Association of prenatal urinary phthalate metabolite concentrations and childhood BMI and obesity

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Abstract

BACKGROUND—Although experiments in animals suggest that phthalates may have obesogenic effects, studies on prenatal exposure in children show inconsistent results.

METHODS—We measured urinary concentrations of 11 phthalate metabolites collected twice during pregnancy from mothers participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort study ($N = 345$). Height, weight, waist circumference, and percent body fat were assessed in their children between 5 and 12 years of age. We used generalized estimating equations to examine associations at each age and tested for interaction by sex.

RESULTS—Metabolites of diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP), butyl benzyl phthalate, and di(2-ethylhexyl) phthalate (DEHP) were positively associated with BMI *z*-score, waist circumference *z*-score, and percent body fat at multiple ages. At age 12, we observed increased odds of being overweight/obese with each doubling of prenatal concentrations of DEP (odds ratio = 1.3; 95% confidence intervals: 1.1, 1.4), DBP (1.2; 1.0, 1.4), and DEHP (1.3; 1.0, 1.6) metabolites. Results were similar in boys and girls except for DBP metabolites and the non-specific metabolite mono-(3-carbox-ypropyl) phthalate, which showed positive associations only in boys.

CONCLUSION—*In utero* exposure to certain phthalates is associated with increased BMI and risk for overweight/obesity in childhood.

The prevalence of obesity in children and adults has increased worldwide in recent decades (1), such that 35% of men and 40% of women in the United States are currently obese (2). Evidence suggests that increased caloric intake and reduced physical activity may not be sufficient to explain the current obesity epidemic (3). Exposure to endocrine-disrupting chemicals (EDCs), including phthalates—a class of chemicals widely used in personal care products, fragrances, medication coatings, adhesives, and polychlorinated vinyl (PVC) plastics—has been hypothesized as a possible contributor to the etiology of obesity (4). The prenatal period may be a critical developmental window for exposure to "obesogenic" chemicals to impact BMI later in life (5).

Exposure to phthalates is almost ubiquitous, with metabolites of eight common phthalates (Table 1) detected in 94% or more of Americans participating in the 2001–2010 cycles of the National Health and Nutrition Examination Survey (NHANES) (6). Low-molecular-weight phthalates, including diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP), and di-isobutyl phthalate (DiBP), are used in personal care products as carriers for fragrance and in the coatings of some medications. High-molecular-weight phthalates, including butyl benzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP), and di-isononyl phthalate (DiNP), are used to soften plastics, particularly PVC building materials. These phthalates break down into monoester metabolites that are eliminated in urine.

Several phthalates, including the metabolites of DBP, BBzP, and DEHP, have been shown to bind to and activate peroxisome proliferator-activated receptor-alpha (PPAR-α) and -gamma (PPAR-γ), nuclear receptors involved in fatty acid oxidation, adipogenesis, and fat storage (7). DEHP has also been associated with reduced thyroid hormone levels in rodent studies, which may interrupt energy homeostasis and increase body fat (8). Much of the rodent research focuses on DEHP, whereas other phthalates have been less studied with regard to body weight. Studies on adult male (8) and female (9) mice show that exposure to DEHP at doses ranging from 0.05 mg/kg per day (similar to occupational exposure levels) to 500 mg/kg per day were associated with increased food intake, body weight, and visceral fat. Prenatal and lactational exposure to DEHP at doses ranging from 0.05 to 300 mg/kg per day has also been associated with increased body weight and fat mass (9,10), which may not manifest until the animal reaches adulthood. For example, in male rat offspring, prenatal and lactational exposure of dams to 300 mg/kg per day of DEHP was associated with decreased body weight at birth but with significantly higher body weight at puberty and adulthood in the exposed group compared with controls (10).

Cross-sectional studies in humans have also linked urinary metabolites of various phthalates to increased BMI, waist circumference, and obesity in children (11) and adults (12). However, only a few longitudinal studies have examined the associations of prenatal exposure and later BMI (13–17), and these studies have shown inconsistent results and often sex-specific associations. A study in France that examined only boys found that prenatal urinary concentrations of the main DEP metabolite were associated with increased BMI at age 5 years (17); however, three other studies have found prenatal phthalate metabolites to

be associated with decreased BMI in boys (13–15). Specifically, a study on Spanish children found that urinary concentrations of high-molecular-weight phthalates in mothers during pregnancy were negatively associated with BMI z-score in boys at age 4 and 7 years but were positively (although non-significantly) associated with BMI z-score in girls at the same ages (16). Two different cohort studies in New York City also found negative associations of maternal urinary metabolites with BMI in boys (14,15). A pooled study (13) of three US cohorts, including the two previously mentioned New York cohorts, found that prenatal urinary concentrations of mono-3-carboxypropyl phthalate (MCPP), a metabolite of DBP and of several high-molecular-weight phthalates, were associated with increased risk for overweight/obesity in boys and girls at ages 4–7 years, whereas metabolites of DEP and DEHP were associated with decreased BMI z-scores in girls. In addition, a study that examined only girls found that urinary concentrations of low-molecular-weight phthalates at ages 6–8 years were associated with increased BMI and waist circumference at ages 7–13 years (18).

To further examine prenatal phthalate exposure and BMI in childhood, we assessed the association of maternal prenatal exposure with eight phthalates (described by concentrations of 11 phthalate metabolites in maternal urine) with BMI, waist circumference, and percent body fat in their children in a longitudinal birth cohort study. We examined anthropometric outcomes between 5 and 12 years of age, with a particular focus on age 12, as animal studies suggest that the obesogenic effects of phthalates may not manifest until puberty.

METHODS

Study Population

Study participants were mothers and children enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal cohort study examining the effects of early life environmental exposures on children's growth, health, and development. The study is based in the Salinas Valley, an agricultural region of California with a large Mexican immigrant population. Recruitment and enrollment in the study were conducted in 1999–2000. Pregnant women receiving prenatal care at partnering clinics that served predominantly low-income, Latina patients were screened for eligibility and were invited to participate. Eligible women were at least 18 years of age, spoke English or Spanish, qualified for low-income health insurance (Medicaid), and planned to deliver at the county hospital.

