Published in final edited form as:

Environ Res. 2019 May ; 172: 604–614. doi:10.1016/j.envres.2019.03.009.

Identifying Periods of Susceptibility to the Impact of Phthalates on Children's Cognitive Abilities

Nan Li^a, George D. Papandonatos^b, Antonia M. Calafat^c, Kimberly Yolton^d, Bruce P. Lanphear^{e,f}, Aimin Chen^g, and Joseph M. Braun^a

^aDepartment of Epidemiology, Brown University, 121 South Main Street, Providence, Rhode Island, United States

^bDepartment of Biostatistics, Brown University, 121 South Main Street, Providence, Rhode Island, United States

^cNational Center for Environmental Health, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, Georgia, United States

^dDepartment of Pediatrics, Division of General and Community Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, 3333 Burnet Avenue, Cincinnati, Ohio, United States

^eChild and Family Research Institute, British Columbia Children's Hospital, 950 West 28th Ave, Vancouver, British Columbia, Canada

^fFaculty of Health Sciences, Simon Fraser University, 8888 University Drive, Burnaby, British Columbia, Canada

^gDivision of Epidemiology, Department of Environmental Health, University of Cincinnati College of Medicine, 160 Panzeca Way, Cincinnati, Ohio, United States

Abstract

Background: Early-life phthalate exposures may adversely affect children's neurodevelopment by disrupting thyroid function, reducing gonadal hormone levels, or altering fatty acid concentrations in the brain. This study aimed to identify periods of heightened susceptibility during gestation, infancy, and childhood to the impact of phthalates on children's cognitive abilities.

Methods: We used data from 253 mother-child pairs in the Health Outcomes and Measures of the Environment (HOME) Study (Cincinnati, Ohio), a longitudinal pregnancy and birth cohort. We

Corresponding Author: Nan Li, Brown University, Box G-S121-2, Providence, RI 02912, Telephone: +1 401-863-1806, nan_li1@brown.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Declarations of interest: None.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

quantified urinary concentrations of 11 phthalate metabolites in samples collected twice during gestation and 6 times during study visits when children were aged 1–8 years using a modified method of on-line solid phase extraction coupled with isotope dilution-high performance liquid chromatography-tandem mass spectrometry. We assessed children's intelligence (IQ) at ages 5 and 8 years using the Wechsler Preschool and Primary Scale of Intelligence-III and Wechsler Intelligence Scale for Children-IV, respectively. We estimated covariate-adjusted associations between a 1-standard deviation increase in log₁₀-transformed urinary phthalate metabolite concentrations at each visit and children's IQ, adjusting for demographic, perinatal, and child factors; we tested for differences in these associations across visits using multiple informant models.

Results: Associations between some phthalate metabolites and IQ varied by visit (phthalate × visit interaction p-values < 0.20). The sum of di(2-ethylhexyl) phthalate metabolites (ΣDEHP), mono(3-carboxypropyl) phthalate, and monoethyl phthalate at age 3 years, and monobenzyl phthalate at 16 weeks gestation and child ages 3, 5, and 8 years were inversely associated with children's full-scale IQ. For example, each 1-standard deviation increase in ΣDEHP at age 3 was associated with a 1.9-point decrease in full-scale IQ (95% confidence interval: −3.7, −0.2). Mono-n-butyl phthalate and mono-isobutyl phthalate at age 4 years were positively associated with children's full-scale IQ.

Conclusion: Urinary concentrations of several phthalate metabolites at age 3 years, compared to other time periods, were more strongly associated with decreased cognitive abilities in these children.

Keywords

phthalate metabolites; cognitive abilities; IQ; children; periods of susceptibility

1. Introduction

Phthalates are a class of endocrine disrupting chemicals (EDCs) that are used in some personal care products, vinyl flooring, medical supplies, food packaging, toys, and other plastics (Braun et al., 2014; Carlstedt et al., 2013; Hauser and Calafat, 2005; Rudel et al., 2011). Phthalate exposure can occur through dermal absorption, inhalation, ingestion (Bornehag et al., 2005; Braun et al., 2014; Rudel et al., 2011). Despite the relatively short biological half-lives (<24 hours) of phthalate metabolites in the human body, there is often repeated and long-term phthalate exposure due to the ubiquity of sources (Hauser and Calafat, 2005). Exposure to phthalates is nearly universal, even among pregnant women, infants, and children; some phthalates can cross the placenta (Braun et al., 2014; Carlstedt et al., 2013; Lewis et al., 2013; Mose et al., 2007; Rudel et al., 2011; Silva et al., 2004; Watkins et al., 2014). Several studies have found that urinary concentrations of some phthalate metabolites were higher in children than in adults, possibly due to children's specific physiology, diet, and age-specific behaviors (Koch et al., 2004; Koch et al., 2005; Silva et al., 2004; Sørensen, 2006; Watkins et al., 2014).

Exposure to some phthalates during gestation and childhood may disrupt children's neurodevelopment (Braun, 2017; Braun et al., 2013). Several potential mechanisms may

explain how different phthalates affect neurodevelopment. Some phthalates (i.e. di(2-ethylhexyl)-phthalate [DEHP], di-n-butyl phthalate [DnBP], and benzyl butyl phthalate [BBzP]) may disrupt the production or function of thyroid hormones, which play an essential role in hippocampal function and neurodevelopment (Akaike et al., 1991; Breous et al., 2005; Huang et al., 2007; Meeker et al., 2007; Miodovnik et al., 2014; Moog et al., 2017; Poon et al., 1997; Stein et al., 1991; Sugiyama et al., 2005). DEHP may also interfere with lipid signal transduction pathways and alter lipid profiles in the brain, which in turn may adversely influence brain development (Xu et al., 2007). Finally, the anti-androgenic properties of certain phthalates (i.e. DEHP, BBzP, DnBP, di-isobutyl phthalate [DiBP]) may affect gonadal hormone mediated neurodevelopmental process (Andrade et al., 2006; Howdeshell et al., 2008b).

Previous studies have examined the associations of gestational or childhood urinary phthalate metabolite concentrations with children's cognitive abilities (Braun et al., 2017a; Cho et al., 2010; Doherty et al., 2017; Factor-Litvak et al., 2014; Gascon et al., 2015; Huang et al., 2015; Huang et al., 2017; Ipapo et al., 2017; Kim et al., 2017; Kim et al., 2018; Kim et al., 2011; Nakiwala et al., 2018; Polanska et al., 2014; Tellez-Royo et al., 2013; Whyatt et al., 2012). However, many of these studies focused on prenatal period, and collected only one urine sample during pregnancy or childhood, which may not be representative of phthalate exposure during all of pregnancy or childhood (Cho et al., 2010; Doherty et al., 2017; Huang et al., 2017; Ipapo et al., 2017; Kim et al., 2018; Nakiwala et al., 2018; Tellez-Royo et al., 2013; Whyatt et al., 2012). Only four studies examined both gestational and childhood urinary phthalate metabolite concentrations; two found that childhood, but not gestational urinary phthalate metabolite concentrations were inversely associated with cognitive abilities (Huang et al., 2015; Kim et al., 2017), and two studies reported the opposite (Factor-Litvak et al., 2014; Polanska et al., 2014). Inconsistencies across studies may relate to differences in study design, timing of exposure or outcome assessment, or instruments used for cognition assessment. To our knowledge, only one study to date has assessed the associations of children's cognitive abilities with urinary phthalate metabolite concentrations at >1 time points in childhood; however, that study neither assessed urinary phthalate metabolite concentrations in early life (age <3 years) nor formally evaluated periods of heightened susceptibility (Factor-Litvak et al., 2014).

To address the literature gaps regarding periods of heightened susceptibility to the impact of phthalates on cognitive abilities, we investigated the associations of eight urinary phthalate metabolite concentrations (from 16 weeks of gestation to age 8 years) with child cognitive abilities using a longitudinal cohort study.

2. Materials and Methods

2.1. Study Participants

We used data from the Health Outcomes and Measures of the Environment (HOME) Study, a pregnancy and birth cohort that recruited pregnant women from nine prenatal clinics in the Cincinnati, OH, metropolitan area from 2003 to 2006, and conducted follow-up visits with their children through age 8 years (Braun et al., 2017b). Details on eligibility criteria, recruitment, and follow up for the HOME Study have been described previously (Braun et

al., 2017b). Briefly, eligibility requirements included that women were at least 18 years of age, 16±3 weeks of gestation, and living in the Cincinnati, Ohio area in a home built before 1978. Of 1,263 eligible women, 468 enrolled in our study. Among 401 mothers who remained in the study until delivery, 389 had live singleton births. The current analysis was restricted to 253 mother-child pairs who had at least one gestational and at least one childhood measurement of urinary phthalate metabolite concentrations, complete covariate information, as well as at least one measurement of cognitive abilities at age 5 or 8 years.

The HOME Study protocols were approved by the institutional review boards (IRBs, # 2015–6165) at Cincinnati Children's Hospital Medical Center (CCHMC) and participating delivery hospitals. Brown University and the Centers for Disease Control and Prevention (CDC) IRBs deferred to the CCHMC IRB. All mothers provided informed consent for themselves and their children.

