Published in final edited form as:

Environ Res. 2019 April ; 171: 416–427. doi:10.1016/j.envres.2019.01.046.

Prenatal and Childhood Exposure to Phthalates and Motor Skills at Age 11 Years

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Abstract

Background—Previous reports suggest that prenatal phthalate exposure is associated with lower scores on measures of motor skills in infants and toddlers. Whether these associations persist into later childhood or preadolescence has not been studied.

Methods—In a follow up study of 209 inner-city mothers and their children the concentrations of mono-*n*-butyl phthalate (MnBP), monobenzyl phthalate (MBzP), monoisobutyl phthalate (MiBP), monomethyl phthalate (MEP), mono-carboxy-isooctyl phthalate (MCOP), and four di-2-ethylhexyl phthalate metabolites (DEHP) were measured in spot urine sample collected from the women in late pregnancy and from their children at ages 3, 5, and 7 years. The Bruininks-Oseretsky Test of Motor Proficiency short form (BOT-2) was administered at child age 11 to assess gross and fine motor skills.

Results—The total number of children included in the study was 209. Of the 209 children, 116(55.5%) were girls and 93 were (45%) boys. Among girls, prenatal MnBP($b=-2.09$; 95% CI: $[-3.43, -0.75]$), MBzP ($b=-1.14$; [95% CI: $-2.13, -0.14]$), and MiBP($b=-1.36$; 95% CI: $[-2.51,$

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Institutional review boards at the Columbia University Medical Center approved the study and all consent procedures for the study. Written informed consent was obtained from all participating mothers, who also provided written informed consent on behalf of their children, and informed assent was obtained from all children starting at age 7 years.

Declaration of Interest:

None.

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−0.21] and MEP($b = -1.23$ [95% CI: −2.36, −0.11]) were associated with lower total BOT-2 composite score. MnBP ($b = -1.43$; 95% CI: [−2.44, −0.42]) was associated with lower fine motor scores and MiBP ($b = -0.56$; 95% CI: [−1.12, −0.01]) and MEP ($b = -0.60$; 95% CI: [−1.14, −0.06]) was associated with lower gross motor scores. Among boys, prenatal MBzP ($b = -0.79$; 95% CI: [−1.40, −0.19]) was associated with lower fine motor composite score.

The associations between MEP measured at age 3 and the BOT-2 gross motor, fine motor and total motor score differed by sex. In boys, there was an inverse association between DEHP metabolites measured in childhood at ages 3 ($b = -1.30$; 95% CI: [−2.34, −0.26]) and 7 years ($b = -0.96$; 95% CI: [−1.79, −0.13]), and BOT-2 fine motor composite scores.

Conclusions—Higher prenatal exposure to specific phthalates was associated with lower motor function among 11- year old girls while higher postnatal exposure to DEHP metabolites was associated with lower scores among boys. As lower scores on measures of motor development have been associated with more problems in cognitive, socioemotional functioning and behavior, the findings of this study have implications related to overall child development.

Keywords

perinatal exposure; motor development; phthalates; adolescence development

1. Introduction

Phthalates are a class of industrial chemicals widely used as plasticizers and additives in a variety of consumer products, such as personal care products, plastic containers, and, children's toys (Net et al., 2015) and are found in foods, due to their use in packaging materials (Schechter et al., 2013). Once absorbed, phthalates are rapidly metabolized and eliminated in urine (Heudorf et al., 2007) within hours after exposure (Wittassek and Angerer, 2008). Urinary concentrations of phthalate metabolites are used as internal dosimeters since urinary enzymatic activity is negligible (Kato et al., 2004); thus, metabolite concentrations in urine reflect an individual's internal exposure, rather than external contaminants. (Calafat et al., 2015). A growing body of literature finds associations between prenatal exposure to phthalates and a wide spectrum of adverse pregnancy and neurodevelopmental outcomes, ranging from preterm birth (Ferguson et al., 2014), low birth weight (Wolff et al., 2008), altered male reproductive tract development (Suzuki et al., 2012; Swan et al., 2005; Swan et al., 2015) to poorer cognitive and behavioral outcomes in infants and young children (Ejaredar et al., 2015; Factor-Litvak et al., 2014; Gascon et al., 2015; Whyatt et al., 2012). Consistent with experimental studies (Borch et al., 2006; Kiyama and Wada-Kiyama, 2015), epidemiologic studies find sex specific associations with several of these outcomes (Engel et al., 2009; Swan et al., 2010; Whyatt et al., 2012; Wolff et al., 2008).