Follow-up of this prospective cohort study is ongoing. Maternal interviews and child developmental assessments have been conducted every 1–2 years through early adolescence. A total of 601 women were enrolled during pregnancy, 537 remained in the study through delivery, and 365 children completed anthropometric measurements at least once between 5 and 12 years of age. For this analysis, we randomly dropped one twin from each pair of twins in the study ($N = 3$) to maintain independent observations. We excluded 17 children who were missing prenatal phthalate biomarker measurements, for a final sample size of 345. All study activities were approved by the Institutional Review Board (IRB) of the University of California, Berkeley. The Centers for Disease Control and Prevention (CDC) IRB deferred approval to the IRB at the University of California, Berkeley. Informed consent

was obtained from all mothers; oral assent was obtained from children beginning at age 7 years and written assent was obtained at age 12 years.

Data Collection

The data for this analysis were collected from interviews with mothers near the end of the first and second trimesters of pregnancy and when their children were 5 (N = 313), 7 (N = 322), 9 (N = 321), 10 ½ (N = 303), and 12 (N = 320) years of age. All interviews were conducted in English or Spanish using structured questionnaires. At the baseline interview, conducted near the end of the first trimester of pregnancy, mothers were asked their age, marital status, education level, number of years residing in the United States, and household income, as well as information about smoking, soda consumption, and drug and alcohol use during pregnancy. Information on pregnancy weight gain, gestational duration, and infant birth weight was gathered from medical records. We calculated pre-pregnancy BMI using measured height and self-reported pre-pregnancy weight, if available, or imputed based on weight at first prenatal care visit if pre-pregnancy weight was unknown or out of range (n = 39). At the interviews when the children were between 5 and 12 years of age, mothers were asked about dietary and physical activity behaviors of their children, including household food security and fast food consumption.

Phthalate Biomarker Measurements

Urine samples were collected from mothers at the time of the two pregnancy interviews (mean ± SD: 14.0 ± 4.8 and 26.9 ± 2.5 weeks gestation). Samples were collected in polypropylene urine cups, aliquoted into glass vials, and stored at −80 °C until shipment to the CDC in Atlanta, Georgia, for analysis.

Samples were analyzed using solid-phase extraction coupled with isotope dilution high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry to quantify concentrations of the following 11 phthalate metabolites of 8 parent compounds (Table 1): monoethyl phthalate (MEP, a metabolite of DEP); mono-*n*-butyl phthalate (MBP, a metabolite of DBP); mono-isobutyl phthalate (MiBP, a metabolite of di-isobutyl phthalate (DiBP)); monobenzyl phthalate (MBzP, a metabolite of BBzP); four metabolites of DEHP (mono-2-ethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECCP)); mono(carboxyoctyl) phthalate (MCOP; a metabolite of di-isononyl phthalate (DiNP)); mono(carboxynonyl) phthalate (MCNP; a metabolite of di-isodecyl phthalate (DiDP)); and mono(3-carboxypropyl) phthalate (MCPP; a metabolite of several high-molecular-weight phthalates and a minor metabolite of DBP). Analytic methods have been published previously (19). Phthalate metabolite concentrations were reported in ng/ml of urine. Limits of detection (LOD) ranged from 0.2 to 0.6 ng/ml. Concentrations less than LOD were assigned the instrumental reading values, if available, or an imputed value less than LOD randomly selected from the log-normal distribution using maximum likelihood estimation (20), if not.

Urinary-specific gravity was measured using a hand-held refractometer (National Instrument Company Inc., Baltimore, Maryland). We corrected for urinary dilution using the formula

(analyte concentration $\times$ 0.24)/(sample specific gravity -1) (21). For 65 women missing specific gravity measures, urinary-specific gravity was imputed on the basis of urinary creatinine concentrations.

Anthropometric Measurements

At ages 5, 7, 9, 10½, and 12 years, children were weighed and measured without shoes or jackets. Standing height was measured using a stadiometer (Seca 222, Chino, California) and waist circumference was measured using a measuring tape held at the level of the iliac crest. Height and waist circumference were measured in triplicate and averaged. Body weight (kg) was measured using an electronic scale at ages 5 and 7 years (Tanita 1582, Arlington Heights, Illinois) and using a foot-to-foot bioimpedence scale (Tanita TBF 300A, Arlington Heights, Illinois) that provided both weight and percent body fat at ages 9, 10½, and 12 years. BMI was calculated as weight/height^2 (kg/m^2) and classified as underweight, normal weight, overweight, or obese according to the CDC's age- and sex-specific percentiles (22). Age- and sex-standardized BMI and waist circumference *z*-scores were calculated using CDC norms (23).

Statistical Analysis

Prenatal phthalate exposure was analyzed as the average of the two pregnancy phthalate metabolite concentration measures. Average phthalate metabolite concentrations were examined continuously as log$_2$-transformed variables and categorically by quartiles. DEHP devolves to several highly correlated metabolites (including MEHP, MEHHP, MEOHP, and MECCP) that individually account for only a fraction of total DEHP exposure but may represent >60% of the DEHP dose when taken together (24); thus, we summed the molar concentrations of MEHP, MEHHP, MEOHP, and MECCP to obtain a ΣDEHP variable. All other metabolites were examined individually. Although other studies have also generated summed variables for low-molecular-weight (MEP, MBP, MiBP) and high-molecular-weight (MBzP, ΣDEHP, MCPP, MCOP, MCNP) metabolites, we chose not to do so because we have no evidence that these compounds have similar mechanisms of action and because the low-and high-molecular-weight sums are dominated by MEP and ΣDEHP metabolite concentrations, respectively.