2.2. Urinary Phthalate Metabolite Concentration Assessment

We collected maternal urine samples in polypropylene specimen cups twice, at approximately 16- and 26-week gestation. Among children, we collected urine samples annually from ages 1–5 years and then at age 8 years. We collected urine samples in surgical inserts placed into a clean diaper for children who were not toilet-trained, in a training potty lined with inserts for children who were in the process of being toilet-trained, or in polypropylene specimen cups for children who were already toilet-trained. Urine was then expressed from the insert with a syringe into a urine collection cup in the laboratory. All urine samples were refrigerated for less than 24 hours prior to processing, and they were stored at –20 °C until chemical analysis at the CDC.

We used a modified method of on-line solid phase extraction coupled with isotope dilution-high performance liquid chromatography-tandem mass spectrometry to measure the urinary phthalate metabolite concentrations (Silva et al., 2007). We measured urinary concentrations of monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono(3-carboxypropyl) phthalate (MCP), monobenzyl phthalate (MBzP), monocarboxyethyl phthalate (MCOP), monocarboxynonyl phthalate (MCNP), and 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 (MECPP). We were not able to measure MCOP or MCNP in prenatal urine samples because the method including these biomarkers had not been developed yet. We were unable to use concentrations of MnBP, MiBP, and MEHP in urine samples collected at ages 1–3 years because we detected these metabolites in the diaper inserts (Watkins et al., 2014). Thus, we used three oxidative DEHP metabolites (MEOHP, MEHHP, and MECPP) to create a summary DEHP metabolite measure (i.e., Σ DEHP) for both gestational and childhood samples. To calculate concentrations of Σ DEHP (in ng/mL), we divided each DEHP metabolite concentration by its molar mass, summed the individual concentrations, and then multiplied the molar sum by the molar mass of MECPP. The limits of detection (LODs) for the phthalate metabolites ranged from ~0.1 to ~1 ng/mL. Values below the LOD were given a value of the LOD/ 2 (Hornung and Reed, 1990). Phthalate metabolite concentrations (ng/mL) were log₁₀-transformed in statistical analyses.

To make the different phthalate metabolite effect sizes more comparable to each other, we standardized each phthalate metabolite concentration to its mean and standard deviation on the $\log_{10}$ scale (Buckley et al., 2016).

2.3. Cognitive Outcomes

Three trained examiners assessed children's cognitive abilities at ages 5 and 8 years, using the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) and Wechsler Intelligence Scale for Children-IV (WISC-IV), respectively (Wechsler, 2002, 2003). One investigator (Kimberly Yolton) performed quality checks and recertified the examiners every 6 months to ensure proper administration and scoring of the IQ measures. Both instruments assess children's overall intellectual abilities (Full-Scale Intelligence Quotient [FSIQ]), verbal abilities (Verbal IQ [WPPSI-III] and Verbal Comprehension Index [WISC-IV]), perceptual reasoning and organization skills (Performance IQ [WPPSI-III] and Perceptual Reasoning Index [WISC-IV]), and speed of mental and graphomotor processing (Processing Speed Quotient [WPPSI-III] and Processing Speed Index [WISC-IV]). Additionally, working memory (Working Memory Index [WMI]) was measured using the WISC-IV. FSIQ, Verbal IQ, Performance IQ, and Processing Speed Quotient scores from the WPPSI-III are comparable to FSIQ, Verbal Comprehension Index, Perceptual Reasoning Index, and Processing Speed Index scores from the WISC-IV, respectively (Wechsler, 2002, 2003). FSIQ scores were normalized to a mean of 100 and standard deviation (SD) of 15 based on U.S. population-based reference data. Higher scores on these tests indicate better cognitive performance.

2.4. Covariate Assessment

We used directed acyclic graphs to identify potential confounders that may be both associated with urinary phthalate metabolite concentrations and IQ, but not causal intermediates or colliders (Supplemental Figure S1) (Watkins et al., 2014). Maternal age, education, household income, marital status, and children's race were assessed using standardized questionnaires administered by trained interviewers. Children's sex and maternal pregnancy-induced hypertension (PIH) were abstracted from hospital medical charts (Werner et al., 2015). We calculated pre-pregnancy body mass index (BMI) using self-reported height and weight (or imputed weight for mothers with missing data) (van der Laan et al., 2007). We measured mothers' FSIQ using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). We assessed maternal gestational exposure to tobacco smoke using the mean of the $\log_{10}$ -transformed serum cotinine concentrations measured at 16- and 26- week gestation. Study staff assessed caregiving environment using the Home Observation for Measurement of the Environment when children were age 1 year (Caldwell and Bradley, 2003). In addition, we accounted for urine dilution by adjusting for $\log_{10}$ -transformed urinary creatinine concentrations in our models (Barr et al., 2005).

2.5. Statistical Analyses

We explored the distribution of urinary phthalate metabolite concentrations across visits by calculating univariate statistics and creating violin plots (Hintze and Nelson, 2012). We then calculated mean child 5-year and 8-year FSIQ scores by strata of the key covariates and compared the FSIQ scores across these strata using a one-way analysis of variance test.

Given that the concentrations of different phthalate metabolites could be correlated due to shared exposure sources, we calculated Pearson's correlation coefficients between each of the eight phthalate metabolites by each visit, and constructed a series of correlation matrix heatmaps.

We used a previously described multiple informant method to investigate associations of repeated gestational and childhood urinary phthalate metabolite concentrations with the repeated IQ measurements (Buckley et al., 2019; Jackson-Browne et al., 2018; Sanchez et al., 2011; Stacy et al., 2017). This method can be used when there are repeated and sparsely sampled environmental exposure measures at different time points and information gathered from multiple sources is used to measure the same construct (Sanchez et al., 2011). The multiple informant model utilizes generalized estimating equations to jointly estimate the exposure-outcome association for each exposure period and also tests whether the estimates for exposure-outcome association are equal at all exposure periods. The assumptions of this model include: there are predefined exposure periods; all participants have the same timing of exposure; there is a homogenous exposure effect within each exposure period; there is at least one exposure sample per participant (Sánchez et al., 2011).

Urinary phthalate concentrations at 16- and 26-week gestation, and ages 1, 2, 3, 4, 5, and 8 years, were treated as informants and repeated child IQ measures as the outcome. We estimated the difference in IQ scores for a 1-standard deviation increase in $\log_{10}$ -transformed concentrations of a specific phthalate metabolite for each time period. The multiple informant model allowed us to test whether phthalate-FSIQ associations differed by exposure period, using the p-value of the phthalate $\times$ visit interaction term (the heterogeneity p-value). The null hypothesis is that the associations are the same across all time periods, and we considered those with p-values <0.20 as evidence that at least one of the phthalate-FSIQ associations differed from the rest.

The multiple informant model included visit, phthalate $\times$ visit, and covariates. Because IQ measurements are relatively stable during childhood, we used both 5-year and 8-year IQ measurements as the outcome to increase precision of measurement (Braun et al., 2017c; Moffitt et al., 1993). However, we did not estimate associations between 8-year phthalates and 5-year IQ due to the reverse causation. In all multiple informant models, we adjusted for children's race and mother's age, education, household income, marital status, FSIQ, pre-pregnancy BMI, gestational serum cotinine, Home Observation for Measurement of the Environment Score, and $\log_{10}$ urinary creatinine concentrations.

2.6. Secondary and Sensitivity Analyses

First, we used the three-way visit $\times$ phthalate $\times$ sex interaction term p-value from our multiple informant models to determine if the phthalates-FSIQ associations differed by sex at any of the visits under investigation (p-values <0.20). Furthermore, for significant inverse associations between some phthalate metabolites and FSIQ scores at some exposure period, we examined the dose-response relationships using 3-knot restricted cubic polynomial splines (Desquilbet and Mariotti, 2010). In addition, we specified a weighted quantile sum regression model to estimate the overall impact of phthalate metabolites collected at a certain periods of development (characterized by a weighted phthalate index estimated with

a set of identified phthalate metabolites) on children's average FSIQ assessed at ages 5 and 8 years and to estimate the relative weights of each individual phthalate metabolites to children's FSIQ (Czarnota et al., 2015). We used 40% of the sample for estimating weights and 60% to estimate the relation between the weighted phthalate index and children's FSIQ. Moreover, for phthalate metabolites that were inversely associated with FSIQ during a certain exposure period, we also examined their associations with individual IQ components. In addition, maternal PIH may be associated with both urinary phthalate metabolite concentrations and child neurodevelopment (Tuovinen et al., 2014; Werner et al., 2015). However, it is unclear if PIH is a mediator of the association between phthalates and IQ (Tuovinen et al., 2014; Werner et al., 2015). Therefore, we additionally adjusted for PIH to test the robustness of our results. We also additionally adjusted for test examiner in sensitivity analysis to determine whether this influenced our results. Finally, given the variation of creatinine concentrations among participants, we conducted a sensitivity analysis excluding participants whose urinary creatinine concentrations were in the top or bottom 2.5% for each visit. We performed all analyses using SAS version 9.4 (SAS Institute Inc., USA).

