, serum cotinine, and log-transformed creatinine
29	M.M. Amin	2018	Urine of participants	When assessing phthalates exposure	Multivariate linear regression	β and *p*-value	(BMI z-score) β (*p*-value*)* of MEOHP, MEHHP, MEHP, MBzP, and MnBP were 0.17 (0.005), 0.3 (<0.001), 0.23 (<0.001), 0.18 (0.002), and 0.22 (<0.001).	Sex, age, and physical activity

BMI, body mass index; OR, odds ratio; CI, confidence interval; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate; LMW, low molecular weight; WC, waist circumference; IQR, interquartile range; WQS, weight quantile sum; MiBP, monoisobutyl phthalate

Table 11. Statistical significance of associations of phthalates exposure at children with BMI, obese, and obesity in children

No	Author	∑phthalate	∑DEHP	MECCP	MEHHP	MEOHP	MnBP	MiBP	Remarks
6	M. C. Buser		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	Obesity (BMI z-score ≥ 95th percentile) and overweight (BMI z-score ≥ 85th percentile) at 6-19 years old
7	C. H. Chang		n.s.				n.s.	n.s.	MEP and MBzP were significantly and positively associated with BMI of children (mean age=9.9 y)
8	A. L. Deierlein		n.s.	n.s.	n.s.	(+)	n.s.	n.s.	Predicted differences in BMI at ages 7-13 years according to quartiled phthalates at 6-8 years
10	J. W. Hou		n.s.	n.s.	(+)	n.s.	n.s.	n.s.	Overweight defined by BMI by phthalates (<25th, 25-75th, and ≥75th percentile)
12	S. H. Kim		n.s.	n.s.	(+)	n.s.			BMI percentile by percentage fractions of DEHP metabolites
16	T. Saengkaew						n.s.		No differences in MMP and MnBP between normal-weight children (n=70) and overweight/obesity children (n=85)
17	J. Shoaff		n.s.				n.s.	n.s.	Multiple informants model estimates of the difference in BMI z-score per 10-fold increase in urinary phthalate metabolite concentration during pregnancy and childhood at 1, 2, 3, 4, 5, and 8 years of age
19	L. Trasande		n.s.						Among non-Hispanic black children, there was a significant association of MEP and MBP with obesity
23	M. Vrijheid		n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	Obesity defined by BMI z-score
24	B. Wu							(+)	MEP and MiBP were positively associated with obesity in children aged 6-19 in NHANES 2005-2010
27	A. Zettergren		n.s.	n.s.	n.s.	n.s.	n.s.		DiNP metabolites were associated with overweight/obesity
28	Y. Zhang	(+)			(+)		(+)		MBP and the sum of LMP were positively associated with BMI z-score and fat distribution among boys >10 years of age, and MEHP was negatively associated with fat distribution in girls <10 years of age.
29	M.M. Amin				(+)	(+)	(+)		BMI z-score as a continuous variable

n.s., not statistically significant; (+), a statistically significant and positive association; (-), a statistically significant and negative association; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; MnBP, mono-n-butyl phthalate (MnBP); MiBP, Monoisobutyl phthalate; LMP, low molecular weight phthalate

Postnatal exposure to phthalates and other body composition indices

Table 12 summarizes the studies on the association between postnatal exposure to phthalates and BMI. Chang et al. cross-sectionally studied 132 children and reported no association between phthalate metabolites and body fat percentage (48). Hou et al. studied 308 Taiwanese children and reported a significant association of MnBP and MiBP with waist-to-hip ratio (51). Shaoff et al. analyzed the data of 219 children from the HOME study and showed significant associations between WC at 8 years of age and sum of DEHP metabolites at 5 years of age; there were significant associations between body fat percentage at 8 years of age and sum of DEHP metabolites at 1 and 5 years of age. A case-control study performed in China with 57 boys with constitutional delay of growth and puberty and 110 controls reported that higher urinary phthalate metabolites were associated with constitutional delay of growth and puberty (66). Another cohort study with 100 children reported no significant associations between DEHP and DBP metabolites at 4 years of age and their WC, body fat percentage, and trunk fat percentage until 24 years of age (67). Zhang et al. performed a cross-sectional study with 497 children in China and reported significant associations between phthalate exposure and fat distribution (69).

Table 12. Description of studies on the association between postnatal exposure to phthalates and body indices other than BMI

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
7	C. H. Chang	2020	Urine of the participants	5 y	Logistic regression	OR and 95% CI	(CDGP) OR (the highest tertile vs. the lowest tertile) of MnBP, MEP, MEHP, and total phthalates were 8.30 (95% CI: 1.97, 34.44), 5.43 (95% CI: 2.02, 14.55), 3.83 (95% CI: 1.59, 8.68), and 9.09 (95% CI: 3.16, 26.31), respectively.	age, BMI, other phthalate metabolites
10	J. W. Hou	2015	Urine of the participants	When assessing phthalates exposure (6.5–8.5 y)	Generalized estimating equations and multivariate linear regression	β and 95% CI	(WC) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (3.44 [95% CI: -0.45, 7.33] and MnBP (0.36, [95% CI: -3.77, 4.48]) (Body fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.62 [95% CI: -0.97, 4.20]) and MnBP (-0.77, [95% CI: -3.47, 1.94]) (Trunk fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.61 [95% CI: -1.26, 4.49]) and MnBP (-1.05 [95% CI: -4.05, 1.95])	sex, maternal smoking during pregnancy, socioeconomic status, breastfeeding duration, physical activity, smoking, and urinary cotinine.
16	T. Saengkaew	2017	Urine of the participants	When assessing phthalates exposure	Logistic regression	OR and 95% CI	(Obesity vs normal) OR of MBP (highest quartile vs. lowest quartile) among boys, 5.768 (95% CI: 1.622, 20.515); OR of the sum of DEHP metabolites (highest quartile vs. lowest quartile) among girls, 0.078 (95% CI: 0.008, 0.791)	socioeconomic level, physical activity, dietary nutriment intake and puberty onset, phthalate metabolite concentrations.
17	J. Shoaff	2017	Up to two times prenatally and six times from 1 to 8 years of age	8 y	Logistic regression	OR and 95% CI	(CDGP) OR (highest tertile vs. lowest tertile) of MBP, MEP, MEHP, and total phthalates were 8.30 (95% CI: 1.97, 34.44), 5.43 (95% CI: 2.02, 14.55), 3.83 (95% CI: 1.59, 8.68), and 9.09 (95% CI: 3.16, 26.31), respectively.	age, BMI, other phthalates metabolites

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
18	A. Smerieri	2015	Urine of the participants	When assessing phthalate exposure	Generalized estimating equations and multivariate linear regression	β and 95% CI	(WC) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (3.44 [95% CI: -0.45, 7.33] and MnBP (0.36, [95% CI: -3.77, 4.48]) (Body fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.62 [95% CI: -0.97, 4.20]) and MnBP (-0.77, [95% CI: -3.47, 1.94]) (Trunk fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.61 [95% CI: -1.26, 4.49]) and MnBP (-1.05 [95% CI: -4.05, 1.95])	sex, maternal smoking during pregnancy, socioeconomic status, breastfeeding duration, physical activity, smoking, and urinary cotinine.
26	C. Xie	2015	Urine of the participants	When assessing phthalate exposure	Logistic regression	OR and 95% CI	(CDGP) OR (the highest tertile vs. the lowest tertile) of MBP, MEP, MEHP, and total phthalates were 8.30 (95% CI: 1.97, 34.44), 5.43 (95% CI: 2.02, 14.55), 3.83 (95% CI: 1.59, 8.68), and 9.09 (95% CI: 3.16, 26.31), respectively.	age, BMI, other phthalate metabolites
27	A. Zettergren	2021	Urine of the participants at 4 years of age	24 y	Generalized estimating equations and multivariate linear regression	β and 95% CI	(WC) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (3.44 [95% CI: -0.45, 7.33] and MnBP (0.36, [95% CI: -3.77, 4.48]) (Body fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.62 [95% CI: -0.97, 4.20]) and MnBP (-0.77, [95% CI: -3.47, 1.94]) (Trunk fat %) β of one unit increase in log-transformed phthalate metabolite concentrations of the sum of DEHP (1.61 [95% CI: -1.26, 4.49]) and MnBP (-1.05 [95% CI: -4.05, 1.95])	sex, maternal smoking during pregnancy, socioeconomic status, breastfeeding duration, physical activity, smoking, and urinary cotinine.

ID	First author	Year	Exposure assessment	Timing of outcome assessment	Statistical analysis	Estimates Type	Estimates	Adjustment variables
29	M.M. Amin	2018	Urine of participants	When assessing phthalates exposure	Multivariate linear regression	β and *p*-value	(WC) β (*p*-value) of MEOHP, MEHHP, MEHP, MBzP, and MiBP were 0.19 (0.003), 0.39 (<0.001), 0.37 (<0.001), 0.22 (<0.001), and 0.29 (<0.001).	sex, age, and physical activity

BMI, body mass index; OR, odds ratio; CI, confidence interval; CDGP, constitutional delay of growth and puberty; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate; WC, waist circumference; IQR, interquartile range

3.2. A mother-child cohort study in South Korea

Table 13 shows the demographic characteristics of the study participants. A total of 726 mother-child pairs were included in the study, and 445, 645, 574, and 527 children were followed up at 2, 4, 6, and 8 years of age, respectively. Among the mother-child pairs followed up at 8 years of age, there were 277 (52.6%) boys and 250 (47.4%) girls. Most mothers attended college (71.9 %), had normal BMIs before pregnancy (65.3%), and gave birth at the age of 31–35 years (49.5 %). Most children had normal birth weight (89.2%), were born full-term (92.0%), and did not do strengthening exercise (67.4%).

Table 13. Demographics of the study participants and excluded participants

Variable	2 y	4 y	6 y	8 y
	n (%)	n (%)	n (%)	n (%)
Total	445 (100.0)	645 (100.0)	574 (100.0)	527 (100.0)
Sex				
Boy	223 (52.5)	338 (52.4)	300 (52.3)	277 (52.6)
Girls	202 (47.5)	307 (47.6)	274 (47.7)	250 (47.4)
Household income (1,000 KRW)				
Missing	425 (100.0)	645 (100.0)		1 (0.2)
< 4,000 (≒ 3,333 US$)			174 (30.3)	105 (19.9)
4,000–6,000 (≒5,000 US$)			224 (39.0)	213 (40.4)
≥ 6,000			176 (30.7)	208 (39.5)
Maternal education level				
Missing				1 (0.2)
≤ High school graduate	79 (18.6)	118 (18.3)	93 (16.2)	79 (15.0)
College graduate	299 (70.4)	452 (70.1)	411 (71.6)	379 (71.9)
Above college	47 (11.1)	75 (11.6)	70 (12.2)	68 (12.9)
Maternal age at birth (y)				
Records unavailable	2 (0.5)	2 (0.3)	2 (0.4)	1 (0.2)
18 – 25	14 (3.3)	30 (4.7)	23 (4.0)	19 (3.6)
26 – 30	147 (34.6)	234 (36.3)	204 (35.5)	189 (35.9)
31 – 35	210 (49.4)	316 (49.0)	284 (49.5)	261 (49.5)
36 – 45	52 (12.2)	63 (9.8)	61 (10.6)	57 (10.8)
Maternal pre-pregnancy BMI (kg/m^2)				
< 23	298 (70.1)	459 (71.2)	383 (66.7)	344 (65.3)
23–25	74 (17.4)	96 (14.9)	103 (17.9)	99 (18.8)
≥ 25	53 (12.5)	90 (14.0)	88 (15.3)	84 (15.9)
Birth weight (g)				
< 2500	31 (7.3)	45 (7.0)	41 (7.1)	37 (7.0)
2500 – 3999	376 (88.5)	577 (89.5)	512 (89.2)	470 (89.2)
≥ 4000	18 (4.2)	23 (3.6)	21 (3.7)	20 (3.8)
Gestational age at delivery (weeks)				
≥ 37	389 (91.5)	595 (92.3)	527 (91.8)	485 (92.0)
< 37	36 (8.5)	50 (7.8)	47 (8.2)	42 (8.0)
Energy intake per day of children (kcal)				
Records unavailable	425 (100.0)	95 (14.7)	1 (0.2)	
1Q		137 (21.2)	143 (24.9)	131 (24.9)
2Q		138 (21.4)	143 (24.9)	132 (25.1)
3Q		138 (21.4)	144 (25.1)	132 (25.1)
4Q		137 (21.2)	143 (24.9)	132 (25.1)
Strengthening exercise				
Records unavailable	425 (100.0)	645 (100.0)		1 (0.2)
0			396 (69.0)	355 (67.4)
1–2 times/week			122 (21.3)	102 (19.4)
≥ 3 times/week			56 (9.8)	69 (13.1)

BMI, body mass index

Body composition indices of children are presented in **Table 14**. Mean values (± SD) of body compositions at 2 years of age were as follows: height=86.3 cm (± 3.0), weight=12.3 kg (± 1.4), BMI=16.5 kg/m^2 (± 1.4), and BMI z-score=-0.2 (± 0.9). Mean values (± SD) of body compositions at 4 years of age were as follows: height=102.0 cm (± 3.7), weight=16.3 kg (± 1.9), BMI=15.6 kg/m^2 (± 1.3), and BMI z-score=-0.1 (S± 1.1). Mean values (± SD) of body compositions at 6 years of age were as follows: height=115.6 cm (± 4.3), weight=21.2 kg (± 3.2), BMI=15.6 kg/m^2 (± 1.8), BMI z-score=-0.1 (± 1.0), FMI=2.9 kg/m^2 (± 1.4), and SMI=6.0 kg/m^2 (± 0.5). Mean values (± SD) of body compositions at 8 years of age were as follows: height=128.0 cm (± 4.8), weight=27.7 kg (± 5.2), BMI=16.0 kg/m^2 (± 2.8), BMI z-score=0 (± 1.1), FMI=3.4 kg/m^2 (± 1.9), and SMI=6.2 kg/m^2 (± 0.8).

Table 14. Body composition indices of the study participants

	Total			Boys		Girls	
	n	**missing**	**mean ± SD**	**n**	**mean ± SD**	**n**	**mean ± SD**
2 y							
Height (cm)	424	21	86.3 ± 3.0	222	86.9 ± 3.0	202	85.6 ± 2.8
Weight (kg)	425	20	12.3 ± 1.4	223	12.7 ± 1.4	202	11.9 ± 1.2
BMI (kg/m^2)	424	21	16.5 ± 1.4	222	16.8 ± 1.5	202	16.2 ± 1.3
BMI z-score	424	21	-0.2 ± 0.9	222	-0.1 ± 1.0	202	-0.2 ± 0.9
4 y							
Height (cm)	645	0	102.0 ± 3.7	338	102.4 ± 3.8	307	101.5 ± 3.6
Weight (kg)	645	0	16.3 ± 1.9	338	16.4 ± 1.8	307	16.1 ± 1.9
BMI (kg/m^2)	645	0	15.6 ± 1.3	338	15.6 ± 1.2	307	15.6 ± 1.3
BMI z-score	645	0	-0.1 ± 1.1	338	-0.2 ± 1.0	307	-0.1 ± 1.1
6 y							
Height (cm)	574	0	115.6 ± 4.3	300	116.1 ± 4.6	274	115.2 ± 4.0
Weight (kg)	574	0	21.2 ± 3.2	300	21.3 ± 3.2	274	21 ± 3.2
BMI (kg/m^2)	574	0	15.6 ± 1.8	300	15.6 ± 1.6	274	15.6 ± 1.9
BMI z-score	574	0	-0.1 ± 1.0	300	-0.2 ± 1.0	274	0 ± 1.1
FMI (kg/m^2)	570	0	2.9 ± 1.4	299	2.7 ± 1.3	271	3.1 ± 1.5
SMI (kg/m^2)	570	0	6.0 ± 0.5	299	6.1 ± 0.5	271	5.9 ± 0.4
8 y							
Height (cm)	527	0	128.0 ± 4.8	277	128.5 ± 5.0	250	127.4 ± 4.7
Weight (kg)	527	0	27.7 ± 5.2	277	28.2 ± 5.6	250	27.1 ± 4.6
BMI (kg/m^2)	527	0	16.0 ± 2.8	277	16.2 ± 2.8	250	15.8 ± 2.8
BMI z-score	527	0	0 ± 1.1	277	0 ± 1.1	250	0 ± 1.1
FMI (kg/m^2)	526	1	3.4 ± 1.9	276	3.3 ± 2.0	250	3.5 ± 1.8
SMI (kg/m^2)	526	1	6.2 ± 0.8	276	6.4 ± 0.8	250	6 ± 0.8

SD, standard deviation; BMI, body mass index; FMI, fat mass index; SMI, skeletal muscle index

Table 15 shows geometric means (GMs) and percentiles of concentration of phthalate metabolites in prenatal maternal urine and children's urine. It was below LOD that nine samples of 637 prenatal maternal urine samples (1.4 %) were measured for MEHHP, 4 samples (0.6%) of 637 prenatal maternal urine samples measured for MnBP, and 2 samples (0.4%) of measured 454 prenatal maternal urine. The number of samples below LOD of MBzP was 4 samples (1.4%) of 275 children's urine measured at 2 years of age, 4 samples (0.7%) of 569 children's urine measured at 4 years of age, 16 samples (4.5%) of 573 children's urine measured at 6 years of age, and 109 samples (20.7%) of 525 children's urine measured at 8 years of age (20.7). GMs (± SDs) of creatinine-adjusted MEHHP in prenatal maternal urine, urine at 2, 4, 6, and 8 years of age were 15.5 μg/g Cr (± 1.2), 91.2 μg/g Cr (± 0.9), 70.7 μg/g Cr (± 1.0), 58.0 μg/g Cr (± 0.8), and 30.9 μg/g Cr (± 1.0), respectively. GMs (± SDs) of creatinine-adjusted MnBP in prenatal maternal urine, urine at 2, 4, 6, and 8 years of age were 41.9 μg/g Cr (± 1.1), 113.2 μg/g Cr (± 0.8), 83.7 μg/g Cr (± 0.9), 72.0 μg/g Cr (± 0.8), and 51.7 μg/g Cr (± 1.1), respectively. GMs (± SDs) of creatinine-adjusted MBzP in prenatal maternal urine, urine at 2, 4, 6, and 8 years of age were 5.9 μg/g Cr (± 1.6), 11.9 μg/g Cr (± 1.5), 8.3 μg/g Cr (± 2.0), 4.9 μg/g Cr (± 2.2), and 2.3 μg/g Cr (± 3.8), respectively. The distribution of phthalate metabolites was presented as boxplots in **Figure 12**, and as histograms in **Figure 13**–**Figure 18**.

Table 15. Distribution of the creatinine-adjusted urinary concentration of phthalate metabolites

		Records				Percentile				
	n	unavailable	<LOD	GM	SD	5th	25th	50th	75th	95th
MEHHP (μg/g Cr)										
Prenatal	637	89	9	15.5	2.3	4.1	9.4	16.7	26.1	53.0
2 y	320	125		91.2	1.9	33.3	60.8	92.6	137.8	261.3
4 y	644	1		70.7	2.0	26.8	49.4	68.7	102.6	186.6
6 y	573	1		58.0	1.8	24.0	40.1	57.2	80.6	159.0
8 y	525	2		30.9	2.0	10.8	20.1	31.4	47.3	91.2
MEOHP (μg/gCr)										
Prenatal	637	89		16.0	2.1	4.9	10.3	16.2	25.5	49.4
2 y	320	125		74.4	1.9	27.7	48.8	73.5	108.4	224.6
4 y	644	1		55.7	1.9	21.9	39.1	54.3	80.7	141.0
6 y	573	1		39.4	1.8	15.5	26.5	38.8	56.1	108.7
8 y	525	2		21.8	2.0	7.3	14.9	21.9	33.2	61.8
MECCP (μg/gCr)										
Prenatal	511	215		22.3	1.9	7.9	14.7	21.4	33.0	68.4
2 y	303	142		105.6	2.3	27.4	65.0	105.1	177.1	370.6
4 y	554	91		95.0	2.0	30.2	68.7	96.5	143.1	267.8
6 y	573	1		77.5	1.8	32.1	51.3	72.6	112.7	218.7
8 y	525	2		45.3	2.0	16.2	31.4	46.4	66.1	126.0
∑DEHP (μmol/gCr)										
Prenatal	494			0.2	1.9	0.1	0.1	0.2	0.3	0.6
2 y	303			0.9	1.8	0.4	0.6	0.9	1.4	2.2
4 y	554			0.7	1.7	0.3	0.5	0.7	1.0	1.7
6 y	573			0.6	1.8	0.2	0.4	0.6	0.8	1.6
8 y	525			0.3	1.9	0.1	0.2	0.3	0.5	0.9
MnBP (μg/gCr)										
Prenatal	637	89	4	41.9	2.1	13.3	27.1	40.1	59.6	153.9
2 y	383	62		113.2	1.7	46.0	77.5	117.7	157.8	280.3
4 y	642	3		83.7	1.9	29.8	57.4	84.6	125.4	225.8
6 y	573	1		72.0	1.7	31.9	48.7	69.5	96.6	176.9
8 y	525	2		51.7	2.1	15.5	34.8	55.1	81.4	158.6
MBzP (μg/gCr)										
Prenatal	454	272	2	5.9	2.4	1.6	3.3	5.3	9.7	29.1
2 y	275	170	4	11.9	3.5	1.3	5.2	11.8	27.0	79.9
4 y	569	76	4	8.3	2.6	1.9	4.5	7.7	14.3	45.7
6 y	573	1	16	4.9	2.8	1.1	2.5	4.4	8.6	32.8
8 y	525	2	109	2.3	3.8	0.2	1.0	2.7	5.7	21.5

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate;

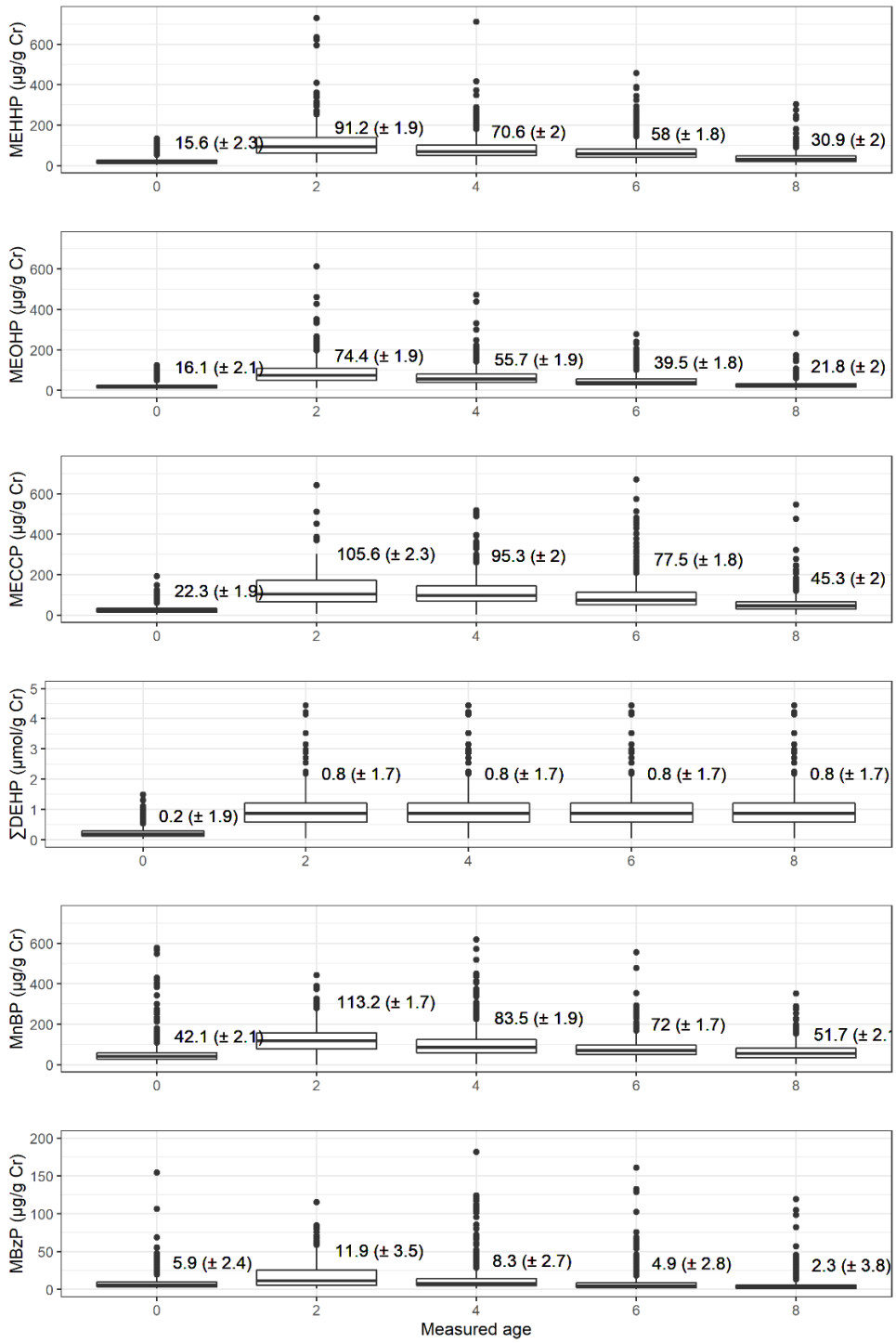

Figure 12. Phthalate metabolites across the different timing of measurement
MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate;

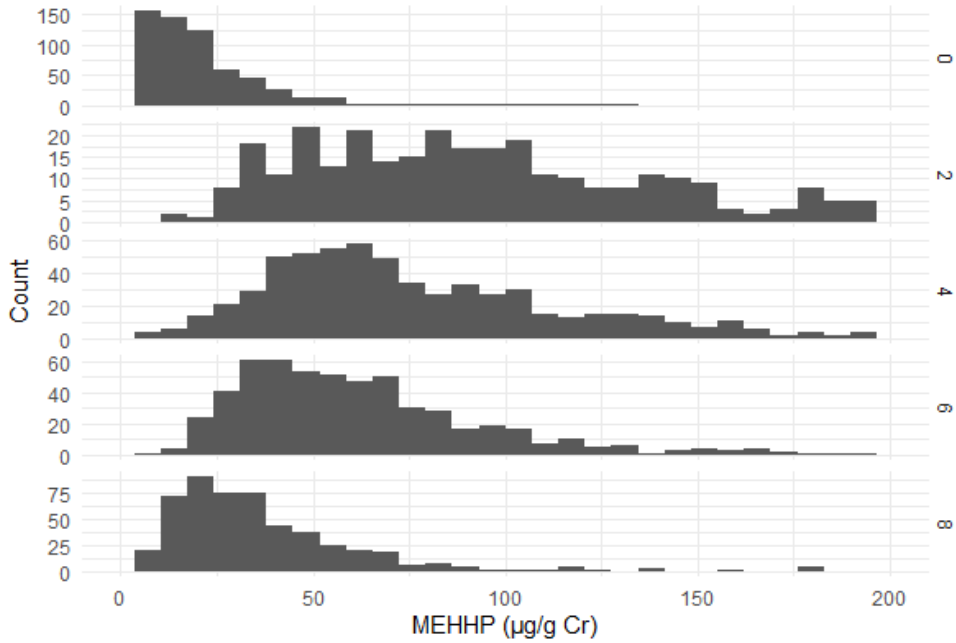

Figure 13. The distribution of mono-(2-ethyl-5-hydroxy-hexyl) (MEHHP) in prenatal urine and urine at 2, 4, 6, and 8 years

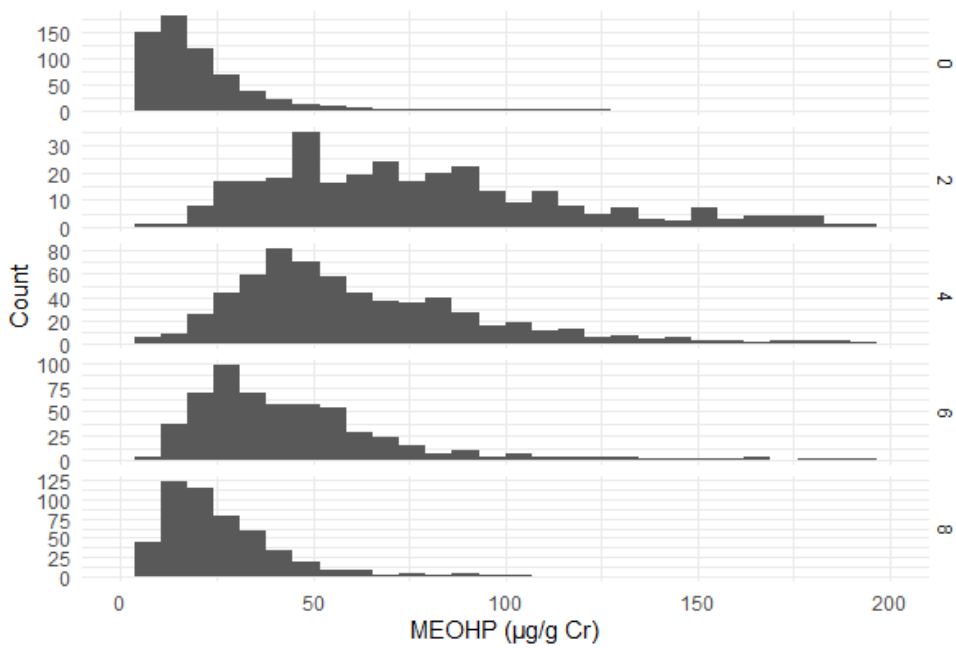

Figure 14. The distribution of mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP) in prenatal urine and urine at 2, 4, 6, and 8 years