To date, associations between prenatal phthalate exposure and motor development have been examined in eight studies of children ranging in age from newborns to preschoolers (Doherty et al., 2016; Engel et al., 2009; Gascon et al., 2015; Kim et al., 2011; Polanska et al., 2014; Tellez-Rojo et al., 2013; Whyatt et al., 2012; Yolton et al., 2011). Among the four studies that examined the association in newborns, two U.S. birth cohorts reported that

phthalate exposure was associated with better motor performance among male infants (Engel et al., 2009; Yolton et al., 2011). In contrast, a Korean birth cohort found that phthalate exposure was associated with worse psychomotor scores in boys at six months (Kim et al., 2011) and a Spanish cohort found no association at the age of 1 year and at the age of 4 years (Gascon et al., 2015). Similarly, inconsistencies were observed among the five studies that examined the associations in toddlers and preschoolers (Doherty et al., 2016; Gascon et al., 2015; Polanska et al., 2014; Tellez-Rojo et al., 2013; Whyatt et al., 2012). Three studies found lower psychomotor scores in both boys and girls (Gascon et al., 2015; Polanska et al., 2014; Whyatt et al., 2012), one reported higher psychomotor scores in boys (Tellez-Rojo et al., 2013), and another reported higher psychomotor scores in boys and lower psychomotor scores in girls (Doherty et al., 2016). These inconsistencies could be due to the different ages of the children included in each study; different timing of sample collection during pregnancy and different socioeconomic profiles of the participants of these studies. Given these inconsistencies in reported associations among young children, we explored associations in older children.

Here, we expand our previous finding (Whyatt et al., 2012) to investigate the associations between phthalate metabolites in pre- and postnatal urine samples and child motor performance at 11 years of age. We measured metabolites of six phthalates: di(*n*-butyl) phthalate (DnBP), butylbenzyl phthalate (BBzP), di-isobutyl phthalate (DiBP), diethyl phthalate (DEP), diisononyl phthalate (DiNP), and di-2-ethylhexyl phthalate (DEHP).

2. Methods

2.1. Cohort and study design

Our sample was selected from participants in the ongoing longitudinal birth cohort study of 727 mothers and newborns conducted by the Columbia Center for Children's Environmental Health (CCCEH). Enrollment and exclusion criteria were described previously (Perera et al., 2003). Briefly, the CCCEH cohort was restricted to nonsmoking women 18–35 years of age who self-identified as either African American or Dominican, who had resided in northern Manhattan or the South Bronx in New York City for at least 1 year before pregnancy and who delivered between 1999 and 2006. Women were excluded if they used illicit drugs, had diabetes, hypertension, or known HIV, or had their first prenatal visit after the 20th week of pregnancy. Women with active smoking during pregnancy verified by maternal and/or umbilical cord plasma cotinine >15 ng/ml at delivery ($n=30$), no or insufficient prenatal urine for measurement of phthalate metabolites ($n=286$), and those lost to follow-up prior to child age 11 years ($n=202$) were also excluded. We selected mother-child pairs ($n=209$) for the study if phthalate metabolite concentrations had been measured in spot urine samples collected during the third trimester of pregnancy and if the child completed the short form of the Bruininks-Oseretsky Test of Motor Proficiency-2 (BOT-2) at the child age 11-year visit.

2.2. Urine sample collection and phthalate measurements.

Spot urine samples were collected during the third trimester of pregnancy (average 33.7 ± 3.2 weeks, median 33.4). Child spot urine samples were collected at the age 3 visit ($n=166$; between years 2002–2008), age 5 visit ($n=199$; between years 2004–2009) and age 7 visit