3. Results

In total, we included children who had at least one phthalate metabolite measurement during gestation and at least one during childhood, at least one measurement of FSIQ at ages 5 or 8 years, and complete covariate data in the analysis (Supplemental Table S1). Urinary MCOP concentrations increased with children's age, whereas the urinary concentrations of other phthalate metabolites were relatively stable (Supplemental Table S2 and Figure 1). Gestational concentrations of MnBP and MEP were higher than childhood concentrations, whereas MiBP and MCPP were lower. For gestational phthalate metabolite concentrations, the correlations between MCPP and MnBP (Pearson's r ranges 0.3–0.6) and MCPP and MiBP (Pearson's r ranges 0.4–0.6) were moderate to strong. Urinary concentrations of MCOP and MCPP were moderately to strongly correlated at ages 1–5 years (Pearson's r ranges 0.6–0.9, Supplemental Figure S2). The correlations between MBzP and MnBP (Pearson's r ranges 0.3–0.8) and MCOP and MCNP (Pearson's r ranges 0.3–0.6) concentrations at childhood visits were moderate to strong as well.

On average, children's mean FSIQ scores were lower among those who were Non-Hispanic Black, had lower caregiving environment scores, or were born to mothers who were 25 years old at delivery, unmarried, overweight or obese (BMI ≥ 25 kg/m²), less educated (high school education), actively smoked during pregnancy, had lower household income, or had lower FSIQ (Table 1).

After adjusting for covariates, several urinary phthalate metabolites were associated with children's FSIQ scores; these associations varied with the timing of urinary phthalate metabolite concentration measurement. Each 1-standard deviation increase in log₁₀-transformed urinary MBzP concentrations at 16-week gestation (β : -1.6; 95% confidence interval [CI]: -3.4, 0.1), and child ages 3 years (β : -2.5; 95% CI: -4.4, -0.6), 5 years (β : -1.6; 95% CI: -3.3, 0.1), and 8 years (β : -1.8; 95% CI: -3.5, -0.1) was inversely associated with children's FSIQ scores (Table 2 and Figure 2). Each 1-standard deviation increase in

log₁₀-transformed urinary concentrations of Σ DEHP, MEP, and MCPP assessed at age 3 years was associated with a 1.9 (95% CI: -3.7, -0.2), 2.1 (95% CI: -3.6, -0.6), and 2.4 (95% CI: -4.2, -0.7) points decrease in FSIQ, respectively. MEP and MCPP at age 2 years were also inversely associated with FSIQ, although the 95% CIs included the null. In contrast, urinary concentrations of MnBP and MiBP at age 4 years were positively associated with children's FSIQ (MnBP 2.1 [0.3, 3.9]; MiBP 1.8 [0.0, 3.6]). The associations of MBzP, MCPP, MEP, and MCNP concentrations with FSIQ varied by visit (phthalate $\times$ visit interaction p-values < 0.20) (Table 2). The associations between phthalate metabolite concentrations and FSIQ did not differ by child sex (all three-way interaction term p-values > 0.20) (Supplemental Table S3).

We observed linear decreases in children's FSIQ scores with increasing urinary concentrations of Σ DEHP, MBzP, MEP, and MCPP at age 3 years (all non-linearity p-values = 0.29) (Figure 3). When examining the overall impact of Σ DEHP, MBzP, MEP, and MCPP assessed at age 3 years, the weighted phthalate index was inversely associated with children's average FSIQ assessed at ages 5 and 8 years (β = -2.2, 95% CI = -3.6, -0.8). The relative weights (i.e., relative contribution) of the four metabolites were 0.40, 0.33, 0.18, and 0.09, for MCPP, Σ DEHP, MBzP, and MEP, respectively. When further examining the associations of Σ DEHP, MBzP, MEP, and MCPP concentrations at age 3 years with individual IQ components, associations were generally of similar magnitude to the associations with FSIQ (Supplemental Table S4). The pattern of results was not substantially different from our main analysis after additionally adjusting for PIH, test examiner, or excluding participants in the top or bottom 2.5% of urinary creatinine concentrations (Supplemental Figures S3–S5).

4. Discussion

We estimated the associations of repeated measurements of urinary phthalate metabolite concentrations from 16 weeks of gestation to age 8 years with IQ scores in school-age children using a longitudinal cohort study. These associations varied depending on specific phthalate metabolite and timing of the metabolite assessment. Urinary concentrations of MBzP at 16-week gestation, and ages 3, 5, and 8 years, and concentrations of Σ DEHP, MEP, and MCPP at age 3 years were inversely associated with children's FSIQ. In contrast, urinary concentrations of MnBP and MiBP at age 4 years were positively associated with children's FSIQ.

We found that urinary concentrations of Σ DEHP, MBzP, MEP, and MCPP around age 2–3 years were inversely associated with children's IQ, although the 95% CIs included the null for the associations at age 2 years. This age range is a critical period for brain development, including synaptogenesis, synaptic pruning, and myelination (Rice and Barone, 2000; Tierney and Nelson, 2009). Therefore, during this period, the rapidly developing brain may be more sensitive to toxic chemicals and other insults, which may play a detrimental role in neurodevelopment and adversely influence children's cognitive abilities later in life. An experimental study has shown that early-life exposure to a mixture of phthalates decreased the number of neurons and synapses in the medial prefrontal cortex and was associated with

decreased cognitive flexibility in adult rats (Kougias et al., 2018), which supports our observations.

Some epidemiological studies have reported inverse associations of gestational or childhood urinary concentrations of Σ DEHP, MBzP, MEP, and MCPP with children's cognitive abilities (Doherty et al., 2017; Factor-Litvak et al., 2014; Huang et al., 2015; Kim et al., 2017; Kim et al., 2018; Polanska et al., 2014). Consistent with our findings, a study conducted in New York City found that urinary MBzP concentration assessed at age 3 was inversely associated with FSIQ at age 7 years (Factor-Litvak et al., 2014). In contrast, another study that examined urinary concentrations of DEHP metabolites, MBzP, and MEP assessed at age 2 years reported null associations (Polanska et al., 2014). However, given that the urinary phthalate metabolite concentrations and outcome were both assessed at age 2 years, these associations were cross-sectional, thus limiting causal inference (Polanska et al., 2014). The inconsistencies in findings may also be explained by differences in age at outcome assessment (from ages 2 to 8 years), and instruments used to assess cognitive abilities (i.e., Wechsler's versus Bayley Scales of Infant Development).

In our cohort, urinary concentrations of MBzP collected at multiple time points of gestation and childhood were inversely associated with children's IQ. The inverse association between MBzP concentration at age 3 years and IQ was similar when we examined individual IQ components. Consistent with our findings, the study conducted in New York City found inverse associations of FSIQ and PIQ scores at age 7 years with urinary MBzP concentrations at gestation and age 3 years, although they reported null association with MBzP assessed at age 5 years (Factor-Litvak et al., 2014). Another U.S. study found prenatal urinary MBzP concentrations were inversely associated with visual recognition memory, assessed with the Fagan Test of Infant Intelligence, at 27 weeks in girls (Ipapo et al., 2017). Visual recognition memory has been shown to be predictive of childhood IQ (McCall and Carriger, 1993). Three other studies found null associations between MBzP (gestational or childhood) and children's cognitive abilities (Doherty et al., 2017; Polanska et al., 2014; Tellez-Rojo et al., 2013). However, these three studies assessed MBzP concentrations using a single gestational urine sample collected in late pregnancy, or a single childhood urine sample collected at the time of outcome assessment (i.e., cross-sectional association). Given the short half-life of phthalate metabolites and episodic nature of phthalate exposures, the use of one single measurement may not accurately capture urinary phthalate metabolite concentrations during entire pregnancy or childhood. In the present study, we assessed MBzP concentration at multiple exposure periods, including early and late pregnancy, ages 1–5 years and 8 years, which allowed us to better capture the phthalate exposure and identify multiple periods of susceptibility.

We found that urinary concentrations of MnBP and MiBP at age 4 years were positively associated with children's IQ. Other studies that investigated the associations of childhood urinary MnBP and MiBP concentrations with cognitive abilities reported null associations (Factor-Litvak et al., 2014; Huang et al., 2007; Kim et al., 2017; Polanska et al., 2014). We are uncertain about the reasons for the observed positive associations at 4 years of age. An experimental study indicated that perinatal exposure to DnBP (parent chemical of MnBP) in rats impaired the spatial learning and memory of their offspring (Li et al., 2013). However,

prior studies examining the associations of gestational MnBP and MiBP concentrations with IQ in children have been inconsistent (Doherty et al., 2017; Factor-Litvak et al., 2014; Huang et al., 2015; Ipapo et al., 2017; Kim et al., 2017; Polanska et al., 2014; Tellez-Rojo et al., 2013). A pregnancy-birth cohort from New York City found that MnBP and MiBP concentrations measured in third trimester maternal urine samples were positively associated with mental development index scores among 2-year-old boys (Doherty et al., 2017). Another U.S. study found inverse associations between gestational urinary MnBP and MiBP concentrations with children's IQ at age 7 years (Factor-Litvak et al., 2014). Other studies found null associations for gestational urinary MnBP and MiBP concentrations, which are consistent with our findings (Huang et al., 2015; Ipapo et al., 2017; Kim et al., 2017; Polanska et al., 2014; Tellez-Rojo et al., 2013). The reasons for these discrepancies are unclear. One possibility is that the biological activity of MnBP and MiBP with regard to neurodevelopment is relatively weak, and thus the studies with relatively small sample sizes may have limited statistical power to detect potential effects (Miodovnik et al., 2014). In addition, differences in timing of metabolite/outcome assessment, instruments used for outcome assessment, and concentrations of MnBP and MiBP in the specific populations may also explain the inconsistent findings. Additional studies are needed to further investigate these associations.