We examined the association of prenatal phthalate metabolites with repeated continuous (BMI *z*-score, waist circumference z-score, percent body fat) and binary (overweight/obese) outcomes using generalized estimating equations with Gaussian or binomial specification, respectively. Separate models were constructed for each phthalate metabolite. We included interaction terms for metabolite*visit point to allow the associations to differ by child age. In many cases we have chosen to report results for age 12 years, the oldest age for which we have body size data for this study, because it reflects the longest term impact of phthalate exposure *in utero*. In subsequent models, we also included interaction terms for metabolite*sex to determine whether associations differed between boys and girls, using the nlcom command in Stata to obtain coefficients for the sex-specific associations at each visit point.

Potential confounders were selected *a priori* using directed acyclic graphs (Supplementary Figure S1 online). All models controlled for maternal age, education, marital status; mother's years of residence in the United States and family income (below vs. at or above poverty threshold) at the time of pregnancy; smoking during pregnancy; and repeated measures of family food insecurity and child's fast food consumption at each time point. Measures of food insecurity and fast food intake were included because diet, particularly highly processed food and fast food, may be a source of exposure to high-molecular-weight phthalates (25,26). We have previously reported associations between childhood BMI and prenatal exposure to bisphenol A (BPA) (27), which—similar to some phthalates—is found in food, plastics, and food containers and was correlated with phthalate concentrations in this data set; thus, all models also controlled for maternal BPA concentrations. All covariates were categorized as shown in Table 2. Because maternal pre-pregnancy BMI, birth weight, and age at onset of puberty might be on the causal pathway between prenatal phthalate exposure and child BMI, we did not include these variables in the main models but did include them in sensitivity analyses. We have previously reported associations of prenatal serum concentrations of the pesticide dichlorodiphenyltrichloroethane (28) and polybrominated diphenyl ether flame retardants (29) with BMI in this cohort. Because we do not have reason to expect these chemicals to be associated with prenatal phthalate exposures and because a significant number of women were missing these variables, we controlled for dichlorodiphenyltrichloroethane and polybrominated diphenyl ether exposure in sensitivity analyses but not in the main models. Associations of prenatal phthalates and body size were very consistent at each time point throughout childhood, and hence, for simplicity, all sensitivity analyses were conducted using models of prenatal exposure and 12-year-old outcomes (the oldest age available), rather than on the repeated-measures models.

In addition, to begin to elucidate the effects of simultaneous exposure to all metabolites measured in this population, we implemented Bayesian Kernel Machine Regression (BKMR) on the continuous outcomes at 12 years, an approach that models the health outcome as a flexible kernel function of the exposure variables, adjusted for covariates (30). The phthalate metabolite concentrations were all moderately correlated with each other ($r =$ 0.18–0.71), precluding their inclusion in the same regression model, but making them good candidates for BKMR. We used BKMR as an approach for variable selection to determine which phthalate concentration variables are influential enough to include in the analysis and to determine the influence of each exposure variable on the outcome when other variables are held at specified values. Although BKMR can also examine interaction effects, this was beyond the scope of the present analysis.

All regression analyses were performed using Stata 13 (College Station, Texas), and BKMR analyses were conducted using the BKMR package in R (Vienna, Austria).

RESULTS

Mothers in the study tended to be Latinas of low-income and low-education level (high-school education or less) (Table 2). Most women were married or living as married, under the age of 30 years, and had been living in the United States for 10 years or less at the time of their pregnancy. More than 65% of mothers were overweight or obese before pregnancy

and 58.5% of their children were overweight or obese by 12 years of age. Mothers whose children were not included in the analysis (i.e., did not have phthalate measurements and at least one anthropometric measurement) were younger, more likely to live in the United States for less than 5 years, and were less likely to be obese (Supplementary Table S1). Mean BMI, waist circumference, and percent body fat for boys and girls at each age are shown in Supplementary Table S2. BMI measurements across ages 5–12 years were highly and significantly correlated. The lowest correlation, between BMI at 5 and that at 12 years of age, was 0.78. (Data not shown.)

The distribution of urinary phthalate metabolites during pregnancy is shown in Table 3. Phthalate metabolites were detected in most women (range: 87.5–100% detection), with MEP exhibiting considerably higher concentrations than the other phthalate metabolites. Analyte concentrations were similar to those measured in women of reproductive age in the NHANES data set for a similar time period (1999–2000 or 2001–2002) (31).

Table 4 shows the association of prenatal phthalate meta-bolites with odds of being overweight or obese at 5, 7, 9, 10½, and 12 years of age, by all children together and separately for boys and girls. We saw no evidence of interaction by sex for any metabolites except MBP (P value for sex interaction = 0.04). For MEP, MBzP, and ΣDEHP, we observed a consistent 20–30% increase in odds of overweight/obesity with each doubling of prenatal urinary metabolite concentration at each age point in both boys and girls. For MBP, we observed a 30–40% increase in odds in boys only (Table 4).

Table 5 shows the associations of phthalate metabolite concentrations with BMI z-score, waist circumference z-score, and percent body fat as continuous variables. Results were very similar in boys and girls (Supplementary Table S3), and hence results are shown for all children combined. We observed consistent positive associations of MEP with BMI, waist circumference, and percent body fat at each time point. At age 12 years, each doubling in urinary MEP concentrations was associated with increases in BMI z-score ($\beta = 0.09$, 95% confidence interval (CI): 0.04, 0.15), waist circumference z-score ($\beta = 0.10$, 95% CI: 0.04, 0.15), and percent body fat ($\beta = 1.0$, 95% CI: 0.2, 1.6), and results were similar at younger ages. We also observed positive associations with other metabolites, including MBP, MiBP, MBzP, and ΣDEHP, with BMI, waist circumference, and percent body fat (Table 5), but these associations were less consistent over time and were stronger at younger ages. Only MBP and MCPP showed some evidence of sex interaction (sex interaction P values <0.1) in both cases, with positive associations seen for boys and associations close to null for girls (Supplementary Table S3). For example, at age 12 years, each doubling of MBP was associated with a change in BMI z-score of 0.13 (95% CI: 0.02, 0.24) in boys vs. −0.01 (95% CI: −0.14, 0.12) in girls (sex interaction P value = 0.08) and a change in waist circumference z-score of 0.10 (95% CI: 0.01, 0.20) in boys vs. −0.03 (95% CI: −0.15, 0.08) in girls (sex interaction P value = 0.08).