($n=156$; between years 2005-2009). Samples were initially analyzed for metabolites of 5 phthalates (DnBP, BBzP, DiBP, DEHP and DEP) at the Center for Disease Control (CDC) as previously described (Kato et al., 2005). In 2009, the CDC began to measure the metabolites of DINP; as a result, 34% of the prenatal samples had mono-carboxy-isooctyl phthalate (MCOP) (a metabolite of DINP) measures, and all child samples had MCOP measures at age 7. To correct for urinary dilution, we used specific gravity (Hauser et al., 2004) measured with a handheld refractometer (Atago PAL 10-S; Atago U.S.A. Inc., Bellevue, WA). For concentrations of phthalate metabolites below the limit of detection (LOD), we assigned a value of $\text{LOD}/2$ (Hornung and Reed 1990), as we have done previously (Factor-Litvak et al., 2014). The DEHP metabolites concentrations (in ng/mL) were converted into their respective molar concentrations and summed to obtain DEHP (Meeker and Ferguson 2014). To assess reliability, we calculated intraclass correlation coefficients (ICCs) for the phthalate metabolites in serial spot urine samples collected biweekly from 48 women in the CCCEH cohort over 6–8 weeks late in pregnancy ($n=135$ samples, 2–4 repeats per woman). Adjusting for specific gravity, the ICCs were 0.77 for monobenzyl phthalate (MBzP), 0.65 for mono-*n*-butyl phthalate (MnBP), and 0.60 for monoisobutyl phthalate (MiBP) and ranged from 0.27 to 0.42 for the DEHP metabolites (Whyatt et al., 2012).

2.3. Measure of child motor development.

We assessed motor function using the short form of the Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition (BOT-2). The BOT-2 is a widely used individually administered test that measures a wide range of motor skills in children and young adults, and was standardized on a U.S. nationally representative sample of $>1,500$ individuals 4–21 years of age (Bruininks and Bruininks, 2005). It has excellent psychometric reliability and validity (Cairney et al., 2009; Deitz et al., 2007; Rodger et al., 2003; Wang et al., 2009; Wilson et al., 1995). In this study, we used the short form of the BOT-2, which is recommended as a screening tool (Spironello et al., 2010) (Bruininks and Bruininks, 2005). The total, fine and gross motor composite point scores that are provided by the short form of BOT-2 were used in this study. The fine motor composite score, which evaluates tasks that require precise movement of the small muscles, combines items that were selected from the following four motor subtests: fine motor precision, fine motor integration, manual dexterity, and upper-limb coordination. These subtests include seven items. The gross motor composite score, also includes seven items and assesses tasks involving larger, stronger muscle groups, contains items that were selected from four motor subtests: bilateral body coordination, balance, strength, and running speed and agility. Point scores of the fourteen items are summed to obtain a total point score, which provides a comprehensive index of motor proficiency. The range of the point scores is 0–45 for fine and 0–43 for gross motor composites. The maximum total point score in the short form of BOT-2 is 88 which corresponds to well above average motor performance (Bruininks and Bruininks 2005). The point scores for the total composite, fine motor composite and gross motor composite can be converted to standard scores (mean=50, standard deviation=10) (Deitz et al., 2007). The reliability of the short form of BOT-2 has been assessed by investigating test-retest and interrater reliability. The Pearson correlation coefficient was reported to be 0.84 and 0.97 for the short form of BOT-2 respectively, indicating good to excellent reliability (Bruininks and Bruininks 2005). Validation studies reported significant correlation of the items in short

form of BOT-2 with overall subtest scores in the original BOT-2 (Carmosino et al., 2014; Lucas et al., 2013).

2.4. Questionnaire and medical record data.

We obtained information on potential confounders using questionnaires administered to the mother during pregnancy and at postnatal intervals and by review of maternal and infant medical records. Variables of interest included maternal race/ethnicity, maternal education and marital status, household income, parity, gestational age, birth weight, child sex, breastfeeding history, exposure to tobacco smoke in the home, prenatal alcohol consumption, and prenatal psychosocial factors including maternal self-report of hardship during pregnancy (i.e., lack of food, clothing, housing, gas or electricity, or medicines) and satisfaction with overall living conditions. Maternal demoralization was assessed by the 27-item Psychiatric Epidemiology Research Instrument-Demoralization Scale (Dohrenwend et al., 1978). The quality of proximal care-taking environment was determined by the Home Observation for Measurement of the Environment (HOME) scale at child age 39.8 ± 7.1 months (Caldwell and Bradley, 1979). Bayley Scales of Infant Development II (BSID-II) and Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) were administered at age 3 and age 7 respectively.