Some animal studies have shown that perinatal phthalate exposure was inversely associated with learning and memory in offspring (Arcadi et al., 1998; Li et al., 2013; Li et al., 2009). Both laboratory-based and epidemiologic studies have provided evidence for the potential biological mechanisms underlying associations between phthalate exposure and neurodevelopment. Phthalates disrupt thyroid hormones and androgen homeostasis, both of which were associated with diverse neurodevelopmental outcomes, including cognitive abilities and behaviors (Cohen-Bendahan et al., 2005; Ghassabian et al., 2011; Haddow et al., 1999; Rovet, 2014). It is well established that thyroid hormones are critical for fetal and infant brain development, including cognitive abilities (Akaike et al., 1991; Chan and Kilby, 2000; Miodovnik et al., 2014; Moog et al., 2017; Stein et al., 1991; Zoeller and Rovet, 2004). Exposure to DEHP, DnBP, and BBzP (the parent chemical of MBzP and, to a lesser extent, MnBP) have been shown to influence thyroid function and thyroid hormone levels (Breous et al., 2005; Meeker et al., 2007; Poon et al., 1997; Stein et al., 1991; Sugiyama et al., 2005). In a large Danish study, urinary phthalate metabolite concentrations were inversely associated with serum levels of free and total triiodothyronine in children (Boas et al., 2010). These findings suggest that disruption of thyroid homeostasis may partly explain the adverse cognitive effects of phthalates. Further, animal studies suggest that some phthalates (i.e. DEHP, BBzP, DnBP, DiBP) diminish fetal testosterone production by altering Leydig cell differentiation and function (Fisher et al., 2003; Foster et al., 2001; Howdeshell et al., 2008a; Kavlock et al., 2002). Epidemiologic studies have also suggested that phthalates may alter endogenous reproductive hormones in humans (Lin et al., 2011; Main et al., 2006). Because reproductive hormones are important for brain development, alterations in gonadal hormones may partly explain the cognitive effects of phthalates (Gore et al., 2014; Nguon et al., 2005). Another potential pathway is via disturbance of lipid metabolism. Lipids and their fatty acid substituents are essential for normal fetal brain development including neurodevelopment (Helland et al., 2003). Studies suggest that

gestational exposure to DEHP in rats altered transfer of essential fatty acids across the placenta and reduced concentrations of lipids (e.g. free cholesterol, sphingomyelin) in the fetal rat brain (Xu et al., 2007, 2008). Therefore, some of our findings (e.g., Σ DEHP, MBzP) are supported by the previous animal and *in vitro* studies, whereas some were not (e.g., MnBP, MiBP).

Given the anti-androgenic properties of phthalates, we speculated that the influences of phthalates on fetal brain development might differ between boys and girls (Doherty et al., 2017). Some studies reported that sex modified the associations between certain phthalate metabolites and child cognitive abilities (Doherty et al., 2017; Kim et al., 2011), whereas other studies did not (Factor-Litvak et al., 2014; Huang et al., 2015). In the present study, we did not identify sex-specific patterns of associations between phthalate metabolites and cognition, but acknowledge that we had limited statistical power to study this. Future studies with larger sample sizes are needed to explore the potential for sex to modify these associations.

There are some strengths and limitations to our study. First, to our knowledge, most studies used a single measurement of phthalate metabolites when examining its impact on children's cognition. The longitudinal design of our study enabled us to be the first to examine the associations of children's cognitive abilities with urinary phthalate metabolite concentrations assessed at multiple important periods of neurodevelopment, including gestation, infancy, and childhood (Rice and Barone, 2000). The novel approach of the multiple informant model enabled us to utilize these repeated metabolite assessments, and be the first to formally test differences in the associations between phthalate metabolites and children's IQ across visits, and identify potential periods of susceptibility (Sanchez et al., 2011). However, it is noteworthy that the associations of urinary phthalate metabolite concentrations at ages 5 and 8 years with children's IQ assessed at ages 5 and 8 years, respectively, in the present study are cross-sectional and need to be interpreted with caution. In addition, we were not able to measure concentrations of MCNP and MCOP in gestational urine samples, or use concentrations of MnBP, MiBP, and MEHP in urine samples collected at ages 1–3 years, which to some extent limited our ability to identify windows of susceptibility for these phthalates. It is also worth noting that not all phthalates share a common toxicological profile. Animal and *in vitro* studies suggest that the specific endocrine disrupting effects of various phthalates may vary (Howdeshell et al., 2008a; Romano et al., 2018). Therefore, it is plausible that different phthalates have different periods of susceptibility or opposite impact on neurodevelopment. Second, our study had a modest sample size, and the multiple informant model has relatively low power to detect metabolite-time period interactions. Regardless, we were still able to detect effect measure modification of associations between certain phthalate metabolites and child IQ by exposure period. Third, phthalate metabolite concentrations assessed using a single urine sample may not represent long-term exposure, particularly during infancy and childhood when there are rapid changes in physiology, diet, and personal care product use (Adibi et al., 2008; Braun et al., 2012; Watkins et al., 2014). In our study, we quantified urinary phthalate metabolite concentrations twice during gestation and six times in childhood, which enabled us to examine repeated measures of phthalate metabolites. However, we cannot rule out the possibility of exposure misclassification. Future studies should consider collecting several urine samples in each

time period to obtain a more accurate estimation of urinary phthalate metabolite concentrations. Fourth, we used repeated IQ measurements to increase the precision of our estimates. The WPPSI-III and WISC-IV tests, which were developed to assess cognitive abilities in preschool and school-aged children (Wechsler, 2002, 2003), respectively, have been shown to have very good reproducibility during childhood (Braun et al., 2017c; Moffitt et al., 1993). Fifth, while we did not adjust for multiple comparisons because it may have undeservedly reduced power (Rothman, 1990), the consistency of the associations of multiple phthalate metabolites at ages 2 and 3 years with FSIQ, and the consistency of the inverse associations across individual IQ components suggest that these results may not be solely due to chance. Finally, we collected detailed information on demographic factors, perinatal factors, and child factors, which allowed us to adjust for a variety of potential confounders. However, there may be some residual confounding from other correlated neurotoxicants (e.g., lead, mercury) and maternal/child diet.

In this study, the associations of gestational and childhood urinary Σ DEHP, MBzP, MEP, and MCPP concentrations with children's FSIQ scores depended on the timing of exposure. Specifically, our results suggest that urinary concentrations of several phthalate metabolites at age 3 years, compared to other time periods, were more strongly associated with children's cognitive abilities. Future epidemiologic studies are needed to confirm our findings and laboratory studies could investigate the underlying mechanisms of the time-dependent associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work was supported by National Institute of Environmental Health Sciences [grant numbers P01 ES011261, R01 ES024381, and R01 ES020349]. We acknowledge the technical assistance of M. Silva, E. Samandar, J. Preau, and J. Tao (Centers for Disease Control and Prevention, Atlanta, Georgia) in measuring the urinary concentrations of phthalate metabolites.

Funding: This work was supported by National Institute of Environmental Health Sciences [grant numbers P01 ES011261, R01 ES024381, and R01 ES020349].

The HOME Study protocols were approved by the institutional review boards (IRBs, # 2015–6165) at Cincinnati Children's Hospital Medical Center (CCHMC) and participating delivery hospitals. Brown University and the Centers for Disease Control and Prevention (CDC) IRBs deferred to the CCHMC IRB.