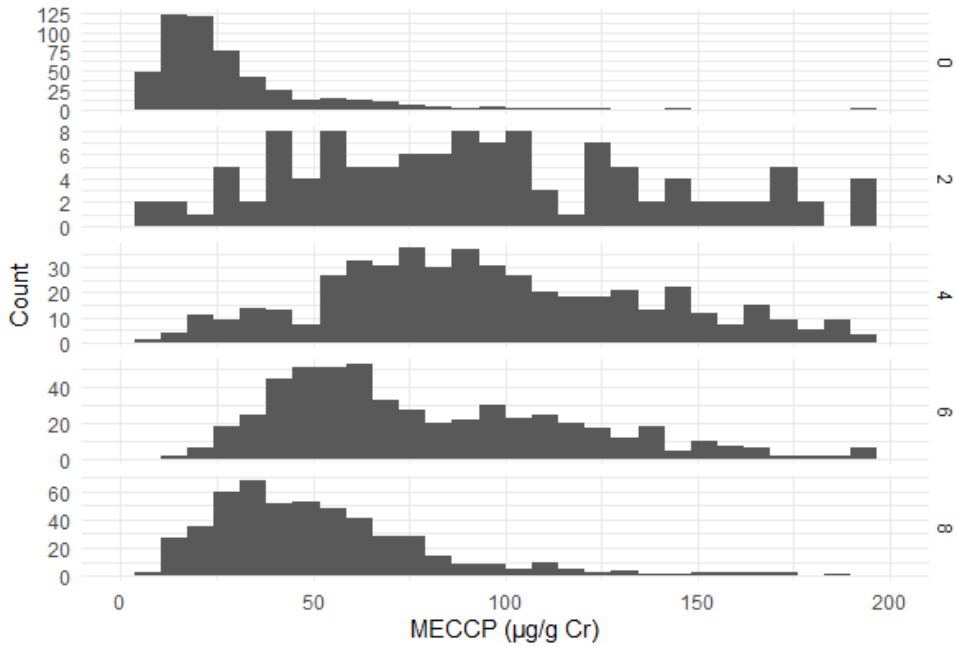

Figure 15. The distribution of Mono-2-ethyl-5-carboxypentyl phthalate (MECCP) in prenatal urine and urine at 2, 4, 6, and 8 years

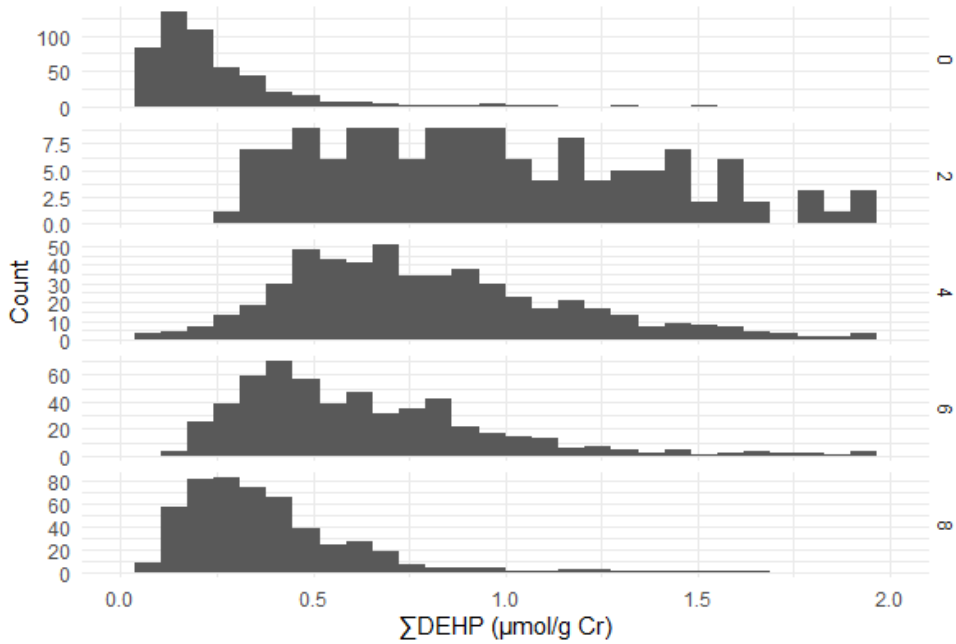

Figure 16. The distribution of the sum of di-2-ethylhexyl phthalate metabolites (∑DEHP) in prenatal urine and urine at 2, 4, 6, and 8 years

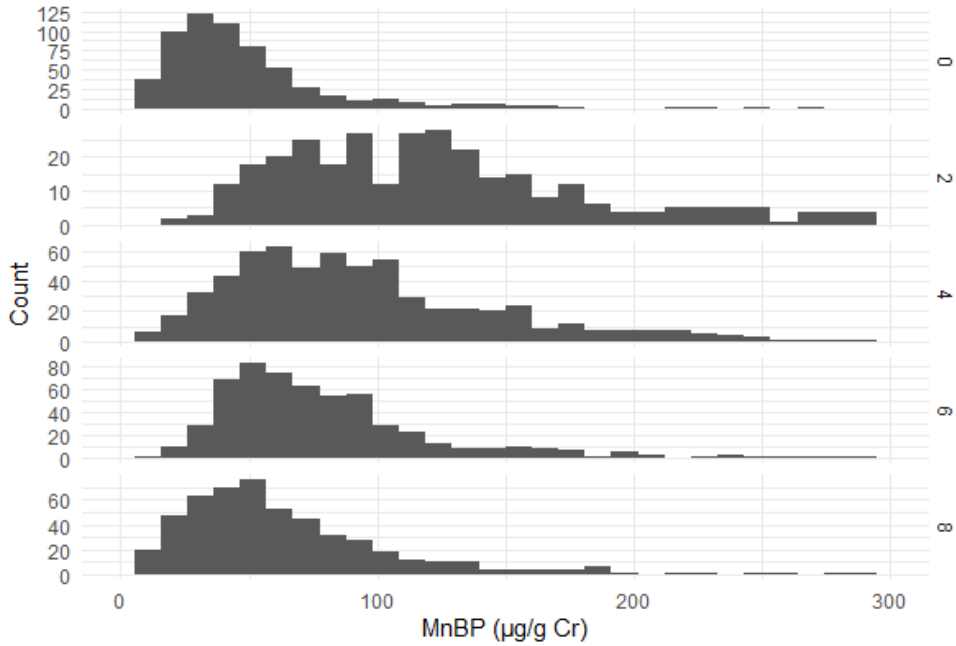

Figure 17. The distribution of mono-n-butyl phthalate (MnBP) in prenatal urine and urine at 2, 4, 6, and 8 years

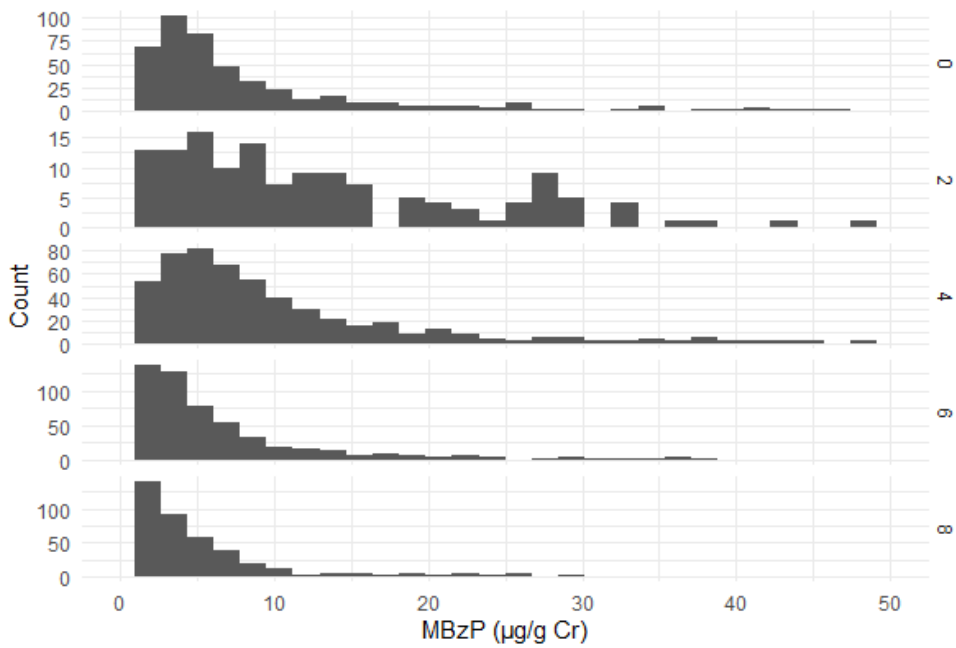

Figure 18. The distribution of monobenzyl phthalate (MBzP) in prenatal urine and urine at 2, 4, 6, and 8 years

Nonparametric associations between phthalates and body composition indices

It was shown that the nonparametric associations between phthalates metabolites measured at a different time and BMI z-score at 6 years (**Figure 19**) and 8 years (**Figure 20**). BMI z-score at 8 years was significantly, negatively, and linearly associated with MECCP and ∑DEHP in prenatal maternal urine, and MEOHP, MECCP, and, ∑DEHP in childrens' urine at 8 years. Decreased SMI at 6 years was significantly associated with increased MEHHP, ∑DEHP in prenatal maternal urine, and MEHHP at 2 years (**Figure 21**). Increased SMI at 8 years was associated with increased MEOHP at 6 years and ∑DEHP at 8 years (**Figure 22**).

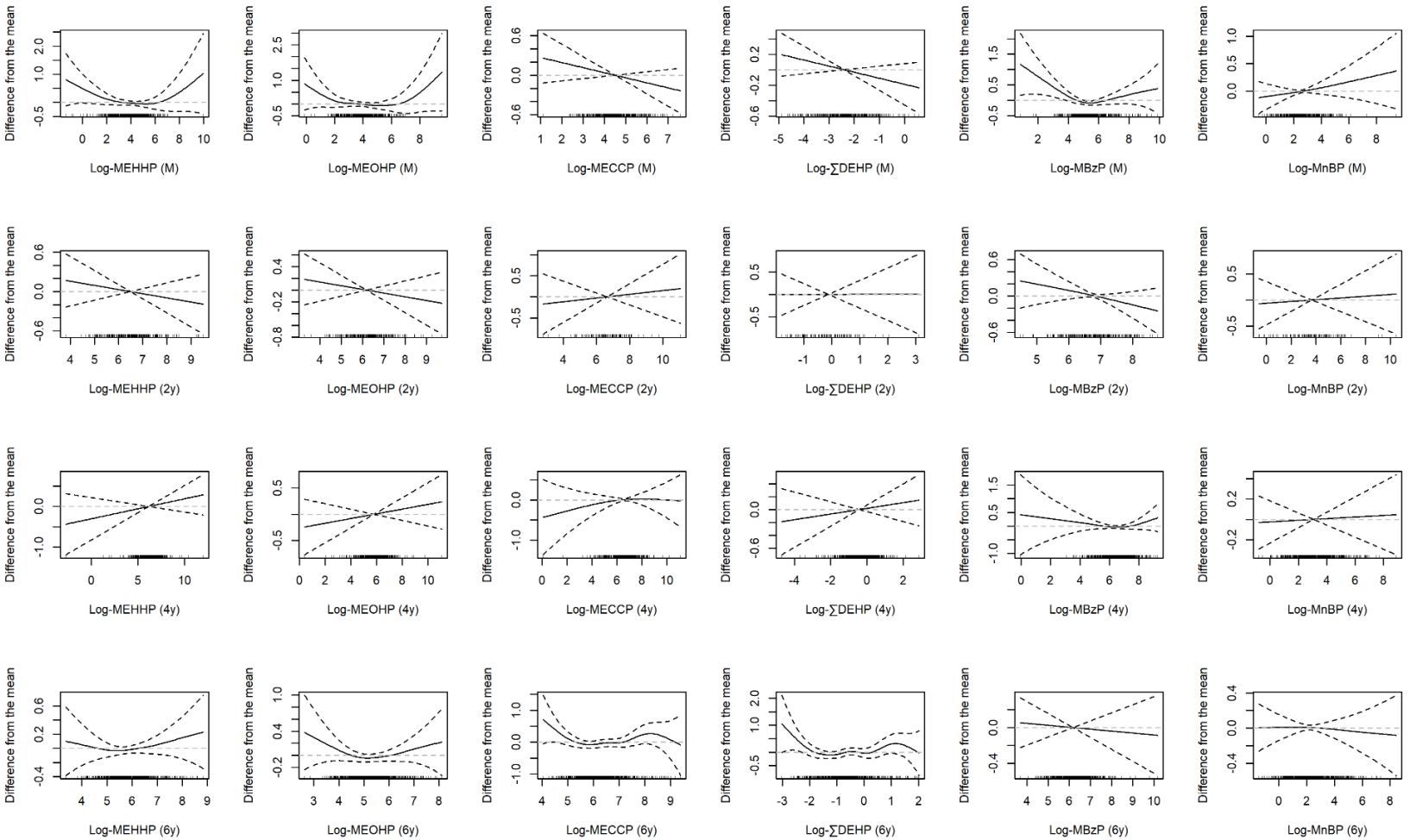

Figure 19. Nonparametric association between phthalates and BMI z-score at 6 years

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate;

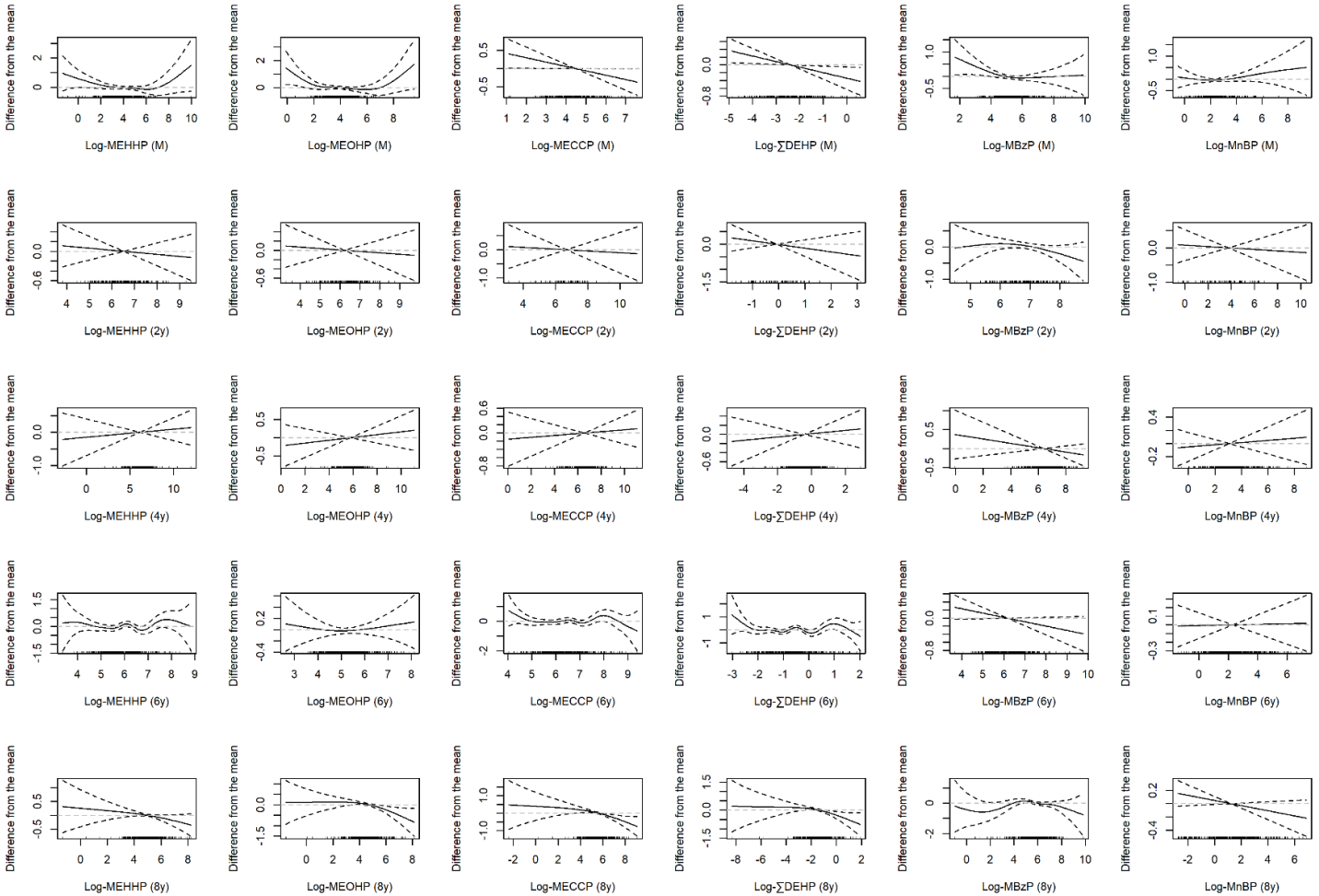

Figure 20. Nonparametric association between phthalates and BMI z-score at 8 years

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate;

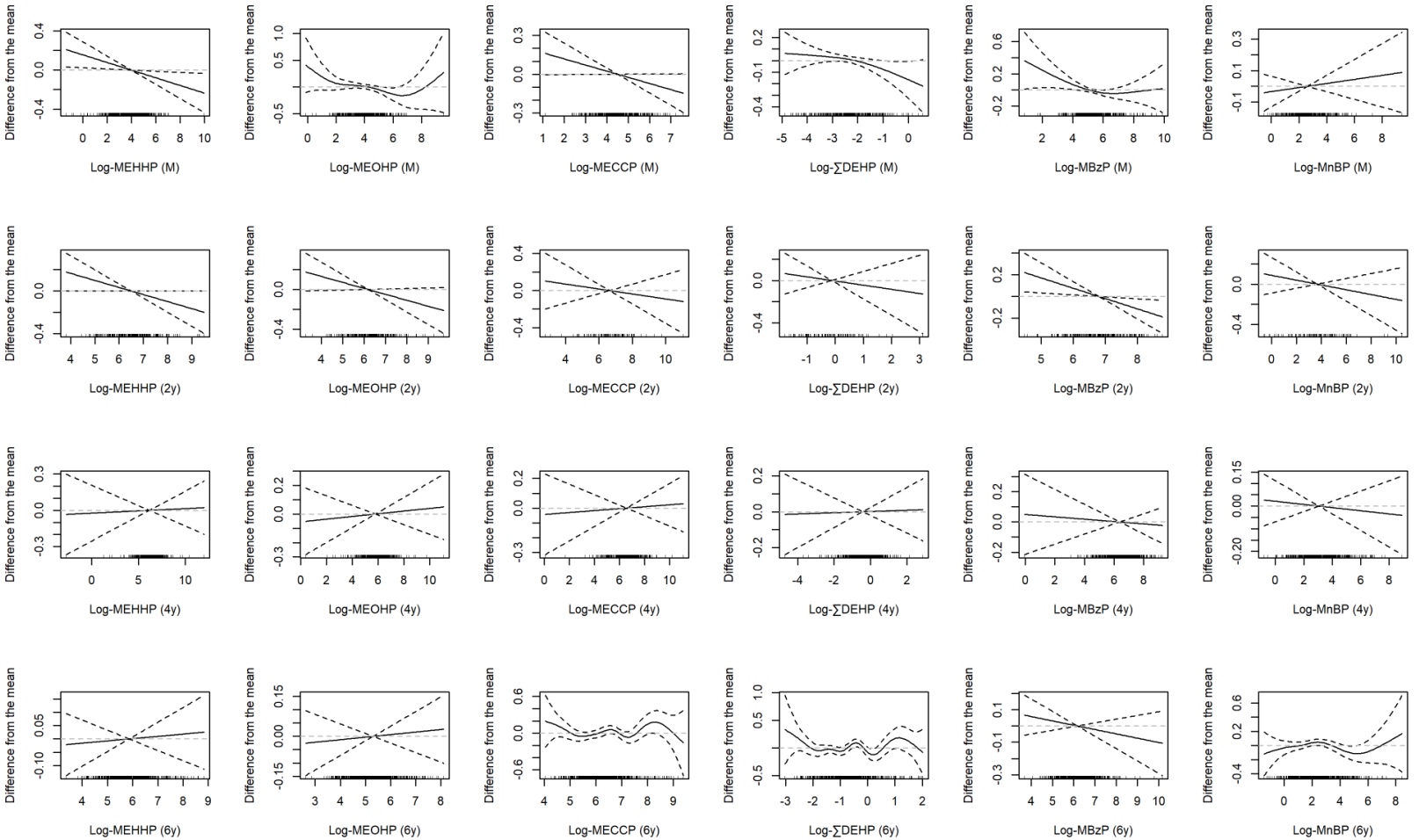

Figure 21. Nonparametric association between phthalates and SMI at 6 years

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate;

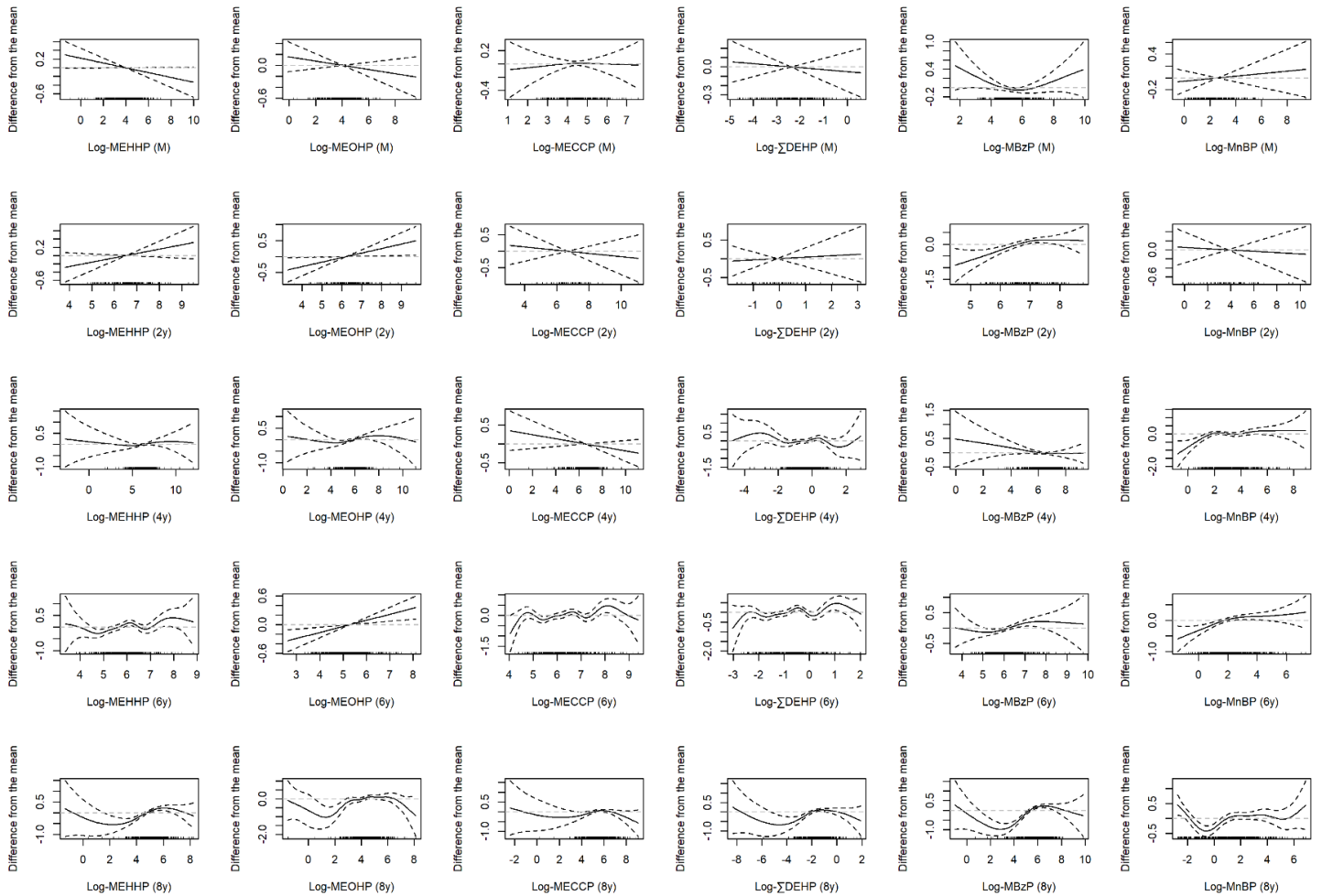

Figure 22. Nonparametric association between phthalates and SMI at 8 years

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate;

Hypothesis testing using multivariate linear regression models

Table 16 shows the association of concentrations of DEHP metabolites in prenatal maternal urine and BMI z-score and SMI at 6 and 8 years of age. There were significant associations between prenatal DEHP exposure and decreased SMI, especially among girls. Decreased SMI of girls at 6 year was associated with two-fold increase of MEHHP (-0.06 [95% CI: -0.10, -0.02], $p\text{-}_{FDR}$=0.032), MEOHP (-0.07 [95% CI: -0.11, -0.02], $p\text{-}_{FDR}$=0.032), MECCP (-0.09 [95% CI: -0.14, -0.03], $p\text{-}_{FDR}$=0.032), and ∑DEHP (-0.08 [95% CI: -0.13, -0.02], $p\text{-}_{FDR}$=0.044) in prenatal maternal urine. Among boys, it was not found that significant associations between phthalate metabolites in prenatal maternal urine, BMI z-score, and SMI.

Table 16. The results of multivariate linear regression for associations of prenatal exposure to DEHP with BMI z-score and SMI

	Total			Boys			Girls		
	n	Change per two-fold inc. of metabolite (95% CI)	p-$_{FDR}$	n	Change per two-fold inc. of metabolite (95% CI)	p-$_{FDR}$	n	Change per two-fold inc. of metabolite (95% CI)	p-$_{FDR}$
BMI z-score (6y)									
MEHHP	501	-0.04 (-0.13, 0.04)	0.338	267	0.01 (-0.11, 0.13)	0.790	234	-0.12 (-0.22, -0.02)	0.177
MEOHP	501	-0.04 (-0.14, 0.06)	0.372	267	0 (-0.14, 0.15)	0.790	234	-0.11 (-0.23, 0.02)	0.430
MECCP	400	-0.09 (-0.20, 0.02)	0.098	202	-0.04 (-0.18, 0.10)	0.488	198	-0.14 (-0.31, 0.02)	0.225
∑DEHP	501	-0.02 (-0.10, 0.06)	0.098	195	-0.05 (-0.19, 0.09)	0.488	190	-0.13 (-0.29, 0.03)	0.177
BMI z-score (8y)									
MEHHP	241	-0.06 (-0.20, 0.08)	0.399	132	0 (-0.18, 0.19)	0.956	109	-0.15 (-0.37, 0.08)	0.064
MEOHP	241	-0.06 (-0.20, 0.08)	0.581	132	0 (-0.18, 0.18)	0.956	109	-0.14 (-0.38, 0.10)	0.177
MECCP	104	0.04 (-0.13, 0.21)	0.198	50	0.06 (-0.19, 0.32)	0.817	54	-0.08 (-0.34, 0.18)	0.177
∑DEHP	104	-0.04 (-0.32, 0.24)	0.672	50	0.05 (-0.38, 0.49)	0.790	54	-0.23 (-0.59, 0.14)	0.177
SMI (6y)									
MEHHP	497	-0.04 (-0.07, -0.01)	0.098	266	-0.03 (-0.08, 0.02)	0.790	231	**-0.06 (-0.10, -0.02)**	**0.032**
MEOHP	497	-0.04 (-0.08, -0.01)	0.098	266	-0.04 (-0.10, 0.02)	0.790	231	**-0.07 (-0.11, -0.02)**	**0.032**
MECCP	397	-0.05 (-0.09, -0.01)	0.098	202	-0.01 (-0.08, 0.05)	0.817	195	**-0.09 (-0.14, -0.03)**	**0.032**
∑DEHP	382	-0.05 (-0.09, -0.002)	0.098	195	-0.03 (-0.09, 0.04)	0.790	187	**-0.08 (-0.13, -0.02)**	**0.044**
SMI (8y)									
MEHHP	460	-0.06 (-0.11, -0.001)	0.098	246	-0.02 (-0.09, 0.06)	0.817	272	-0.11 (-0.19, -0.02)	0.051
MEOHP	460	-0.04 (-0.11, 0.03)	0.372	246	-0.01 (-0.10, 0.08)	0.956	272	-0.09 (-0.20, 0.02)	0.177
MECCP	366	0 (-0.08, 0.09)	0.957	187	0.05 (-0.08, 0.17)	0.790	272	-0.03 (-0.15, 0.10)	0.666
∑DEHP	352	-0.03 (-0.11, 0.06)	0.634	180	0.05 (-0.07, 0.16)	0.790	272	-0.11 (-0.25, 0.03)	0.177

BMI, body mass index; SMI, skeletal muscle index; CI, confidence interval; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income.

Exploring associations between phthalates metabolites and body composition indices

Table 17 shows the association of concentrations of urinary phthalate metabolites at different time points with BMI z-score of children of 6 years of age. MEHHP, MEOHP, MECCP, ∑DEHP, MnBP, and MBzP in prenatal maternal urine and children's urine (at 2 y, 4 y, and 6 y) were not significantly associated. In the analyses with stratification based on the sex of the children, the concentration of MEHHP in maternal urine was significantly associated with BMI z-score at 6 years of age, as a two-fold increase in MEHHP was associated with a 0.12 unit decrease in BMI z-score (95% CI: -0.22, -0.02). Among boys, there was no significant association between phthalate metabolites and BMI z-score.