Similar results were seen when phthalate metabolites were examined as categorical variables by quartiles at age 12 years (Figure 1). Being in the highest concentration quartile of prenatal phthalate biomarkers was associated with increased odds of overweight/obesity for MEP (odds ratio (OR) = 2.0, 95% confidence interval (CI): 1.0, 3.9), MBP (OR = 2.1, 95%

CI: 1.1, 4.2), MBzP (OR = 1.9, 95% CI: 0.9, 3.7), and ΣDEHP (OR = 2.2, 95% CI: 1.1, 4.5). There was no indication of sex interaction for overweight/obesity at age 12 when phthalate metabolites were considered as categorical variables, and hence the results are for boys and girls combined.

In sensitivity analyses, associations with outcomes at age 12 were very similar when we additionally controlled for maternal pre-pregnancy BMI, birth weight, or age at onset of puberty (Supplementary Table S4). Results were virtually unchanged when we additionally controlled for dichlorodiphenyltrichloroethane or polybrominated diphenyl ethers (not shown).

The BKMR analysis of simultaneous phthalate exposure identified all phthalate metabolite variables as important contributors to BMI z-score. Figure 2 illustrates that the trend of positive associations of MEP, MBP, MBzP, and ΣDEHP with BMI z-score at age 12 observed in the single metabolite linear regression models persists in the BKMR models including all other phthalates held at their median values, and also controlling for other covariates. Both MCPP and MCOP demonstrated negative associations with BMI z-score that were not apparent in the linear regression models, although in the case of MCPP this was strongly influenced by sparse data at rather low values. No other phthalate metabolites showed a remarkable change in slope.

DISCUSSION

We found that higher concentrations of urinary MEP, MBzP, and ΣDEHP metabolites in pregnant mothers were associated with increased odds of their children being overweight or obese between 5 and 12 years of age. Higher prenatal MEP concentrations were consistently associated with increased BMI, waist circumference, and percent body fat in children between 5 and 12 years of age. Higher prenatal MBP, MBzP, and ΣDEHP concentrations were also associated with larger body size over the same time period but less consistently. Results were similar at multiple ages between 5 and 12 years of age, suggesting that onset of puberty did not affect our findings. In addition, unlike previous studies, our results were quite similar between boys and girls. We saw some evidence of sex interaction with MBP and MCPP, with boys showing stronger positive associations with body size than girls, but not with other metabolites.

Five other investigations (13–17) have used similar study designs as ours, measuring phthalate metabolites in prenatal urine and body weight in childhood, although no other study followed up children beyond 7 years of age. Our findings are consistent with those of Botton *et al.* (17), who reported that prenatal urinary concentrations of MEP were associated with increased weight growth velocity at ages 2 and 4 years and increased BMI at 5 years in French boys (N = 520). The study by Botton *et al.* did not include girls and could not examine interaction by sex. Like Botton *et al.*, we found associations of prenatal MEP with increased BMI at 5 years of age; we also found that these associations persisted through age 12. However, our findings are not consistent with three other studies that have found different prenatal phthalate metabolites to be associated with decreased BMI in boys (14–16)

or with the pooled study that found increased odds of overweight/obesity with MCPP and decreased odds of overweight/obesity with MEP and ΣDEHP in girls (13).

Reasons for the inconsistency of study findings may relate to the difficulty in characterizing ongoing phthalate exposure during pregnancy. Phthalates are non-persistent compounds with short biological half-lives that are rapidly excreted from the body (32); thus, urinary metabolites reflect only recent exposure. Previous studies have shown that spot urine measures of phthalate metabolites have weak to moderate temporal reliability with interclass correlation coefficients often ranging from ~ 0.2 to 0.5 (33), which is consistent with our study. With the exception of the study by Valvi *et al.* (16), the previous studies assessed exposure during pregnancy with a single spot urine sample, which may not have been adequate to characterize phthalate exposure throughout pregnancy. In the current study, we averaged measures in two pregnancy urine samples to better characterize ongoing exposure, although this too may be insufficient to account for the temporal variability across pregnancy.

Another source of inconsistency with previous studies may relate to timing of exposure. Although we measured phthalate exposure in the prenatal period, we have no information about phthalate exposure during childhood, which may also be relevant to later risk for obesity. Our study population also differs from those of previous studies in terms of demographics. The vast majority of mothers in our study were recent immigrants from Mexico who were of low income and did not complete high school. These unique demographics may affect the generalizability of our results.

It is also possible that previous studies assessed BMI too early in childhood to detect associations with later obesity. On the basis of animal studies that only observed increased fat mass in offspring after the animals reached sexual maturity (9,10), we hypothesized that we might not detect associations between phthalate exposure and body size until age 12 or later. However, the fact that we found consistent positive associations of phthalate metabolites with BMI, waist circumference, percent body fat, and overweight/obesity consistently, beginning at age 5, argues against this hypothesis and suggests that puberty did not play a strong role in this association.

Possible biological mechanisms for our observed associations of several phthalates with increased BMI and risk for obesity include PPAR activation, adipocyte differentiation, and thyroid hormone disruption. MEHP, MBzP, and MBP activate PPAR-α and PPAR-γ nuclear receptors, key regulators of adipogenesis and energy storage, in both rodent and human cell lines (34). MEHP has been shown to stimulate lipid accumulation in differentiating adipocytes *in vitro* via PPAR-γ activation, leading to increased release of leptin, resistin, and adiponectin (35). In addition, DEHP has been shown to induce hypothyroidism in mice, leading to energy metabolism imbalance and increased white adipose tissue (8). In epidemiologic studies, several phthalate metabolites are also negatively associated with thyroid hormone levels (36), which could impact the regulation of resting energy expenditure and increase body weight. Various phthalates have demonstrated anti-androgenic or weak estrogenic properties (37), which can also impact fat quantity and distribution (38).