References

- Adibi JJ, Whyatt RM, Williams PL, Calafat AM, Camann D, Herrick R, Nelson H, Bhat HK, Perera FP, Silva MJ, Hauser R, 2008 Characterization of phthalate exposure among pregnant women assessed by repeat air and urine samples. *Environ. Health Perspect* 116, 467–473. [PubMed: 18414628]
- Akaike M, Kato N, Ohno H, Kobayashi T, 1991 Hyperactivity and spatial maze learning impairment of adult rats with temporary neonatal hypothyroidism. *Neurotoxicol. Teratol* 13, 317–322. [PubMed: 1886541]
- Andrade AJ, Grande SW, Talsness CE, Gericke C, Grote K, Golombiewski A, Sterner-Kock A, Chahoud I, 2006 A dose response study following in utero and lactational exposure to di-(2-

- ethylhexyl) phthalate (DEHP): reproductive effects on adult male offspring rats. *Toxicology* 228, 85–97. [PubMed: 16996189]
- Arcadi FA, Costa C, Imperatore C, Marchese A, Rapisarda A, Salemi M, Trimarchi GR, Costa G, 1998 Oral toxicity of bis(2-ethylhexyl) phthalate during pregnancy and suckling in the Long-Evans rat. *Food Chem. Toxicol* 36, 963–970. [PubMed: 9771559]
- Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL, 2005 Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. *Environ. Health Perspect* 113, 192–200. [PubMed: 15687057]
- Boas M, Frederiksen H, Feldt-Rasmussen U, Skakkebaek NE, Hegedüs L, Hilsted L, Juul A, Main KM, 2010 Childhood exposure to phthalates: associations with thyroid function, insulin-like growth factor I, and growth. *Environ. Health Perspect* 118, 1458–1464. [PubMed: 20621847]
- Bornehag CG, Lundgren B, Weschler CJ, Sigsgaard T, Hagerhed-Engman L, Sundell J, 2005 Phthalates in indoor dust and their association with building characteristics. *Environ. Health Perspect* 113, 1399–1404. [PubMed: 16203254]
- Braun JM, 2017 Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nat. Rev. Endocrinol* 13, 161–173. [PubMed: 27857130]
- Braun JM, Bellinger DC, Hauser R, Wright RO, Chen A, Calafat AM, Yoltan K, Lanphear BP, 2017a Prenatal phthalate, triclosan, and bisphenol A exposures and child visual-spatial abilities. *Neurotoxicology* 58, 75–83. [PubMed: 27888119]
- Braun JM, Just AC, Williams PL, Smith KW, Calafat AM, Hauser R, 2014 Personal care product use and urinary phthalate metabolite and paraben concentrations during pregnancy among women from a fertility clinic. *Journal of exposure science & environmental epidemiology* 24, 459–466. [PubMed: 24149971]
- Braun JM, Kalloo G, Chen A, Dietrich KN, Liddy-Hicks S, Morgan S, Xu Y, Yoltan K, Lanphear BP, 2017b Cohort Profile: The Health Outcomes and Measures of the Environment (HOME) study. *Int. J. Epidemiol* 46, 24. [PubMed: 27006352]
- Braun JM, Sathyanarayana S, Hauser R, 2013 Phthalate exposure and children's health. *Curr. Opin. Pediatr* 25, 247–254. [PubMed: 23429708]
- Braun JM, Smith KW, Williams PL, Calafat AM, Berry K, Ehrlich S, Hauser R, 2012 Variability of urinary phthalate metabolite and bisphenol A concentrations before and during pregnancy. *Environmental health perspectives* 120, 739–745. [PubMed: 22262702]
- Braun JM, Yoltan K, Stacy SL, Erar B, Papandonatos GD, Bellinger DC, Lanphear BP, Chen A, 2017c Prenatal environmental chemical exposures and longitudinal patterns of child neurobehavior. *Neurotoxicology* 62, 192–199. [PubMed: 28736150]
- Breous E, Wenzel A, Loos U, 2005 The promoter of the human sodium/iodide symporter responds to certain phthalate plasticisers. *Mol. Cell Endocrinol* 244, 75–78. [PubMed: 16257484]
- Buckley JP, Hamra GB, Braun JM, 2019 Statistical Approaches for Investigating Periods of Susceptibility in Children's Environmental Health Research. *Curr. Environ. Health Rep*
- Buckley JP, Herring AH, Wolff MS, Calafat AM, Engel SM, 2016 Prenatal exposure to environmental phenols and childhood fat mass in the Mount Sinai Children's Environmental Health Study. *Environment international* 91, 350–356. [PubMed: 27037776]
- Caldwell B, Bradley R, 2003 Home Inventory Administration Manual University of Arkansas at Little Rock, Little Rock, AK.
- Carlstedt F, Jönsson BA, Bornehag CG, 2013 PVC flooring is related to human uptake of phthalates in infants. *Indoor Air* 23, 32–39. [PubMed: 22563949]
- Chan S, Kilby MD, 2000 Thyroid hormone and central nervous system development. *J. Endocrinol* 165, 1–8. [PubMed: 10750030]
- Cho SC, Bhang SY, Hong YC, Shin MS, Kim BN, Kim JW, Yoo HJ, Cho IH, Kim HW, 2010 Relationship between environmental phthalate exposure and the intelligence of school-age children. *Environ. Health Perspect* 118, 1027–1032. [PubMed: 20194078]
- Cohen-Bendahan CC, van de Beek C, Berenbaum SA, 2005 Prenatal sex hormone effects on child and adult sex-typed behavior: methods and findings. *Neurosci. Biobehav. Rev* 29, 353–384. [PubMed: 15811504]

- Czarnota J, Gennings C, Wheeler DC, 2015 Assessment of weighted quantile sum regression for modeling chemical mixtures and cancer risk. *Cancer Inform* 14, 159–171. [PubMed: 26005323]
- Desquilbet L, Mariotti F, 2010 Dose-response analyses using restricted cubic spline functions in public health research. *Statistics in medicine* 29, 1037–1057. [PubMed: 20087875]
- Doherty BT, Engel SM, Buckley JP, Silva MJ, Calafat AM, Wolff MS, 2017 Prenatal phthalate biomarker concentrations and performance on the Bayley Scales of Infant Development-II in a population of young urban children. *Environ. Res* 152, 51–58. [PubMed: 27741448]
- Factor-Litvak P, Insel B, Calafat AM, Liu X, Perera F, Rauh VA, Whyatt RM, 2014 Persistent Associations between Maternal Prenatal Exposure to Phthalates on Child IQ at Age 7 Years. *PLoS one* 9, e114003. [PubMed: 25493564]
- Fisher JS, Macpherson S, Marchetti N, Sharpe RM, 2003 Human ‘testicular dysgenesis syndrome’: a possible model using in-utero exposure of the rat to dibutyl phthalate. *Hum. Reprod* 18, 1383–1394. [PubMed: 12832361]
- Foster PM, Mylchreest E, Gaido KW, Sar M, 2001 Effects of phthalate esters on the developing reproductive tract of male rats. *Hum. Reprod. Update* 7, 231–235. [PubMed: 11392369]
- Gascon M, Valvi D, Fornes J, Casas M, Martínez D, Júlvez J, Monfort N, Ventura R, Sunyer J, Vrijheid M, 2015 Prenatal exposure to phthalates and neuropsychological development during childhood. *Int. J. Hyg. Environ. Health* 218, 550–558. [PubMed: 26095249]
- Ghassabian A, Bongers-Schokking JJ, Henrichs J, Jaddoe VW, Visser TJ, Visser W, de Muinck Keizer-Schrama SM, Hooijkaas H, Steegers EA, Hofman A, Verhulst FC, van der Ende J, de Rijke YB, Tiemeier H, 2011 Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. *Pediatr. Res* 69, 454–459. [PubMed: 21471776]
- Gore AC, Martien KM, Gagnidze K, Pfaff D, 2014 Implications of prenatal steroid perturbations for neurodevelopment, behavior, and autism. *Endocr. Rev* 35, 961–991. [PubMed: 25211453]
- Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O’Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ, 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N. Engl. J. Med* 341, 549–555. [PubMed: 10451459]
- Hauser R, Calafat AM, 2005 Phthalates and human health. *Occup Environ Med* 62, 806–818. [PubMed: 16234408]
- Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA, 2003 Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children’s IQ at 4 years of age. *Pediatrics* 111, e39–44. [PubMed: 12509593]
- Hintze J, Nelson R, 2012 Violin Plots: A Box Plot-Density Trace Synergism. *The American Statistician* 52, 181–184.
- Hornung R, Reed L, 1990 Estimation of Average Concentration in the Presence of Nondetectable Values. *Applied Occupational and Environmental Hygiene* 5, 46–51.
- Howdeshell KL, Rider CV, Wilson VS, Gray LE, 2008a Mechanisms of action of phthalate esters, individually and in combination, to induce abnormal reproductive development in male laboratory rats. *Environ. Res* 108, 168–176. [PubMed: 18949836]
- Howdeshell KL, Wilson VS, Furr J, Lambright CR, Rider CV, Blystone CR, Hotchkiss AK, Gray LE Jr., 2008b A mixture of five phthalate esters inhibits fetal testicular testosterone production in the sprague-dawley rat in a cumulative, dose-additive manner. *Toxicol. Sci* 105, 153–165. [PubMed: 18411233]
- Huang HB, Chen HY, Su PH, Huang PC, Sun CW, Wang CJ, Hsiung CA, Wang SL, 2015 Fetal and Childhood Exposure to Phthalate Diesters and Cognitive Function in Children Up to 12 Years of Age: Taiwanese Maternal and Infant Cohort Study. *PLoS One* 10, e0131910. [PubMed: 26121592]
- Huang PC, Kuo PL, Guo YL, Liao PC, Lee CC, 2007 Associations between urinary phthalate monoesters and thyroid hormones in pregnant women. *Hum. Reprod* 22, 2715–2722. [PubMed: 17704099]
- Huang PC, Tsai CH, Chen CC, Wu MT, Chen ML, Wang SL, Chen BH, Lee CC, Jaakkola JJK, Wu WC, Chen MK, Hsiung CA, Group R, 2017 Intellectual evaluation of children exposed to phthalate-tainted products after the 2011 Taiwan phthalate episode. *Environ. Res* 156, 158–166. [PubMed: 28342962]