Table 17. Associations of BMI z-score at 6 years of age with different time windows of phthalate exposure

	Total			Boys			Girls		
	n	△BMI z-score at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△BMI z-score at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△BMI z-score at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*
Prenatal									
MEHHP	501	-0.04 (-0.13, 0.04)	0.299	267	0.01 (-0.11, 0.13)	0.901	234	**-0.12 (-0.22, -0.02)**	**0.024**
MEOHP	501	-0.04 (-0.14, 0.06)	0.472	267	0 (-0.14, 0.15)	0.956	234	-0.11 (-0.23, 0.02)	0.102
MECCP	400	-0.09 (-0.20, 0.02)	0.099	202	-0.04 (-0.18, 0.10)	0.574	198	-0.14 (-0.31, 0.02)	0.089
∑DEHP	501	-0.02 (-0.10, 0.06)	0.630	195	-0.05 (-0.19, 0.09)	0.494	190	-0.13 (-0.29, 0.03)	0.115
MnBP	385	-0.08 (-0.19, 0.02)	0.121	267	0.04 (-0.07, 0.16)	0.452	234	-0.11 (-0.23, 0.01)	0.077
MBzP	352	0.03 (-0.05, 0.11)	0.432	185	0.07 (-0.02, 0.15)	0.127	167	-0.03 (-0.17, 0.12)	0.694
2 y									
MEHHP	241	-0.06 (-0.20, 0.08)	0.417	132	0 (-0.18, 0.19)	0.958	109	-0.15 (-0.37, 0.08)	0.204
MEOHP	241	-0.06 (-0.20, 0.08)	0.416	132	0 (-0.18, 0.18)	0.989	109	-0.14 (-0.38, 0.10)	0.269
MECCP	104	0.04 (-0.13, 0.21)	0.659	50	0.06 (-0.19, 0.32)	0.631	54	-0.08 (-0.34, 0.18)	0.540
∑DEHP	104	-0.04 (-0.32, 0.24)	0.786	50	0.05 (-0.38, 0.49)	0.816	54	-0.23 (-0.59, 0.14)	0.234
MnBP	241	-0.13 (-0.32, 0.07)	0.211	132	-0.06 (-0.31, 0.20)	0.673	109	-0.20 (-0.51, 0.12)	0.229
MBzP	113	0.01 (-0.08, 0.10)	0.824	56	-0.02 (-0.15, 0.11)	0.788	57	0.04 (-0.11, 0.19)	0.602
4 y									
MEHHP	554	0.06 (-0.02, 0.13)	0.142	288	0.03 (-0.09, 0.14)	0.641	266	0.09 (-0.02, 0.20)	0.108
MEOHP	554	0.05 (-0.04, 0.14)	0.237	288	0.01 (-0.12, 0.14)	0.925	266	0.11 (-0.02, 0.23)	0.095
MECCP	477	0.04 (-0.05, 0.13)	0.384	246	0.01 (-0.09, 0.11)	0.834	231	0.07 (-0.08, 0.22)	0.350
∑DEHP	552	-0.01 (-0.10, 0.09)	0.877	246	0.02 (-0.12, 0.16)	0.789	231	0.10 (-0.09, 0.28)	0.304
MnBP	477	0.05 (-0.06, 0.17)	0.366	288	-0.06 (-0.18, 0.05)	0.289	264	0.04 (-0.10, 0.18)	0.595
MBzP	490	0.01 (-0.05, 0.07)	0.759	255	-0.03 (-0.11, 0.04)	0.354	235	0.08 (-0.03, 0.18)	0.167
6 y									
MEHHP	572	0.03 (-0.08, 0.13)	0.616	300	0.13 (-0.01, 0.27)	0.079	272	-0.10 (-0.27, 0.07)	0.263
MEOHP	572	-0.01 (-0.11, 0.10)	0.927	300	0.09 (-0.06, 0.23)	0.235	272	-0.12 (-0.29, 0.04)	0.142
MECCP	572	0 (-0.10, 0.11)	0.971	300	0.07 (-0.07, 0.22)	0.327	272	-0.09 (-0.24, 0.07)	0.288
∑DEHP	572	-0.03 (-0.14, 0.08)	0.579	300	0.09 (-0.05, 0.24)	0.204	272	-0.10 (-0.27, 0.06)	0.228
MnBP	572	0.01 (-0.10, 0.11)	0.897	300	-0.11 (-0.24, 0.03)	0.122	272	0.07 (-0.10, 0.24)	0.403
MBzP	572	-0.01 (-0.07, 0.05)	0.745	300	-0.05 (-0.11, 0.02)	0.164	272	0.06 (-0.04, 0.16)	0.265

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Table 18 shows the association of concentrations of urinary phthalate metabolites at different time points with the BMI z-score of children at 8 years of age. A two-fold increase of ∑DEHP in prenatal maternal urine, and children's urine at 8 years of age was associated with changes in BMI z-score of -0.15 (95% CI: -0.26, -0.03), and -0.12 (95% CI: -0.21, -0.02), respectively. Among boys, a two-fold increase in ∑DEHP in prenatal maternal urine and children's urine at 8 years of age was associated with a -0.17 (95% CI: -0.34, -0.01) and -0.16 unit change (95% CI: -0.31, -0.01) in BMI z-score at 8 years of age, respectively.

Table 18. Associations of BMI z-score at 8 years of age with different time windows of phthalate exposure

	Total			Boys			Girls		
	n	△BMI z-score at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△BMI z-score at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△BMI z-score at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*
Prenatal									
MEHHP	461	-0.06 (-0.15, 0.03)	0.190	247	-0.05 (-0.19, 0.09)	0.457	214	-0.09 (-0.21, 0.03)	0.144
MEOHP	461	-0.06 (-0.18, 0.05)	0.256	247	-0.08 (-0.24, 0.09)	0.364	214	-0.06 (-0.21, 0.08)	0.403
MECCP	366	**-0.12 (-0.24, -0.01)**	**0.034**	187	-0.16 (-0.32, 0.01)	0.061	179	-0.11 (-0.28, 0.06)	0.197
∑DEHP	352	**-0.15 (-0.26, -0.03)**	**0.016**	180	**-0.17 (-0.34, -0.01)**	**0.037**	172	-0.14 (-0.31, 0.04)	0.139
MnBP	461	-0.06 (-0.16, 0.03)	0.190	247	-0.05 (-0.18, 0.09)	0.485	214	-0.09 (-0.23, 0.05)	0.210
MBzP	327	0.03 (-0.05, 0.11)	0.480	172	0.06 (-0.04, 0.17)	0.228	155	-0.03 (-0.18, 0.12)	0.733
2 y									
MEHHP	224	-0.04 (-0.19, 0.11)	0.622	124	0 (-0.19, 0.19)	0.991	100	-0.05 (-0.30, 0.20)	0.702
MEOHP	224	-0.03 (-0.18, 0.12)	0.722	124	-0.01 (-0.19, 0.17)	0.945	100	-0.03 (-0.29, 0.23)	0.816
MECCP	93	-0.04 (-0.27, 0.19)	0.749	45	-0.05 (-0.38, 0.28)	0.767	48	0.04 (-0.34, 0.43)	0.827
∑DEHP	93	-0.16 (-0.47, 0.14)	0.297	45	0 (-0.54, 0.53)	0.988	48	-0.16 (-0.58, 0.26)	0.451
MnBP	224	-0.12 (-0.33, 0.08)	0.236	124	-0.07 (-0.32, 0.18)	0.580	100	-0.17 (-0.51, 0.17)	0.333
MBzP	102	-0.02 (-0.14, 0.10)	0.713	51	-0.11 (-0.27, 0.06)	0.218	51	0.11 (-0.06, 0.28)	0.222
4 y									
MEHHP	510	0.03 (-0.06, 0.12)	0.542	267	0.02 (-0.10, 0.14)	0.759	243	0.04 (-0.11, 0.18)	0.621
MEOHP	510	0.04 (-0.06, 0.15)	0.396	267	0.02 (-0.12, 0.16)	0.778	243	0.07 (-0.09, 0.23)	0.366
MECCP	441	0.02 (-0.07, 0.12)	0.627	229	-0.01 (-0.12, 0.09)	0.819	212	0.05 (-0.11, 0.21)	0.538
∑DEHP	441	0.04 (-0.09, 0.16)	0.569	229	0.01 (-0.14, 0.16)	0.897	212	0.06 (-0.15, 0.26)	0.587
MnBP	508	-0.05 (-0.15, 0.04)	0.272	267	-0.11 (-0.24, 0.03)	0.118	241	-0.01 (-0.16, 0.13)	0.848
MBzP	452	0.01 (-0.06, 0.08)	0.796	237	-0.05 (-0.13, 0.03)	0.255	215	0.09 (-0.03, 0.20)	0.154
6 y									
MEHHP	525	0.05 (-0.07, 0.16)	0.440	276	0.15 (-0.01, 0.31)	0.063	249	-0.09 (-0.24, 0.07)	0.286
MEOHP	525	0.03 (-0.08, 0.15)	0.594	276	0.14 (-0.02, 0.30)	0.095	249	-0.09 (-0.25, 0.06)	0.233
MECCP	525	0.01 (-0.10, 0.12)	0.805	276	0.10 (-0.05, 0.26)	0.197	249	-0.09 (-0.24, 0.05)	0.222
∑DEHP	525	0.03 (-0.09, 0.14)	0.629	276	0.13 (-0.03, 0.30)	0.115	249	-0.09 (-0.25, 0.06)	0.235
MnBP	525	-0.11 (-0.21, 0.003)	0.043	276	-0.11 (-0.24, 0.02)	0.090	249	-0.12 (-0.29, 0.06)	0.188
MBzP	525	0.01 (-0.05, 0.07)	0.753	276	-0.03 (-0.11, 0.04)	0.406	249	0.08 (-0.02, 0.17)	0.136
8 y									
MEHHP	524	-0.07 (-0.16, 0.02)	0.105	276	-0.04 (-0.18, 0.10)	0.564	248	-0.08 (-0.20, 0.03)	0.154
MEOHP	524	**-0.10(-0.19, -0.01)**	**0.033**	276	-0.07 (-0.22, 0.08)	0.366	248	-0.11 (-0.23, 0.01)	0.078
MECCP	524	**-0.13 (-0.22, -0.04)**	**0.007**	276	**-0.16 (-0.31, -0.01)**	**0.036**	248	-0.1 (-0.21, 0.02)	0.098
∑DEHP	524	**-0.12 (-0.21, -0.02)**	**0.020**	276	-0.11 (-0.27, 0.05)	0.188	248	-0.1 (-0.22, 0.02)	0.088
MnBP	524	-0.03 (-0.11, 0.05)	0.519	276	-0.09 (-0.24, 0.06)	0.226	248	0.03 (-0.06, 0.12)	0.543
MBzP	524	-0.04 (-0.08, 0.01)	0.141	276	-0.06 (-0.13, 0.003)	0.065	248	0 (-0.07, 0.07)	0.948

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Table 19 shows the association of concentrations of urinary phthalate metabolites at different time points with BMI of children of 6 years of age. MEHHP, MEOHP, MECCP, ∑DEHP, MnBP, and MBzP in prenatal maternal urine and children's urine (at 2 y, 4 y, and 6 y) were not significantly associated. In the analyses with stratification based on the sex of the children, girls showed the significant association between a two-fold increase in MEHHP, MEOHP, and ∑DEHP in maternal urine with decreased BMI at 6 years of age as -0.21 kg/m^2 (95% CI: -0.38, -0.05), -0.22 kg/m^2 (95% CI: -0.42, -0.01), and -0.21 kg/m^2 (-0.41, -0.003), respectively. Among boys, there was no significant association between phthalate metabolites and BMI.

Table 19. Associations of BMI at 6 years of age with different time windows of phthalate exposure

	Total			Boys			Girls		
	n	△BMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△BMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△BMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*
Prenatal									
MEHHP	501	-0.04 (-0.21, 0.12)	0.623	267	0.08 (-0.17, 0.33)	0.534	234	**-0.21 (-0.38, -0.05)**	**0.013**
MEOHP	501	-0.03 (-0.23, 0.16)	0.736	267	0.08 (-0.22, 0.37)	0.619	234	**-0.22 (-0.42, -0.01)**	**0.041**
MECCP	400	-0.17 (-0.38, 0.03)	0.091	202	-0.03 (-0.24, 0.18)	0.761	198	-0.31 (-0.65, 0.02)	0.069
∑DEHP	385	-0.13 (-0.29, 0.03)	0.119	195	-0.05 (-0.27, 0.16)	0.635	190	-0.23 (-0.48, 0.02)	0.070
MnBP	501	-0.04 (-0.20, 0.11)	0.596	267	0.08 (-0.15, 0.30)	0.497	234	**-0.21 (-0.41, -0.003)**	**0.048**
MBzP	352	0.05 (-0.07, 0.17)	0.445	185	0.11 (-0.02, 0.24)	0.101	167	-0.06 (-0.29, 0.17)	0.610
2 y									
MEHHP	241	-0.16 (-0.37, 0.06)	0.157	132	-0.06 (-0.34, 0.23)	0.703	109	-0.28 (-0.62, 0.06)	0.111
MEOHP	241	-0.16 (-0.38, 0.05)	0.146	132	-0.07 (-0.34, 0.20)	0.594	109	-0.26 (-0.63, 0.10)	0.155
MECCP	104	0.18 (-0.18, 0.54)	0.331	50	0.26 (-0.28, 0.81)	0.348	54	-0.07 (-0.49, 0.34)	0.732
∑DEHP	104	0.04 (-0.51, 0.59)	0.896	50	0.24 (-0.66, 1.14)	0.602	54	-0.30 (-0.88, 0.29)	0.325
MnBP	241	-0.29 (-0.61, 0.03)	0.074	132	-0.20 (-0.59, 0.20)	0.335	109	-0.37 (-0.90, 0.16)	0.177
MBzP	113	0.03 (-0.11, 0.18)	0.670	56	0.01 (-0.19, 0.20)	0.939	57	0.04 (-0.19, 0.28)	0.711
4 y									
MEHHP	554	0.10 (-0.01, 0.22)	0.086	288	0.07 (-0.11, 0.25)	0.472	266	0.14 (-0.02, 0.31)	0.082
MEOHP	554	0.10 (-0.04, 0.24)	0.155	288	0.05 (-0.17, 0.26)	0.675	266	0.17 (-0.02, 0.36)	0.087
MECCP	477	0.07 (-0.06, 0.21)	0.268	246	0.04 (-0.12, 0.19)	0.641	231	0.12 (-0.10, 0.34)	0.293
∑DEHP	477	0.11 (-0.07, 0.28)	0.226	246	0.06 (-0.15, 0.27)	0.578	231	0.16 (-0.11, 0.44)	0.245
MnBP	552	0 (-0.17, 0.16)	0.956	288	-0.14 (-0.33, 0.05)	0.143	264	0.11 (-0.16, 0.39)	0.416
MBzP	490	0.01 (-0.09, 0.11)	0.850	255	-0.06 (-0.17, 0.05)	0.287	235	0.11 (-0.06, 0.28)	0.190
6 y									
MEHHP	572	0.04 (-0.15, 0.23)	0.674	300	0.22 (-0.03, 0.47)	0.088	272	-0.19 (-0.49, 0.11)	0.214
MEOHP	572	-0.01 (-0.19, 0.18)	0.935	300	0.17 (-0.09, 0.42)	0.204	272	-0.24 (-0.52, 0.04)	0.100
MECCP	572	0.01 (-0.16, 0.19)	0.895	300	0.15 (-0.11, 0.40)	0.252	272	-0.17 (-0.43, 0.09)	0.208
∑DEHP	572	0.01 (-0.17, 0.20)	0.879	300	0.18 (-0.08, 0.44)	0.178	272	-0.20 (-0.48, 0.08)	0.170
MnBP	572	-0.04 (-0.20, 0.13)	0.672	300	-0.17 (-0.38, 0.04)	0.111	272	0.14 (-0.12, 0.41)	0.296
MBzP	572	-0.01 (-0.10, 0.09)	0.915	300	-0.08 (-0.18, 0.02)	0.120	272	0.11 (-0.07, 0.29)	0.237

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Table 20 shows the association of concentrations of urinary phthalate metabolites at different time points with the BMI of children at 8 years of age. A two-fold increase of MECCP and ∑DEHP in prenatal maternal urine was associated with changes in BMI of -0.31 kg/m^2 (95% CI: -0.55, -0.06) and -0.37 kg/m^2 (95% CI: -0.64, -0.10), respectively. MECCP at 8 y were significantly associated with BMI z-score at 8 y (-0.26 kg/m^2 per two-fold increase; 95% CI: -0.47, -0.05). Among boys, a two-fold increase in MEHHP and MEOHP in children's urine at 6 years of age was associated with a 0.45 kg/m^2 (95% CI: 0.03, 0.87) and 0.43 kg/m^2 (0.004, 0.86) increase in BMI at 8 years of age.

Table 20. Associations of BMI at 8 years of age with different time windows of phthalate exposure

	Total			Boys			Girls		
	n	△BMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△BMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△BMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*
Prenatal									
MEHHP	461	-0.13 (-0.40, 0.14)	0.355	247	-0.07 (-0.51, 0.36)	0.748	214	-0.22 (-0.49, 0.05)	0.109
MEOHP	461	-0.14 (-0.47, 0.19)	0.403	247	-0.12 (-0.64, 0.40)	0.646	214	-0.19 (-0.52, 0.13)	0.247
MECCP	366	**-0.31 (-0.55, -0.06)**	**0.015**	187	**-0.36 (-0.72, -0.01)**	**0.047**	179	-0.28 (-0.63, 0.07)	0.122
∑DEHP	352	**-0.37 (-0.64, -0.10)**	**0.007**	180	**-0.42 (-0.81, -0.04)**	**0.032**	172	-0.35 (-0.74, 0.03)	0.076
MnBP	461	-0.17 (-0.42, 0.07)	0.169	247	-0.13 (-0.51, 0.26)	0.521	214	-0.25 (-0.57, 0.06)	0.111
MBzP	327	0.07 (-0.12, 0.25)	0.492	172	0.15 (-0.09, 0.39)	0.234	155	-0.06 (-0.38, 0.25)	0.685
2 y									
MEHHP	224	-0.13 (-0.47, 0.20)	0.436	124	-0.08 (-0.54, 0.38)	0.729	100	-0.15 (-0.65, 0.36)	0.567
MEOHP	224	-0.11 (-0.44, 0.22)	0.511	124	-0.08 (-0.51, 0.35)	0.702	100	-0.11 (-0.63, 0.40)	0.666
MECCP	93	0.04 (-0.50, 0.58)	0.884	45	0.12 (-0.77, 1.02)	0.790	48	0.13 (-0.61, 0.87)	0.732
∑DEHP	93	-0.27 (-0.99, 0.44)	0.452	45	0.16 (-1.23, 1.55)	0.824	48	-0.29 (-1.14, 0.56)	0.506
MnBP	224	-0.25 (-0.68, 0.19)	0.270	124	-0.16 (-0.72, 0.41)	0.588	100	-0.29 (-0.96, 0.39)	0.402
MBzP	102	-0.02 (-0.28, 0.24)	0.889	51	-0.13 (-0.50, 0.23)	0.479	51	0.17 (-0.19, 0.52)	0.355
4 y									
MEHHP	510	0.10 (-0.11, 0.31)	0.342	267	0.12 (-0.18, 0.42)	0.440	243	0.08 (-0.21, 0.37)	0.597
MEOHP	510	0.16 (-0.07, 0.40)	0.170	267	0.17 (-0.19, 0.53)	0.356	243	0.17 (-0.16, 0.49)	0.313
MECCP	441	0.07 (-0.13, 0.26)	0.501	229	-0.02 (-0.25, 0.22)	0.900	212	0.13 (-0.19, 0.45)	0.420
∑DEHP	441	0.13 (-0.14, 0.39)	0.343	229	0.10 (-0.26, 0.46)	0.586	212	0.14 (-0.26, 0.54)	0.502
MnBP	508	-0.13 (-0.34, 0.08)	0.231	267	-0.27 (-0.59, 0.04)	0.093	241	-0.01 (-0.32, 0.29)	0.932
MBzP	452	0.01 (-0.14, 0.17)	0.862	237	-0.13 (-0.32, 0.07)	0.196	215	0.20 (-0.05, 0.44)	0.113
6 y									
MEHHP	525	0.17 (-0.11, 0.44)	0.235	276	**0.45 (0.03, 0.87)**	**0.035**	249	-0.17 (-0.50, 0.16)	0.311
MEOHP	525	0.15 (-0.12, 0.42)	0.283	276	**0.43 (0.004, 0.86)**	**0.049**	249	-0.17 (-0.49, 0.14)	0.282
MECCP	525	0.10 (-0.16, 0.36)	0.438	276	0.35 (-0.06, 0.76)	0.098	249	-0.17 (-0.47, 0.12)	0.255
∑DEHP	525	0.14 (-0.14, 0.41)	0.326	276	0.42 (-0.01, 0.85)	0.059	249	-0.18 (-0.49, 0.14)	0.269
MnBP	525	-0.23 (-0.47, 0.01)	0.058	276	-0.26 (-0.58, 0.06)	0.112	249	-0.22 (-0.59, 0.14)	0.233
MBzP	525	0.05 (-0.10, 0.19)	0.522	276	-0.04 (-0.23, 0.14)	0.653	249	0.17 (-0.04, 0.39)	0.119
8 y									
MEHHP	524	-0.13 (-0.33, 0.08)	0.236	276	-0.06 (-0.42, 0.30)	0.745	248	-0.16 (-0.40, 0.08)	0.193
MEOHP	524	-0.18 (-0.39, 0.02)	0.083	276	-0.10 (-0.46, 0.27)	0.599	248	-0.22 (-0.47, 0.03)	0.085
MECCP	524	**-0.26 (-0.47, -0.05)**	**0.015**	276	-0.35 (-0.74, 0.04)	0.077	248	-0.19 (-0.42, 0.04)	0.103
∑DEHP	524	-0.22 (-0.44, 0.0002)	0.051	276	-0.22 (-0.64, 0.20)	0.305	248	-0.20 (-0.45, 0.04)	0.099
MnBP	524	-0.06 (-0.23, 0.11)	0.521	276	-0.21 (-0.53, 0.11)	0.195	248	0.07 (-0.12, 0.25)	0.482
MBzP	524	-0.05 (-0.16, 0.06)	0.372	276	-0.11 (-0.26, 0.03)	0.133	248	0.02 (-0.14, 0.18)	0.808

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Table 21 shows the association between phthalate metabolites for different time windows of phthalate exposure and SMI at 6 years of age. A 2-fold increase in prenatal exposure to MEHHP, MEOHP, MECCP and ∑DEHP was significantly associated with -0.04 kg/m^2 (95% CI: -0.07, -0.01), -0.04 kg/m^2 (95% CI: -0.08, -0.01), -0.05 kg/m^2 (95% CI: -0.09, -0.01), and -0.05 kg/m^2 (95% CI: -0.09, -0.002) change in SMI at 6 years of age. In the sex-stratification analyses, these associations were significant only among girls. In girls, A 2-fold increase in prenatal exposure to MEHHP, MEOHP, MECCP and ∑DEHP was significantly associated with -0.06 kg/m^2 (95% CI: -0.10, -0.02), -0.07 kg/m^2 (95% CI: -0.11, -0.02), -0.09 kg/m^2 (95% CI: -0.14, -0.03), and -0.08 kg/m^2 (95% CI: -0.13, -0.02) change in SMI at 6 years of age. A 2-fold increase in MEHHP and MEOHP exposure at 2 years of age were also significantly associated with decreased SMI at 6 years of age (-0.07 kg/m^2 [95% CI: -0.12, -0.01], -0.06 kg/m^2 [95% CI: -0.12, -0.001], respectively).

Table 21. Associations of SMI at 6 years of age with different time windows of phthalate exposure

	Total			Boys			Girls		
	n	△SMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△SMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△SMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*
Prenatal									
MEHHP	497	**-0.04 (-0.07, -0.01)**	**0.019**	266	-0.03 (-0.08, 0.02)	0.268	231	**-0.06 (-0.10, -0.02)**	**0.005**
MEOHP	497	**-0.04 (-0.08, -0.01)**	**0.024**	266	-0.04 (-0.10, 0.02)	0.221	231	**-0.07 (-0.11, -0.02)**	**0.006**
MECCP	397	**-0.05 (-0.09, -0.01)**	**0.025**	202	-0.01 (-0.08, 0.05)	0.664	195	**-0.09 (-0.14, -0.03)**	**0.003**
∑DEHP	382	**-0.05 (-0.09, -0.002)**	**0.038**	195	-0.03 (-0.09, 0.04)	0.395	187	**-0.08 (-0.13, -0.02)**	**0.011**
MnBP	497	-0.03 (-0.07, 0.01)	0.097	266	-0.02 (-0.07, 0.03)	0.431	231	-0.05 (-0.10, 0.01)	0.083
MBzP	351	0.01 (-0.03, 0.04)	0.594	185	0.02 (-0.02, 0.06)	0.319	166	-0.01 (-0.07, 0.05)	0.705
2 y									
MEHHP	241	**-0.07 (-0.12, -0.01)**	**0.029**	132	-0.04 (-0.12, 0.04)	0.340	109	**-0.09 (-0.19, -0.004)**	**0.042**
MEOHP	241	**-0.06 (-0.12, -0.001)**	**0.047**	132	-0.04 (-0.11, 0.04)	0.342	109	-0.08 (-0.18, 0.02)	0.104
MECCP	104	-0.04 (-0.11, 0.04)	0.353	50	-0.09 (-0.18, 0.01)	0.085	54	0.04 (-0.08, 0.17)	0.489
∑DEHP	104	-0.06 (-0.18, 0.05)	0.288	50	-0.11 (-0.29, 0.07)	0.228	54	0 (-0.19, 0.18)	0.982
MnBP	241	-0.10 (-0.18, -0.02)	0.014	132	-0.08 (-0.18, 0.01)	0.095	109	-0.1 (-0.24, 0.03)	0.145
MBzP	113	-0.03 (-0.08, 0.02)	0.285	56	-0.06 (-0.13, -0.001)	0.052	57	0.02 (-0.06, 0.09)	0.683
4 y									
MEHHP	550	0 (-0.03, 0.04)	0.787	287	-0.03 (-0.09, 0.03)	0.308	263	0.03 (-0.01, 0.07)	0.102
MEOHP	550	0.01 (-0.03, 0.05)	0.604	287	-0.03 (-0.09, 0.03)	0.375	263	0.05 (-0.004, 0.10)	0.073
MECCP	475	0.01 (-0.03, 0.04)	0.655	246	0.02 (-0.04, 0.07)	0.511	229	0 (-0.05, 0.04)	0.924
∑DEHP	475	0.01 (-0.04, 0.05)	0.837	246	0 (-0.08, 0.07)	0.969	229	0.01 (-0.05, 0.07)	0.716
MnBP	548	-0.01 (-0.05, 0.03)	0.622	287	-0.03 (-0.09, 0.03)	0.369	261	0 (-0.05, 0.06)	0.865
MBzP	487	-0.01 (-0.03, 0.02)	0.660	254	-0.02 (-0.06, 0.02)	0.257	233	0.02 (-0.02, 0.06)	0.409
6 y									
MEHHP	568	0.01 (-0.04, 0.05)	0.822	299	0.04 (-0.03, 0.10)	0.282	269	-0.04 (-0.11, 0.03)	0.301
MEOHP	568	0.01 (-0.04, 0.05)	0.783	299	0.03 (-0.03, 0.10)	0.310	269	-0.03 (-0.10, 0.03)	0.334
MECCP	568	0.01 (-0.03, 0.06)	0.640	299	0.04 (-0.03, 0.10)	0.263	269	-0.03 (-0.09, 0.04)	0.415
∑DEHP	568	0.01 (-0.04, 0.06)	0.748	299	0.04 (-0.03, 0.10)	0.284	269	-0.03 (-0.10, 0.04)	0.346
MnBP	568	-0.03 (-0.08, 0.01)	0.171	299	-0.06 (-0.12, 0.01)	0.088	269	0 (-0.06, 0.06)	0.991
MBzP	568	-0.01 (-0.03, 0.02)	0.485	299	-0.03 (-0.06, 0.002)	0.057	269	0.03 (-0.02, 0.07)	0.231

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Table 22 shows the association between exposure to phthalate metabolites at different time windows and SMI at 8 years of age. A two-fold increase in prenatal maternal MEHHP was significantly associated with decreased SMI at 8 years of age (-0.06 kg/m^2; 95% CI: -0.11, -0.001), and this association was significant among girls (-0.11 kg/m^2; 95% CI: -0.19, -0.02) but not significant among boys. The associations between increased SMI at 8 years of age and a two-fold increase in MEOHP (0.14 kg/m^2; 95% CI: 0.02, 0.26) and MnBP (0.26 kg/m^2; 95% CI: 0.11, 0.42) at 2 years of age, and MEHHP (0.15 kg/m^2; 95% CI: 0.07, 0.23), MEOHP (0.14 kg/m^2; 95% CI: 0.06, 0.22), MECCP (0.11 kg/m^2; 95% CI: 0.03, 0.19), ∑DEHP (0.14 kg/m^2; 95% CI: 0.06, 0.22), MnBP (0.14 kg/m^2; 95% CI: 0.05, 0.22), MBzP (0.09 kg/m^2; 95% CI: 0.04, 0.14) at 6 years of age, and MEHHP (0.16 kg/m^2; 95% CI: 0.08, 0.24), MEOHP (0.08 kg/m^2; 95% CI: 0.004, 0.16), MnBP (0.21 kg/m^2; 95% CI: 0.14, 0.29) at 8 years of age were statistically significant.