Exposure to the phthalates linked to obesity in this study is pervasive. Between 2001 and 2010, almost all Americans sampled in NHANES had detectable concentrations of metabolites of DEHP (e.g., MEOHP, MEHHP, MECCP), DEP (i.e., MEP), and DBP (i.e., MBP) in their urine (6). The primary routes of exposure to the high-molecular-weight phthalates used in plastics, including DEHP, DiNP, and BBzP, appear to be via diet (39), possibly a result of contact with plastics during food processing, packaging, and storage (40). A recent study found higher urinary metabolites of DEHP among individuals consuming more fast food (41), highlighting the difficulty in separating the effects of diet vs. high-molecular-weight phthalates on obesity. In contrast, the main sources of exposure to DEP and DBP are thought to be personal care product use and some medications (42–44); thus, diet is less likely to be a confounding factor in these associations. We found associations of prenatal exposure to DEP, DBP, BBzP, and DEHP with increased BMI, waist circumference, percent body fat, and increased risk of being overweight or obese in late childhood. These associations persisted when the joint impact of all phthalates was considered. This is the first study to demonstrate these associations, and findings will need to be replicated in other populations. Future studies should assess the trajectory of body size over time to determine in greater detail whether an increased BMI at a young age stays consistent throughout childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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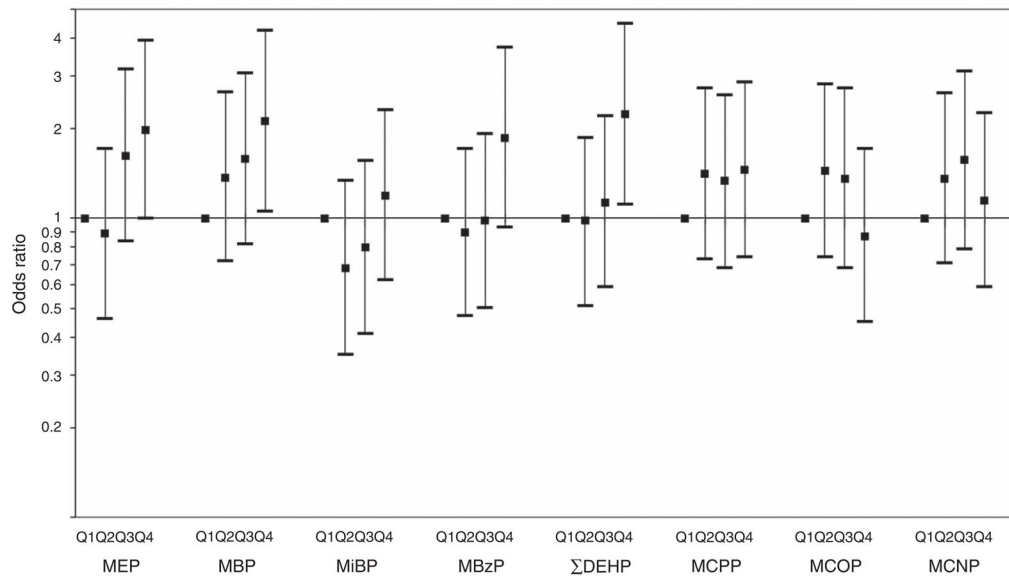
Figure 1.
Adjusted odds ratios of overweight/obesity at age 12 years comparing maternal quartile of urinary phthalate metabolites during pregnancy.
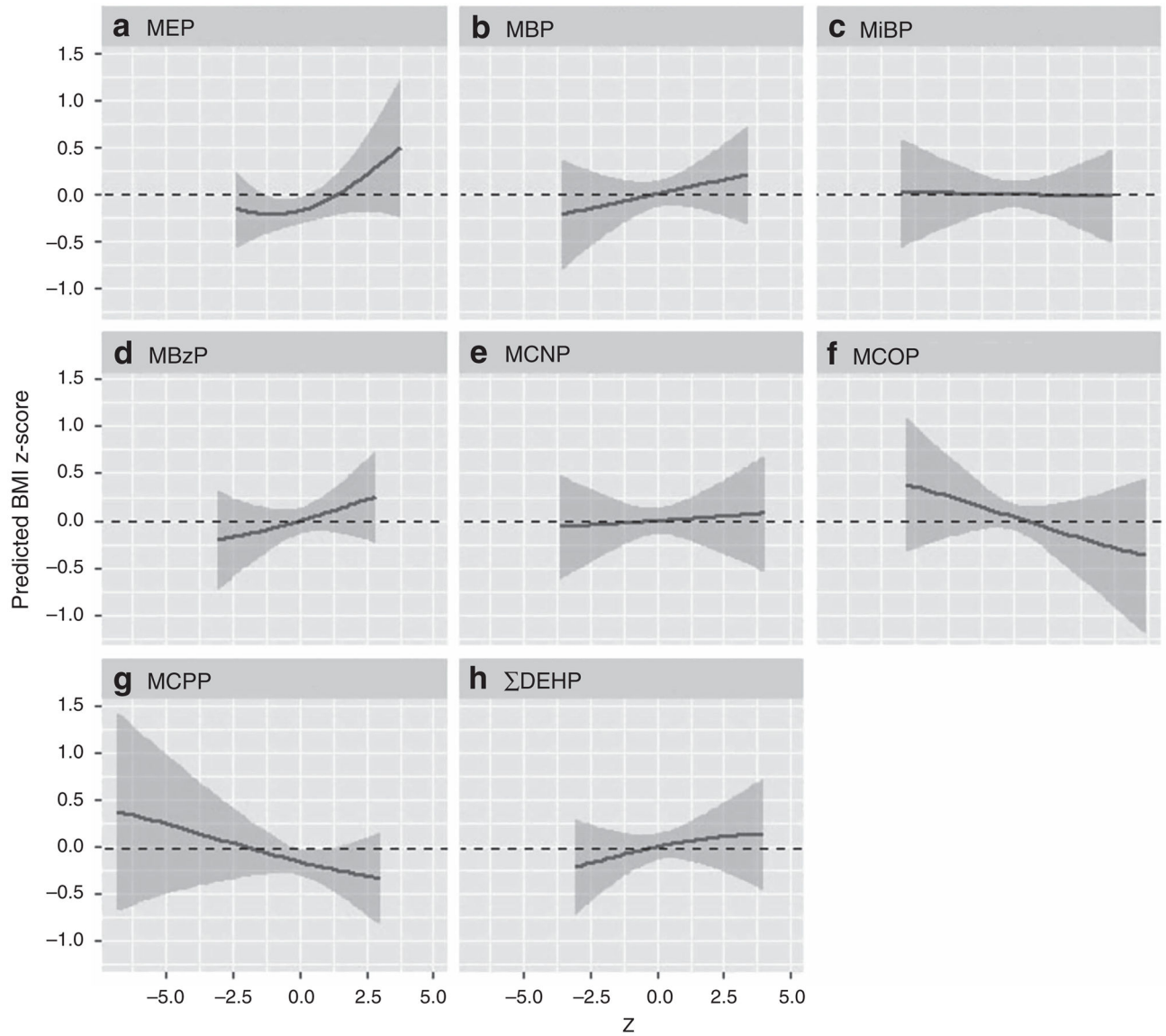
Figure 2.
Adjusted associations and 95% credible intervals for concentrations of MEP (**a**), MBP (**b**), MiBP (**c**), MBzP (**d**), MCNP (**e**), MCOP (**f**), MCPP (**g**), and ΣDEHP metabolites (**h**) with BMI *z*-score at age 12, holding all other phthalate metabolite concentrations at their median.