2.5. Statistical analysis.

Summary statistics means and proportions were used to describe the sample characteristics. Chi-square test and Wilcoxon rank-sum test and Kruskal-Wallis test were used to detect differences in categorical and quantitative variables, respectively, between specific groups. We used linear regression model to examine the associations between BOT-2 scores and each phthalate metabolite, measured prenatally or postnatally at specific ages, controlling for covariates. The phthalate metabolite concentrations had right skewed distributions with some values below LOD. In the primary analysis using the continuous phthalate metabolite measures, we used $LOD/2$ for values below LOD and a natural logarithmic transformation to the variable to reduce the impact of extreme values. We identified potential confounders using a directed acyclic graph (DAG) based on previous literature suggesting that the variables were associated with phthalate exposure and/or with motor outcomes (Supplementary Figure 1). Potential confounders were then included in the final models if their inclusion changed the estimated regression coefficient of the main predictor (i.e. specific phthalate variable) by more than 0.5 standard error of the coefficient estimate. Covariates selected for the linear models for the whole sample included child age (in months) at the time of BOT-2 administration, maternal race/ethnicity, maternal prenatal alcohol consumption (yes/no), maternal prenatal demoralization scale score, HOME score, child body mass index (BMI) z-score, and specific gravity. We used the same set of covariates in the models stratified by child sex.

We identified the predictors of the variables with missing observations using simple linear regression. The predictors that were significantly associated with covariates at $p < 0.2$ were included in our final prediction model. We imputed missing values for the following three covariates using imputation methods: a) three missing values for maternal prenatal demoralization were imputed by a linear regression model with maternal education, maternal

satisfaction, maternal hardship, maternal demoralization at child age 5 and 11 as predictors (model $R^2 = 0.41$, $n = 194$); *b*) nine missing observations from the HOME scale were imputed by linear regression with maternal race/ethnicity, maternal education and intelligence quotient (IQ), and household income as predictors (model $R^2 = 0.14$, $n = 200$); and *c*) nine missing observations for child BMI z-score at age 11 were imputed based on a linear regression with child BMI z-score at age 9 as predictor (model $R^2 = 0.87$; $n = 192$). To assess effect modification by sex, we first examined the estimated regression coefficient of the phthalate variable from the models separately for boys and girls, and then used a Wald test to detect sex differences in the estimated coefficients. We a priori defined effect measure modification by sex as $p < 0.05$.

To assess possible non-linear relationships between phthalate metabolite concentrations and the BOT-2 outcomes, we conducted an alternative analysis with specific gravity (SG) adjusted phthalate metabolites (Hauser et al., 2004) categorized at quartiles, with the lowest quartile as a reference category.

All analyses were conducted using SAS (version 9.4 SAS Institute Inc., Cary, NC).

2.6. Ethics Statement

Institutional review boards at the Columbia University Medical Center approved the study and all consent procedures for the study. Written informed consent was obtained from all participating mothers, who also provided written informed consent on behalf of their children, and informed assent was obtained from all children starting at age 7 years.

3. Results

The 209 study women did not differ significantly from the 147 women whose children had BOT-2 scores but who did not have prenatal phthalate measures in terms of basic demographics (race/ethnicity, prenatal marital status, education level, household income, and proportion on Medicaid or other public assistance. (all p -values > 0.10) (Table 1). Birth outcomes were likewise similar among children who did and did not complete the BOT-2. Among 356 children with motor function measured at age 11 years, those with prenatal exposure measures ($n=209$) differed in number of BSID-2, WISC-V and BOT-2 total composite point scores compared to those without prenatal exposure measures. The children with prenatal exposure measures performed significantly better on the psychomotor development scale (PDI) (mean: 102.1 vs. 98.6; $p < 0.0001$), and mental development index (MDI) (mean: 92.0 vs. 88.5; $p < 0.01$) of the BSID-II at age 3 as well as on the full scale composite (mean: 98.7 vs. 94.7; $p < 0.01$), and the verbal comprehension composite (mean: 96.5 vs. 91.1; $p < 0.001$) of the WISC-IV at age 7 (Table 1). There were a higher proportion of children having below than average BOT-2 total composite point scores among those with prenatal exposure measures compared to those without prenatal exposure measures (Table 1). We further compared participants with available BOT-2 measures with the participants without measures ($n=359$) (Supplementary table 1). The participants who had available BOT-2 measures ($n=368$) did not differ from the participants without the BOT-2 measures in terms of maternal age, child sex, ethnicity, marital status, maternal demoralization score, HOME scale, maternal IQ, weight at birth, or gestational age. The participants with available