Table 22. Associations of SMI at 8 years of age with different time windows of phthalate exposure

	Total			Boys			Girls		
	n	△SMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△SMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△SMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*
Prenatal									
MEHHP	460	**-0.06 (-0.11, -0.001)**	**0.043**	246	-0.02 (-0.09, 0.06)	0.661	214	**-0.11 (-0.19, -0.02)**	**0.016**
MEOHP	460	-0.04 (-0.11, 0.03)	0.235	246	-0.01 (-0.10, 0.08)	0.886	214	-0.09 (-0.20, 0.02)	0.120
MECCP	366	0 (-0.08, 0.09)	0.957	187	0.05 (-0.08, 0.17)	0.466	179	-0.03 (-0.15, 0.10)	0.666
∑DEHP	352	-0.03 (-0.11, 0.06)	0.555	180	0.05 (-0.07, 0.16)	0.436	172	-0.11 (-0.25, 0.03)	0.142
MnBP	460	-0.02 (-0.08, 0.05)	0.583	246	0.01 (-0.07, 0.09)	0.893	214	-0.06 (-0.16, 0.05)	0.307
MBzP	327	0.02 (-0.04, 0.08)	0.567	172	0.04 (-0.03, 0.11)	0.311	155	-0.02 (-0.14, 0.09)	0.687
2 y									
MEHHP	224	0.10 (-0.02, 0.23)	0.114	124	0.10 (-0.03, 0.24)	0.136	100	0.11 (-0.12, 0.34)	0.341
MEOHP	224	**0.14 (0.02, 0.26)**	**0.029**	124	0.13 (0.004, 0.26)	0.059	100	0.16 (-0.06, 0.39)	0.161
MECCP	93	-0.07 (-0.24, 0.11)	0.450	45	-0.15 (-0.36, 0.07)	0.179	48	0.13 (-0.16, 0.43)	0.381
∑DEHP	93	0.01 (-0.22, 0.24)	0.927	45	0.05 (-0.28, 0.37)	0.787	48	0.21 (-0.14, 0.56)	0.254
MnBP	224	**0.26 (0.11, 0.42)**	**0.001**	124	0.16 (-0.02, 0.35)	0.091	100	**0.40 (0.13, 0.68)**	**0.005**
MBzP	102	-0.02 (-0.13, 0.09)	0.744	51	-0.04 (-0.18, 0.10)	0.567	51	0.03 (-0.12, 0.18)	0.701
4 y									
MEHHP	509	0.02 (-0.04, 0.09)	0.484	266	0.03 (-0.06, 0.12)	0.542	243	0.02 (-0.08, 0.11)	0.700
MEOHP	509	0.07 (-0.01, 0.16)	0.094	266	0.07 (-0.03, 0.18)	0.170	243	0.07 (-0.06, 0.20)	0.272
MECCP	440	-0.05 (-0.12, 0.01)	0.103	228	-0.08 (-0.17, 0.005)	0.066	212	-0.03 (-0.12, 0.07)	0.574
∑DEHP	440	0.01 (-0.08, 0.10)	0.772	228	-0.01 (-0.14, 0.12)	0.881	212	0.04 (-0.09, 0.17)	0.590
MnBP	507	-0.05 (-0.11, 0.02)	0.171	266	-0.01 (-0.10, 0.09)	0.893	241	-0.09 (-0.18, 0.005)	0.065
MBzP	451	0.07 (0.02, 0.12)	0.007	236	0.06 (-0.01, 0.12)	0.079	215	**0.09 (0.003, 0.18)**	**0.043**
6 y									
MEHHP	524	**0.15 (0.07, 0.23)**	**<0.001**	275	**0.21 (0.09, 0.32)**	**<0.001**	249	0.09 (-0.03, 0.22)	0.135
MEOHP	524	**0.14 (0.06, 0.22)**	**0.001**	275	**0.19 (0.08, 0.30)**	**0.001**	249	0.09 (-0.03, 0.21)	0.146
MECCP	524	**0.11 (0.03, 0.19)**	**0.006**	275	**0.15 (0.05, 0.25)**	**0.004**	249	0.07 (-0.04, 0.19)	0.214
∑DEHP	524	**0.14 (0.06, 0.22)**	**0.001**	275	**0.19 (0.08, 0.30)**	**0.001**	249	0.09 (-0.03, 0.21)	0.161
MnBP	524	**0.14 (0.05, 0.22)**	**0.002**	275	**0.12 (0.01, 0.24)**	**0.035**	249	0.15 (0.02, 0.28)	0.028
MBzP	524	**0.09 (0.04, 0.14)**	**<0.001**	275	**0.07 (0.01, 0.13)**	**0.016**	249	**0.12 (0.04, 0.20)**	**0.003**
8 y									
MEHHP	523	**0.16 (0.08, 0.24)**	**<0.001**	275	**0.19 (0.08, 0.30)**	**0.001**	248	**0.15 (0.02, 0.27)**	**0.020**
MEOHP	523	**0.08 (0.004, 0.16)**	**0.039**	275	0.08 (-0.05, 0.20)	0.229	248	0.10 (-0.01, 0.20)	0.069
MECCP	523	0.02 (-0.06, 0.10)	0.666	275	-0.06 (-0.18, 0.07)	0.352	248	0.08 (-0.04, 0.19)	0.193
∑DEHP	523	0.09 (-0.0004, 0.18)	0.052	275	0.07 (-0.06, 0.19)	0.319	248	0.11 (-0.01, 0.24)	0.079
MnBP	523	**0.21 (0.14, 0.29)**	**<0.001**	275	**0.26 (0.16, 0.36)**	**<0.001**	248	**0.18 (0.08, 0.29)**	**0.001**
MBzP	523	0.02 (-0.01, 0.06)	0.177	275	0.01 (-0.04, 0.06)	0.663	248	0.04 (-0.01, 0.10)	0.121

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Table 23 shows the association of the concentrations of urinary phthalate metabolites at different time points with FMI of 6-year-old children. There were no significant associations between phthalate exposure at prenatal, 2 y, 4 y, 6 y, and 8 years of age and FMI.

Table 23. Associations of FMI at 6 years of age with different time windows of phthalate exposure

	Total			Boys			Girls		
	n	△FMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△FMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△FMI at 6 years of age per two-fold inc. of metabolite (95% CI)	*p*
Prenatal									
MEHHP	497	0.02 (-0.12, 0.15)	0.807	266	0.10 (-0.11, 0.30)	0.341	231	-0.10 (-0.25, 0.05)	0.187
MEOHP	497	0.02 (-0.14, 0.18)	0.800	266	0.09 (-0.16, 0.33)	0.484	231	-0.09 (-0.27, 0.09)	0.315
MECCP	397	-0.12 (-0.29, 0.05)	0.163	202	-0.06 (-0.24, 0.11)	0.488	195	-0.18 (-0.46, 0.11)	0.224
∑DEHP	382	-0.09 (-0.22, 0.05)	0.200	195	-0.07 (-0.25, 0.11)	0.456	187	-0.11 (-0.32, 0.10)	0.303
MnBP	497	-0.04 (-0.17, 0.09)	0.574	266	0.05 (-0.15, 0.25)	0.647	231	-0.15 (-0.30, 0.003)	0.055
MBzP	351	0.03 (-0.08, 0.13)	0.618	185	0.07 (-0.05, 0.19)	0.259	166	-0.05 (-0.24, 0.14)	0.614
2 y									
MEHHP	241	-0.08 (-0.25, 0.09)	0.375	132	-0.02 (-0.23, 0.19)	0.874	109	-0.16 (-0.46, 0.13)	0.271
MEOHP	241	-0.09 (-0.25, 0.08)	0.318	132	-0.04 (-0.23, 0.16)	0.716	109	-0.15 (-0.46, 0.15)	0.319
MECCP	104	0.21 (-0.09, 0.51)	0.171	50	0.37 (-0.07, 0.81)	0.110	54	-0.14 (-0.43, 0.15)	0.350
∑DEHP	104	0.08 (-0.37, 0.54)	0.719	50	0.36 (-0.36, 1.08)	0.332	54	-0.31 (-0.73, 0.11)	0.156
MnBP	241	-0.14 (-0.39, 0.11)	0.284	132	-0.06 (-0.38, 0.25)	0.702	109	-0.21 (-0.63, 0.21)	0.324
MBzP	113	0.06 (-0.05, 0.18)	0.289	56	0.08 (-0.08, 0.23)	0.328	57	0.04 (-0.15, 0.22)	0.703
4 y									
MEHHP	550	0.06 (-0.03, 0.16)	0.163	287	0.08 (-0.06, 0.21)	0.267	263	0.06 (-0.06, 0.18)	0.340
MEOHP	550	0.05 (-0.06, 0.16)	0.346	287	0.05 (-0.12, 0.21)	0.583	263	0.07 (-0.08, 0.22)	0.383
MECCP	475	0.03 (-0.07, 0.14)	0.540	246	0 (-0.12, 0.11)	0.939	229	0.08 (-0.10, 0.26)	0.386
∑DEHP	475	0.07 (-0.07, 0.20)	0.329	246	0.04 (-0.11, 0.20)	0.600	229	0.10 (-0.12, 0.32)	0.367
MnBP	548	0 (-0.13, 0.14)	0.950	287	-0.1 (-0.24, 0.05)	0.188	261	0.10 (-0.13, 0.32)	0.406
MBzP	487	0.01 (-0.06, 0.09)	0.722	254	-0.03 (-0.12, 0.05)	0.422	233	0.09 (-0.05, 0.23)	0.204
6 y									
MEHHP	568	0.03 (-0.12, 0.18)	0.704	299	0.17 (-0.04, 0.38)	0.105	269	-0.15 (-0.38, 0.08)	0.213
MEOHP	568	-0.02 (-0.16, 0.13)	0.826	299	0.12 (-0.09, 0.33)	0.254	269	-0.20 (-0.43, 0.03)	0.088
MECCP	568	0 (-0.14, 0.14)	0.969	299	0.10 (-0.11, 0.30)	0.361	269	-0.13 (-0.34, 0.07)	0.199
∑DEHP	568	0 (-0.15, 0.15)	0.968	299	0.13 (-0.08, 0.35)	0.234	269	-0.16 (-0.38, 0.06)	0.163
MnBP	568	-0.01 (-0.14, 0.11)	0.826	299	-0.10 (-0.26, 0.06)	0.228	269	0.10 (-0.12, 0.31)	0.386
MBzP	568	0.02 (-0.06, 0.09)	0.649	299	-0.03 (-0.10, 0.05)	0.502	269	0.08 (-0.06, 0.22)	0.244

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Table 24 shows the association of the concentrations of urinary phthalate metabolites at different time points with FMI of children at 8 years of age. ∑DEHP in prenatal maternal urine was associated with decreased FMI at 8 years of age (-0.25 kg/m^2; 95% CI: -0.47, -0.03). A two-fold increase in MnBP measured at 8 years of age was significantly associated with FMI at 8 years of age in all children (0.16 kg/m^2; 95% CI: 0.04, 0.28). In the sex-stratified analyses, a two-fold increase in MEHHP, MEOHP, and ∑DEHP at 6 years of age was associated with 0.25 kg/m^2 (95% CI: 0.05, 0.45), 0.23 kg/m^2 (95% CI: 0.03, 0.43), and 0.22 kg/m^2 (95% CI: 0.22, 0.42) increase in FMI at 8 years of age, respectively.

Table 24. Associations of FMI at 8 years of age with different time windows of phthalate exposure

	Total			Boys			Girls		
	n	△FMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△FMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*	n	△FMI at 8 years of age per two-fold inc. of metabolite (95% CI)	*p*
Prenatal									
MEHHP	460	-0.13 (-0.30, 0.05)	0.162	246	-0.10 (-0.36, 0.15)	0.429	214	-0.16 (-0.39, 0.07)	0.172
MEOHP	460	-0.11 (-0.33, 0.11)	0.321	246	-0.12 (-0.44, 0.20)	0.460	214	-0.11 (-0.39, 0.17)	0.461
MECCP	366	-0.15 (-0.34, 0.04)	0.132	187	-0.20 (-0.48, 0.08)	0.158	179	-0.11 (-0.39, 0.18)	0.464
∑DEHP	352	**-0.25 (-0.47, -0.03)**	**0.027**	180	-0.26 (-0.57, 0.05)	0.106	172	-0.24 (-0.57, 0.09)	0.149
MnBP	460	-0.13 (-0.33, 0.06)	0.184	246	-0.08 (-0.38, 0.23)	0.611	214	-0.23 (-0.47, 0.01)	0.063
MBzP	327	0.02 (-0.11, 0.16)	0.722	172	0.06 (-0.12, 0.24)	0.535	155	-0.03 (-0.26, 0.2)	0.789
2 y									
MEHHP	224	0.09 (-0.16, 0.34)	0.491	124	0.09 (-0.22, 0.40)	0.588	100	0.08 (-0.33, 0.5)	0.693
MEOHP	224	0.10 (-0.14, 0.34)	0.403	124	0.09 (-0.21, 0.39)	0.574	100	0.12 (-0.29, 0.52)	0.578
MECCP	93	0.03 (-0.26, 0.32)	0.837	45	0.09 (-0.29, 0.46)	0.653	48	0.13 (-0.39, 0.65)	0.632
∑DEHP	93	-0.10 (-0.51, 0.3)	0.615	45	0.09 (-0.47, 0.66)	0.748	48	-0.06 (-0.69, 0.58)	0.859
MnBP	224	0.24 (-0.07, 0.55)	0.127	124	0.21 (-0.19, 0.61)	0.311	100	0.32 (-0.18, 0.82)	0.211
MBzP	102	-0.01 (-0.18, 0.15)	0.862	51	-0.08 (-0.3, 0.13)	0.458	51	0.19 (-0.09, 0.47)	0.192
4 y									
MEHHP	509	0.02 (-0.15, 0.18)	0.830	266	0.07 (-0.17, 0.31)	0.573	243	-0.02 (-0.24, 0.20)	0.848
MEOHP	509	0.08 (-0.11, 0.27)	0.392	266	0.14 (-0.14, 0.41)	0.327	243	0.04 (-0.22, 0.29)	0.775
MECCP	440	-0.03 (-0.18, 0.12)	0.668	228	-0.13 (-0.31, 0.04)	0.140	212	0.06 (-0.19, 0.30)	0.638
∑DEHP	440	0.04 (-0.15, 0.24)	0.662	228	0.01 (-0.24, 0.27)	0.917	212	0.07 (-0.25, 0.39)	0.670
MnBP	507	-0.07 (-0.24, 0.1)	0.419	266	-0.13 (-0.37, 0.11)	0.277	241	-0.01 (-0.27, 0.25)	0.942
MBzP	451	0.04 (-0.07, 0.16)	0.444	236	-0.07 (-0.21, 0.07)	0.310	215	0.20 (0.004, 0.39)	0.047
6 y									
MEHHP	524	**0.25 (0.05, 0.45)**	**0.016**	275	**0.49 (0.19, 0.80)**	**0.002**	249	-0.02 (-0.28, 0.23)	0.853
MEOHP	524	**0.23 (0.03, 0.43)**	**0.024**	275	**0.47 (0.16, 0.77)**	**0.003**	249	-0.05 (-0.29, 0.20)	0.710
MECCP	524	0.17 (-0.02, 0.36)	0.078	275	**0.37 (0.07, 0.67)**	**0.015**	249	-0.05 (-0.28, 0.18)	0.657
∑DEHP	524	**0.22 (0.02, 0.42)**	**0.034**	275	**0.45 (0.14, 0.77)**	**0.005**	249	-0.04 (-0.29, 0.20)	0.733
MnBP	524	-0.01 (-0.2, 0.18)	0.925	275	-0.06 (-0.31, 0.20)	0.658	249	0.03 (-0.26, 0.31)	0.848
MBzP	524	0.10 (-0.01, 0.21)	0.069	275	0.02 (-0.12, 0.15)	0.801	249	0.21 (0.04, 0.37)	0.013
8 y									
MEHHP	523	0.06 (-0.09, 0.22)	0.428	275	0.21 (-0.05, 0.48)	0.118	248	-0.06 (-0.25, 0.12)	0.515
MEOHP	523	-0.03 (-0.18, 0.13)	0.736	275	0.11 (-0.17, 0.39)	0.447	248	-0.12 (-0.30, 0.07)	0.215
MECCP	523	-0.09 (-0.25, 0.06)	0.243	275	-0.14 (-0.45, 0.18)	0.396	248	-0.07 (-0.24, 0.10)	0.399
∑DEHP	523	-0.03 (-0.19, 0.14)	0.747	275	0.05 (-0.27, 0.37)	0.748	248	-0.09 (-0.27, 0.10)	0.364
MnBP	523	**0.16 (0.04, 0.28)**	**0.010**	275	0.16 (-0.05, 0.37)	0.134	248	**0.15 (0.01, 0.29)**	**0.036**
MBzP	523	0.02 (-0.06, 0.10)	0.662	275	-0.01 (-0.12, 0.10)	0.866	248	0.04 (-0.08, 0.16)	0.497

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Figure 23 summarizes the associations of body composition indices at 6 years of age with phthalate metabolites in prenatal maternal urine, and urine at 2, 4, 6 years of age. MEHHP, MEOHP, and MnBP in prenatal maternal urine were significantly associated with decreased BMI of girls at 6 years of age, and prenatal exposure to MEHHP was significantly associated with decreased BMI z-score of girls at 6 years of age. The association of FMI with phthalates was not significantly across different exposure timing. SMI at 6 years of age were associated with MEHHP, MEOHP, MECCP, and ∑DEHP in prenatal maternal urine, and MEHHP, MEOHP, and MnBP measured at 2 years of age. Among girls, MEHHP, MEOHP, MECCP, and ∑DEHP in prenatal maternal urine, and MEHHP in children's urine at 2 years of age were significantly associated with decreased SMI at 6 years of age. There was no significant association among boys, although the direction of association was identical to the girls.

Figure 24 summarizes the associations of body composition indices at 8 years of age with phthalate metabolites in prenatal maternal urine, and urine at 2, 4, 6, 8 years of age. MECCP and ∑DEHP in prenatal maternal urine and MECCP in 8 years of age were associated with decreased BMI and decreased BMI z-score at 8 years of age. Among boys, MECCP and ∑DEHP in prenatal maternal urine were associated with decreased BMI at 8 years of age. This association was not significant among girls, although the direction of associations was identical with boys. MEHHP and MEOHP at 6 years of age were significantly associated with increased BMI at 8 years of age among boys. ∑DEHP in prenatal maternal urine was associated with decreased FMI at 8 years, but MEHHP, MEOHP, and ∑DEHP in children's urine at 6 years, and MnBP in children's urine at 8 years were

associated with increased FMI at 8 years. Among boys, a significant association between MEHHP, MEOHP, MECCP, and ∑DEHP in children's urine at 6 years and increased FMI at 8 years was found. Among girls, increased FMI at 8 years was significantly associated with MBzP at 4 years, MBzP at 6 years, and MnBP at 8 years. MEHHP in prenatal maternal urine was associated with decreased SMI at 8 years, and this association was only significant among girls in the sex-stratified analyses. MEOHP and MnBP at 2 years, MBzP at 4 years, and MEHHP, MEOHP, MECCP, ∑DEHP, MBzP, and MnBP at 6 years, and MEHHP, MOEHP, and MnBP at 8 years were associated with increased SMI at 8 years of age. In the sex-stratified analyses, MEHHP, MEOHP, MECCP, ∑DEHP, MBzP, and MnBP at 6 years and MEHHP, MnBP at 8 years were significantly associated with increased SMI among boys. Among girls, increased SMI was significantly associated with MnBP at 2 years, MBzP at 4 years, MBzP and MnBP at 6 years, and MEHHP and MnBP at 8 years.

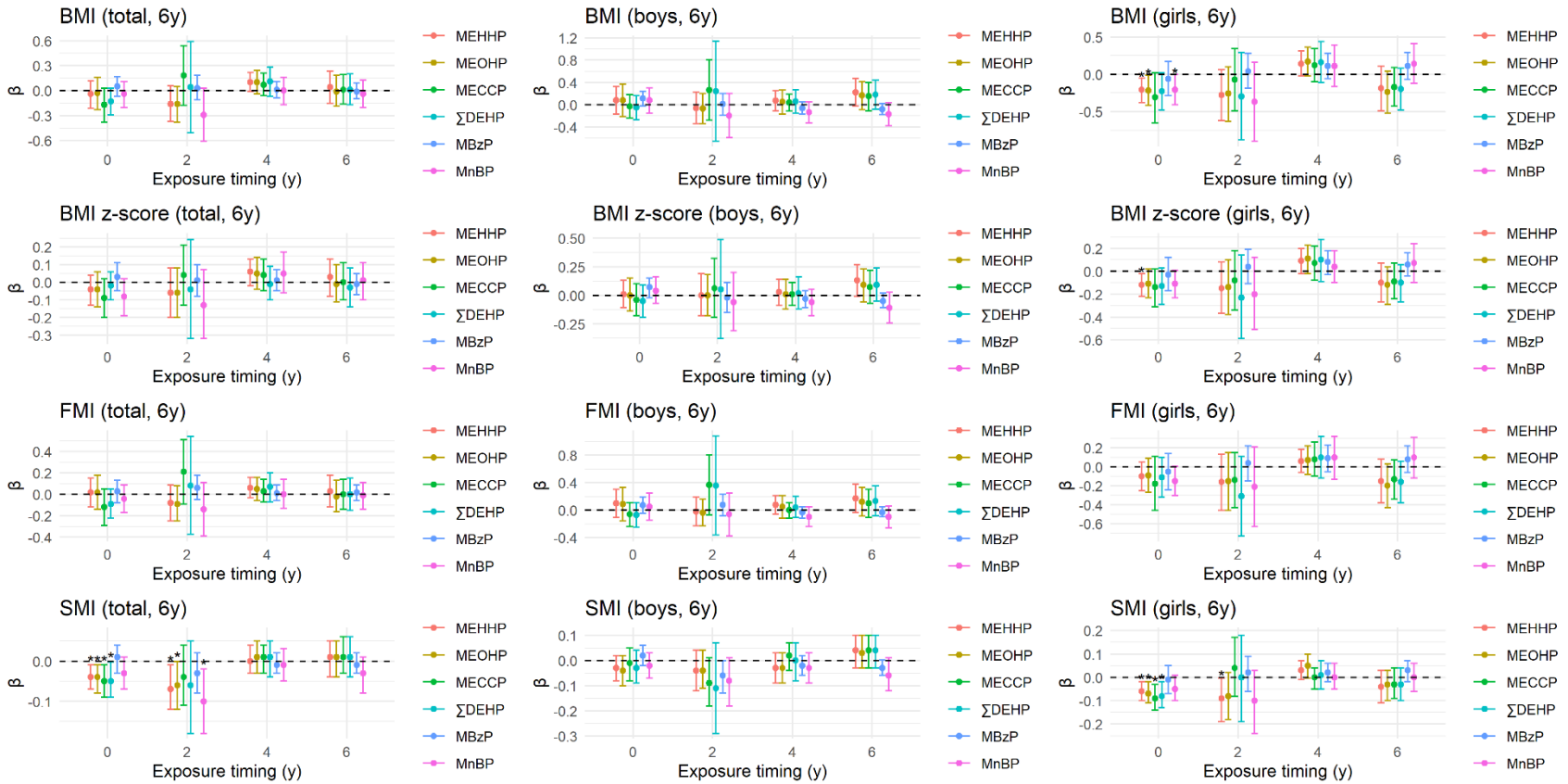

Figure 23. The associations between phthalate metabolites and body composition indices at 6 years of age

The X-axis shows the age of children when urine was collected for measuring phthalate metabolites, and '0' presents phthalate metabolites measured in prenatal maternal urine. The multivariate linear regressions between phthalate metabolites and body composition indices were adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices. MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

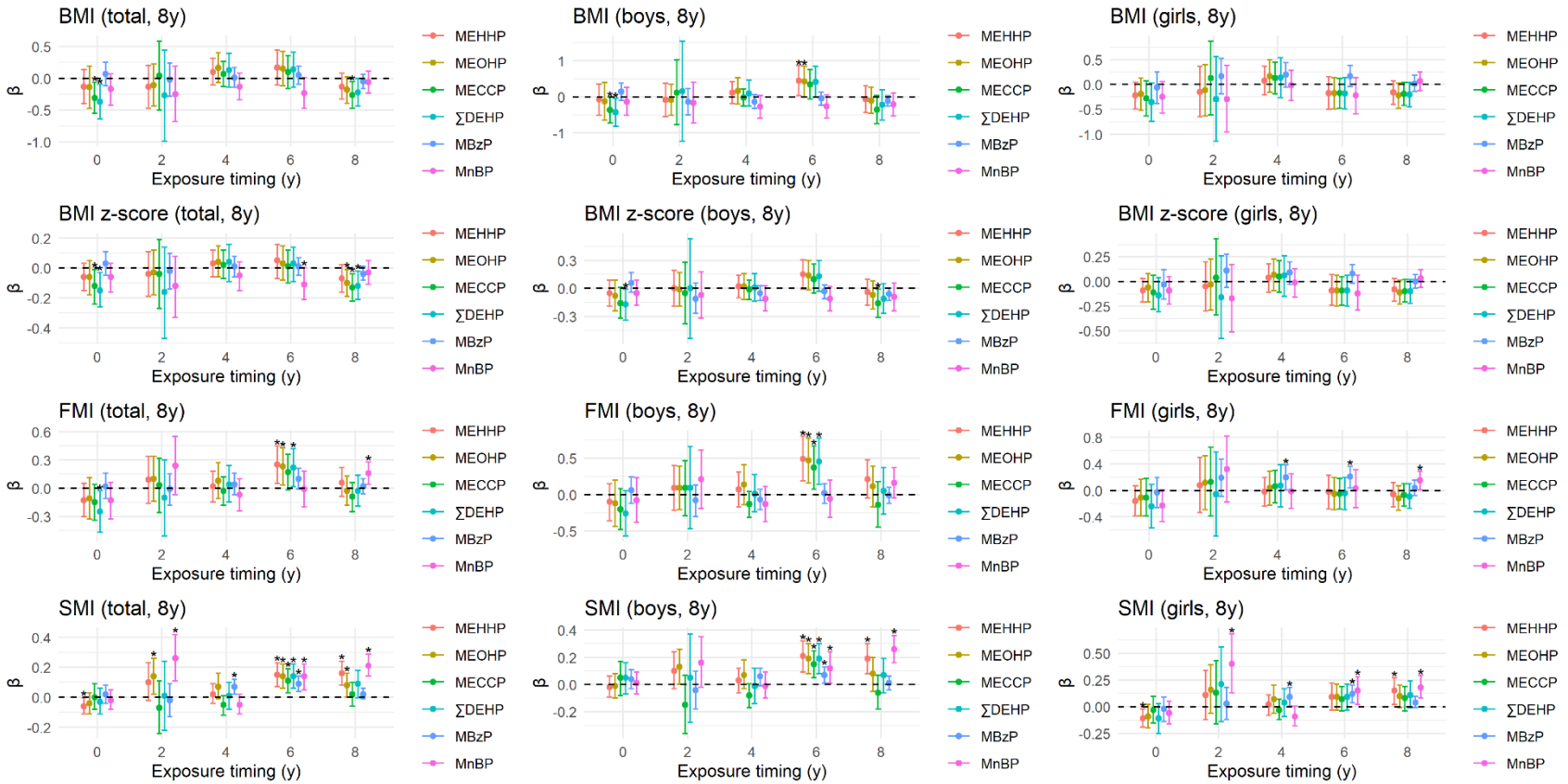

Figure 24. The associations between phthalate metabolites and body composition indices at 8 years of age

The X-axis shows the age of children when urine was collected for measuring phthalate metabolites, and '0' presents phthalate metabolites measured in prenatal maternal urine. The multivariate linear regressions between phthalate metabolites and body composition indices were adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices. MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Table 25 and **Table 26** present the results of logistic regression for the association between quartiled prenatal phthalate metabolites and SMI at 6 years and 8 years, respectively. There were no significant findings between the association of phthalates with dichotomized SMI. MnBP 3rd quartile showed higher OR for low SMI at 8 years defined as <25th percentile (2.48, 95% CI: 1.29, 4.77) and MBzP 4th quartile showed lower OR for low SMI at 8 years defined as <25th percentile (0.50, 95% CI: 0.28, 0.88), but these associations were not robust and not statistically significant when low SMI was defined as <50th percentile.

Table 25. The results of logistic regression for the association between quartiled prenatal phthalate metabolites and SMI at 6 years

	n	Mean SMI (±SD)	SMI < 25th percentile		SMI < 50th percentile	
			n (%)	OR	n (%)	OR
MEHHP						
Q1	125	6.08 (±0.47)	26 (20.3)	1 (Reference)	57 (23.1)	1 (Reference)
Q2	125	6.01 (±0.50)	31 (24.2)	1.39 (0.76, 2.55)	59 (23.9)	1.12 (0.67, 1.85)
Q3	127	5.98 (±0.47)	34 (26.6)	1.38 (0.76, 2.49)	66 (26.7)	1.30 (0.79, 2.15)
Q4	124	5.94 (±0.46)	37 (28.9)	1.65 (0.92, 2.95)	65 (26.3)	1.35 (0.82, 2.22)
p for trend				0.116		0.197
MEOHP						
Q1	124	6.03 (±0.45)	30 (23.4)	1 (Reference)	60 (24.3)	1 (Reference)
Q2	126	6.04 (±0.52)	30 (23.4)	1.03 (0.58, 1.86)	60 (24.3)	0.98 (0.60, 1.62)
Q3	126	6.02 (±0.49)	31 (24.2)	1.04 (0.58, 1.87)	58 (23.5)	0.93 (0.57, 1.54)
Q4	125	5.92 (±0.44)	37 (28.9)	1.29 (0.73, 2.27)	69 (27.9)	1.33 (0.80, 2.19)
p for trend				0.398		0.326
MECCP						
Q1	99	6.01 (±0.45)	27 (27.0)	1 (Reference)	47 (23.4)	1 (Reference)
Q2	101	5.99 (±0.48)	23 (23.0)	0.81 (0.42, 1.55)	53 (26.4)	1.23 (0.70, 2.16)
Q3	101	6.06 (±0.46)	20 (20.0)	0.66 (0.34, 1.29)	41 (20.4)	0.74 (0.42, 1.31)
Q4	99	5.90 (±0.44)	30 (30.0)	1.15 (0.61, 2.14)	60 (29.9)	1.68 (0.95, 2.97)
p for trend				0.799		0.252
∑DEHP						
Q1	95	6.02 (±0.43)	24 (24.0)	1 (Reference)	48 (24.4)	1 (Reference)
Q2	97	5.98 (±0.50)	25 (25.0)	1.07 (0.55, 2.08)	50 (25.4)	1.00 (0.57, 1.78)
Q3	97	6.03 (±0.47)	22 (22.0)	0.88 (0.45, 1.73)	42 (21.3)	0.74 (0.42, 1.32)
Q4	96	5.89 (±0.42)	29 (29.0)	1.28 (0.67, 2.43)	57 (28.9)	1.44 (0.81, 2.58)
p for trend				0.591		0.402
MnBP						
Q1	124	6.09 (±0.46)	27 (21.1)	1 (Reference)	56 (22.7)	1 (Reference)
Q2	126	6.02 (±0.52)	33 (25.8)	1.37 (0.76, 2.48)	61 (24.7)	1.22 (0.74, 2.02)
Q3	126	5.94 (±0.50)	38 (29.7)	1.61 (0.90, 2.89)	68 (27.5)	1.45 (0.88, 2.41)
Q4	125	5.97 (±0.42)	30 (23.4)	1.10 (0.61, 2.01)	62 (25.1)	1.19 (0.72, 1.97)
p for trend				0.640		0.390
MBzP						
Q1	143	5.97 (±0.46)	39 (27.5)	1 (Reference)	71 (25.0)	1 (Reference)
Q2	143	6.03 (±0.47)	32 (22.5)	0.78 (0.45, 1.35)	59 (20.8)	0.74 (0.46, 1.19)
Q3	144	6.06 (±0.51)	30 (21.1)	0.72 (0.41, 1.24)	67 (23.6)	0.90 (0.57, 1.44)
Q4	143	5.93 (±0.47)	41 (28.9)	1.06 (0.63, 1.80)	87 (30.6)	1.57 (0.98, 2.53)
p for trend				0.907		**0.048**

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Table 26. The results of logistic regression for the association between quartiled prenatal phthalate metabolites and SMI at 8 years

	n	Mean SMI (±SD)	SMI < 25th percentile		SMI < 50th percentile	
			n (%)	OR	n (%)	OR
MEHHP						
Q1	115	3.99 (±8.67)	20 (20.8)	1 (Reference)	48 (22.12)	1 (Reference)
Q2	115	4.30 (±7.93)	24 (25.0)	1.23 (0.63, 2.40)	53 (24.42)	1.26 (0.74, 2.14)
Q3	116	4.02 (±8.17)	28 (29.2)	1.55 (0.81, 2.96)	57 (26.27)	1.36 (0.80, 2.29)
Q4	115	3.91 (±7.94)	24 (25.0)	1.29 (0.66, 2.50)	59 (27.19)	1.51 (0.89, 2.56)
p for trend				0.354		0.121
MEOHP						
Q1	114	3.99 (±8.67)	21 (21.9)	1 (Reference)	48 (22.12)	1 (Reference)
Q2	116	4.02 (±7.81)	26 (27.1)	1.27 (0.66, 2.41)	56 (25.8)	1.28 (0.76, 2.15)
Q3	116	4.25 (±8.17)	28 (29.2)	1.41 (0.75, 2.67)	56 (25.8)	1.27 (0.75, 2.15)
Q4	115	3.91 (±7.94)	21 (21.9)	1.01 (0.51, 1.98)	57 (26.3)	1.36 (0.81, 2.31)
p for trend				0.885		0.275
MECCP						
Q1	90	3.99 (±7.59)	26 (29.2)	1 (Reference)	46 (25.4)	1 (Reference)
Q2	92	4.02 (±8.01)	20 (22.5)	0.67 (0.34, 1.32)	42 (23.2)	0.81 (0.45, 1.46)
Q3	92	4.25 (±7.74)	20 (22.5)	0.69 (0.35, 1.37)	42 (23.2)	0.78 (0.43, 1.40)
Q4	92	3.91 (±7.80)	23 (25.8)	0.84 (0.44, 1.63)	51 (28.2)	1.16 (0.65, 2.09)
p for trend				0.638		0.660
∑DEHP						
Q1	88	3.99 (±8.01)	19 (25.3)	1 (Reference)	41 (24.6)	1 (Reference)
Q2	88	4.02 (±7.81)	20 (26.7)	1.10 (0.53, 2.28)	41 (24.6)	0.97 (0.53, 1.77)
Q3	88	4.25 (±7.80)	20 (26.7)	1.08 (0.53, 2.23)	40 (24.0)	0.92 (0.51, 1.68)
Q4	88	3.91 (±7.68)	16 (21.3)	0.82 (0.39, 1.75)	45 (27.0)	1.16 (0.63, 2.11)
p for trend				0.624		0.688
MnBP						
Q1	114	4.30 (±8.01)	18 (18.8)	1 (Reference)	49 (22.6)	1 (Reference)
Q2	116	3.99 (±8.67)	23 (24.0)	1.32 (0.67, 2.61)	58 (26.7)	1.37 (0.81, 2.31)
Q3	116	3.91 (±7.93)	35 (36.5)	**2.48 (1.29, 4.77)**	62 (28.6)	1.56 (0.92, 2.66)
Q4	115	4.39 (±7.70)	20 (20.8)	1.12 (0.56, 2.27)	48 (22.1)	0.93 (0.55, 1.58)
p for trend				0.343		0.919
MBzP						
Q1	131	3.99 (±7.93)	43 (32.8)	1 (Reference)	68 (25.9)	1 (Reference)
Q2	131	3.91 (±8.67)	40 (30.5)	0.86 (0.51, 1.46)	67 (25.5)	0.95 (0.58, 1.55)
Q3	132	4.02 (±8.17)	22 (16.8)	0.40 (0.22, 0.72)	62 (23.6)	0.82 (0.50, 1.33)
Q4	131	4.44 (±8.01)	26 (19.9)	**0.50 (0.28, 0.88)**	66 (25.1)	0.97 (0.59, 1.59)
p for trend				**0.002**		0.752

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine, adjusted for maternal education, household income, energy intake per day, sex of the child, and urinary creatinine for the association between phthalates and children's body composition indices.