Table 1

Phthalates and their monoester metabolites

Phthalate	Used in	Urinary metabolite
Diethyl phthalate (DEP)	Personal care products, fragrance	Monoethyl phthalate (MEP)
Di-*n*-butyl phthalate (DBP)	Personal care products, medications	Mono-*n*-butyl phthalate (MBP)
Di-isobutyl phthalate (DiBP)	Personal care products, medications	Mono-isobutyl phthalate (MiBP)
Benzylbutyl phthalate (BzBP)	Polychlorinated vinyl (PVC), adhesives, sealants, car care products	Monobenzyl phthalate (MBzP)
Di-2-ethylhexyl phthalate (DEHP)	PVC, flexible plastics (toys, film packaging, medical devices, building materials, garden hoses, and so on)	Mono-2-ethylhexyl phthalate (MEHP)
		Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
		Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)
		Mono-(2-ethyl-5-carboxypentyl) phthalate (MECCP)
Di-*n*-octyl phthalate (DOP)	PVC, flexible plastics	Mono-(3-carboxypropyl) phthalate (MCPP)[a]
Di-isononyl phthalate (DiNP)	PVC, flexible plastics	Mono-(carboxyoctyl) phthalate (MCOP)
Di-isodecyl phthalate (DiDP)	PVC, flexible plastics	Mono-(carboxynonyl) phthalate (MCNP)

Adapted from CDC National Biomonitoring Program, Phthalate Biomonitoring Summaries http://www.cdc.gov/biomonitoring/biomonitoring_summaries.html.

[a]MCPP is also a minor metabolite of DBP and a non-specific metabolite of several high-molecular-weight phthalates

Table 2

Demographic characteristics of the study population, CHAMACOS Study, Salinas, CA (*N* = 345)

	N	(%)
Maternal characteristics at time of pregnancy		
Race/ethnicity		
Latina	339	(98.3)
Non-Latina, White	3	(0.9)
Other	3	(0.9)
Age (years)		
18–24	149	(43.2)
25–29	111	(32.2)
30–34	55	(15.9)
35+	30	(8.7)
Marital status		
Married/living as married	284	(82.3)
Single	61	(17.7)
Education		
6th grade	153	(44.4)
7–12th grade	118	(34.2)
High school graduate	74	(21.5)
Years of residence in the USA		
5 years	162	(47.0)
6–10 years	88	(25.5)
11+ years	56	(16.2)
Entire life	39	(11.3)
Household income		
Below or equal to poverty	213	(61.7)
Above poverty	132	(38.3)
Pre-pregnancy BMI		
Underweight	2	(0.6)
Normal	120	(34.8)
Overweight	133	(38.6)
Obese	90	(26.1)
Smoked during pregnancy		
No	331	(95.9)
Yes	14	(4.1)
Child Characteristics		
Birth weight		
<2,500 g	15	(4.4)
2,500 g	330	(95.7)
BMI at age 12		
Underweight (<5th percentile)	1	(0.3)

	N	(%)
Normal (5th–85th percentile)	131	(40.9)
Overweight (85th–95th percentile)	58	(18.1)
Obese (>95th percentile)	130	(40.6)
Food insecurity at age 12		
Food secure	224	(71.6)
Insecure without hunger	70	(22.4)
Insecure with hunger	19	(6.1)
Fast food consumption at age 12		
<1 time per week	97	(30.9)
1–2 times per week	206	(65.6)
3+ times per week	11	(3.5)

Table 3

Distribution of uncorrected and specific-gravity-corrected (italics) phthalate metabolites in maternal urine collected at two time points during pregnancy (*N* = 345)