BOT-2 measures performed slightly better on PDI scale of Bayley Scales of Infant Development II as well as on the full scale composite and the verbal comprehension of the WISC-IV at age 7. The maternal alcohol consumption was less common among the participants with BOT-2 measures compared to those who did not have BOT-2 measures.

The mean age at the BOT-2 administration was 11.0 ± 0.4 (range, 10.1–13.4) years. As expected, boys and girls scored comparably on the three BOT-2 measures: the BOT-2 total composite score (68.2 ± 5.3 vs. 67.4 ± 6.1 ; $p=0.31$), BOT-2 fine motor composite score (38.8 ± 3.3 vs. 38.5 ± 4.4 ; $p=0.47$) and BOT-2 gross motor composite score (29.3 ± 3.0 vs. 28.9 ± 2.9 ; $p=0.30$).

The three BOT-2 composite scores were weakly correlated with the measures of neurodevelopment, the BSID-II at age 3 and the WISC-IV at age 7 (Spearman correlation coefficient r -values ranged from 0.04 to 0.31) (see Supplementary Table S2).

The distributions of the urinary phthalate metabolite concentrations in prenatal spot samples are shown in Table 2. Prenatal phthalate metabolites were detected in 99.5–100% of the samples, except for MEHP where 17% of the measures were below the LOD. The four DEHP metabolite concentrations, adjusted for specific gravity, were strongly correlated (Spearman's correlation (r -values ranged from 0.65 to 0.97). MnBP, MBzP, and MiBP concentrations were moderately correlated (r -values ranged from 0.46 to 0.67). In contrast, the DEHP and non-DEHP (MnBP, MBzP, and MiBP) metabolite concentrations were weakly correlated (r -values ranged from 0.14 to 0.37). MCOP concentrations were moderately correlated with the others, ranging from $r=0.33$ with MEP to $r=0.57$ with MEOHP. The prenatal specific gravity-adjusted phthalate metabolite concentrations did not significantly differ by child sex. The prenatal phthalate metabolites concentrations were weakly correlated with postnatal measures at age 3, age 5 and age 7 (r -values ranged from -0.03 to 0.30) (see Supplementary Table S3). The weak correlations between postnatal phthalate metabolite concentrations persisted when stratified by child sex (Supplementary Table S4).

3.1. Prenatal Phthalate Exposure

After adjusting for covariates, among girls, the BOT-2 total composite score was lower with higher prenatal concentrations of $\log_e$ MnBP ($b=-2.09$; 95% CI: $[-3.43, -0.75]$), $\log_e$ MBzP ($b=-1.14$; [95% CI: $-2.13, -0.14]$), $\log_e$ MiBP ($b=-1.36$; 95% CI: $[-2.51, -0.21]$) and $\log_e$ MEP ($b=-1.23$ [95% CI: $-2.36, -0.11]$). BOT-2 fine motor composite score was lower with higher prenatal $\log_e$ MnBP ($b=-1.43$; 95% CI: $[-2.44, -0.42]$). The gross motor composite score was also inversely associated with the prenatal concentrations of $\log_e$ MiBP ($b=-0.56$; 95% CI: $[-1.12, -0.01]$), and $\log_e$ MEP ($b=-0.60$; 95% CI: $[-1.14, -0.06]$).

Among boys, BOT-2 fine motor composite score was associated inversely with prenatal concentrations of $\log_e$ MBzP ($b=-0.79$; 95% CI: $[-1.40, -0.19]$). A similar association was found between prenatal concentrations of $\log_e$ MnBP ($b=-0.78$; 95% CI: $[-1.63, 0.07]$) and BOT-2 fine motor composite score.

No significant association between any prenatal phthalate metabolite concentration and BOT-2 gross motor score was found among boys. The associations between $\log_e$ MEP and BOT-2 gross motor composite score significantly differed by sex ($p=0.03$). No other effect measure modification by sex was found. Figure 1 illustrates the findings.