Latent growth class model

Figure 25 shows six distinct mean trajectories of the BMI z-score among boys by using the latent growth class model. It was found that 36.4%, 25.2%, and 23.0% of boys were grouped as relatively normal stable (Class 2), relatively lower stable (Class 3), and relatively high stable (Class 5), respectively. A relatively smaller number of boys were classified into low and decreasing (Class 1, 2.7%), high and increasing (Class 6, 4.4%), and normal-to-high (Class 4, 8.3%) groups. **Figure 26** shows the four distinct mean trajectories identified using the BMI z-score among girls. It was found that 6.8%, 38.8%, 38.3%, and 16.0% of girls were classified into the lowest BMI z-score group (Class 1), lower BMI z-score group (Class 2), normal BMI z-score group (Class 3), and high and increasing BMI z-score group (Class 4); GM and SD of phthalate metabolites at the different time windows according to trajectory groups were presented in **Table 27** and **Table 28**. Among boys, MBzP in prenatal maternal urine, MEOHP at 2 years of age, and MEOHP and MECCP at 8 years of age were significantly different by trajectory groups, but the increased phthalate metabolites level was not found in increasing trajectory patterns. When increasing classes (Class 4 and 6) were compared with other classes (Class 1, 2, 3, and 5), there was no significant difference of phthalates metabolites between them. Among girls, there were no significant associations between phthalate metabolites and trajectory groups. It was found that significantly lower levels of MEOHP and ∑DEHP at 8 years of the increasing BMI z-score class (Class 4) than those of other classes (Class 1, 2, and 3).

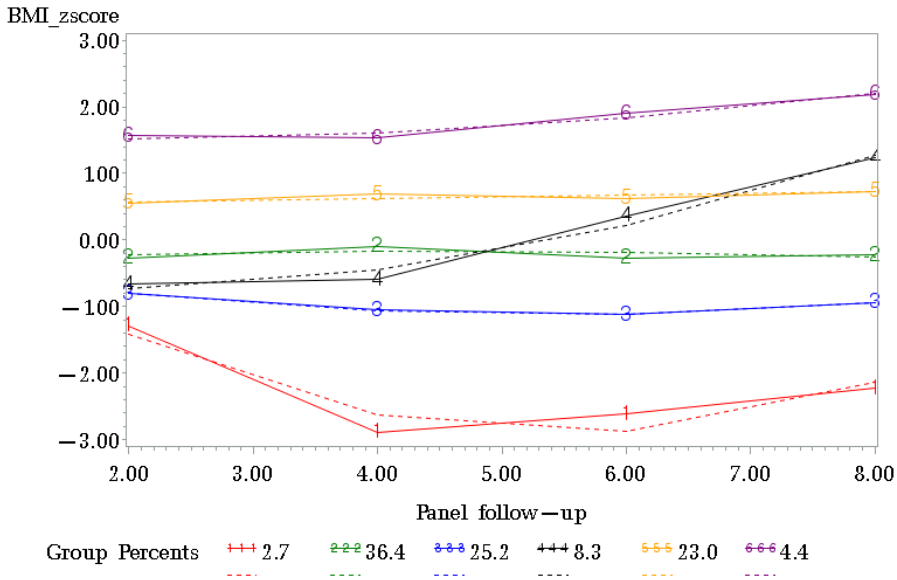

Figure 25. BMI z-score trajectories determined by a six-group latent growth class model among boys

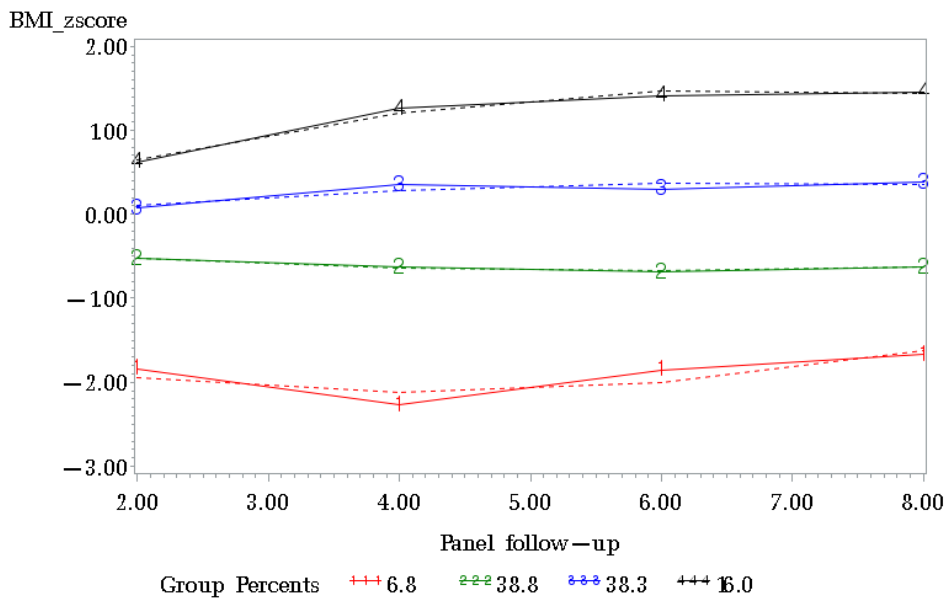

Figure 26. BMI z-score trajectories determined by a four-group latent growth class model among girls

Table 27. GM and SD of phthalate metabolites at the different time windows of phthalate exposure by BMI z-score trajectory groups among boys

	Class 1 (n=7)			Class 2 (n=102)			Class 3 (n=70)			Class 4 (n=20)			Class 5 (n=66)			Class 6 (n=12)			
	n	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	***p***
Prenatal maternal urine																			
MEHHP	7	21.9	1.7	86	14.8	2.2	60	17.9	2.7	20	14.7	2.3	63	16.9	2.2	11	19.5	5.3	0.374
MEOHP	7	22.6	1.5	86	15.1	2.0	60	18.4	2.3	20	16.4	2.1	63	17.4	2.0	11	18.9	4.9	0.357
MECCP	6	25.2	1.4	71	21.9	1.8	45	27.6	2.0	17	18.5	1.9	43	25.3	2.0	5	27.9	1.5	0.115
∑DEHP	6	0.2	1.5	68	0.2	1.9	43	0.2	2.1	17	0.2	2.0	41	0.2	2.0	5	0.2	2.2	0.235
MnBP	7	49.3	1.7	86	47.3	2.2	60	39.0	1.8	20	44.0	2.4	63	41.6	2.2	11	44.7	3.4	0.742
MBzP	7	4.5	5.2	102	2.4	3.9	70	3.4	3.6	20	3.0	5.1	65	1.7	3.7	12	2.3	2.9	**0.011**
2 y																			
MEHHP	4	62.8	1.7	41	86.5	2.0	30	101.2	1.8	8	135.0	2.2	37	98.0	2.0	4	51.7	1.4	0.098
MEOHP	4	51.0	1.7	41	69.9	2.0	30	82.1	1.8	8	115.2	2.0	37	78.2	2.1	4	40.4	1.5	**0.049**
MECCP	3	102.1	1.6	12	109.8	3.8	11	126.3	1.8	3	158.7	1.8	13	81.5	2.1	3	168.5	2.4	0.590
∑DEHP	3	0.7	1.6	12	1.0	2.6	11	1.2	1.4	3	1.5	1.5	13	0.9	1.5	3	0.8	2.0	0.281
MnBP	4	88.4	2.3	41	110.7	1.8	30	122.1	1.7	8	141.6	1.7	37	115.3	1.6	4	71.4	1.5	0.344
MBzP	3	24.4	2.1	12	13.5	7.7	12	16.2	3.4	4	9.0	2.2	17	11.4	5.9	3	17.6	1.7	0.846
4 y																			
MEHHP	7	61.3	2.1	94	65.3	2.0	69	69.7	2.0	20	71.7	1.7	65	74.4	1.9	12	81.4	1.7	0.956
MEOHP	7	46.2	1.8	94	51.0	1.9	69	57.6	1.8	20	58.8	1.7	65	56.2	1.8	12	68.0	1.7	0.825
MECCP	7	102.7	2.0	82	88.7	2.3	58	88.7	1.7	17	79.1	1.9	58	106.5	1.7	7	99.5	1.5	0.631
∑DEHP	7	0.7	1.8	82	0.7	1.9	58	0.7	1.6	17	0.7	1.6	58	0.8	1.6	7	0.8	1.5	0.916
MnBP	7	77.6	1.9	94	85.9	2.0	69	83.1	1.9	20	87.9	1.9	65	84.3	1.8	12	63.3	1.5	0.529
MBzP	7	9.0	1.8	82	8.8	3.2	63	9.9	2.9	17	7.6	3.1	59	9.4	2.6	9	6.6	2.1	0.592
6 y																			
MEHHP	7	50.2	1.5	102	57.8	1.6	69	53.8	1.8	20	58.4	2.0	66	59.2	1.8	12	58.1	2.1	0.939
MEOHP	7	34.3	1.5	102	39.2	1.7	69	37.9	1.8	20	39.4	2.0	66	40.4	1.8	12	41.1	2.3	0.935
MECCP	7	67.9	1.6	102	74.2	1.7	69	76.4	1.8	20	70.8	1.9	66	79.1	1.9	12	84.7	2.2	0.946
∑DEHP	7	0.5	1.5	102	0.6	1.7	69	0.6	1.8	20	0.6	1.9	66	0.6	1.8	12	0.6	2.2	0.971
MnBP	7	83.0	1.4	102	80.2	1.8	69	78.0	1.8	20	67.1	1.6	66	70.3	1.6	12	66.1	1.6	0.560
MBzP	7	11.2	2.8	102	5.1	3.1	69	6.1	3.2	20	5.6	3.6	66	4.4	2.5	12	4.4	2.3	0.320
8 y																			
MEHHP	7	31.3	1.9	102	30.1	1.8	70	39.5	2.1	20	36.2	2.0	65	30.1	1.8	12	37.5	2.2	0.165
MEOHP	7	21.4	1.9	102	21.1	1.9	70	29.1	1.9	20	24.1	2.1	65	21.5	1.7	12	26.9	1.8	**0.044**
MECCP	7	48.0	1.5	102	43.5	1.8	70	58.5	1.8	20	48.5	1.9	65	41.0	1.8	12	51.4	2.0	**0.022**
∑DEHP	7	0.3	1.7	102	0.3	1.7	70	0.4	1.9	20	0.4	1.8	65	0.3	1.6	12	0.4	2.0	**0.037**
MnBP	7	71.9	1.9	102	54.6	1.9	70	58.9	2.3	20	64.0	1.5	65	45.8	2.0	12	46.2	1.8	0.156
MBzP	7	4.5	5.2	102	2.4	3.9	70	3.4	3.6	20	3.0	5.1	65	1.7	3.7	12	2.3	2.9	**0.017**

GM, geometric mean; SD, standard devation; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

$p < 0.05$ was in bold; differences among groups were tested using Kruskal-Wallis test.

Table 28. GM and SD of phthalate metabolites at the different time windows of phthalate exposure by BMI z-score trajectory groups among girls

	Class 1 (n=7)			Class 2 (n=102)			Class 3 (n=70)			Class 4 (n=20)			
	n	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	***p***
Prenatal maternal urine													
MEHHP	17	13.0	2.1	80	15.8	2.1	81	16.0	2.4	36	12.3	2.6	0.252
MEOHP	17	11.8	1.9	80	16.1	2.0	81	17.3	1.9	36	12.6	2.2	0.058
MECCP	15	17.4	1.9	70	23.2	2.0	65	20.6	1.9	29	19.1	2.1	0.517
∑DEHP	15	0.1	1.9	66	0.2	1.9	62	0.2	1.7	29	0.2	2.0	0.234
MnBP	17	31.2	1.6	80	44.0	2.1	81	41.8	2.1	36	34.4	2.0	0.101
MBzP	17	2.3	2.6	95	2.3	3.6	98	2.1	4.0	39	2.2	4.1	0.469
2 y													
MEHHP	7	71.6	1.5	36	102.2	1.8	43	91.1	2.0	14	75.1	1.7	0.294
MEOHP	7	53.9	1.9	36	83.1	1.8	43	73.1	1.9	14	63.8	1.7	0.312
MECCP	2	88.8	1.2	20	96.9	2.2	20	91.4	2.1	6	104.2	1.8	0.981
∑DEHP	2	0.7	1.1	20	1.0	1.8	20	0.8	1.6	6	0.8	1.8	0.667
MnBP	7	90.5	2.2	36	124.0	1.6	43	109.5	1.6	14	101.9	1.8	0.261
MBzP	3	11.2	6.6	21	10.6	2.8	21	15.2	3.4	6	18.4	2.5	0.514
4 y													
MEHHP	17	48.1	2.4	93	70.9	1.8	97	74.0	2.7	37	72.9	1.8	0.127
MEOHP	17	40.5	1.9	93	55.4	1.7	97	57.6	2.2	37	57.3	1.7	0.156
MECCP	15	69.8	3.4	82	94.7	2.2	84	103.3	1.8	32	101.1	1.8	0.194
∑DEHP	15	0.6	2.6	82	0.7	1.8	84	0.8	1.7	32	0.8	1.7	0.424
MnBP	17	69.7	2.0	93	80.5	1.8	95	89.5	2.2	37	84.5	2.2	0.377
MBzP	14	6.4	3.0	82	6.9	2.2	86	8.5	2.6	34	9.7	2.6	0.192
6 y													
MEHHP	17	62.6	2.0	96	60.2	1.8	98	57.8	1.8	39	54.7	1.6	0.816
MEOHP	17	40.9	2.1	96	41.3	1.8	98	38.5	1.8	39	37.0	1.6	0.783
MECCP	17	81.4	2.3	96	82.6	1.8	98	75.6	1.9	39	73.9	1.6	0.852
∑DEHP	17	0.6	2.1	96	0.6	1.8	98	0.6	1.8	39	0.6	1.6	0.832
MnBP	17	64.1	1.8	96	67.6	1.7	98	69.1	1.7	39	68.8	1.6	0.855
MBzP	17	4.2	2.8	96	4.3	2.3	98	5.0	2.6	39	4.9	2.5	0.664
8 y													
MEHHP	17	35.3	2.4	95	31.4	1.9	98	26.9	2.2	39	25.1	1.7	0.255
MEOHP	17	25.6	2.6	95	22.4	2.2	98	18.8	2.2	39	16.7	2.0	0.075
MECCP	17	53.3	2.6	95	49.8	2.0	98	38.2	2.3	39	38.8	1.6	**0.043**
∑DEHP	17	0.4	2.5	95	0.4	1.9	98	0.3	2.2	39	0.3	1.6	0.084
MnBP	17	51.9	1.6	95	48.4	2.4	98	48.7	2.5	39	51.5	1.8	0.938
MBzP	17	2.3	2.6	95	2.3	3.6	98	2.1	4.0	39	2.2	4.1	0.976

GM, geometric mean; SD, standard devation; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

$p < 0.05$ was in bold; differences among groups were tested using Kruskal-Wallis test.

Table 29. GM and SD of phthalate metabolites at the different time windows of phthalate exposure by BMI z-score trajectory groups

	Boys							Girls						
	Increasing classes (4, 6)			Other classes (1, 2, 3, 5)				Increasing class (4)			Other classes (1,2,3)			
	n	GM	SD	n	GM	SD	*p*	n	GM	SD	n	GM	SD	*p*
Prenatal maternal urine														
MEHHP	31	16.2	3.3	216	16.4	2.3	0.558	36	12.3	2.6	178	15.6	2.3	0.220
MEOHP	31	17.2	3.0	216	16.8	2.1	0.805	36	12.6	2.2	178	16.1	2.0	0.092
MECCP	22	20.3	1.8	165	24.4	1.9	0.134	29	19.1	2.1	150	21.4	1.9	0.576
∑DEHP	22	0.2	2.0	158	0.2	2.0	0.147	29	0.2	2.0	143	0.2	1.9	0.248
MnBP	31	44.2	2.7	216	43.2	2.1	0.853	36	34.4	2.0	178	41.6	2.0	0.147
MBzP	32	2.7	4.2	244	2.5	3.9	0.998	39	2.2	4.1	210	2.2	3.7	0.252
2 y														
MEHHP	12	98.0	2.3	112	93.0	1.9	0.886	14	75.1	1.7	86	93.7	1.9	0.193
MEOHP	12	81.2	2.2	112	74.9	2.0	0.612	14	63.8	1.7	86	75.2	1.9	0.237
MECCP	6	163.5	2.0	39	102.8	2.5	0.142	6	104.2	1.8	42	93.8	2.1	0.926
∑DEHP	6	1.1	1.8	39	1.0	1.9	0.443	6	0.8	1.8	42	0.9	1.7	0.685
MnBP	12	112.7	1.8	112	114.3	1.7	0.886	14	101.9	1.8	86	113.6	1.7	0.538
MBzP	7	12.0	2.1	44	13.9	5.2	0.702	6	18.4	2.5	45	12.6	3.2	0.242
4 y														
MEHHP	32	75.2	1.7	235	68.9	2.0	0.653	37	72.9	1.8	207	70.1	2.3	0.610
MEOHP	32	62.1	1.7	235	54.2	1.8	0.289	37	57.3	1.7	207	55.0	2.0	0.520
MECCP	24	84.6	1.8	205	93.9	2.0	0.360	32	101.1	1.8	181	96.2	2.1	0.789
∑DEHP	24	0.8	1.5	205	0.7	1.7	0.871	32	0.8	1.7	181	0.7	1.8	0.995
MnBP	32	77.7	1.8	235	84.3	1.9	0.209	37	84.5	2.2	205	83.6	2.0	0.950
MBzP	26	7.2	2.7	211	9.3	2.9	0.165	34	9.7	2.6	182	7.6	2.5	0.135
6 y														
MEHHP	32	58.3	2.0	244	56.8	1.7	0.908	39	54.7	1.6	211	59.2	1.8	0.476
MEOHP	32	40.0	2.1	244	39.0	1.8	0.660	39	37.0	1.6	211	40.0	1.8	0.482
MECCP	32	75.7	2.0	244	75.9	1.8	0.981	39	73.9	1.6	211	79.1	1.9	0.582
∑DEHP	32	0.6	2.0	244	0.6	1.7	0.862	39	0.6	1.6	211	0.6	1.8	0.504
MnBP	32	66.8	1.6	244	76.9	1.7	0.313	39	68.8	1.6	211	68.0	1.7	0.783
MBzP	32	5.1	3.1	244	5.3	3.0	0.776	39	4.9	2.5	211	4.6	2.5	0.764
8 y														
MEHHP	32	36.7	2.0	244	32.6	1.9	0.450	39	25.1	1.7	210	29.5	2.1	0.078
MEOHP	32	25.1	2.0	244	23.3	1.9	0.438	39	16.7	2.0	210	20.8	2.2	**0.030**
MECCP	32	49.6	1.9	244	46.7	1.8	0.682	39	38.8	1.6	210	44.3	2.2	0.059
∑DEHP	32	0.4	1.9	244	0.4	1.8	0.636	39	0.3	1.6	210	0.3	2.1	**0.044**
MnBP	32	56.7	1.7	244	53.7	2.1	0.869	39	51.5	1.8	210	48.8	2.3	0.543
MBzP	32	2.7	4.2	244	2.5	3.9	0.727	39	2.2	4.1	210	2.2	3.7	0.813

GM, geometric mean; SD, standard deviation; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

$p < 0.05$ was in bold; differences among groups were tested using Wilcoxon rank-sum test.

Figure 27 shows 5 distinct mean trajectories identified using the weight z-score among boys. It was found that 3.2%, 18.7%, 37.0%, 33.3%, and 7.7% of boys were classified as those with low birth weight and catch-up growth (Class 1), low decreasing (Class 2), low stable (Class 3), normal increasing (Class 4), and increasing growth (Class 5). **Figure 28** shows the 4 distinct mean trajectories identified using the weight z-score among girls. It was found that 6.6%, 15.6%, 49.6%, and 28.2% of girls were classified into the low birth weight and catch-up growth (Class 1), low decreasing (Class 2), normal stable (Class 3), and increasing growth (Class 4). GM and SD of phthalate metabolites at different time windows of phthalate exposure according to trajectory groups are presented in **Table 30** and **Table 31**. Among boys, MBzP at 4 y and MECCP and MBzP at 8 y were significantly different by trajectory groups, and increasing trajectory patterns were associated with decreased levels of phthalate metabolites. Among girls, there were only significant differences in MECCP at 8 y by trajectory groups, and increasing trajectory patterns were associated with decreasing levels of phthalate metabolites.

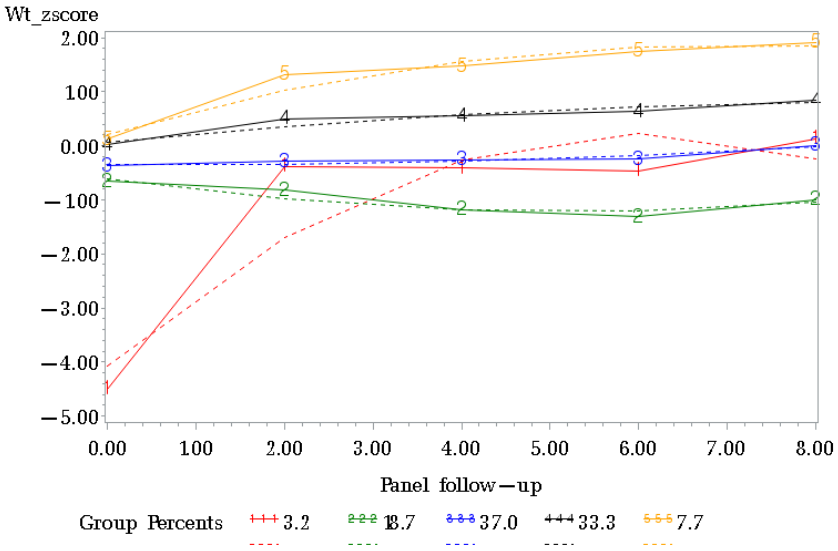

Figure 27. Weight z-score trajectories determined by a five-group latent growth class model among boys

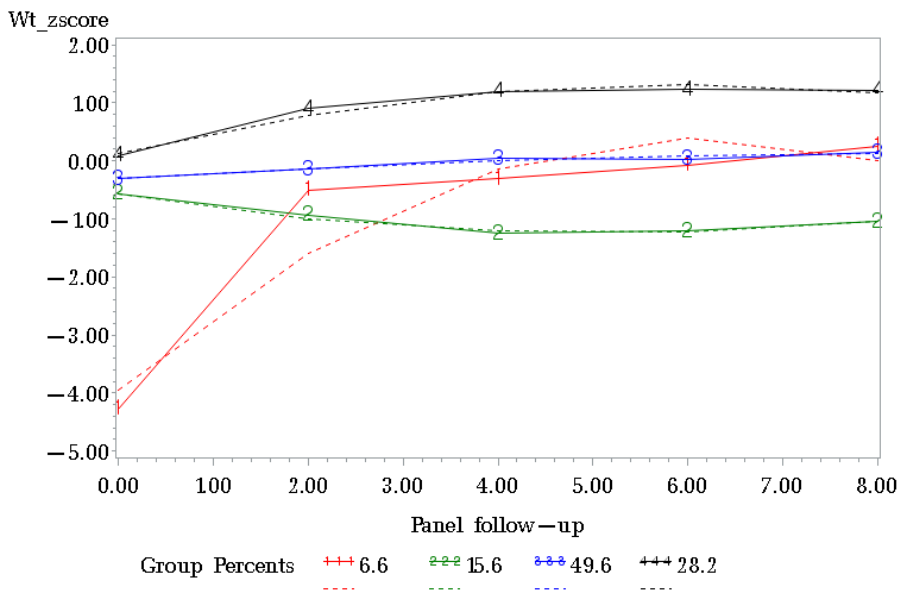

Figure 28. Weight z-score trajectories determined by a four-group latent growth class model among girls

Table 30. GM and SD of phthalate metabolites at the different time windows of weight z-score trajectory groups among boys

	Class 1 (n=9)			Class 2 (n=52)			Class 3 (n=102)			Class 4 (n=96)			Class 5 (n=18)			
	n	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	***p***
Prenatal maternal urine																
MEHHP	9	11.5	2.2	46	19.5	2.1	89	15.3	2.5	86	16.1	2.2	17	19.4	3.9	0.264
MEOHP	9	14.7	1.8	46	19.7	2.1	89	15.9	2.2	86	16.5	2.1	17	18.6	3.6	0.228
MECCP	5	17.6	1.4	32	26.3	1.7	73	22.8	2.1	68	24.4	1.9	9	24.0	1.8	0.422
∑DEHP	5	0.1	1.3	31	0.2	1.9	70	0.2	2.1	65	0.2	2	9	0.2	2.0	0.437
MnBP	9	34.5	2.2	46	45.4	1.9	89	43.6	2.0	86	42.3	2.3	17	47.3	2.7	0.740
MBzP	9	1.0	3.8	52	3.0	4.2	102	3.1	4.0	95	2.1	3.6	18	1.9	3.5	0.498
2 y																
MEHHP	4	99.9	2.5	26	85.5	1.7	43	101.7	2.1	42	96.8	1.9	9	66.6	2.0	0.390
MEOHP	4	78.8	3.3	26	65.7	1.8	43	84.8	2.1	42	78.8	1.8	9	52.1	1.9	0.260
MECCP	1	27.4		12	149.2	2.7	11	99.7	1.6	16	90.4	2.7	5	154.3	2.2	0.367
∑DEHP	1	0.3		12	1.1	2.1	11	1.0	1.6	16	1.0	1.7	5	0.9	2.3	0.536
MnBP	4	120.9	2.1	26	102.1	1.9	43	126.2	1.6	42	115.5	1.7	9	89.5	1.6	0.393
MBzP	1	1.3		12	26.0	4.8	15	17.0	3.1	17	6.6	4.5	6	24.3	5.6	0.119
4 y																
MEHHP	8	49.4	1.7	50	67.4	2.3	99	71.7	1.9	93	69.1	1.9	17	78.9	1.9	0.485
MEOHP	8	37.1	1.8	50	57.0	1.9	99	55.5	1.8	93	54.0	1.8	17	63.7	1.8	0.413
MECCP	8	68.2	1.8	44	98.2	1.7	84	92.1	2.0	84	93.7	2.1	9	92.6	1.4	0.669
∑DEHP	8	0.5	1.7	44	0.8	1.7	84	0.7	1.7	84	0.8	1.7	9	0.8	1.4	0.477
MnBP	8	54.3	1.6	50	80.1	2.0	99	91.7	1.9	93	83.9	1.8	17	65.6	1.9	**0.037**
MBzP	8	4.8	1.5	46	12.6	2.9	87	8.9	3.0	83	8.8	2.7	13	5.4	1.8	0.004
6 y																
MEHHP	9	61.1	1.7	52	54.8	1.6	101	58.6	1.7	96	55.5	1.8	18	60.0	2.0	0.755
MEOHP	9	43.7	1.8	52	37.8	1.7	101	40.0	1.7	96	38.2	1.8	18	40.4	2.2	0.869
MECCP	9	92.1	2.2	52	73.7	1.7	101	77.6	1.7	96	72.8	1.8	18	82.5	2.2	0.820
∑DEHP	9	0.7	2	52	0.6	1.7	101	0.6	1.7	96	0.6	1.8	18	0.6	2.1	0.803
MnBP	9	64.5	1.8	52	82.7	1.6	101	79.0	1.9	96	72.0	1.6	18	64.4	1.6	0.287
MBzP	9	3.4	2.1	52	6.7	3.3	101	5.8	3.1	96	4.8	2.7	18	3.3	2.5	0.109
8 y																
MEHHP	9	35.8	2.1	52	34.9	1.9	102	35.0	2.0	95	29.7	1.8	18	34.0	1.9	0.313
MEOHP	9	22.4	2.2	52	25.4	2.0	102	24.9	1.9	95	21.2	1.7	18	23.2	1.7	0.188
MECCP	9	47.2	1.9	52	57.3	1.7	102	48.7	1.9	95	42.7	1.8	18	36.2	2.1	**0.023**
∑DEHP	9	0.4	1.9	52	0.4	1.7	102	0.4	1.9	95	0.3	1.7	18	0.3	1.8	0.055
MnBP	9	61.6	1.6	52	54.9	2.4	102	58.7	2.0	95	47.9	1.9	18	56.7	1.9	0.306
MBzP	9	1.0	3.8	52	3.0	4.2	102	3.1	4.0	95	2.1	3.6	18	1.9	3.5	**0.028**

GM, geometric mean; SD, standard devation; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

$p < 0.05$ was in bold; differences among groups were tested using Kruskal-Wallis test.