Phthalate metabolite	%>LOD		Average of two measurements						
	1st measurement[a]	2nd measurement[b]	Geo. mean	10th%	25th%	50th%	75th%	90th%	95th%
MEP (ng/ml)	100.0%	99.5%	183.7	34.4	80.3	185.0	413.0	795.5	1,280.0
			236.0	*47.7*	*106.0*	*231.0*	*500.3*	*953.5*	*1,620.4*
MBP (ng/ml)	98.4%	100.0%	22.8	6.4	12.2	22.1	45.5	80.0	107.3
			28.5	*9.1*	*15.9*	*27.5*	*51.7*	*93.4*	*128.1*
MiBP (ng/ml)	92.8%	95.0%	2.7	0.8	1.5	2.8	5.4	9.5	16.5
			3.4	*1.1*	*1.9*	*3.5*	*6.5*	*11.0*	*16.3*
MBzP (ng/ml)	97.2%	98.8%	7.3	1.7	3.8	8.0	15.4	26.5	35.1
			9.1	*2.5*	*4.9*	*9.5*	*18.4*	*29.4*	*44.1*
ΣDEHP (nmol/ml)	NA	NA	0.2	0.1	0.1	0.2	0.3	0.6	0.8
			0.2	*0.1*	*0.1*	*0.2*	*0.4*	*0.6*	*0.9*
MEHP (ng/ml)	88.0%	91.4%	3.6	1.0	2.1	3.7	7.0	12.8	20.8
			4.5	*1.4*	*2.6*	*4.4*	*7.6*	*15.7*	*20.3*
MEHHP (ng/ml)	100.0%	99.3%	15.1	4.5	8.6	15.2	27.8	49.1	72.8
			18.8	*6.4*	*11.3*	*18.4*	*32.9*	*55.3*	*75.7*
MECPP (ng/ml)	100.0%	100.0%	25.9	9.1	15.7	25.2	43.1	70.2	92.8
			32.4	*12.9*	*21.0*	*31.1*	*50.5*	*78.3*	*110.3*
MEOHP (ng/ml)	98.2%	98.6%	11.2	3.4	6.6	11.2	20.8	35.4	51.1
			13.8	*5.0*	*8.0*	*14.1*	*22.6*	*39.0*	*53.6*
MCPP (ng/ml)	88.0%	93.5%	1.7	0.6	1.0	2.1	3.2	4.9	6.6
			2.2	*0.8*	*1.4*	*2.4*	*3.8*	*5.3*	*7.6*
MCOP (ng/ml)	96.8%	96.6%	3.0	1.0	1.7	3.2	5.0	7.5	11.0
			3.7	*1.5*	*2.4*	*3.9*	*5.5*	*8.9*	*12.2*
MCNP (ng/ml)	95.1%	96.7%	1.8	0.6	1.2	1.9	2.9	4.5	6.2
			2.3	*0.9*	*1.5*	*2.3*	*3.5*	*5.5*	*7.6*

LOD, limit of detection.

[a]Mean ± s.d. = 14.0 ± 5.0 weeks gestation.

[b]Mean ± s.d. = 26.9 ± 2.5 weeks gestation.

Table 4

Association of $\log_2$ prenatal urinary phthalate metabolite concentrations with odds of overweight/obesity in all children and separately by boys and girls (N = 341 children, 1,552 observations)

	5 year	7 year	9 year	10.5 year	12 year	Sex interaction
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	P value
MEP						
All	1.3 (1.1, 1.5)*	1.3 (1.1, 1.4)*	1.3 (1.1, 1.4)*	1.3 (1.1, 1.4)*	1.3 (1.1, 1.5)*	
Boys	1.3 (1.1, 1.5)*	1.3 (1.1, 1.5)*	1.3 (1.1, 1.5)*	1.3 (1.1, 1.5)*	1.3 (1.1, 1.5)*	
Girls	1.3 (1.1, 1.5)*	1.3 (1.1, 1.5)*	1.3 (1.1, 1.5)†	1.3 (1.1, 1.5)†	1.3 (1.0, 1.5)†	0.93
MBP						
All	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	1.2 (1.0, 1.4)	
Boys	1.3 (1.1, 1.7)†	1.3 (1.1, 1.6)*	1.4 (1.1, 1.7)*	1.4 (1.1, 1.7)*	1.4 (1.1, 1.8)*	
Girls	1.0 (0.7, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	0.04†
MiBP						
All	1.1 (0.9, 1.3)	1.1 (0.9, 1.2)	1.1 (1.0, 1.3)	1.1 (0.9, 1.3)	1.1 (1.0, 1.3)	
Boys	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)	
Girls	1.1 (0.9, 1.4)	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.00
MBzP						
All	1.2 (1.0, 1.4)†	1.2 (1.0, 1.4)†	1.2 (1.0, 1.4)†	1.2 (1.0, 1.4)†	1.2 (1.0, 1.4)†	
Boys	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)†	1.2 (1.0, 1.5)†	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)†	
Girls	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.2 (0.9, 1.4)	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	0.81
ΣDEHP						
All	1.1 (0.9, 1.4)	1.2 (1.0, 1.5)†	1.2 (1.0, 1.5)†	1.2 (1.0, 1.5)†	1.3 (1.0, 1.6)†	
Boys	1.1 (0.8, 1.6)	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)	1.3 (0.9, 1.7)	1.3 (1.0, 1.7)	
Girls	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.2 (0.9, 1.6)	1.3 (0.9, 1.7)	0.89
MCPP						
All	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.1 (0.9, 1.3)	
Boys	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)	1.1 (0.9, 1.4)	1.1 (0.8, 1.4)	1.2 (0.9, 1.5)	
Girls	0.9 (0.7, 1.2)	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	1.0 (0.8, 1.2)	0.24
MCOP						

	5 year	7 year	9 year	10.5 year	12 year	Sex interaction
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	P value
All	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)	1.0 (0.8, 1.3)	1.1 (0.8, 1.3)	
Boys	1.1 (0.9, 1.5)	1.1 (0.9, 1.5)	1.1 (0.9, 1.5)	1.1 (0.9, 1.4)	1.1 (0.9, 1.5)	
Girls	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)	1.0 (0.7, 1.3)	0.43
MCNP						
All	1.2 (1.0, 1.6)[†]	1.2 (1.0, 1.5)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.1 (0.8, 1.4)	
Boys	1.4 (1.0, 1.9)[†]	1.4 (1.0, 1.8)[†]	1.3 (1.0, 1.7)[‡]	1.2 (0.9, 1.7)	1.2 (0.9, 1.7)	
Girls	1.2 (0.9, 1.5)	1.1 (0.9, 1.5)	1.1 (0.8, 1.4)	1.0 (0.8, 1.4)	1.0 (0.8, 1.4)	0.33

Separate models created for each phthalate metabolite or sum of metabolites (ΣDEHP); coefficients for boys and girls obtained from model with sex interaction term.