- Ipapo KN, Factor-Litvak P, Whyatt RM, Calafat AM, Diaz D, Perera F, Rauh V, Herbstman JB, 2017 Maternal prenatal urinary phthalate metabolite concentrations and visual recognition memory among infants at 27 weeks. *Environmental research* 155, 7–14. [PubMed: 28171772]
- Jackson-Browne MS, Papandonatos GD, Chen A, Calafat AM, Yolton K, Lanphear BP, Braun JM, 2018 Identifying Vulnerable Periods of Neurotoxicity to Triclosan Exposure in Children. *Environmental health perspectives* 126, 057001. [PubMed: 29727133]
- Kavlock R, Boekelheide K, Chapin R, Cunningham M, Faustman E, Foster P, Golub M, Henderson R, Hinberg I, Little R, Seed J, Shea K, Tabacova S, Tyl R, Williams P, Zacharewski T, 2002 NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-n-butyl phthalate. *Reprod. Toxicol* 16, 489–527. [PubMed: 12406493]
- Kim JI, Hong YC, Shin CH, Lee YA, Lim YH, Kim BN, 2017 The effects of maternal and children phthalate exposure on the neurocognitive function of 6-year-old children. *Environmental research* 156, 519–525. [PubMed: 28431379]
- Kim S, Eom S, Kim HJ, Lee JJ, Choi G, Choi S, Kim SY, Cho G, Kim YD, Suh E, Kim SK, Kim GH, Moon HB, Park J, Choi K, Eun SH, 2018 Association between maternal exposure to major phthalates, heavy metals, and persistent organic pollutants, and the neurodevelopmental performances of their children at 1 to 2years of age- CHECK cohort study. *Sci. Total Environ* 624, 377–384. [PubMed: 29258038]
- Kim Y, Ha EH, Kim EJ, Park H, Ha M, Kim JH, Hong YC, Chang N, Kim BN, 2011 Prenatal exposure to phthalates and infant development at 6 months: prospective Mothers and Children's Environmental Health (MOCEH) study. *Environ. Health Perspect* 119, 1495–1500. [PubMed: 21737372]
- Koch HM, Drexler H, Angerer J, 2004 Internal exposure of nursery-school children and their parents and teachers to di(2-ethylhexyl)phthalate (DEHP). *Int. J. Hyg. Environ. Health* 207, 15–22. [PubMed: 14762970]
- Koch HM, Preuss R, Drexler H, Angerer J, 2005 Exposure of nursery school children and their parents and teachers to di-n-butylphthalate and butylbenzylphthalate. *Int. Arch. Occup. Environ. Health* 78, 223–229. [PubMed: 15776263]
- Kougiass DG, Sellinger EP, Willing J, Juraska JM, 2018 Perinatal exposure to an environmentally relevant mixture of phthalates results in a lower number of neurons and synapses in the medial prefrontal cortex and decreased cognitive flexibility in adult male and female rats. *J. Neurosci*
- Lewis RC, Meeker JD, Peterson KE, Lee JM, Pace GG, Cantoral A, Tellez-Rojo MM, 2013 Predictors of urinary bisphenol A and phthalate metabolite concentrations in Mexican children. *Chemosphere* 93, 2390–2398. [PubMed: 24041567]
- Li XJ, Jiang L, Chen L, Chen HS, Li X, 2013 Neurotoxicity of dibutyl phthalate in brain development following perinatal exposure: a study in rats. *Environ. Toxicol. Pharmacol* 36, 392–402. [PubMed: 23736097]
- Li Y, Zhuang M, Li T, Shi N, 2009 Neurobehavioral toxicity study of dibutyl phthalate on rats following in utero and lactational exposure. *J. Appl. Toxicol* 29, 603–611. [PubMed: 19533667]
- Lin LC, Wang SL, Chang YC, Huang PC, Cheng JT, Su PH, Liao PC, 2011 Associations between maternal phthalate exposure and cord sex hormones in human infants. *Chemosphere* 83, 1192–1199. [PubMed: 21272909]
- Main KM, Mortensen GK, Kaleva MM, Boisen KA, Damgaard IN, Chellakooty M, Schmidt IM, Suomi AM, Virtanen HE, Petersen DV, Andersson AM, Toppari J, Skakkebaek NE, 2006 Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. *Environ. Health Perspect* 114, 270–276. [PubMed: 16451866]
- McCall RB, Carriger MS, 1993 A meta-analysis of infant habituation and recognition memory performance as predictors of later IQ. *Child. Dev* 64, 57–79. [PubMed: 8436038]
- Meeker JD, Calafat AM, Hauser R, 2007 Di(2-ethylhexyl) phthalate metabolites may alter thyroid hormone levels in men. *Environ. Health Perspect* 115, 1029–1034. [PubMed: 17637918]
- Miodovnik A, Edwards A, Bellinger DC, Hauser R, 2014 Developmental neurotoxicity of ortho-phthalate diesters: review of human and experimental evidence. *Neurotoxicology* 41, 112–122. [PubMed: 24486776]

- Moffitt TE, Caspi A, Harkness AR, Silva PA, 1993 The natural history of change in intellectual performance: who changes? How much? Is it meaningful? *J. Child. Psychol. Psychiatry* 34, 455–506. [PubMed: 8509490]
- Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C, 2017 Influence of maternal thyroid hormones during gestation on fetal brain development. *Neuroscience* 342, 68–100. [PubMed: 26434624]
- Mose T, Knudsen LE, Hedegaard M, Mortensen GK, 2007 Transplacental transfer of monomethyl phthalate and mono(2-ethylhexyl) phthalate in a human placenta perfusion system. *Int. J. Toxicol* 26, 221–229. [PubMed: 17564903]
- Nakiwala D, Peyre H, Heude B, Bernard JY, Béranger R, Slama R, Philippat C, group, E.m.-c.s., 2018 In-utero exposure to phenols and phthalates and the intelligence quotient of boys at 5 years. *Environ. Health* 17, 17. [PubMed: 29458359]
- Nguon K, Ladd B, Baxter MG, Sajdel-Sulkowska EM, 2005 Sexual dimorphism in cerebellar structure, function, and response to environmental perturbations. *Prog. Brain Res* 148, 341–351. [PubMed: 15661202]
- Polanska K, Ligocka D, Sobala W, Hanke W, 2014 Phthalate exposure and child development: the Polish Mother and Child Cohort Study. *Early Hum. Dev* 90, 477–485. [PubMed: 25038557]
- Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG, Chu I, 1997 Subchronic oral toxicity of di-n-octyl phthalate and di(2-Ethylhexyl) phthalate in the rat. *Food Chem. Toxicol* 35, 225–239. [PubMed: 9146736]
- Rice D, Barone S, 2000 Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ. Health Perspect* 108 Suppl 3, 511–533. [PubMed: 10852851]
- Romano ME, Eliot MN, Zoeller RT, Hoofnagle AN, Calafat AM, Karagas MR, Yolton K, Chen A, Lanphear BP, Braun JM, 2018 Maternal urinary phthalate metabolites during pregnancy and thyroid hormone concentrations in maternal and cord sera: The HOME Study. *Int. J. Hyg. Environ. Health* 221, 623–631. [PubMed: 29606598]
- Rothman KJ, 1990 No adjustments are needed for multiple comparisons. *Epidemiology* 1, 43–46. [PubMed: 2081237]
- Rovet JF, 2014 The role of thyroid hormones for brain development and cognitive function. *Endocr. Dev* 26, 26–43. [PubMed: 25231442]
- Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, Rizzo J, Nudelman JL, Brody JG, 2011 Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention. *Environ. Health Perspect* 119, 914–920. [PubMed: 21450549]
- Sanchez BN, Hu H, Litman HJ, Tellez-Rojo MM, 2011 Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. *Environmental health perspectives* 119, 409–415. [PubMed: 21362588]
- Sánchez BN, Hu H, Litman HJ, Téllez-Rojo MM, 2011 Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. *Environ. Health Perspect* 119, 409–415. [PubMed: 21362588]
- Silva MJ, Barr DB, Reidy JA, Malek NA, Hodge CC, Caudill SP, Brock JW, Needham LL, Calafat AM, 2004 Urinary levels of seven phthalate metabolites in the U.S. population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. *Environ. Health Perspect* 112, 331–338. [PubMed: 14998749]
- Silva MJ, Samandar E, Preau JL, Reidy JA, Needham LL, Calafat AM, 2007 Quantification of 22 phthalate metabolites in human urine. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci* 860, 106–112.
- Sørensen LK, 2006 Determination of phthalates in milk and milk products by liquid chromatography/tandem mass spectrometry. *Rapid Commun. Mass. Spectrom* 20, 1135–1143. [PubMed: 16521163]
- Stacy SL, Papandonatos GD, Calafat AM, Chen A, Yolton K, Lanphear BP, Braun JM, 2017 Early life bisphenol A exposure and neurobehavior at 8 years of age: Identifying windows of heightened vulnerability. *Environ. Int* 107, 258–265. [PubMed: 28764921]