Table 31. GM and SD of phthalate metabolites at the different time windows of weight z-score trajectory groups among girls

	Class 1 (n=18)			Class 2 (n=37)			Class 3 (n=125)			Class 4 (n=70)			
	n	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	**n**	**GM**	**SD**	***p***
Prenatal maternal urine													
MEHHP	13	13.8	1.6	35	14.9	0.8	105	15.5	1.3	61	14.5	1.3	0.744
MEOHP	13	14.9	1.3	35	13.5	0.7	105	16.7	1.0	61	14.8	1.1	0.256
MECCP	9	20.7	1.3	29	19.4	0.9	93	23.7	0.8	48	17.5	1.1	**0.022**
∑DEHP	8	0.2	1.3	29	0.2	0.8	89	0.2	0.9	46	0.2	1.0	0.090
MnBP	13	41.0	1.2	35	39.3	0.9	105	41.6	1.1	61	38.5	1.0	0.972
MBzP	18	1.8	2.0	37	2.1	1.9	124	2.4	1.8	70	2.0	2.0	0.749
2 y													
MEHHP	8	152.7	1.1	11	88.7	0.7	50	92.7	0.9	31	77.7	0.9	0.174
MEOHP	8	120.5	1.1	11	67.4	1.0	50	74.7	0.9	31	65.0	0.8	0.285
MECCP	4	126.4	0.6	4	114.1	1.2	26	83.4	1.2	14	106.1	0.8	0.451
∑DEHP	4	1.5	1.2	4	1.0	0.9	26	0.8	0.7	14	0.9	0.6	0.589
MnBP	8	126.5	0.6	11	105.2	1.1	50	114.7	0.7	31	106.5	0.7	0.618
MBzP	6	12.6	1.8	4	11.0	2.0	27	10.6	1.8	14	21.5	1.0	0.124
4 y													
MEHHP	18	55.4	0.5	37	64.2	1.2	122	75.1	1.2	67	70.5	1.1	0.034
MEOHP	18	44.3	0.6	37	52.3	1.0	122	58.5	1.0	67	54.8	1.0	0.109
MECCP	18	76.6	0.8	33	89.1	1.3	104	109.4	1.0	58	87.9	0.9	0.063
∑DEHP	18	0.6	0.6	33	0.7	1.0	104	0.8	0.8	58	0.7	0.8	**0.044**
MnBP	18	62.4	0.6	37	91.9	1.0	121	84.6	1.0	66	84.3	1.0	0.058
MBzP	15	5.4	0.9	35	7.6	1.3	106	8.6	1.4	60	7.6	1.2	0.319
6 y													
MEHHP	18	64.0	0.9	37	57.2	0.8	125	60.8	0.8	70	54.0	0.8	0.401
MEOHP	18	41.4	0.9	37	37.5	0.8	125	41.7	0.9	70	36.3	0.8	0.410
MECCP	18	85.9	1.0	37	74.8	0.8	125	82.2	0.9	70	71.8	0.8	0.515
∑DEHP	18	0.6	1.0	37	0.6	0.8	125	0.6	0.9	70	0.5	0.8	0.487
MnBP	18	59.1	0.8	37	75.5	0.7	125	65.8	0.8	70	71.3	0.7	0.554
MBzP	18	3.9	1.1	37	4.1	1.4	125	4.6	1.4	70	5.1	1.3	0.614
8 y													
MEHHP	18	36.9	1.1	37	30.5	1.0	124	30.4	0.9	70	23.7	1.2	0.197
MEOHP	18	24.6	1.1	37	21.3	1.2	124	21.7	1.0	70	16.2	1.3	0.091
MECCP	18	61.4	1.0	37	45.2	1.2	124	45.5	0.9	70	35.6	1.3	0.029
∑DEHP	18	0.4	1.0	37	0.3	1.1	124	0.3	0.9	70	0.3	1.2	0.056
MnBP	18	72.7	0.9	37	55.5	1.1	124	46.2	1.1	70	46.7	1.3	**0.028**
MBzP	18	1.8	2.0	37	2.1	1.9	124	2.4	1.8	70	2.0	2.0	0.803

GM, geometric mean; SD, standard devation; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

$p < 0.05$ was in bold; differences among groups were tested using Kruskal-Wallis test.

Multiple informant models

Table 32–**Table 34** shows results of the multiple informant models for the association between phthalate metabolites at different time points and body composition indices at 6 years of age. There was no significant association between BMI z-score at 6 years of age and phthalate metabolites at different time points. The association between SMI and phthalate metabolites in prenatal maternal urine was significant, as a two-fold increase in MEHHP, MEOHP, and MECCP was significant and negatively associated with -0.04 kg/m^2 (95% CI: -0.07, -0.01), -0.05 kg/m^2 (95% CI: -0.08, -0.01), and -0.05 (95% CI: -0.10, -0.003) change in SMI at 6 years of age. The association between phthalates metabolites and SMI at 6 years of age did not differ by the timing of exposure. Among girls, it was found that suggestive different associations of MEHHP ($p_{\text{int-FDR}} = 0.080$) and MEOHP ($p_{\text{int-FDR}} = 0.066$) with BMI by the timing of exposure.

Table 35–Table 37 shows results of the multiple informant models for the association between phthalate metabolites at different time points and body composition indices at 8 years of age. After adjusting for maternal age at birth, maternal education levels, and sex of children as covariates, I found significant inverse associations between BMI z-score at 8 years of age and MECCP in prenatal maternal urine at 2 and 8 years of age. Specifically, for a two-fold increase in MECCP concentration in prenatal maternal urine and children's urine at ages of 2 and 8 y, there was on average -0.12 kg/m^2 (95% CI: -0.23, -0.003), -0.15 kg/m^2 (95% CI: -0.30, -0.004), and -0.14 kg/m^2 (95% CI: -0.23, -0.05) change in BMI z-score at 8 years of age. The association between SMI at 8 years and phthalate metabolites at 6 years was significant, as two-fold increase in MEHHP, MEOHP, MECCP, ∑DEHP, MnBP, and MBzP was significantly associated with 0.13 kg/m^2

(95% CI: 0.05, 0.22), 0.13 kg/m^2 (95% CI: 0.04, 0.21), 0.14 kg/m^2 (95% CI: 0.05, 0.23), 0.10 kg/m^2 (95% CI: 0.02, 0.18), and 0.09 kg/m^2 (0.04, 0.14) increase in SMI at 8 years of age. Prenatal exposure to MEHHP was negatively associated with SMI, but it was marginally significant (-0.06 kg/m^2 per two-fold increase; 95% CI: -0.12, 0.004). The association of urinary MEHHP and MnBP with SMI at 8 years of age was different across the timing of exposure ($p_{\text{int-FDR}}$ = 0.012, and $p_{\text{int-FDR}}$ = 0.012, respectively). Among boys, the association of urinary MECPP and MnBP with SMI at 8 years of age was different across different periods of exposure ($p_{\text{int-FDR}}$ = 0.048, and $p_{\text{int-FDR}}$ = 0.024, respectively). Among girls, the association of urinary MnBP with SMI at 8 years of age was different across the timing of exposure ($p_{\text{int-FDR}}$ = 0.012).

Table 32. Results of multiple informant models for the association between phthalate metabolites at different time points and body composition indices at 6 years of age

	MEHHP		MEOHP		MECPP		∑DEHP		MnBP		MBzP	
	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***
BMI Z-score												
Prenatal	-0.04 (-0.12, 0.03)	0.253	-0.04 (-0.12, 0.05)	0.411	-0.09 (-0.20, 0.02)	0.101	0 (-0.14, 0.15)	0.970	-0.02 (-0.11, 0.06)	0.568	0.04 (-0.05, 0.12)	0.408
2y	-0.08 (-0.22, 0.07)	0.305	-0.08 (-0.22, 0.06)	0.284	0.05 (-0.11, 0.22)	0.516	0 (-0.24, 0.24)	0.975	-0.14 (-0.31, 0.03)	0.115	0.02 (-0.08, 0.12)	0.702
4y	0.04 (-0.04, 0.13)	0.320	0.04 (-0.06, 0.13)	0.456	0.03 (-0.06, 0.13)	0.497	0.04 (-0.08, 0.15)	0.527	-0.02 (-0.11, 0.07)	0.655	0 (-0.06, 0.07)	0.955
6y	0.02 (-0.09, 0.12)	0.719	-0.01 (-0.12, 0.09)	0.796	-0.01 (-0.11, 0.09)	0.896	0 (-0.11, 0.10)	0.962	-0.04 (-0.15, 0.07)	0.521	-0.02 (-0.07, 0.04)	0.610
$p_{int\text{-}FDR}$	0.830		0.997		0.978		0.966		0.939		0.986	
BMI												
Prenatal	-0.02 (-0.12, 0.07)	0.630	0 (-0.11, 0.11)	0.953	**-0.15 (-0.29, -0.01)**	**0.037**	0.10 (-0.10, 0.29)	0.338	**0.13 (0.02, 0.23)**	**0.021**	-0.05 (-0.16, 0.06)	0.364
2y	**-0.20 (-0.38, -0.02)**	**0.030**	**-0.19 (-0.37, -0.01)**	**0.037**	0.03 (-0.17, 0.24)	0.748	-0.18 (-0.48, 0.12)	0.247	**-0.25 (-0.46, -0.03)**	**0.024**	0 (-0.13, 0.13)	0.996
4y	0.09 (-0.03, 0.20)	0.131	0.07 (-0.06, 0.20)	0.303	0.07 (-0.05, 0.19)	0.272	0.09 (-0.07, 0.25)	0.289	0.05 (-0.07, 0.17)	0.418	-0.02 (-0.1, 0.07)	0.732
6y	0.03 (-0.12, 0.18)	0.693	-0.02 (-0.17, 0.13)	0.787	0 (-0.15, 0.14)	0.974	0 (-0.16, 0.15)	0.979	-0.05 (-0.21, 0.11)	0.546	-0.02 (-0.11, 0.06)	0.599
$p_{int\text{-}FDR}$	0.328		0.264		0.642		0.645		0.360		0.960	
SMI												
Prenatal	**-0.04 (-0.07, -0.01)**	**0.018**	**-0.05 (-0.08, -0.01)**	**0.019**	**-0.05 (-0.10, -0.003)**	**0.036**	-0.01 (-0.07, 0.05)	0.730	-0.03 (-0.07, 0.004)	0.080	0.01 (-0.03, 0.05)	0.614
2y	**-0.06 (-0.13, -0.001)**	**0.047**	-0.06 (-0.12, 0.003)	0.063	-0.02 (-0.09, 0.05)	0.575	-0.03 (-0.13, 0.08)	0.598	**-0.10 (-0.17, -0.03)**	**0.008**	-0.02 (-0.07, 0.02)	0.264
4y	0 (-0.04, 0.04)	0.974	0.01 (-0.04, 0.05)	0.800	0 (-0.04, 0.04)	0.865	0 (-0.05, 0.05)	0.895	-0.01 (-0.05, 0.03)	0.508	-0.01 (-0.04, 0.02)	0.556
6y	0 (-0.04, 0.05)	0.877	0 (-0.04, 0.05)	0.861	0.01 (-0.04, 0.05)	0.712	0 (-0.04, 0.05)	0.854	-0.03 (-0.08, 0.02)	0.195	-0.01 (-0.04, 0.01)	0.401
$p_{int\text{-}FDR}$	0.372		0.288		0.689		0.988		0.282		0.971	
FMI												
Prenatal	0.02 (-0.08, 0.12)	0.712	0.02 (-0.09, 0.14)	0.709	-0.12 (-0.27, 0.02)	0.101	0.07 (-0.13, 0.28)	0.468	-0.04 (-0.15, 0.07)	0.493	0.03 (-0.08, 0.14)	0.624
2y	-0.09 (-0.28, 0.10)	0.343	-0.1 (-0.29, 0.08)	0.278	**0.24 (0.02, 0.46)**	**0.032**	0.14 (-0.20, 0.47)	0.418	-0.15 (-0.37, 0.08)	0.201	0.08 (-0.05, 0.21)	0.218
4y	0.05 (-0.07, 0.16)	0.416	0.03 (-0.10, 0.16)	0.624	0.03 (-0.10, 0.16)	0.661	0.05 (-0.11, 0.21)	0.531	-0.01 (-0.14, 0.11)	0.815	0 (-0.09, 0.09)	0.985
6y	0.01 (-0.13, 0.15)	0.877	-0.04 (-0.17, 0.10)	0.614	-0.02 (-0.16, 0.11)	0.751	-0.02 (-0.16, 0.13)	0.807	-0.02 (-0.17, 0.12)	0.754	0 (-0.07, 0.08)	0.910
$p_{int\text{-}FDR}$	0.906		0.955		0.943		0.989		0.944		0.970	

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine.

Table 33. Results of multiple informant models for the association between phthalate metabolites at different time points and body composition indices in boys at 6 years of age

	MEHHP		MEOHP		MECPP		∑DEHP		MnBP		MBzP	
	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***
BMI Z-score												
Prenatal	0.01 (-0.09, 0.11)	0.857	0.01 (-0.10, 0.12)	0.924	-0.05 (-0.20, 0.10)	0.552	0.02 (-0.20, 0.23)	0.884	0.04 (-0.07, 0.15)	0.484	0.07 (-0.03, 0.18)	0.188
2y	0 (-0.19, 0.18)	0.963	-0.02 (-0.20, 0.16)	0.856	0.11 (-0.08, 0.31)	0.259	0.13 (-0.18, 0.44)	0.426	-0.07 (-0.29, 0.16)	0.563	0.01 (-0.11, 0.13)	0.864
4y	0 (-0.12, 0.13)	0.958	-0.02 (-0.15, 0.12)	0.806	0 (-0.13, 0.13)	0.963	0 (-0.17, 0.17)	0.997	-0.08 (-0.22, 0.05)	0.223	-0.05 (-0.13, 0.04)	0.281
6y	0.10 (-0.04, 0.24)	0.157	0.06 (-0.07, 0.20)	0.374	0.04 (-0.09, 0.18)	0.519	0.07 (-0.07, 0.21)	0.337	-0.12 (-0.27, 0.02)	0.098	-0.06 (-0.13, 0.02)	0.122
$p_{\text{int-FDR}}$	0.894		0.823		0.963		0.953		0.696		0.999	
BMI												
Prenatal	0 (-0.12, 0.12)	0.999	0.02 (-0.12, 0.16)	0.761	-0.18 (-0.38, 0.01)	0.065	0.09 (-0.19, 0.37)	0.529	**0.18 (0.04, 0.32)**	**0.013**	-0.01 (-0.15, 0.12)	0.838
2y	-0.15 (-0.39, 0.09)	0.220	-0.12 (-0.35, 0.11)	0.305	-0.03 (-0.30, 0.23)	0.807	-0.27 (-0.68, 0.14)	0.194	-0.09 (-0.38, 0.21)	0.565	-0.05 (-0.21, 0.12)	0.565
4y	-0.01 (-0.18, 0.15)	0.901	-0.03 (-0.2, 0.15)	0.768	0.04 (-0.13, 0.21)	0.640	0.04 (-0.19, 0.26)	0.748	-0.03 (-0.21, 0.14)	0.701	-0.05 (-0.16, 0.06)	0.404
6y	0.20 (-0.002, 0.40)	0.053	0.14 (-0.05, 0.34)	0.157	0.12 (-0.08, 0.31)	0.244	0.15 (-0.06, 0.36)	0.157	-0.18 (-0.39, 0.03)	0.085	-0.09 (-0.19, 0.02)	0.097
$p_{\text{int-FDR}}$	0.648		0.782		0.765		0.999		0.999		0.754	
SMI												
Prenatal	-0.03 (-0.07, 0.02)	0.241	-0.04 (-0.09, 0.02)	0.172	-0.01 (-0.08, 0.05)	0.680	-0.04 (-0.13, 0.06)	0.474	-0.02 (-0.07, 0.03)	0.446	0.02 (-0.03, 0.07)	0.357
2y	-0.04 (-0.13, 0.05)	0.348	-0.04 (-0.13, 0.04)	0.304	-0.06 (-0.15, 0.03)	0.223	-0.06 (-0.20, 0.08)	0.398	-0.09 (-0.20, 0.02)	0.098	-0.04 (-0.10, 0.02)	0.156
4y	-0.03 (-0.09, 0.03)	0.283	-0.03 (-0.09, 0.04)	0.392	0.01 (-0.05, 0.08)	0.629	-0.01 (-0.08, 0.07)	0.869	-0.03 (-0.09, 0.03)	0.340	-0.02 (-0.06, 0.02)	0.230
6y	0.03 (-0.04, 0.09)	0.386	0.03 (-0.04, 0.09)	0.422	0.03 (-0.03, 0.09)	0.379	0.03 (-0.04, 0.09)	0.401	-0.06 (-0.13, 0.01)	0.095	-0.03 (-0.07, 0.0002)	0.052
$p_{\text{int-FDR}}$	0.768		0.858		0.857		0.879		0.999		0.989	
FMI												
Prenatal	0.10 (-0.02, 0.23)	0.109	0.09 (-0.05, 0.23)	0.210	-0.07 (-0.26, 0.11)	0.439	0.21 (-0.07, 0.48)	0.136	0.05 (-0.10, 0.19)	0.526	0.07 (-0.06, 0.20)	0.291
2y	-0.02 (-0.26, 0.22)	0.855	-0.04 (-0.27, 0.19)	0.732	**0.40 (0.15, 0.64)**	**0.002**	0.37 (-0.04, 0.78)	0.074	-0.08 (-0.37, 0.21)	0.596	0.10 (-0.05, 0.25)	0.186
4y	0.06 (-0.11, 0.22)	0.505	0.03 (-0.15, 0.21)	0.762	0 (-0.17, 0.16)	0.961	0.04 (-0.17, 0.26)	0.703	-0.12 (-0.29, 0.06)	0.184	-0.04 (-0.15, 0.06)	0.426
6y	0.15 (-0.03, 0.34)	0.098	0.1 (-0.08, 0.28)	0.264	0.08 (-0.09, 0.24)	0.385	0.11 (-0.08, 0.29)	0.247	-0.11 (-0.30, 0.08)	0.249	-0.03 (-0.12, 0.06)	0.477
$p_{\text{int-FDR}}$	0.855		0.912		0.724		0.845		0.728		0.856	

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine.

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Table 34. Results of multiple informant models for the association between phthalate metabolites at different time points and body composition indices in girls at 6 years of age

	MEHHP		MEOHP		MECPP		∑DEHP		MnBP		MBzP	
	β (95% CI)	*p*	*β* (95% CI)	*p*	*β* (95% CI)	*p*	*β* (95% CI)	*p*	*β* (95% CI)	*p*	*β* (95% CI)	*p*
BMI Z-score												
Prenatal	**-0.12 (-0.23, -0.003)**	**0.045**	-0.11 (-0.24, 0.03)	0.131	-0.14 (-0.30, 0.02)	0.087	-0.01 (-0.21, 0.19)	0.946	-0.11 (-0.24, 0.01)	0.081	-0.02 (-0.16, 0.12)	0.786
2y	-0.18 (-0.40, 0.05)	0.123	-0.17 (-0.39, 0.06)	0.141	-0.07 (-0.35, 0.22)	0.649	-0.20 (-0.58, 0.18)	0.303	-0.22 (-0.47, 0.03)	0.090	0.04 (-0.13, 0.21)	0.632
4y	0.08 (-0.04, 0.19)	0.178	0.09 (-0.04, 0.23)	0.181	0.07 (-0.07, 0.20)	0.322	0.09 (-0.08, 0.25)	0.307	0.03 (-0.10, 0.16)	0.640	0.07 (-0.03, 0.17)	0.181
6y	-0.08 (-0.24, 0.08)	0.312	-0.11 (-0.26, 0.05)	0.177	-0.06 (-0.21, 0.08)	0.391	-0.08 (-0.24, 0.07)	0.290	0.07 (-0.10, 0.24)	0.429	0.05 (-0.04, 0.15)	0.263
$p_{int\text{-}FDR}$	0.134		0.141		0.452		0.477		0.373		0.742	
BMI												
Prenatal	-0.06 (-0.21, 0.09)	0.430	-0.03 (-0.21, 0.15)	0.732	-0.13 (-0.33, 0.08)	0.233	0.10 (-0.17, 0.37)	0.461	0.05 (-0.11, 0.21)	0.553	-0.10 (-0.28, 0.07)	0.246
2y	-0.27 (-0.55, 0.01)	0.056	**-0.30 (-0.57, -0.02)**	**0.037**	0.11 (-0.22, 0.43)	0.510	-0.13 (-0.59, 0.32)	0.570	**-0.43 (-0.74, -0.12)**	**0.007**	0.08 (-0.14, 0.29)	0.483
4y	**0.18 (0.02, 0.34)**	**0.029**	0.17 (-0.02, 0.35)	0.074	0.11 (-0.08, 0.29)	0.253	0.16 (-0.08, 0.39)	0.193	0.14 (-0.04, 0.32)	0.119	0.05 (-0.10, 0.19)	0.514
6y	-0.15 (-0.37, 0.07)	0.183	-0.2 (-0.42, 0.02)	0.075	-0.13 (-0.35, 0.08)	0.233	-0.17 (-0.39, 0.06)	0.153	0.16 (-0.09, 0.41)	0.204	0.10 (-0.04, 0.24)	0.176
$p_{int\text{-}FDR}$	0.080		0.066		0.437		0.429		0.144		0.455	
SMI												
Prenatal	**-0.06 (-0.10, -0.01)**	**0.016**	**-0.06 (-0.12, -0.01)**	**0.027**	**-0.09 (-0.15, -0.02)**	**0.010**	0.01 (-0.07, 0.09)	0.814	-0.05 (-0.10, 0.0003)	0.052	-0.01 (-0.07, 0.05)	0.768
2y	**-0.10 (-0.19, -0.004)**	**0.042**	-0.08 (-0.17, 0.01)	0.084	0.05 (-0.06, 0.17)	0.370	0.02 (-0.14, 0.18)	0.788	**-0.11 (-0.22, -0.01)**	**0.034**	0.01 (-0.07, 0.08)	0.865
4y	0.03 (-0.02, 0.07)	0.264	0.04 (-0.02, 0.09)	0.189	-0.01 (-0.06, 0.05)	0.789	0 (-0.07, 0.07)	0.973	0 (-0.05, 0.05)	0.993	0.01 (-0.03, 0.05)	0.598
6y	-0.03 (-0.09, 0.04)	0.386	-0.02 (-0.09, 0.04)	0.448	-0.02 (-0.08, 0.05)	0.629	-0.02 (-0.09, 0.04)	0.476	0 (-0.07, 0.07)	0.940	0.02 (-0.02, 0.06)	0.235
$p_{int\text{-}FDR}$	0.108		0.120		0.312		0.958		0.386		0.857	
FMI												
Prenatal	-0.10 (-0.26, 0.06)	0.210	-0.09 (-0.28, 0.10)	0.332	-0.18 (-0.41, 0.05)	0.120	-0.04 (-0.33, 0.26)	0.808	-0.15 (-0.33, 0.02)	0.083	-0.03 (-0.23, 0.16)	0.728
2y	-0.18 (-0.49, 0.13)	0.244	-0.19 (-0.49, 0.12)	0.226	-0.13 (-0.53, 0.28)	0.543	-0.30 (-0.85, 0.26)	0.293	-0.23 (-0.57, 0.12)	0.200	0.04 (-0.20, 0.28)	0.731
4y	0.06 (-0.10, 0.21)	0.490	0.06 (-0.13, 0.24)	0.555	0.07 (-0.12, 0.26)	0.472	0.09 (-0.15, 0.34)	0.455	0.08 (-0.10, 0.25)	0.395	0.08 (-0.07, 0.22)	0.288
6y	-0.14 (-0.36, 0.07)	0.192	-0.19 (-0.4, 0.02)	0.081	-0.13 (-0.34, 0.09)	0.245	-0.15 (-0.38, 0.08)	0.192	0.10 (-0.14, 0.34)	0.413	0.08 (-0.06, 0.21)	0.265
$p_{int\text{-}FDR}$	0.375		0.353		0.413		0.350		0.329		0.756	

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine.

Table 35. Results of multiple informant models for the association between phthalate metabolites at different time points and body composition indices at 8 years of age

	MEHHP		MEOHP		MECPP		∑DEHP		MnBP		MBzP	
	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***
BMI Z-score												
Prenatal	-0.06 (-0.14, 0.02)	0.117	-0.07 (-0.16, 0.02)	0.135	**-0.12 (-0.23, -0.003)**	**0.045**	**-0.14 (-0.26, -0.02)**	**0.019**	-0.07 (-0.16, 0.02)	0.139	0.03 (-0.06, 0.12)	0.493
2y	-0.05 (-0.20, 0.10)	0.540	-0.04 (-0.19, 0.11)	0.612	-0.03 (-0.22, 0.16)	0.761	-0.13 (-0.40, 0.14)	0.340	-0.11 (-0.29, 0.07)	0.231	-0.02 (-0.13, 0.08)	0.663
4y	0.01 (-0.08, 0.10)	0.804	0.03 (-0.07, 0.13)	0.577	0.02 (-0.08, 0.12)	0.702	0.03 (-0.10, 0.15)	0.652	-0.07 (-0.17, 0.03)	0.152	0.01 (-0.06, 0.08)	0.757
6y	0.02 (-0.10, 0.13)	0.789	0.01 (-0.10, 0.12)	0.877	-0.01 (-0.11, 0.10)	0.927	0 (-0.11, 0.12)	0.932	-0.11 (-0.23, 0.01)	0.061	0 (-0.06, 0.07)	0.903
8y	-0.08 (-0.17, 0.01)	0.093	**-0.11 (-0.20, -0.02)**	**0.021**	**-0.14 (-0.23, -0.05)**	**0.003**	**-0.12 (-0.22, -0.03)**	**0.013**	-0.03 (-0.11, 0.06)	0.536	-0.04 (-0.08, 0.01)	0.130
$p_{int\text{-}FDR}$	0.253		0.127		0.060		0.062		0.253		0.561	
BMI												
Prenatal	-0.03 (-0.14, 0.08)	0.654	0 (-0.13, 0.13)	0.982	-0.15 (-0.32, 0.01)	0.070	-0.07 (-0.24, 0.10)	0.414	**0.13 (0.004, 0.25)**	**0.043**	-0.05 (-0.18, 0.08)	0.431
2y	-0.20 (-0.41, 0.004)	0.055	-0.19 (-0.40, 0.01)	0.063	0.03 (-0.21, 0.27)	0.787	-0.17 (-0.52, 0.17)	0.326	**-0.25 (-0.5, -0.01)**	**0.044**	0 (-0.15, 0.15)	0.982
4y	0.09 (-0.04, 0.22)	0.187	0.07 (-0.08, 0.21)	0.374	0.07 (-0.08, 0.21)	0.351	0.09 (-0.10, 0.28)	0.345	0.05 (-0.09, 0.19)	0.494	-0.02 (-0.12, 0.09)	0.749
6y	0.03 (-0.15, 0.20)	0.772	-0.03 (-0.19, 0.14)	0.763	-0.01 (-0.18, 0.16)	0.920	-0.01 (-0.18, 0.17)	0.953	-0.05 (-0.24, 0.13)	0.561	-0.02 (-0.12, 0.07)	0.624
8y	-0.11 (-0.26, 0.04)	0.155	**-0.16 (-0.31, -0.02)**	**0.025**	**-0.26 (-0.42, -0.11)**	**0.001**	**-0.21 (-0.37, -0.05)**	**0.012**	-0.04 (-0.17, 0.1)	0.575	-0.04 (-0.12, 0.03)	0.276
$p_{int\text{-}FDR}$	0.083		0.083		0.089		0.229		0.078		0.871	
SMI												
Prenatal	-0.06 (-0.12, 0.004)	0.069	-0.04 (-0.11, 0.03)	0.266	0 (-0.09, 0.09)	0.967	-0.03 (-0.12, 0.06)	0.564	-0.02 (-0.09, 0.05)	0.548	0.02 (-0.05, 0.09)	0.623
2y	0.08 (-0.03, 0.20)	0.156	**0.12 (0.01, 0.23)**	**0.039**	-0.07 (-0.21, 0.08)	0.348	0.04 (-0.17, 0.24)	0.723	**0.27 (0.13, 0.41)**	**<0.001**	-0.02 (-0.10, 0.06)	0.616
4y	0.02 (-0.05, 0.09)	0.539	0.07 (-0.01, 0.15)	0.088	-0.06 (-0.14, 0.02)	0.118	0.01 (-0.09, 0.10)	0.915	-0.05 (-0.12, 0.03)	0.203	**0.07 (0.02, 0.13)**	**0.009**
6y	**0.13 (0.05, 0.22)**	**0.002**	**0.13 (0.04, 0.21)**	**0.003**	**0.10 (0.02, 0.18)**	**0.016**	**0.13 (0.04, 0.21)**	**0.004**	**0.14 (0.05, 0.23)**	**0.003**	**0.09 (0.04, 0.13)**	**0.001**
8y	**0.15 (0.08, 0.22)**	**<0.001**	**0.08 (0.01, 0.15)**	**0.028**	0.01 (-0.06, 0.08)	0.822	**0.08 (0.003, 0.16)**	**0.041**	**0.21 (0.15, 0.27)**	**<0.001**	0.02 (-0.01, 0.06)	0.216
$p_{int\text{-}FDR}$	**0.012**		0.056		0.075		0.074		**0.012**		0.056	
FMI												
Prenatal	-0.12 (-0.26, 0.01)	0.074	-0.12 (-0.27, 0.04)	0.148	-0.13 (-0.33, 0.06)	0.183	**-0.24 (-0.43, -0.04)**	**0.021**	-0.15 (-0.30, 0.01)	0.070	0.03 (-0.12, 0.18)	0.675
2y	0.06 (-0.20, 0.32)	0.650	0.07 (-0.19, 0.33)	0.590	0.04 (-0.28, 0.36)	0.819	-0.04 (-0.50, 0.41)	0.850	0.26 (-0.06, 0.58)	0.109	0 (-0.19, 0.18)	0.964
4y	-0.01 (-0.17, 0.14)	0.889	0.06 (-0.12, 0.23)	0.536	-0.04 (-0.21, 0.13)	0.647	0.03 (-0.18, 0.25)	0.748	-0.1 (-0.27, 0.07)	0.261	0.05 (-0.07, 0.17)	0.396
6y	0.18 (-0.02, 0.37)	0.078	0.18 (-0.01, 0.37)	0.071	0.13 (-0.05, 0.31)	0.170	0.16 (-0.03, 0.35)	0.094	-0.01 (-0.22, 0.19)	0.892	0.09 (-0.02, 0.20)	0.100
8y	0.06 (-0.10, 0.22)	0.494	-0.04 (-0.19, 0.12)	0.632	-0.12 (-0.28, 0.04)	0.139	-0.04 (-0.21, 0.12)	0.603	**0.16 (0.02, 0.31)**	**0.029**	0.02 (-0.06, 0.10)	0.615
$p_{int\text{-}FDR}$	0.369		0.3367		0.242		0.238		0.060		0.688	

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine.