Models control for 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 log2 prenatal BPA.

*
P<0.01.

†
P<0.05.

‡
P<0.10.

Table 5

Association of $\log_2$ prenatal urinary phthalate metabolite concentrations with BMI *z*-score, waist circumference *z*-score, and percent body fat in children at various ages

	5 year β (95% CI)	7 year β (95% CI)	9 year β (95% CI)	10.5 year β (95% CI)	12 year β (95% CI)
BMI *z*-score (*n* = 341 children, 1,551 observations)					
MEP	0.12 (0.06, 0.18)*	0.11 (0.06, 0.17)*	0.10 (0.05, 0.16)*	0.10 (0.04, 0.15)*	0.10 (0.04, 0.16)*
MBP	0.09 (0.00, 0.19)†	0.07 (−0.01, 0.16)‡	0.06 (−0.02, 0.14)	0.06 (−0.03, 0.14)	0.06 (−0.03, 0.15)
MiBP	0.06 (−0.02, 0.14)	0.04 (−0.03, 0.11)	0.04 (−0.04, 0.11)	0.05 (−0.03, 0.12)	0.06 (−0.02, 0.14)
MBzP	0.08 (−0.02, 0.17)	0.07 (−0.02, 0.16)	0.07 (−0.02, 0.16)	0.08 (−0.01, 0.17)†	0.09 (0.00, 0.19)†
ΣDEHP	0.05 (−0.05, 0.16)	0.08 (−0.02, 0.18)	0.09 (−0.01, 0.20)‡	0.09 (−0.02, 0.19)	0.08 (−0.03, 0.19)
MCPP	0.02 (−0.09, 0.13)	0.00 (−0.09, 0.10)	0.00 (−0.10, 0.09)	0.01 (−0.09, 0.10)	0.02 (−0.07, 0.12)
MCOP	0.08 (−0.04, 0.19)	0.05 (−0.05, 0.16)	0.04 (−0.06, 0.15)	0.05 (−0.05, 0.15)	0.06 (−0.04, 0.17)
MCNP	0.13 (0.01, 0.25)†	0.10 (−0.01, 0.21)‡	0.07 (−0.04, 0.18)	0.05 (−0.06, 0.16)	0.06 (−0.05, 0.17)
Waist circumference *z*-score (*n* = 341 children, 1,551 observations)					
MEP	0.09 (0.04, 0.15)*	0.13 (0.08, 0.18)*	0.14 (0.09, 0.18)*	0.10 (0.05, 0.15)*	0.10 (0.04, 0.16)*
MBP	0.07 (−0.01, 0.14)‡	0.12 (0.05, 0.19)*	0.12 (0.05, 0.19)*	0.05 (−0.03, 0.12)	0.04 (−0.04, 0.13)
MiBP	−0.02 (−0.08, 0.05)	0.10 (0.04, 0.15)*	0.12 (0.06, 0.18)*	0.02 (−0.05, 0.09)	0.03 (−0.05, 0.11)
MBzP	0.01 (−0.06, 0.09)	0.11 (0.04, 0.18)*	0.13 (0.05, 0.20)*	0.05 (−0.02, 0.13)	0.07 (−0.01, 0.15)‡
ΣDEHP	0.14 (0.05, 0.23)*	0.00 (−0.08, 0.09)	0.00 (−0.09, 0.09)	0.10 (0.00, 0.19)‡	0.09 (−0.01, 0.20)‡
MCPP	−0.04 (−0.13, 0.05)	0.08 (0.00, 0.17)‡	0.11 (0.02, 0.19)†	−0.03 (−0.11, 0.05)	−0.01 (−0.09, 0.07)
MCOP	0.00 (−0.09, 0.09)	0.13 (0.05, 0.21)*	0.15 (0.07, 0.23)*	0.01 (−0.08, 0.10)	0.03 (−0.07, 0.13)
MCNP	0.01 (−0.09, 0.11)	0.15 (0.06, 0.24)*	0.16 (0.08, 0.25)*	−0.02 (−0.12, 0.08)	0.01 (−0.10, 0.11)
Percent body fat (*n* = 289 children, 801 observations)					
MEP	—	—	1.2 (0.5, 1.8)*	1.2 (0.5, 1.8)*	1.0 (0.3, 1.7)*
MBP	—	—	0.9 (−0.1, 1.9)	1.0 (0.0, 1.9)‡	0.7 (−0.4, 1.8)‡
MiBP	—	—	0.1 (−0.8, 1.1)	0.6 (−0.3, 1.5)	0.2 (−0.7, 1.2)
MBzP	—	—	0.8 (−0.2, 1.9)	1.0 (0.0, 2.0)‡	0.7 (−0.4, 1.8)

	5 year	7 year	9 year	10.5 year	12 year
	β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
ΣDEHP	—	—	1.0 (−0.2, 2.2)	1.0 (−0.2, 2.2)	1.1 (−0.2, 2.4)
MCPP	—	—	0.1 (−0.8, 1.1)	0.5 (−0.4, 1.5)	0.0 (−1.0, 1.0)
MCOP	—	—	0.2 (−0.9, 1.3)	0.7 (−0.5, 1.8)	0.4 (−0.9, 1.6)
MCNP	—	—	0.3 (−0.8, 1.5)	0.5 (−0.7, 1.6)	0.2 (−1.0, 1.5)

Separate models created for each phthalate metabolite or sum of metabolites (ΣDEHP).

Models control for 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 log2 prenatal BPA.

*
P<0.01.

†
P<0.05.

‡
P<0.10.