- Stein SA, Adams PM, Shanklin DR, Mihailoff GA, Palnitkar MB, 1991 Thyroid hormone control of brain and motor development: molecular, neuroanatomical, and behavioral studies. *Adv. Exp. Med. Biol* 299, 47–105. [PubMed: 1725685]
- Sugiyama S, Shimada N, Miyoshi H, Yamauchi K, 2005 Detection of thyroid system-disrupting chemicals using in vitro and in vivo screening assays in *Xenopus laevis*. *Toxicol. Sci* 88, 367–374. [PubMed: 16179385]
- Tellez-Rojo MM, Cantoral A, Cantonwine DE, Schnaas L, Peterson K, Hu H, Meeker JD, 2013 Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. *The Science of the total environment* 461–462, 386–390.
- Tierney AL, Nelson CA, 2009 Brain Development and the Role of Experience in the Early Years. *Zero Three* 30, 9–13. [PubMed: 23894221]
- Tuovinen S, Eriksson JG, Kajantie E, Räikkönen K, 2014 Maternal hypertensive pregnancy disorders and cognitive functioning of the offspring: a systematic review. *J. Am. Soc. Hypertens* 8, 832–847.e831. [PubMed: 25455009]
- van der Laan MJ, Polley EC, Hubbard AE, 2007 Super learner. *Statistical applications in genetics and molecular biology* 6, Article25.
- Watkins DJ, Eliot M, Sathyanarayana S, Calafat AM, Yolton K, Lanphear BP, Braun JM, 2014 Variability and predictors of urinary concentrations of phthalate metabolites during early childhood. *Environmental science & technology* 48, 8881–8890. [PubMed: 24977926]
- Wechsler D, 1999 Wechsler Abbreviated Scale of Intelligence The Psychological Corporation: Harcourt Brace & Company, New York, NY
- Wechsler D, 2002 Wechsler Preschool and Primary Scale of Intelligence, 3rd ed. The Psychological Corporation, San Antonio, TX.
- Wechsler D, 2003 Wechsler Intelligence Scale for Children-IV, 3rd ed. The Psychological Corporation, San Antonio, TX.
- Werner EF, Braun JM, Yolton K, Khoury JC, Lanphear BP, 2015 The association between maternal urinary phthalate concentrations and blood pressure in pregnancy: The HOME Study. *Environ. Health* 14, 75. [PubMed: 26380974]
- Whyatt RM, Liu X, Rauh VA, Calafat AM, Just AC, Hoepner L, Diaz D, Quinn J, Adibi J, Perera FP, Factor-Litvak P, 2012 Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. *Environ. Health Perspect* 120, 290–295. [PubMed: 21893441]
- Xu Y, Agrawal S, Cook TJ, Knipp GT, 2007 Di-(2-ethylhexyl)-phthalate affects lipid profiling in fetal rat brain upon maternal exposure. *Arch. Toxicol* 81, 57–62. [PubMed: 16951938]
- Xu Y, Agrawal S, Cook TJ, Knipp GT, 2008 Maternal di-(2-ethylhexyl)-phthalate exposure influences essential fatty acid homeostasis in rat placenta. *Placenta* 29, 962–969. [PubMed: 18829104]
- Zoeller RT, Rovet J, 2004 Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *J. Neuroendocrinol* 16, 809–818. [PubMed: 15500540]

Highlights

- Urinary Σ DEHP, MEP and MCPPE at age 3 years were inversely associated with child IQ
- Gestational and childhood urinary MBzP levels were inversely associated with child IQ
- Age 3 years may be a susceptible period of neurodevelopment to several phthalates
- Phthalate exposure at age 3 years was more strongly related to decreased child IQ

Figure 1.

Violin Plots of Urinary Phthalate Metabolite Concentrations (ng/mL) from 16-Week Gestation until Age 8 Years among Mother-Child Pairs from the HOME Study. Σ DEHP, summary di(2-ethylhexyl) phthalate metabolite measure; MnBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MCNP, monocarboxynonyl phthalate; MCOP, monocarboxyoctyl phthalate.

The shaded area represents the density function of phthalate metabolite concentrations, and the four shaded areas represent the four quartiles.

Concentrations of Σ DEHP (in ng/mL) were calculated using the following formula: Σ DEHP (ng/mL) = $[\text{MECPP (ng/mL)} / 308.33 \text{ g/mol} + \text{MEHHP (ng/mL)} / 294.347 \text{ g/mol} + \text{MEOHP (ng/mL)} / 292.331 \text{ g/mol}] * 308.33 \text{ g/mol}$.

Figure 2.

Adjusted Differences in Full-Scale Intelligence Quotient (FSIQ) at ages 5 or 8 Years Per 1-Standard Deviation Increase in $\log_{10}$ -Transformed Urinary Phthalate Metabolite Concentrations.

SD, standard deviation; Σ DEHP, summary di(2-ethylhexyl) phthalate metabolite measure; MnBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MCNP, monocarboxynonyl phthalate; MCOP, monocarboxyoctyl phthalate.

All estimates are from multiple informant models adjusted for: visit, phthalates $\times$ visit, $\log_{10}$ urinary creatinine concentrations, household income (<\$45K, \$45–75K, >\$75K), HOME Inventory Score, maternal age at delivery, mother's pre-pregnancy BMI, maternal gestational smoking (mean of $\log_{10}$ -transformed serum cotinine concentrations during 16 and 26 weeks of pregnancy), mother's FSIQ, maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), and child's race (non-Hispanic White, non-Hispanic Black, other).

Figure 3.

Adjusted Restricted Cubic Polynomial Spline of Urinary Phthalate Metabolite Concentrations (on Log₁₀-Scale) at Age 3 Years, and Children's Full-Scale IQ ΣDEHP, summary di(2-ethylhexyl) phthalate metabolite measure; mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate.

Adjusted for: log₁₀ urinary creatinine concentrations, household income (<\$45K, \$45–75K, >\$75K), HOME Inventory Score, maternal age at delivery, mother's pre-pregnancy BMI, maternal gestational smoking (mean of log₁₀-transformed serum cotinine concentrations during 16 and 26 weeks of pregnancy), mother's FSIQ, maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), and child's race (non-Hispanic White, non-Hispanic Black, other). P-values<0.05 indicate non-linear association between urinary phthalate metabolite concentrations and children's full-scale IQ.

Table 1.

Full-Scale Intelligence Quotient (FSIQ) Scores at Ages 5 and 8 Years According to Covariates among Children from the Health Outcomes and Measures of the Environment (HOME) Study (N=253)

Characteristics	N (%)	5-Year FSIQ (N=202) Mean $\pm$ SD	P-value	N (%)	8-Year FSIQ (N=220) Mean $\pm$ SD	P-value
Overall	202	102 $\pm$ 15		220	102 $\pm$ 16	
Child Sex			0.11			0.71
Male	87 (43)	100 $\pm$ 16		98 (45)	101 $\pm$ 15	
Female	115 (57)	104 $\pm$ 15		122 (55)	102 $\pm$ 16	
Child Race			<0.01			<0.01
Non-Hispanic White	120 (60)	108 $\pm$ 13		126 (57)	108 $\pm$ 12	
Non-Hispanic Black	67 (33)	91 $\pm$ 13		81 (37)	91 $\pm$ 15	
Other	15 (7)	106 $\pm$ 12		13 (6)	110 $\pm$ 16	
Maternal Age at Delivery (years)			<0.01			<0.01
18–25	45 (22)	92 $\pm$ 14		59 (27)	93 $\pm$ 16	
>25–35	127 (63)	104 $\pm$ 14		130 (59)	103 $\pm$ 15	
>35	30 (15)	110 $\pm$ 14		31 (14)	111 $\pm$ 13	
Annual Household Income			<0.01			<0.01
>\$75K	52 (26)	111 $\pm$ 11		56 (26)	112 $\pm$ 12	
\$45–75K	77 (38)	105 $\pm$ 13		71 (32)	104 $\pm$ 14	
<\$45K	73 (36)	92 $\pm$ 15		93 (42)	94 $\pm$ 16	
Maternal Education			<0.01			<0.01
College graduate	100 (49)	110 $\pm$ 12		101 (46)	109 $\pm$ 12	
Tech school/Some College	58 (29)	98 $\pm$ 14		62 (28)	100 $\pm$ 14	
High school graduate	44 (22)	90 $\pm$ 14		57 (26)	90 $\pm$ 16	
Caregiving Environment Score			<0.01			<0.01
<35	35 (17)	90 $\pm$ 12		36 (16)	91 $\pm$ 15	
35–<40	39 (19)	96 $\pm$ 14		58 (27)	94 $\pm$ 15	
40	128 (64)	107 $\pm$ 14		126 (57)	108 $\pm$ 13	
Marital Status			<0.01			<0.01
Married	136 (67)	107 $\pm$ 13		135 (61)	108 $\pm$ 13	
Unmarried	66 (33)	92 $\pm$ 14		85 (39)	92 $\pm$ 16	
Pre-pregnancy BMI (kg/m ²)			<0.01			0.02
<25 (lean)	100 (49)	105 $\pm$ 15		113 (51)	104 $\pm$ 16	
25–30 (overweight)	54 (27)	102 $\pm$ 13		57 (26)	102 $\pm$ 15	
>30 (obese)	48 (24)	96 $\pm$ 15		50 (23)	96 $\pm$ 16	
Maternal Gestational Smoking Status			<0.01			<0.01
Unexposed (<0.015ng/ml)	66 (33)	107 $\pm$ 12		66 (30)	106 $\pm$ 14	
Secondhand Smoke (0.015, <3.0 ng/ml)	121 (60)	100 $\pm$ 15		128 (58)	100 $\pm$ 16	
Active Smoking (3.0 ng/ml)	15 (7)	97 $\pm$ 21		26 (12)	96 $\pm$ 18	
Maternal Full-scale IQ			<0.01			<0.01
1 st Tercile 58–99	69 (34)	91 $\pm$ 13		84 (38)	91 $\pm$ 15	