In the alternative analysis with specific gravity adjusted prenatal phthalate metabolites categorized as quartiles, BOT-2 total composite scores among girls born to mothers with urinary MnBP, MBzP, and MiBP concentrations in the highest compared to the lowest quartile were -3.8 (95% CI = $[-0.64$ to $-6.92]$), -3.3 (95% CI = $[-0.06$ to $-6.49]$) and -3.5 (95% CI = $[-0.56$ to $-6.43]$) points lower, respectively (Table S5b). Similarly, girls whose mothers had MnBP concentrations in the highest compared to the lowest quartile had significantly lower scores on BOT-2 fine motor composite 2.6 (95% CI = $[0.28$ to $4.98]$). BOT-2 gross motor composite scores among girls born to mothers with MBzP and MiBP concentrations in the highest compared to the lowest quartile were -1.6 points lower (95% CI = $[-0.03$ to $-3.13]$ and 95% CI = $[-0.17$ to $-3.01]$, respectively).

Among boys, BOT-2 fine motor composite scores of those born to mothers with MnBP and MBzP concentrations in the highest quartile compared to the lowest quartile of both metabolites were 2.2 points lower (95% CI = $[-0.27$ to $-4.14]$ and 95% CI = $[-0.29$ to $-4.07]$, respectively). No effect measure modification by sex was found for any of these comparisons.

3.2. Postnatal Phthalates

In contrast to the prenatal phthalate results, none of the child MnBP, MiBP and MBzP phthalates were associated with BOT-2 scores, while child DEHP metabolites were associated with BOT-2 scores. After adjusting for the covariates, several significant associations were found for the child age 3 phthalate metabolites. Among girls, none of the age 3 phthalate metabolites were associated with BOT-2 fine motor composite score. Among boys, age 3 $\log_e$ DEHP, $\log_e$ MEHHP, and $\log_e$ MEOHP were significantly inversely associated with BOT-2 fine motor composite score among boys. Age 3 $\log_e$ MEP was positively associated BOT-2 gross motor composite score among girls. Among boys, $\log_e$ MEP and $\log_e$ MCOP were inversely associated with BOT-2 gross motor composite score among boys. The child sex differences in the associations between $\log_e$ MEP at age 3 with the three BOT-2 motor composite scores were statistically significant ($p<0.01$) (figure 2 and table 4).

For metabolites measured at age 5, only $\log_e$ MEP was positively associated with BOT-2 gross motor composite score ($b = 0.59$; 95% CI = $[0.07, 1.11]$) among boys (figure 3 and table 4). In contrast, several phthalates measured at age 7 were associated with BOT-2 outcomes, mostly among boys. Age 7 $\log_e$ DEHP ($b = -0.96$; 95% CI = $[-1.79, -0.13]$), $\log_e$ MEHHP ($b = -0.76$; 95% CI = $[-1.50, -0.02]$), $\log_e$ MECPP ($b = -1.21$; 95% CI = $[-2.13, -0.29]$), and $\log_e$ MEOHP ($b = -0.80$; 95% CI = $[-1.55, -0.04]$) were inversely associated with BOT-2 fine motor composite score among boys (Table S4). Significant child sex differences were found between $\log_e$ DEHP, $\log_e$ MECPP, and BOT-2 fine motor composite score. Among girls, $\log_e$ MEP was inversely associated with BOT-2 total composite score ($b = -1.12$; 95%

CI=[-2.23, -0.02]) and the association was significantly different from that in boys ($p=0.02$) (figure 4 and table 4).

In the analysis comparing second, third and fourth quartiles to the lowest quartile of exposure to phthalates at ages 3, 5 and 7 years (see Supplementary Table S5b-S5d), revealed that BOT-2 total composite scores among boys with urinary MEP and MCOP concentrations measured at age 3 in the highest compared to the lowest quartile were 5.76 (95% CI = [2.09 to 9.43]), and 7.47 (95% CI= [2.34 to 12.60]) points lower, respectively (Table S5b). Similarly, girls with urinary MEP concentrations measured at age 7 in the highest compared to the lowest quartile had significantly lower scores on BOT-2 fine motor composite 3.34 (95% CI= [0.60 to 6.90]).