Table 36. Results of multiple informant models for the association between phthalate metabolites at different time points and body composition indices in boys at 8 years age

	MEHHP		MEOHP		MECPP		∑DEHP		MnBP		MBzP	
	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***
BMI Z-score												
Prenatal	-0.05 (-0.16, 0.05)	0.318	-0.08 (-0.20, 0.04)	0.185	-0.15 (-0.32, 0.01)	0.064	**-0.17 (-0.33, -0.02)**	**0.030**	-0.05 (-0.17, 0.07)	0.431	0.06 (-0.05, 0.17)	0.300
2y	-0.02 (-0.22, 0.17)	0.815	-0.03 (-0.22, 0.16)	0.742	-0.05 (-0.29, 0.19)	0.695	-0.08 (-0.44, 0.27)	0.638	-0.08 (-0.32, 0.16)	0.499	-0.09 (-0.22, 0.04)	0.176
4y	-0.02 (-0.16, 0.12)	0.781	-0.01 (-0.17, 0.14)	0.854	-0.02 (-0.16, 0.13)	0.816	0 (-0.19, 0.18)	0.969	-0.13 (-0.28, 0.01)	0.067	-0.06 (-0.15, 0.03)	0.209
6y	0.09 (-0.06, 0.25)	0.251	0.08 (-0.07, 0.24)	0.271	0.06 (-0.09, 0.21)	0.450	0.08 (-0.08, 0.24)	0.316	-0.15 (-0.30, 0.01)	0.074	-0.05 (-0.13, 0.03)	0.259
8y	-0.06 (-0.19, 0.07)	0.378	-0.09 (-0.23, 0.05)	0.204	-0.17 (-0.32, -0.03)	0.018	-0.13 (-0.28, 0.02)	0.095	-0.10 (-0.23, 0.02)	0.099	**-0.07 (-0.13, -0.003)**	**0.041**
$p_{int\text{-}FDR}$	0.428		0.296		0.216		0.228		0.314		0.238	
BMI												
Prenatal	0 (-0.15, 0.15)	0.978	0.02 (-0.15, 0.19)	0.817	-0.18 (-0.42, 0.05)	0.128	-0.1 (-0.33, 0.13)	0.385	**0.18 (0.01, 0.34)**	**0.036**	-0.01 (-0.18, 0.16)	0.892
2y	-0.15 (-0.43, 0.13)	0.286	-0.13 (-0.40, 0.15)	0.364	-0.03 (-0.35, 0.29)	0.836	-0.25 (-0.74, 0.23)	0.302	-0.09 (-0.44, 0.26)	0.621	-0.05 (-0.25, 0.15)	0.618
4y	-0.01 (-0.21, 0.18)	0.888	-0.03 (-0.24, 0.18)	0.768	0.03 (-0.17, 0.24)	0.744	0.03 (-0.24, 0.30)	0.826	-0.04 (-0.24, 0.17)	0.732	-0.05 (-0.19, 0.09)	0.477
6y	0.19 (-0.05, 0.43)	0.117	0.13 (-0.10, 0.37)	0.259	0.11 (-0.13, 0.34)	0.378	0.14 (-0.10, 0.39)	0.257	-0.19 (-0.43, 0.06)	0.139	-0.09 (-0.22, 0.04)	0.163
8y	-0.06 (-0.28, 0.16)	0.594	-0.11 (-0.34, 0.12)	0.359	-0.35 (-0.59, -0.11)	0.004	-0.22 (-0.47, 0.04)	0.094	**-0.21 (-0.41, -0.003)**	**0.047**	-0.11 (-0.21, 0.001)	0.052
$p_{int\text{-}FDR}$	0.437		0.480		0.228		0.383		0.264		0.453	
SMI												
Prenatal	-0.02 (-0.09, 0.06)	0.707	-0.01 (-0.10, 0.08)	0.894	0.04 (-0.08, 0.17)	0.496	0.04 (-0.08, 0.16)	0.489	0 (-0.09, 0.09)	0.967	0.03 (-0.06, 0.12)	0.485
2y	0.07 (-0.08, 0.22)	0.337	0.09 (-0.06, 0.24)	0.226	-0.14 (-0.33, 0.04)	0.127	-0.01 (-0.28, 0.26)	0.949	0.16 (-0.02, 0.34)	0.075	-0.04 (-0.14, 0.06)	0.396
4y	0.02 (-0.08, 0.13)	0.668	0.07 (-0.05, 0.18)	0.260	-0.1 (-0.21, 0.01)	0.066	-0.03 (-0.17, 0.10)	0.634	-0.01 (-0.12, 0.1)	0.865	0.04 (-0.03, 0.11)	0.233
6y	**0.17 (0.05, 0.28)**	**0.006**	**0.16 (0.05, 0.27)**	**0.006**	**0.12 (0.01, 0.24)**	**0.034**	**0.16 (0.04, 0.27)**	**0.009**	0.11 (-0.01, 0.23)	0.075	**0.06 (0.001, 0.12)**	**0.048**
8y	**0.18 (0.07, 0.28)**	**0.001**	0.07 (-0.04, 0.18)	0.202	-0.06 (-0.17, 0.05)	0.307	0.06 (-0.05, 0.17)	0.306	**0.24 (0.15, 0.34)**	**<0.001**	0.01 (-0.04, 0.06)	0.786
$p_{int\text{-}FDR}$	0.064		0.282		**0.048**		0.257		**0.024**		0.280	
FMI												
Prenatal	-0.11 (-0.30, 0.08)	0.271	-0.12 (-0.34, 0.09)	0.256	-0.21 (-0.5, 0.08)	0.157	-0.27 (-0.54, 0.01)	0.059	-0.08 (-0.3, 0.14)	0.483	0.06 (-0.14, 0.26)	0.577
2y	0.08 (-0.28, 0.43)	0.673	0.07 (-0.28, 0.41)	0.709	0.06 (-0.37, 0.49)	0.787	0 (-0.62, 0.63)	0.993	0.21 (-0.22, 0.65)	0.338	-0.08 (-0.31, 0.16)	0.510
4y	0.02 (-0.23, 0.27)	0.869	0.11 (-0.17, 0.38)	0.452	-0.13 (-0.38, 0.12)	0.307	0.01 (-0.31, 0.33)	0.929	-0.18 (-0.44, 0.08)	0.179	-0.07 (-0.23, 0.09)	0.393
6y	**0.35 (0.07, 0.63)**	**0.015**	**0.36 (0.09, 0.64)**	**0.009**	**0.29 (0.02, 0.55)**	**0.032**	**0.35 (0.07, 0.63)**	**0.013**	-0.1 (-0.39, 0.19)	0.502	0.01 (-0.13, 0.16)	0.849
8y	0.21 (-0.03, 0.46)	0.083	0.11 (-0.15, 0.36)	0.415	-0.13 (-0.38, 0.13)	0.334	0.06 (-0.20, 0.33)	0.642	0.16 (-0.06, 0.39)	0.162	0 (-0.11, 0.12)	0.963
$p_{int\text{-}FDR}$	0.299		0.319		0.210		0.281		0.280		0.636	

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine.

Table 37. Results of multiple informant models for the association between phthalate metabolites at different time points and body composition indices in girls at 8 years of age

	MEHHP		MEOHP		MECPP		∑DEHP		MnBP		MBzP	
	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***	***β* (95% CI)**	***p***
BMI Z-score												
Prenatal	-0.07 (-0.19, 0.04)	0.210	-0.06 (-0.20, 0.09)	0.440	-0.08 (-0.24, 0.08)	0.323	-0.1 (-0.27, 0.08)	0.270	-0.11 (-0.24, 0.03)	0.140	-0.02 (-0.16, 0.12)	0.780
2y	-0.10 (-0.33, 0.14)	0.425	-0.06 (-0.29, 0.17)	0.615	0.01 (-0.29, 0.30)	0.966	-0.2 (-0.61, 0.21)	0.348	-0.16 (-0.44, 0.12)	0.251	0.11 (-0.07, 0.29)	0.232
4y	0.03 (-0.08, 0.15)	0.565	0.07 (-0.07, 0.21)	0.343	0.05 (-0.09, 0.19)	0.480	0.06 (-0.11, 0.23)	0.513	-0.02 (-0.16, 0.11)	0.755	0.10 (-0.01, 0.21)	0.063
6y	-0.08 (-0.24, 0.09)	0.352	-0.08 (-0.24, 0.08)	0.309	-0.07 (-0.22, 0.08)	0.355	-0.08 (-0.24, 0.08)	0.337	-0.08 (-0.26, 0.09)	0.355	0.08 (-0.02, 0.18)	0.109
8y	-0.09 (-0.22, 0.03)	0.144	-0.11 (-0.23, 0.003)	0.056	-0.12 (-0.24, 0.01)	0.064	-0.12 (-0.25, 0.01)	0.069	0.04 (-0.07, 0.15)	0.490	0 (-0.07, 0.07)	0.979
$p_{int\text{-}FDR}$	0.391		0.417		0.471		0.352		0.435		0.452	
BMI												
Prenatal	-0.06 (-0.23, 0.10)	0.471	-0.03 (-0.23, 0.16)	0.749	-0.13 (-0.36, 0.11)	0.285	-0.03 (-0.29, 0.22)	0.788	0.05 (-0.13, 0.23)	0.577	-0.11 (-0.30, 0.09)	0.289
2y	-0.27 (-0.58, 0.04)	0.085	-0.3 (-0.60, 0.01)	0.059	0.11 (-0.25, 0.48)	0.539	-0.12 (-0.63, 0.38)	0.629	**-0.43 (-0.78, -0.09)**	**0.013**	0.08 (-0.16, 0.32)	0.511
4y	**0.18 (0.01, 0.36)**	**0.043**	0.17 (-0.03, 0.38)	0.097	0.11 (-0.1, 0.32)	0.296	0.16 (-0.1, 0.42)	0.223	0.14 (-0.06, 0.34)	0.163	0.05 (-0.11, 0.21)	0.548
6y	-0.16 (-0.40, 0.09)	0.217	-0.2 (-0.45, 0.04)	0.101	-0.14 (-0.37, 0.1)	0.269	-0.16 (-0.41, 0.08)	0.195	0.15 (-0.12, 0.43)	0.269	0.1 (-0.06, 0.26)	0.218
8y	-0.17 (-0.37, 0.03)	0.094	**-0.23 (-0.41, -0.04)**	**0.016**	-0.22 (-0.42, -0.02)	0.032	**-0.23 (-0.44, -0.02)**	**0.035**	0.08 (-0.09, 0.26)	0.351	0.02 (-0.09, 0.14)	0.687
$p_{int\text{-}FDR}$	0.060		0.064		0.406		0.406		0.060		0.573	
SMI												
Prenatal	**-0.10 (-0.19, -0.01)**	**0.028**	-0.08 (-0.19, 0.03)	0.133	-0.03 (-0.16, 0.10)	0.672	-0.10 (-0.24, 0.04)	0.147	-0.06 (-0.17, 0.05)	0.292	-0.01 (-0.13, 0.10)	0.804
2y	0.08 (-0.10, 0.27)	0.380	0.15 (-0.03, 0.33)	0.105	0.07 (-0.16, 0.30)	0.572	0.12 (-0.20, 0.44)	0.454	**0.40 (0.19, 0.62)**	**<0.0001**	0.03 (-0.11, 0.17)	0.652
4y	0.02 (-0.07, 0.11)	0.695	0.07 (-0.04, 0.18)	0.217	-0.03 (-0.14, 0.08)	0.591	0.03 (-0.10, 0.17)	0.634	-0.09 (-0.19, 0.02)	0.100	**0.10 (0.02, 0.19)**	**0.016**
6y	0.09 (-0.04, 0.22)	0.163	0.09 (-0.04, 0.21)	0.179	0.08 (-0.04, 0.20)	0.212	0.09 (-0.04, 0.21)	0.176	**0.16 (0.02, 0.30)**	**0.021**	**0.12 (0.04, 0.20)**	**0.002**
8y	**0.14 (0.04, 0.23)**	**0.008**	0.09 (-0.004, 0.18)	0.061	0.06 (-0.04, 0.15)	0.241	0.01 (-0.01, 0.20)	0.065	**0.19 (0.10, 0.27)**	**<0.001**	0.04 (-0.01, 0.10)	0.125
$p_{int\text{-}FDR}$	0.196		0.448		0.657		0.453		**0.012**		0.250	
FMI												
Prenatal	-0.14 (-0.34, 0.05)	0.150	-0.1 (-0.34, 0.13)	0.394	-0.06 (-0.33, 0.21)	0.648	-0.2 (-0.49, 0.10)	0.188	**-0.24 (-0.48, -0.01)**	**0.038**	-0.01 (-0.25, 0.22)	0.919
2y	0.03 (-0.36, 0.42)	0.886	0.07 (-0.32, 0.46)	0.715	0 (-0.49, 0.49)	0.989	-0.11 (-0.79, 0.57)	0.750	0.31 (-0.15, 0.77)	0.192	0.14 (-0.15, 0.44)	0.347
4y	-0.03 (-0.22, 0.17)	0.764	0.02 (-0.21, 0.25)	0.864	0.04 (-0.19, 0.27)	0.715	0.06 (-0.23, 0.34)	0.691	-0.03 (-0.25, 0.19)	0.799	**0.22 (0.04, 0.40)**	**0.015**
6y	-0.02 (-0.28, 0.25)	0.902	-0.04 (-0.3, 0.23)	0.787	-0.04 (-0.29, 0.22)	0.783	-0.03 (-0.29, 0.24)	0.827	0.08 (-0.21, 0.37)	0.578	**0.21 (0.04, 0.38)**	**0.013**
8y	-0.08 (-0.29, 0.13)	0.443	-0.14 (-0.33, 0.06)	0.176	-0.12 (-0.32, 0.09)	0.260	-0.12 (-0.34, 0.10)	0.271	0.17 (-0.02, 0.35)	0.081	0.04 (-0.07, 0.16)	0.448
$p_{int\text{-}FDR}$	0.740		0.683		0.806		0.651		0.144		0.426	

MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECCP, Mono-2-ethyl-5-carboxypentyl phthalate; ∑DEHP, sum of di-2-ethylhexyl phthalate metabolites; MnBP, mono-n-butyl phthalate (MnBP); MBzP, Monobenzyl phthalate

Adjusted for maternal age as a continuous variable, maternal education, and household income for the association between maternal phthalates and body composition indices of their children, and adjusted for urinary creatinine.

4. Discussion

4.1. Phthalates and physical growth of children

Main findings of the study

The systematic review and meta-analysis, and the mother-child cohort study in South Korea were performed to investigate the association between phthalates and physical growth in children. In the systematic literature review, it was found that a significant and negative association between prenatal exposure to DEHP and BMI z-score of the offspring, but there was no significant association between prenatal exposure to DEHP and DBP and body fat mass percentage of the offspring. In the mother-child cohort study, increased DEHP metabolites in prenatal maternal urine were associated with decreased SMI of the children at 6 years of age. It can be concluded that prenatal phthalates exposure interferes with the normal physical growth of children. Additionally, it was found that previous studies on the association between phthalates exposure in childhood and obesity were inconsistent in the systematic review, and increased FMI and SMI in children were associated with phthalates exposure at childhood in the mother-child cohort study.

Prenatal exposure to phthalates and growth disturbance

It was found that a significant and negative association between prenatal exposure to phthalates and BMI of the offspring in the literature review. In the mother-child cohort study, prenatal phthalates exposure was associated with decreased SMI. These results imply that phthalates could be chemicals disrupting normal muscle development instead of *obesogens*. Thus, the selective association of phthalate exposure with the development of muscle mass than fat mass could

explain the inconsistencies reported in previous studies regarding the association between prenatal exposure to phthalates and childhood BMI.

Increased prenatal exposure to phthalates was associated with decreased SMI, which implied relative lower muscle mass considering the heights of the children. Thus, phthalates could disturb adequate muscle development rather than change body adiposity. Previous studies on prenatal exposure to phthalates and body composition have focused on obesity, but the results were inconsistent. The CHAMACOS study in the U.S. reported that prenatal exposures to DEHP and DBP were associated with increased obesity outcomes at ages of 5–12 y (56). Vafeiadi et al. examined 500 mother-child pairs in Greece and reported that prenatal exposure to phthalates was not associated with obesity at 4–6 years of age (61). Another study involving 707 children in the U.S. reported that prenatal exposure to DEHP could be associated with decreased BMI z-scores in girls aged 4–7 y (46). Although a cross-sectional study in the U.S. reported that decreased lean mass is associated with the increased urinary concentration of phthalate metabolites (24), studies investigating the association of prenatal phthalate exposure with skeletal muscle development in children are lacking. SMI could be independent of body fat percentage or fat mass index because it represents a different compartment in body composition, but SMI is inevitably associated with BMI as it includes both fat mass and lean mass. However, SMI is relatively weakly associated with BMI (R^2=0.112), especially in girls (70). If phthalate exposure is more selectively associated with muscle mass than fat mass, it could explain the inconsistencies reported in previous studies regarding the association between prenatal exposure to phthalates and BMI during childhood.

The mechanism between phthalate exposure and decreased SMI could be

plausibly explained by the antiandrogenic effects of phthalates on muscle development (8, 71). Androgens play an important role in muscle development. In an animal study, androgen withdrawal in mice resulted in decreased myofibrillar protein synthesis, which was reversed by anabolic steroid administration (72). Another study using mice reported that testosterone had positive effects on muscle mass and the ultrastructure of muscles (73). Epidemiologic studies also consistently reported that androgen is positively associated with muscle growth. A study in which the authors followed up 50 boys and 50 girls aged 8 to 17 y reported that increased testosterone levels were significantly associated with muscle strength (74). Another study involving hysterectomized women reported that testosterone is associated with muscle mass and strength in women and there is a dose-response relationship between them (75). Prenatal phthalate exposure is associated with decreased anogenital distance, which is positively related with antiandrogenic properties (76, 77). In an animal study, prenatal DEHP exposure could lead to decreased testosterone production in the offspring both in the fetal and postnatal period (78). Another study involving human participants also reported that increased phthalate metabolites were associated with decreased levels of serum testosterone (79). Among children, the positive association between serum testosterone and SMI has been investigated (80). Given the previous researches, the antiandrogenic properties of phthalates could be an important link between prenatal exposure to phthalates and decreased SMI.

Inflammation is a possible mediator of disruption of muscle development following phthalate exposure. Phthalates exacerbate inflammatory response by increasing inflammatory cytokines (81). A human study reported that DEHP exposure could induce IL-1β production in neonatal neutrophils (82), and an *in*

vitro study reported that increased gene expression of inflammatory cytokines could be induced by DEHP (83). Inflammatory cytokines are associated with inhibition of expression of myogenic miRNA in myoblasts and promoting muscle protein degradation (84, 85). Given this evidence, I could infer that inflammation due to phthalates could be associated with decreased skeletal muscle indices.

Insulin-like growth factor-1 (IGF-1) could be attributed to the negative association between phthalate exposure and decreased muscle mass. IGF-1 pathway acts as a positive regulator of muscle growth processes that take place after birth (86). Few epidemiologic studies have reported that urinary phthalate metabolites are negatively associated with IGF-1. Cross-sectional studies have reported the associations between phthalates and decreased levels of IGF-1 among children (60, 87, 88). These epidemiologic studies imply that phthalates could lead to decreased levels of IGF-1, disturbing normal muscle growth in children.

In the mother-child cohort study, the association between prenatal phthalate exposure and SMI at 6 years of age was significant among girls. Although the association was not statistically significant among boys, our finding was consistent with a recent study on mice wherein perinatal exposure to DEHP was associated with decreased muscle mass only in the female offspring (23). Further research on the mechanism of this association is needed for complete understanding. The differences in hormones and epigenetics between boys and girls are probable explanations for the sex-specific association of phthalates (89, 90). Homeostasis of the thyroid hormone, which is closely related with IGF-1, could be disturbed following phthalate exposure (87, 88), and the study that thyroid hormone disturbances are strongly associated with the female sex suggests that phthalate exposure could affect muscle development in a sex-specific manner (91).

Phthalates exposure at children and body composition indices

It was explored that positive association between phthalate metabolites in children's urine and SMI and FMI of children in the mother-child cohort study. Several researchers reported phthalate exposure in children could be related with obesity, although obesity was inconsistently associated with phthalate metabolites, and the number of studies was limited to perform the meta-analysis. The results of searched studies in the systematic review were inconsistent. As one of the results with a significant association, a cross-sectional study with 845 Danish children aged 4–9 years reported that urinary phthalate metabolites are negatively associated with height and weight (92). The National Health and Nutrition Examination Survey (NHANES) data showed that LMWP could be associated with increased BMI z-score (16), and a longitudinal study in the U.S. also reported that phthalate exposure at 5 years of age was associated with obesity at 8 years of age (58). These studies suggested that the role of peroxisome-proliferator activated receptors (PPARs) is important to induce obesity. PPARs are nuclear hormone receptors that have regulatory roles in adipogenesis and lipid storage and could be affected by DEHP to induce adipogenesis (93-95). As phthalate exposure is associated with decreased thyroid hormone (96), hormonal homeostasis can be disturbed by phthalates, and it can lead to fat accumulation and obesity. A Chinese metabolome study investigated 69 overweight/obese children and 80 normal-weight children. It was reported that urinary MnBP concentration was different between the two groups, and was associated with arginine and proline metabolism and butyraldehyde (97). However, there were several studies with results with no significant associations between phthalates and obesity and/or BMI (16, 47, 48, 57,

58, 63). Some researchers argued that the association between urinary phthalates metabolites and obesity was not derived from the causal association between phthalates exposure in children and obesity. For instance, the recent study to explain the mechanism for cross-sectional studies for the association between phthalates and higher BMI demonstrated that the higher energy intake in the overweight and obese can result in the concomitant higher phthalates exposure and the higher body weight (98). Additionally, ultra-processed food consumption is associated with overweight and weight gain (99), and it is also associated with urinary phthalates metabolites (100). Therefore, there is a possibility that a cross-sectionally observed association between phthalates metabolites and obesity may just reflect the association of the dietary pattern and the amount of consumption with obesity. Additionally, it may be possible that urinary phthalate metabolite can be measured higher among children with more adipose and/or muscle mass. Given absorption, distribution, metabolism and excretion of phthalates, absorbed phthalates in the human body distribute mainly in the intestine and liver, and they are rapidly excreted. On the other hand, a relatively small portion of absorbed phthalates is distributed fat and muscle tissue, but they are excreted slower than those in the intestine and liver, resulting in a relatively higher proportion of phthalates in the human body (101). Therefore, observed cross-sectional associations between phthalates and obesity in children can be just simple associations, rather than causal associations. Inconsistent results and the related factors make it difficult to conclude the association between phthalates exposure in childhood and weight gain. It is needed in the future that studies designed with longitudinal design and studies suggesting plausible mechanism such as hormonal, epigenetic and/or metabolomic changes.

Indices for evaluating skeletal muscle growth in children

It was found that prenatal phthalates exposure was associated with decreased SMI in the mother-child cohort study. Body composition of children may predict adult body composition (102), and later risk for cardiovascular disease (103). However, has yet been defined reference ranges for muscle mass in pediatrics that account for normal growth and development (104). A study consisted of 10,818 Chinese children reported the reference curves of SMI (105). In Chinese boys, ASMI increased slightly until 16 years and slowed down thereafter, and in Chinese girls, ASMI increased slightly until 14 years and slightly decreased after that. In South Korea, a study with 1,919 Korean children established the reference values for skeletal muscle mass, but the study only included adolescents aged 10–18 years (106). This study also showed that SMI increased slightly and steadily until 13 years of age in girls and 14 years of age in boys. Generally, the velocity of change of SMI and FMI does not change suddenly at the age of 6 and 8 years, when SMI and FMI were measured in the mother-child cohort study. However, there is a possibility that phthalates exposure may affect the velocity of change of SMI and FMI in this period. It is expected that more comprehensive results could be derived with the EDC cohort when follow-up for 10-year old and 12-year old are completed in the future.

Phthalates concentrations in South Korea Children

GMs of MEHHP, MEOHP, MECCP, and MnBP of prenatal maternal urine of the mother-cohort study participants were 15.5 μg/g Cr, 16.0 μg/g Cr, 22.3 μg/g Cr, and 41.9 μg/g Cr, respectively. In South Korea, the mean concentrations of phthalate metabolites in prenatal maternal urine were similar to those in previous

studies, which reported mean concentrations of 7.1–22.5 μg/g Cr, 6.9–18.7 μg/g Cr, and 21.1–39.68 μg/g Cr for MEHHP, MEOHP, and MnBP, respectively (46, 56, 61). The children included in this study had higher concentrations of urinary phthalate metabolites than those included in U.S.-based studies, which ranged from 14.0–25.8 μg/g Cr, 9.8–10.0 μg/g Cr, 16.3–21.7 μg/g Cr for MEHHP, MEOHP, and MnBP, respectively (16, 58, 107). Other studies also reported that phthalate levels in South Korean children were higher than those of children in the U.S. (108). The difference could be partially contributed to frequencies of consumption of dairy products and meat using plastic packaging (109). However, the results of our study showed phthalate metabolite levels in children's urine similar to those of studies in Korea, Greece, and Denmark (61, 87, 110). Phthalate metabolites were relatively higher in children's urine than in prenatal maternal urine, and their concentration decreased according to children's age in the mother-child cohort data. GMs of MEHHP in prenatal maternal urine, and children's urine at 2, 4, 6, and 8 years were 91.2 μg/g Cr, 70.7 μg/g Cr, 58.0 μg/g Cr, and 30.9 μg/g Cr, respectively. It is consistent with the observed findings of the Korean National Environmental Health Survey (KoNEHS), the nationally representative data of South Korea. In 2017, GMs of MEHHP in toddlers, elementary school students, and middle- and high-school students were 34.6 μg/g Cr, 28.8 μg/g Cr, and 13.6 μg/g Cr, respectively (111). A Taiwanese study also reported that GMs of total urinary phthalate metabolite in 2 years olds (398.6 ug/L) was higher than those in 5 years olds (333.7) (112).

Exposure assessment for phthalates

There has been an assumption that a single measure of phthalate metabolites

can adequately reflect exposure. All studies included in the meta-analysis and the mother-child cohort study also had the assumption. Assessing exposures to DEHP may not be conclusive since various metabolites of DEHP are rapidly metabolized *in vivo* and quickly excreted. The excretion half-lives of DEHP metabolites can be as short as 0.5–3.0 days (25). Therefore, only recent exposure to DEHP is accurately reflected in urine biomarkers of DEHP. However, all studies included in the meta-analysis considered DEHP metabolites of maternal urine or children's urine. In all longitudinal studies, DEHP metabolites were assessed only once from pregnant women's urine and/or children's urine. Children's urine was repeatedly measured four times with 2-3 y intervals in one study alone. In all cross-sectional studies, DEHP metabolites were measured only once from children's urine. In addition to their short half-lives and rapid excretion, the temporal stability of DEHP metabolites over weeks to months has been studied. Fromme et al. investigated the daily variation of phthalate metabolites by collecting urine from 50 participants on 8 consecutive days and reported intra-class coefficients (ICCs) of creatinine-adjusted DEHP metabolites to be 0.20-0.34. (113) Hauser et al. reported that DEHP metabolites in one spot urine samples could predict 3-mo average DEHP metabolite levels with a sensitivity of 0.56 and specificity of 0.83 (114). DEHP metabolites in the spot urine of pregnant women and children did not have excellent stability, but reasonable temporal stability for weeks to months (115-119). A recent study investigated 805 urine samples of 16 volunteers during 6 months and suggested that adequately classifying the exposure level of participants requires several samples per subject (120). However, no studies used measured phthalates repeatedly in a short-time period to measure phthalates exposure more accurately in the systematic review. With this background, all studies included in

present meta-analyses assumed implicitly or explicitly that a single measurement could reflect exposure over a considerable period.