Characteristics	N (%)	5-Year FSIQ (N=202) Mean $\pm$ SD	P-value	N (%)	8-Year FSIQ (N=220) Mean $\pm$ SD	P-value
2 nd Tercile >99–114	69 (34)	106 $\pm$ 15		68 (31)	106 $\pm$ 13	
3 rd Tercile >114	64 (32)	109 $\pm$ 12		68 (31)	109 $\pm$ 14	
Pregnancy-Induced Hypertension			0.11			0.09
Yes	23 (12)	97 $\pm$ 16		24 (11)	97 $\pm$ 17	
No	176 (88)	103 $\pm$ 15		192 (89)	102 $\pm$ 16	

SD, standard deviation; BMI, body mass index.

A total of 33 children had 5-year FSIQ measurement only, 51 children had 8-year FSIQ measurement only, and 169 children had both measurements.

P values were calculated using a one-way analysis of variance test to compare the mean FSIQ scores across the strata of covariates.

Table 2.

Unadjusted and Adjusted Differences [95% Confidence Intervals (CI)] in Full-Scale Intelligence Quotient at Age 5 or 8 Years with 1 Standard Deviation Increase in Log₁₀-Transformed Gestational and Childhood Urinary Phthalate Metabolite Concentrations.

Metabolite	N	Visit	Unadjusted Estimate (95% CI)	Adjusted Estimate ^a (95% CI)	Heterogeneity P-Value ^b
ΣDEHP	251	16-week	−0.9 (−2.8, 0.9)	0.1 (−1.3, 1.6)	0.27
	245	26-week	−1.3 (−3.2, 0.7)	0.3 (−1.5, 2.1)	
	212	Age 1	0.9 (−1.2, 3.1)	1.0 (−0.6, 2.6)	
	188	Age 2	−0.6 (−2.7, 1.5)	0.2 (−1.5, 1.8)	
	196	Age 3	−3.5 (−5.8, −1.2)	−1.9 (−3.7, −0.2)	
	166	Age 4	−0.6 (−2.7, 1.6)	0.6 (−1.1, 2.3)	
	202	Age 5	−2.0 (−4.3, 0.2)	−0.4 (−2.0, 1.2)	
	218	Age 8	−1.6 (−3.9, 0.7)	−0.5 (−2.2, 1.2)	
MnBP	251	16-week	−2.8 (−4.7, −1.0)	0.6 (−0.9, 2.2)	0.36
	245	26-week	−3.1 (−4.9, −1.4)	0.6 (−0.9, 2.1)	
	166	Age 4	0.6 (−1.6, 2.8)	2.1 (0.3, 3.9)	
	202	Age 5	−1.3 (−3.7, 1.0)	0.4 (−1.3, 2.1)	
	218	Age 8	−1.3 (−3.4, 0.7)	−0.3 (−1.9, 1.3)	
MiBP	251	16-week	−3.0 (−4.8, −1.2)	0.8 (−1.0, 2.5)	0.27
	245	26-week	−3.2 (−4.9, −1.5)	1.4 (−0.3, 3.1)	
	166	Age 4	−0.8 (−2.9, 1.4)	1.8 (0.0, 3.6)	
	202	Age 5	−1.2 (−3.3, 1.0)	0.3 (−1.3, 1.9)	
	218	Age 8	−0.3 (−2.5, 1.8)	0.3 (−1.4, 1.9)	
MBzP	251	16-week	−4.7 (−6.5, −2.9)	−1.6 (−3.4, 0.1)	0.05
	245	26-week	−3.9 (−5.6, −2.2)	−0.5 (−2.2, 1.2)	
	212	Age 1	−0.4 (−2.5, 1.7)	0.3 (−1.3, 1.9)	
	188	Age 2	−2.6 (−4.6, −0.6)	−1.1 (−3.0, 0.7)	
	196	Age 3	−4.8 (−6.8, −2.9)	−2.5 (−4.4, −0.6)	
	166	Age 4	−1.7 (−3.8, 0.5)	0.0 (−1.7, 1.8)	
	202	Age 5	−4.2 (−6.0, −2.3)	−1.6 (−3.3, 0.1)	
	218	Age 8	−4.5 (−6.6, −2.5)	−1.8 (−3.5, −0.1)	
MCPP	251	16-week	−2.1 (−4.0, −0.2)	−1.0 (−2.5, 0.6)	0.17
	245	26-week	−3.0 (−4.8, −1.2)	−0.8 (−2.4, 0.7)	
	212	Age 1	0.7 (−1.4, 2.8)	−0.1 (−1.8, 1.7)	
	188	Age 2	−0.9 (−2.9, 1.1)	−1.4 (−3.0, 0.3)	
	196	Age 3	−3.6 (−5.6, −1.5)	−2.4 (−4.2, −0.7)	
	166	Age 4	−0.5 (−2.8, 1.8)	−0.2 (−2.0, 1.6)	
	202	Age 5	−0.2 (−2.4, 2.1)	−1.3 (−2.9, 0.4)	
	218	Age 8	1.6 (−0.3, 3.4)	−0.5 (−2.2, 1.2)	
MEP	251	16-week	−2.6 (−4.5, −0.6)	−0.3 (−1.9, 1.2)	0.10
	245	26-week	−2.9 (−4.8, −1.1)	0.3 (−1.3, 1.9)	

Metabolite	N	Visit	Unadjusted Estimate (95% CI)	Adjusted Estimate ^a (95% CI)	Heterogeneity P-Value ^b
	212	Age 1	-1.7 (-3.7, 0.3)	0.6 (-0.9, 2.1)	
	188	Age 2	-4.2 (-6.4, -2.1)	-1.5 (-3.3, 0.4)	
	196	Age 3	-6.4 (-8.1, -4.7)	-2.1 (-3.6, -0.6)	
	166	Age 4	-3.8 (-5.9, -1.7)	0.4 (-1.2, 2.0)	
	202	Age 5	-5.2 (-7.0, -3.4)	-0.7 (-2.1, 0.7)	
	218	Age 8	-4.2 (-6.0, -2.4)	-0.4 (-1.8, 1.1)	
MCNP	212	Age 1	1.5 (-0.8, 3.7)	1.3 (-0.6, 3.1)	0.16
	188	Age 2	-1.1 (-3.1, 0.9)	-0.1 (-2.2, 1.9)	
	196	Age 3	-2.1 (-4.2, 0.0)	-0.2 (-2.0, 1.6)	
	166	Age 4	0.0 (-2.2, 2.1)	1.4 (-0.2, 3.0)	
	202	Age 5	-0.2 (-2.5, 2.2)	0.3 (-1.3, 2.0)	
	218	Age 8	-1.3 (-3.4, 0.9)	-1.1 (-2.8, 0.7)	
MCOP	212	Age 1	0.8 (-1.2, 2.9)	0.5 (-1.3, 2.3)	0.27
	188	Age 2	-0.7 (-2.6, 1.1)	-0.4 (-2.4, 1.6)	
	196	Age 3	-2.8 (-5.0, -0.5)	-1.2 (-3.2, 0.9)	
	166	Age 4	0.9 (-1.6, 3.4)	1.4 (-0.7, 3.5)	
	202	Age 5	-0.4 (-2.6, 1.9)	-0.2 (-1.7, 1.2)	
	218	Age 8	1.0 (-0.9, 2.9)	0.2 (-1.5, 1.9)	

ΣDEHP, summary di(2-ethylhexyl) phthalate metabolite measure; MnBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MCNP, monocarboxynonyl phthalate; MCOP, monocarboxyoctyl phthalate.

^aAll estimates are from multiple informant models adjusted for: visit, phthalates × visit, log₁₀ urinary creatinine concentrations, household income (<\$45K, \$45–75K, >\$75K), HOME Inventory Score, maternal age at delivery, mother's pre-pregnancy BMI, maternal gestational smoking (mean of log₁₀-transformed serum cotinine concentrations during 16 and 26 weeks of pregnancy), mother's FSIQ, maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), and child's race (non-Hispanic White, non-Hispanic Black, other).

^bP-values<0.20 indicate the phthalate-FSIQ associations differ by exposure period (at least one of the phthalate-FSIQ associations differed from the rest).