4. Discussion

This is one of the few epidemiologic studies to evaluate the effects of prenatal phthalate exposure on child motor skills and, to our knowledge, is the only study to examine the associations in preadolescents (i.e. children age 11 years). In our follow up study of children prenatally exposed to phthalates, we found significant inverse associations between prenatal exposure to MnBP, MiBP, MBzP, MEP and BOT-2 motor scores assessed at 11 years of age. While girls and boys had similar prenatal phthalate exposure profiles and similar BOT-2 motor scores, the magnitude of inverse associations between prenatal phthalate exposure and BOT-2 motor scores were different among girls and among boys. Nevertheless, there was little evidence for effect measure modification, likely due to small sample sizes. Specifically, BOT-2 fine motor composite scores were estimated to be 2.6 points lower among girls born to women with the highest compared to the lowest quartile of MnBP. Likewise, BOT-2 gross composite scores were estimated to be 1.6 points lower among girls born to women with the highest compared with the lowest quartile of MBzP and MiBP. In. Among boys born to women with highest compared with the lowest quartile MnBP and MBzP, BOT-2 fine motor composite scores were 2.2 points lower.

Postnatal child exposure to phthalates was also associated with BOT-2 motor composite scores. While prenatal DEHP metabolites were not associated with BOT-2 scores among either girls or boys, DEHP metabolites measured at age 3 and 7 years were inversely associated with BOT-2 total composite and BOT-2 fine motor composite scores among boys only. Postnatal MEP was also associated with BOT-2 scores but the direction of this association varied by sex and age. We found a significant sex-difference in association between concentrations of MEP detected at age 3 and the three BOT-2 motor composite scores. Among girls, MEP at age 3 was positively associated with BOT-2 scores, while MEP at age 7 was inversely associated with BOT-2 scores. The associations at age 7 are consistent with the association between BOT-2 scores and prenatal MEP maternal urine concentration. Among boys, MEP at age 3 was inversely associated with the BOT-2 scores. In summary, while prenatal phthalates were inversely associated with BOT-2 scores among girls, child phthalates were inversely associated with BOT-2 scores among boys. These findings suggest a role for prenatal and postnatal exposure to specific phthalates, particularly diethyl phthalate(DEP) and di-2-ethylhexyl phthalate (DEHP) (which are metabolized to MEP and MEHP respectively), that is sex specific. Indeed, controlling for prenatal and postnatal

phthalate metabolites simultaneously, we found that among girls, prenatal phthalate metabolites were more strongly associated with BOT- 2 scores than postnatal phthalates (data not shown). In contrast, among boys, postnatal phthalate metabolites, in particular DEHP metabolites were more strongly associated with BOT-2 scores than prenatal phthalate metabolites.

The study extends our earlier observations of associations between prenatal exposure to phthalates and child psychomotor development at age 3 years (Whyatt et al., 2012). In the previous analysis, we found inverse associations between prenatal urinary concentrations of MnBP and MiBP and the psychomotor development index (PDI) of the Bayley Scales of Infant Development-II among boys and girls. Similar to our current findings, we found no associations between prenatal DEHP concentrations and child psychomotor score.

Further, our data suggest that the associations between prenatal phthalates and motor function persist into preadolescence, with the emergence of sex-specific associations. While it is possible that sex-specific differences were present at earlier ages, motor function at earlier ages was not assessed in our study, making it difficult to determine whether there are persistent associations or whether sex-specific associations truly emerge among pre-adolescents, as these children begin to undergo puberty.