Strengths and Limitations

The study has unique strengths. In the systematic review and meta-analysis study, the associations between classes of phthalates (DEHP and DBP) and body composition indices were investigated by using the properties of the phthalate metabolites. There was a reason for the inconclusive association between phthalate exposure and children's growth (21). It was how best to sum up the different metabolites to assess the total exposure amount. The molar sum of several metabolites of DEHP is considered by far the best estimate of exposure rather than a simple mass sum of DEHP metabolites. Therefore, it was aimed to use the molar sum of multiple metabolites to estimate the exposure amount. However, some studies used a single metabolite rather than the sum of metabolites. Moreover, the phthalate metabolites measured, and the summation methods used varied across studies. Although in each study we selected the association between the most reasonable metabolites of DEHP and DBP and the outcome, the interpretation of our results should be cautious because the different metabolites may not have the same values for estimating exposure. Further, the timing of measurement for phthalate exposure (such as prenatal or postnatal) and the methods for assessing body composition indices including BMI, BMI z-score, and body fat percentage differ across studies. In this study, it was attempted to attempt to analyze the results collectively in a meta-analysis with the abovementioned methods, which was also described in the previous meta-analysis study (15). In the mother-child cohort study, it was used prospective cohort data were used to derive the results.

Biological markers measured in prenatal maternal urine and children's urine at 2, 4, 6, and 8 years of age, and body compositions measured at 2, 4, 6, and 8 years of age among children provide evidence of temporal relationship to infer causality. Furthermore, associations between phthalate exposure and body composition indices were estimated following adjustment for energy intake per day to avoid confounding by food consumption, in addition to adjustments for potential confounders including maternal BMI, household income level, maternal education level, and frequency of strength training exercise per week.

This study has several limitations. First, calibration of the amount of exposure to phthalates considering the duration of exposure is not assessed in the systematic review and meta-analysis, because it isn't practically impossible currently. The fetus is affected through maternal blood or inhalation and the infant is exposed through breast milk and the environment (121). Phthalates are also found in several medical devices such as catheters, medical tubing, and blood bags, which may also be confounding variables regarding phthalate exposures concerning prenatal and postnatal differences (122). Second, the included studies had limited information, and had methodological differences (123), although it was used that standardized values from beta estimates and 95% CIs of DEHP or DBP, the main independent variable. If raw data can be obtained and pooled analysis is carried out, more robust results may be expected. In the mother-child cohort study, phthalate metabolites were measured from spot urine samples of participants. There is no study with repeatitive measurement for accurate phthalates measurement for the association between phthalates and body composition indicies. In the future, more repetitive methods such as using mean levels of various phthalate metabolites assessed at multiple time points could increase the precision and accuracy of predicting

phthalate exposure (124). Third, non-standardized SMI and FMI were used as indicators for skeletal muscle and fat mass of children's bodies, unlike BMI z-score. SMI and FMI are measured by techniques such as magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry, and BIA. As the absence of reference data of SMI and FMI in South Korea, standardized Z-score of SMI and FMI cannot be calculated. SMI and FMI have been used for researches and not been used for clinical purposes. In the future study, it is expected Z-score of SMI and FMI can be calculated by using the reference curve of children in South Korea, such as reference curves presented in the UK and China (105, 125). Fourth, I performed many multivariate linear regression analyses for evaluation of phthalate exposure using maternal and pediatric samples (MEHHP, MEOHP, MECCP, ∑DEHP, MnBP, and MBzP) and considering various outcomes of interest (BMI z-score, BMI, FMI, and SMI). Finally, our results were derived from the EDC cohort dataset, which included participants from South Korea alone. Therefore, the findings of this study cannot be generalized to populations of other countries.

4.2. Regulation and management of phthalate in South Korea

Environmental health services are systematic and scientific activities to protect the health of people from environmental hazards; they involve direct participation and communication of the government, local communities, organizations, and individuals (126). From the perspective of public health, the etiology of a disease is the interaction among 3 factors: agent (and/or pathogen), host, and environment. During the occurrence of a disease, these 3 factors should be investigated concurrently with epidemiologists focusing on the host, microbiologists focusing on the agent, and environmental health specialists focusing on the environment.

Based on the public health service policies suggested by the Institute of Medicine, ten essential services have been suggested under environmental health services (**Table 38**) (127). It was reviewed that the current status of phthalate regulation and biomonitoring system in South Korea, focusing on "6. Enforce laws and regulations that protect environmental health and ensure safety" and "1. Monitor environmental and health status to identify and solve community environmental health problems."

Table 38. The ten essential services of environmental health

1. Monitor environmental and health status to identify and solve community environmental health problems
2. Diagnose and investigate environmental health problems and health hazards in the community
3. Inform, educate, and empower people about environmental health issues
4. Mobilize community partnerships and actions to identify and solve environmental health problems
5. Develop policies and plans that support individual and community environmental health efforts
6. Enforce laws and regulations that protect environmental health and ensure safety
7. Link people to needed personal environmental health services and assure the provision of healthcare when otherwise unavailable
8. Assure competent environmental health and personal healthcare workforce
9. Evaluate effectiveness, accessibility, and quality of personal and population-based environmental health services
10. Research for new insights and innovative solutions to environmental health problems

United Nations defined EDCs as a global threat that needs to be resolved and suggested future needs including increasing the awareness of EDCs, improving their testing, reducing exposures and thereby vulnerability to disease, identifying endocrine active chemicals, creating environments for scientific advances, innovation, and disease prevention, and methods for evaluating evidence (128).

Instead of a specific and exclusive law so-called 'phthalate law', there are many laws and regulations related to phthalate management. Their interrelationship among the laws and regulations is very complex. However, there is an increased necessity for their management and regulation, but the system and policy are still not sufficient.

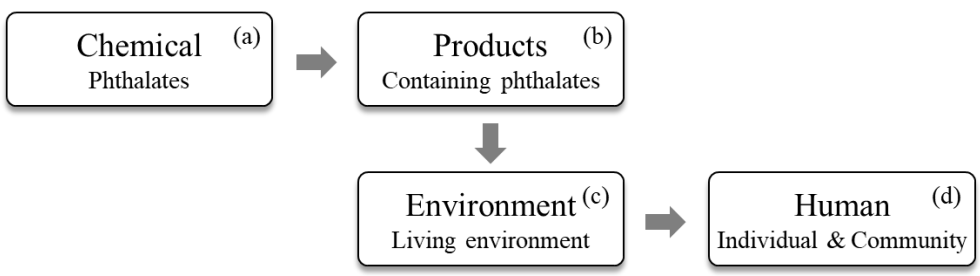

Figure 29. Scheme of the flow of phthalates to the human body

Figure 3 shows the scheme of the flow of phthalates from chemical products to the human body. In South Korea, there currently exists no special law to specifically manage and regulate EDCs. There are many laws and regulations on the management of numerous chemical substances, and the interrelationship of the laws is complicated. Moreover, the detailed methods of regulating chemical substances differ by law. The laws and regulations were reviewed according to the scheme, and the relevant existing laws were as follows: (a) "Act on Registration and Evaluation, etc. of Chemicals' and "Chemical Substance Control Act;' (b) "Food Sanitation Act," "Cleansing and Hygiene Products Control Act," "Special

Act on the Safety of Children's Products,'' and "Medical Devices Act;' (c) "Environmental Health Act"' (related to health impact assessment), and "Food Sanitation Act" (related to cumulative risk assessment); (d) "Environmental Health Act"' (related to the Korean National Environmental Health Survey)

Law and regulation related to phthalate as chemicals

As chemical substances, phthalates including DEHP, DBP, butylbenzyl phthalate (BBP), diisobutyl phthalate (DIBP), and diallyl phthalate (DAP) are designated as *toxic substances* according to a *hazard review*. The act on registration and evaluation of chemicals was to protect public health and the environment by addressing matters regarding registering and reporting chemical substances, reviewing and assessing hazards and risks of chemical substances, and designating hazardous chemical substances. Article 10 of this act designated that any person who intends to manufacture or import at least 100 kilograms of a non-phase-in substance per year or at least 1 ton of a phase-in substance per year should register the chemical substance to the Minister of Environment. The Ministry of Environment shall conduct a *hazard review* of a chemical substance registered according to Article 10 and designate and publicly notify the chemical to be hazardous. *Hazard reviews* shall be conducted by the National Institute of Environmental Research according to subordinate statutes in South Korea. A *toxic substance* is designated and notified in the case of a chemical substance that is found hazardous based on the results of a *hazard review*, according to Article 20. DEHP, DBP, DIBP, BBP, DAP, and a combination containing 0.3% or more of those chemicals are designated as a hazardous substance. Additionally, diallyl phthalate and a combination containing 25% or more are also designated as a

hazardous substance. Chemical substances designated as *toxic substances* are regulated when they are imported. Individuals intending to import hazardous chemicals should report the types and purposes of these substances to the Ministry of Environment as per Article 20 of Chemical Substances Control Act.

Substance subject to intensive control is designated by the Ministry of Environment if a substance causes or be likely to cause cancer, mutation, reproductive disorders, or endocrine system disorders. According to the act on registration and evaluation of chemicals, *substance subject to intensive control* was defined as one of the following: (a) A substance that causes or is likely to cause cancer, mutation, reproductive disorders, or disorders of the endocrine system in humans or animals; (b) A substance that is highly likely to accumulate in the bodies of humans, animals or plants and remains in the environment for an extended period of time; (c) A substance that, when exposed to humans, may cause damage to the internal organs such as lungs, liver, and kidneys; (d) a substance that may pose a risk equivalent to or more serious than the substances referred to in items (a) through (c) to humans, animals or plants (129). If a chemical meets the definition, the Chemicals Evaluation Committee deliberate and discuss the chemical. After that, the Minister of Environment designates and publicly notifies the chemical as a *substance to intensive control*. Phthalates including DEHP, DBP, DIBP, BBP, and dihexyl phthalate are designated as *substances subject to intensive control*. Individuals involved in the manufacture or import of products containing *substances subject to intensive control* should report the name, content, hazard information, exposure information, and uses of the substance to the Ministry of Environment before the manufacture or import. A total of eight phthalate chemicals including DEHP and DBP have been designated as substances subject to intensive

control.

Law and regulation related to products containing phthalates

In South Korea, laws and regulations on products containing phthalates have been strengthened mainly for children's products. For the regulation of products containing phthalates, the following acts are to be considered: Food Sanitation act, Cleansing, and Hygiene Products Control Act, Special Act on the Safety of Children's Products, and Medical Devices Act.

Food Sanitation Act is the standard for improving public health by preventing sanitary risk caused by foods; Article 9 of this act stated that considering public health the Minister of Food and Drug Safety shall determine and publicly announce matters concerning apparatus, containers, and packages sold or used for business. According to the "Public notice on standards of apparatus, containers, and packages," DEHP should not be used in these items for usage in the food industry; it can only be used in the absence of any risk of DEHP eluting and contaminating food items. According to the Public notice, DBP, and BBP should not be used in baby bottles and pacifiers.

Individuals involved in the production of cleansing and hygiene products are under the regulation of Cleansing and Hygiene Products Control Act. According to Article 10 of this act, the Ministry of Food and Drug Safety may determine the standards and specifications concerning the ingredients, manufacturing methods, and purposes of use of cleansing and hygiene products and publicly notify them whenever it is deemed necessary for public health safety. The Ministry of Food and Drug Safety states that a resin shaft of a disposable cotton swab, synthetic resin fixing tape of a disposable diaper, or sanitary mat may contain DEHP, DBP, and

BBP at a concentration of 0.1% (or less) of the total mass of the products.

Recent changes in phthalate regulation included unification of regulations on children's products both by the Ministry of Trade, Industry, and Energy and Ministry of Environment. The Ministry of Trade, Industry, and Energy regulated six types of phthalate plasticizers for use in children's products intended for oral use and three types of phthalate plasticizers for use in children's products that were not intended for oral use following the "Special Act on Children's Product Safety." Additionally, the Ministry of Environment has regulated two types of phthalate plasticizers for use in children's products in accordance with the "Environmental Health Act," but manufacturers had difficulties in complying with the regulations under both laws and following various tests methods as per the regulations. Currently, individuals involved in producing children's products are only regulated by the "Common Safety Standards for Children's Products" for six types of phthalates including DEHP and DBP. The standard defines children's products as goods, parts, or accessories thereof used by or used for, children under 13 years of age, and states that these products should not contain over 0.1% of the six types of phthalates in total.

The Minister of Food and Drug Safety shall designate and publicly notify raw materials which cannot be used for the manufacture, etc. of cosmetics according to the Cosmetics act. Phthalates including DBP, DEHP, and BBP cannot be used in cosmetics, according to the regulation on cosmetic safety standards. However, as it is technically impossible to completely remove phthalates, the detection limit of phthalates in cosmetics is regulated as 100 μg/g.

Individuals intending to manufacture medical devices shall obtain manufacturing business permission from the Ministry of Food and Drug Safety,

manufacturing permission or certification, or file a manufacturing notification for medical devices he/she intends to manufacture. Article 6-3 of Medical Devices Act and Public notice for Regulations on Medical Device Permission, Report, and Review designated that phthalates such as DEHP, DBP, and BBP should not be used in intravascular administration sets (since 2015) and circuits for blood dialysis (since 2021).

Biomonitoring for phthalates in South Korea

The *in vivo* concentration of environmental hazardous factors or their metabolites indicates the quantified data on the subject's exposure. The method of assessing human exposure to environmental compounds is called human biomonitoring (130). This is a rather direct and accurate indicator of exposure compared to the concentrations in the surrounding environment or at the source of exposure.

The Environmental Health Act was enacted with the following purpose (131): "to protect and maintain national health and ecosystem integrity by investigating, diagnosing, and monitoring the effects of environmental pollution, toxic chemicals, etc. on national health and the ecosystem and any damage thereto, thereby preventing threats to national health and establishing measures to reduce these threats."

Article 14 of the Environmental Health Act requires the Ministry of Environment to conduct nationwide investigations once every three years, including assessment of *in vivo* concentrations of environmentally hazardous factors, harmful effects to health resulting from environmental hazardous factors, and the status of an outbreak of environmental diseases (132). Under the law, the

National Institute of Environment Health has performed a survey, named KoNEHS, with nationally representative samples (about 2,000 people) throughout South Korea.

Article 14 (2) of the Environmental Health Act requires a *detailed investigation* to understand how they cause *in vivo* concentrations of environmentally hazardous factors of a specific population group to be higher than *the standard* under Article 9. Article 9 of the Environmental Health Act requires establishing the Environmental Health Council under the jurisdiction of the Ministry of Environment to deliberate on major issues concerning the promotion of environmental health, including the designation of environmental diseases, formulation, and modification of an environmental health master plan and policies promoting environmental health. One of the objectives of the Environmental Health Committee is to define the standards of *in vivo* concentrations of environmentally hazardous factors.

Currently, no *standard* under the law to determine the necessity to conduct a *detailed investigation* for a specific region and/or population according to the results of the KoNEHS. However, it was not developed nor notified that *the standard* for Article 9 and Article 14 in South Korea. The *standard* could be a *reference value* or a *guidance value*. *Reference values* are derived from studies or surveys of a reference population that may represent the general population. Reference values present upper limits of the normal range of exposure to hazardous substances. They are determined as 90^{th} or 95^{th} percentile of the distribution of biomonitoring values of the reference population. If there is a vulnerable population group in the general population, reference values for this population group can be determined separately from the general population. Reference values

are not the basis of toxicological or biological evidence, so they should not be interpreted with respect to health outcomes. When biomonitoring values are above reference values it implies higher exposure to hazardous substances than the general population (133). *Guidance values* imply that there can be detrimental health effects among individuals with exposure levels higher than the guidance values. Guidance values help to interpret the results. These values are determined based on the understanding of absorption, distribution, metabolism, elimination, and toxicity of a substance (134).

Examples of biomonitoring standards for phthalates

Human Biomonitoring Committee in Germany was established in 1992 to collect and provide opinions of experts in the policy decision-making process by the Federal Ministry of Health and the Environment Agency. The members of committees consist of scientists in universities and government institutes and related people in organizations; the members are appointed for a term of three years (135). The committee performs a comprehensive review on the epidemiological and toxicological studies for each substance, determines human biomonitoring values (HBM values) and the recommended levels for human biomonitoring, and publishes a monograph (135).

HBM values are designated based on toxicological and epidemiological evidence; thus, they are guidance values directly related to health effects. HBM committees suggest two HBM values. HBM I level is no adverse effects of substances below the level and HBM II level is that people with biomonitoring values higher than HBM II level can show hazardous health effects in a vulnerable population so immediate action is required. Earlier, HBM values were defined

based only on epidemiological studies, but some substances had insufficient epidemiological evidence and a lacking of human studies. Therefore, a new concept has been introduced to determine HBM values based on the results of risk assessments including acceptable daily intake and tolerable daily intake concerning Biomonitoring Equivalents (BEs) used in the United States.

BEs are concentrations in the blood or urine corresponding to acceptable daily intake or tolerable daily intake, which are external doses determined for regulation. According to the recommendation of the National Research Council of the U.S., BEs have been developed and used since 2008 to interpret the biomonitoring values with respect to public health. First, considering the existing toxicological studies, the no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) is regarded as a point of departure (POD). If LOAEL or NOAEL is derived from animal studies, BE_{POD}-Animal is estimated using the pharmacodynamic characteristics of the animal. Subsequently, BE_{POD} for humans is estimated considering the uncertainty factor (UF) between the animal and humans, along with pharmacodynamic characteristics of humans. BEs are used for determining magnitudes of the public health problem due to hazardous substances, and prioritizing the follow-up biomonitoring tests for public health purposes (136-138).

Suggestion for laws and regulations of phthalate management

It was argued that the level of human exposure to phthalates is relatively low compared to the level of exposure in animal studies reporting detrimental effects, and excessive regulation of phthalates could be meaningless and affect public health negatively because of replacement of phthalates with other compounds,

which have insufficient toxicity data as compared to phthalates (139). However, epidemiologic studies have continuously reported that the detrimental health effects of phthalates are at a level in humans lower than those of the corresponding toxic level in animal studies. Furthermore, a review of risk assessment studies also reported that 85% of the included studies showed that children's exposure to phthalate is higher than the reference dose set by the US EPA for DEHP, although the annual trend for children has declined continuously (140).

The results of this study suggest that prenatal exposure to phthalates may have detrimental effects on children's growth. It is known that prenatal exposure to phthalates is not only associated with children's growth but also associated with children's neurodevelopment (15). However, it has yet emerged that the importance of phthalate regulation for pregnancies. Although more researches are needed on the predictors of phthalate exposures in pregnant women, explored sources of exposure such as perfume (141), and dietary factors (142) should be regulated more strictly and continuously monitored by the Ministry of Food and Drug Safety.

Environmental phthalate exposure is harmful to both children and older adults. Cardiovascular and related risk factors including atherosclerosis (140), insulin resistance (143), and diabetes (144), have been studied for their relationships with phthalate exposure. Additionally, an association between phthalates and muscle strength (145, 146) and frailty (146) was reported, consistent with our finding among children (association between prenatal phthalate exposure and decreased skeletal muscle mass). Phthalate plasticizers are regulated as EDCs but are more favorable than the alternatives because of cost and property: thus, it is difficult to replace them without regulative pressure (147, 148). Furthermore, phthalates are ubiquitous in the environment including dietary sources, personal

care products, dust, and indoor air, vinyl flooring, and medical sources (149, 150). Therefore, phthalates in the environment may contribute to hazardous effects on children and older adults. Thus, the regulatory standards maintained in children's products should be applied to all products. The regulation of all products in the environment cannot be achieved by revising one specific law. Currently, acts related to phthalates are the Food Sanitation Act, Cleansing and Hygiene Products Control Act, Special Act on the Safety of Children's Products', and Medical Devices Act. With reference to the recent revision of laws focusing on protecting children, the revision of listed related laws and regulation should be discussed and implemented.

In short, laws and regulations have focused on the proportion of phthalates in the produces used by children. Furthermore, laws and regulations are complex and have been added one by one when they become issues. Therefore, cases of out-of-regulation have continuously occurred. Children are not only exposed to goods produced only for them but even use the products not designed for children. Prenatal exposure to phthalates is also a considerable environmental hazard, not derived from products for children. In future, the phthalate management should be strengthened as reducing phthalate exposure throughout the living environment, rather than as regulating phthalate in some listed items.

Suggestion for biomonitoring of phthalate

According to the center for disease control and prevention in the U.S., the purposes of measuring the exposure level of hazardous substances are as follows (151): 1) to determine chemicals in the bodies of humans and their concentrations; 2) to determine the prevalence of concentrations above toxicity levels (for

chemicals with known toxicity levels); 3) to establish reference ranges that can be used by physicians and scientists to determine whether an individual or group has an unusually high exposure; 4) to assess the effectiveness of public health efforts to reduce exposure of Americans to specific chemicals; 5) to determine whether exposure levels are higher among minorities, children, women of childbearing age, or other potentially vulnerable groups; 6) to track, over time, trends in exposure levels of the population; 7) to set priorities for research on human health effects.

It is necessary to define standards for human biomonitoring values through a multidisciplinary committee. If biomonitoring (performed according to the Environmental Health Act) shows higher than normal standards, a close investigation articulated by the Environmental Health Act should be conducted. However, there have been no effective standards until now. Additionally, the definition and usage of the standards should be further discussed. Thus, in the first stage, it should be defined as "Standards for close investigation stated in the Environmental Health Act" in a narrow sense. Later, the scope of its application and concepts should be included. Thus, a committee composed of multidisciplinary experts to define standards for *the reference value* is needed. A multidisciplinary approach is required to ensure the assessment of toxicological validity, considerations from the perspective of health and environmental medicine, analysis of biological samples, consideration of social impacts, and acceptance in society from the medical point of view. Therefore, it is suggested to proceed with the establishment of standards for *the reference value* as follows:

Organization of the committee: To set up standards for the *in vivo* reference value of substances, various factors should be considered. This is required because it is often difficult to unambiguously conclude the relation between scientific levels

and reaction when defining standards for *the reference value* of environmentally hazardous substances. Despite existing toxicological study results, their relevance needs to be assessed via a direct human application. Additionally, the usefulness of uniform application to the actual population should be multilaterally discussed despite epidemiological study results. I suggest organizing the committee including experts who have participated in studies evaluating the maximum recommended level to sensitive individuals, experts who have participated in the Korean National Environmental Health Survey, experts who are related to permanent epidemiological surveys in industrial complexes and abandoned mine areas, and officials in the Ministry of Environment as well as in the relevant agencies involved in setting up standards for the reference value.

Selection of priority substances: Priority substances should be defined in all procedures to define standards for the reference value of biomonitoring substances and to select substances that are to be subjected to further biomonitoring. Considering the limited budget and resources, it is impossible to monitor in vivo concentration of all chemical substances or environmentally hazardous substances and to establish standards for the reference value. Moreover, social efforts might be required after setting up standards for the reference value. Therefore, priority substances must be selected. To define the priority of substances that are excluded from biomonitoring, the chemical ranking and scoring method may be applied. To determine the priority of substances for defining standards of the reference value, excess rates should be investigated, and yearly trends should also be considered in comparison to the recommended maximum limits or reference limits already existing in South Korea and other countries, based on which the committee would be able to make decisions.

Identification of toxicity and target organs of substances: The procedure to identify toxicity and target organs of substances is mixed with that of the priority substance selection. This is because the expertise and opinion of experts on toxicity levels are scored or affect the final decision when determining priority substances through the chemical scoring method or committee discussion. Thus, the multidisciplinary committee should decide based on the common data comprehensively summarized from studies on toxicity and target organs of substances.

Selection of populations that need special attention: The comprehensive summary of studies during the identification of toxicity and target organs of substances needs to identify populations that need special attention. When focusing on the effects of environmental exposure at low levels (rather than focusing on the acute effect of exposure at high levels) sensitive populations should be identified, for whom separate standards should be defined for the reference value. For example, lead (Pb) and mercury affect the development of the nervous system in children and adults and the neural development of a fetus in pregnant women and infants, respectively. It should be carefully considered when the populations that need special attention are to be included.

Determination of *in vivo* biomonitoring indices: When establishing standards for *the reference value*, even a single substance may need multiple indices. Of phthalates, DEHP is metabolized in various forms in the body. For example, blood MEHP and urine MEHP, MEOHP, MEHHP, and MECPP, of which the target metabolites and *in vivo* samples must be decided unanimously.

Checking the recommended maximum limits based on toxicological data: The committee must consider the existing recommended maximum limits if any. If

there are reports on the recommended maximum limits by the HBM of Germany, the EPA of the US, and the EFSA and WHO/JEFCA of Europe, these should be carefully reviewed and compared with *the reference value* levels of South Korea.

Identification of *in vivo* biomonitoring indices in populations: Most environmentally hazardous substances show differences in biomonitoring indices *in vivo*, depending on the country and population due to differences in diet, lifestyle, and environment. Instead of direct application of standards from other countries, it is necessary to check levels of *in vivo* indices in South Korea, to find explainable factors, and to propose standards for *in vivo* concentration of substances, based on which the committee should identify ways to improve these aspects rapidly at the policy-making and social level.

Considering all other situations: A standard value for the substances should be set with the consideration of all other situations. For example, since the use of phthalate has been reduced internationally, its concentration in the population has been lowered over time. However, it is predicted that exposure to alternative substances to substitute DEHP may increase. Following discussion and agreement in the committee, these need to be documented and consideration is needed to decide the time points when the standards for the reference value are to be presented and when the standards are to be revised on time.

Establishment of standards for *the standard*: The *standard* should be established after all the mentioned procedures and thorough discussion in the committee, including decisions on the best standards to be used, the guidance values, and the reference values. Although it may often be difficult for all committee members to agree, I suggest that the committee should comprise members with relevant experiences and backgrounds, and standards for *the*

standard should be established based on the level of an agreement after discussion.

4.3. Conclusion

The results of the systematic review and meta-analysis showed that prenatal exposure to phthalates is significantly associated with low BMI in childhood, but not with body fat mass percentage. In the Mother-child cohort study with 726 mother-child pairs, phthalates exposure during pregnancy was associated with low SMI at 6 and 8 years of age after childbirth. Prenatal phthalate exposure may affect the disturbance of normal growth of children, rather than act as an obesogen. Considering the detrimental effects of phthalates on children, it is necessary stricter and broader regulations on phthalates in living environments than now. Additionally, it needs to organize an expert committee under the Environmental Health Committee to set the *standard* for phthalates biomonitoring.

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국문 초록

프탈레이트가 소아의 신체 성장에 미치는 영향

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의학과 예방의학전공

프탈레이트는 플라스틱에 가소성을 부여하는 용도로 널리 사용되는 화학물질의 한 종류로, 내분비계 교란물질으로 작용하여 다양한 건강 영향을 미치는 것으로 알려져 있다. 하지만 소아에서 체질량지수 등 성장 지표와의 연관성은 일관되지 않게 보고되고 있다. 본 연구를 통해 산전 및 출생 후 프탈레이트 노출과 소아에서 성장과 관련된 지표들과의 연관성을 밝히고자 하였다. 이를 위해 본 연구에서는 체계적 문헌 고찰과 메타분석, 그리고 모-자 코호트 자료를 분석을 수행하였다.

가장 많이 사용되는 프탈레이트인 di(2-ethylhexyl) phthalate (DEHP)와 dibutyl phthalate (DBP)와 성장 관련 지표 사이 연구들에 대한 체계적 문헌고찰 및 메타분석을 수행하였다. 포함 기준을 충족하는 17개의 종적 연구와 12개의 단면 연구를 포함한 29개의 연구를 검토하였다. 또한 모-자 코호트 자료인 한국의 Environment and Development of Children (EDC)

코호트에서 추적된 726명의 모자 쌍의 데이터를 이용하여 프탈레이트와 어린이 성장 사이 연관성을 분석였다. 임신 중 산모 및 아이의 2, 4, 6, 8세의 요중 프탈레이트 대사체를 측정하여 이용하였다. 프탈레이트 대사체는 mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxo-hexyl) phthalate (MEOHP), mono(5-carboxy-2-ethylpentyl) phthalate (MECPP), mono-n-butyl phthalate (MnBP), monobenzyl phthalate (MBzP)를 요중에서 측정하였고, 아이의 성장과 관련된 지표는 6세 및 8세 시점에서 체질량지수, 지방지수, 근육량지수를 측정하였다. 여러 시점에서 측정된 프탈레이트 대사체와 성장 관련 지표 사이 연관성을 탐색하기 위해 다변량선형회귀분석, 잠재성장계층모형분석(latent class growth modeling), 다중정보모델(multiple informant model)을 이용하였다.

체계적 문헌고찰 및 메타분석 결과 임신 중 산모의 DEHP 노출은 출생 후 낮은 어린이의 체질량지수 Z 점수와 유의한 연관성을 관찰하였다. 임신 중 산모의 DEHP 노출과 어린이 체중 중 체지방의 비율 사이에는 유의한 연관성이 관찰되지 않았다. 모-자코호트 자료 분석 결과 임신 중 산모의 요중 MEHHP가 2배 증가할 때 6세와 8세에서 0.04 kg/m^2 및 0.06 kg/m^2 의 근육량지수 감소가 유의하게 연관되어 있음을 관찰하였다. 다중정보모델에서는 MEHHP의 태아기 노출과 어린이 시기 근육량지수 사이 음의 연관성이 관찰되었으며, MEHHP와 MECCP의 태아기 노출과 낮은 체질량지수 Z 점수가 연관되어 있음이 관찰되었다.

추가적으로 프탈레이트가 포함된 제품과 관련된 규정을

검토하였으며, 프탈레이트의 생체 내 농도 모니터링과 생체 내 농도 기준에 관련된 내용을 검토하여 정책적 개선이 가능한 부분을 찾아내고자 하였다. 현재 프탈레이트 포함 제품으로 규제되는 아동용 또는 의료용 제품은 소수에 불과한 반면, 프탈레이트 노출은 모든 환경을 통해 이루어질 수 있으며 건강영향 또한 아동에 국한되는 것이 아닌 점을 감안하여 프탈레이트 포함 제품의 제조에 대한 보다 엄격한 규제 및 관리 정책을 제안하였다. 또한 해외의 사례를 참조하여 프탈레이트의 생체 내 농도기준을 설정하기 위한 절차를 제안하였다.

본 연구는 코호트 자료 분석 및 체계적 문헌고찰을 통해 산전 프탈레이트 노출이 비만을 유발하는 것이 아닌 정상적인 성장을 저해하는 방향으로 작용할 수 있음을 발견하였다. 이는 출생 전 프탈레이트 노출이 어린이의 정상적인 발달 과정을 방해할 수 있음을 의미한다. 본 연구에서는 또한 국민 건강 보호를 위해 프탈레이트를 함유한 제품에 대한 개선된 규제 정책과, 환경보건 정책 측면에서 산모의 프탈레이트 노출 저감을 위한 규제 정책의 입안, 그리고 환경보건적 관리를 위한 프탈레이트의 생체 내 농도기준 설정의 방법을 제시하였다.