While no previous study examined the association between prenatal phthalate exposure and motor skills in school age children, several studies investigated the association in infants and toddlers. Our results are consistent with those of some studies (Gascon et al., 2015; Kim et al., 2011; Polanska et al., 2014; Whyatt et al., 2012), but different from others (Engel et al., 2009; Tellez-Rojo et al., 2013; Yolton et al., 2011). . Numerous factors may contribute to the discrepancies. First, the ages of the children in the studies ranged from infants (Engel et al., 2009; Gascon et al., 2015; Kim et al., 2009; Yolton et al., 2011), 2-3 year old toddlers (Polanska et al., 2014; Whyatt et al., 2012), 4 years (Gascon et al., 2015), and 11 years (the present study). For newborns, prenatal phthalate exposure was associated with better motor performance (Engel et al., 2009; Yolton et al., 2011); and from 6 months and older, prenatal phthalate exposure was associated with worse motor performance (Gascon et al., 2015; Kim et al., 2011; Polanska et al., 2014; Whyatt et al., 2012); except for a Mexican birth cohort which found that MBzP and MCPP concentrations were associated with improved psychomotor scores among boys (Tellez-Rojo et al., 2013) (All studies described in Supplementary Table S7). . This suggests that better motor function in late childhood may be associated with better physical outcomes. Furthermore, most of the studies assessed children's motor development using the Bayley Scales of Infant Development (BSID) II or III. Although we acknowledge the excellent reliability and validity of these batteries, several studies have found that BSID-II and BSID-III have poor predictive value in predicting later motor development in preterm and term infants (Burakevych et al., 2017; Luttikhuisen dos Santos et al., 2013; Spittle et al., 2013).

Second, the variability in timing of sample collection during pregnancy between the studies can contribute to heterogeneous results. The timing ranged from first trimester (Gascon et al., 2015), second trimester (Yolton et al., 2011), to third trimester (Engel et al., 2009; Gascon et al., 2015; Kim et al., 2011; Polanska et al., 2014; Tellez-Rojo et al., 2013; Whyatt

et al., 2012). Only two of the studies (Gascon et al., 2015; Yolton et al., 2011) did not use a single spot urine sample to assess prenatal phthalate exposure. Particularly for short-lived chemicals such as phthalates, sampling parameters such as timing of collection and use of single spot samples may introduce measurement error into the estimation of exposure and thereby, bias the results, likely to the null (Smolders et al., 2014). The composition and concentration of the phthalate mixtures in the cohorts can further influence the findings. We found that the prenatal metabolites concentrations in the CCCEH cohort were generally higher than those in other studies.

Third, the discrepancies between the studies may be due to the differences in the socioeconomic composition of the cohorts. Several socioeconomic factors influence diet and personal care product use, thereby affecting phthalate exposure (Belova et al., 2013; Casas et al., 2011; Kobrosly et al., 2012; Tyrrell et al., 2013; Valvi et al., 2015). Motor skills are also associated with socioeconomic factors (Golding et al., 2014). High socioeconomic status children outperform their low socioeconomic status peers on fine and gross motor proficiency (Morley et al., 2015). Socioeconomic status is also associated with children's intelligence and other cognitive functions (Piccolo et al., 2016; von Stumm and Plomin, 2015). Higher maternal education is associated with gross motor maturity (Syrengelas et al., 2014) and earlier development of fine motor skills (Comuk-Balci et al., 2016). In the CCCEH cohort, the women were from minority ethnic groups, younger at pregnancy, more often unmarried, and of lower educational attainment than women in the other studies.

In terms of potential mechanisms, alteration of thyroid function by phthalates is particularly relevant with respect to motor development. Associations between phthalate exposure and alteration of thyroid function have been found in experimental studies (Breous et al., 2005; Pereira et al., 2007; Sugiyama et al., 2005) and in epidemiologic studies (Boas et al., 2010; Huang et al., 2007; Meeker and Ferguson, 2011; Morgenstern et al., 2017). Thyroid hormones are critical for brain development (Moog et al., 2015; Morreale de Escobar, 2001) and in particular, for the cerebellum (Anderson, 2008), which is associated with motor learning and coordination. Studies consistently show that children of women with thyroid abnormalities have significantly lower motor scores than children of euthyroid women (with normally functioning thyroid) (Fan and Wu, 2016; Li et al., 2010; Pop et al., 2003). The possible mediating role of thyroid hormones in the association between prenatal phthalate exposure and motor development should be investigated in future studies. Another pathway is disruption of the brain dopaminergic system by phthalates (Matsuda et al., 2012; Tanida et al., 2009). Experimental studies in laboratory rodents show that acquisition of motor skills is dependent on the integrity of dopaminergic fibers in the primary motor cortex (Hosp and Luft, 2013). Specifically, BBzP exposure produced dose-dependent pathological changes in hippocampal dentate gyrus and reduced locomotion in mice (Min et al., 2014). Other potential mechanisms include the anti-androgenic activity of phthalates (Howdeshell et al., 2008) that may alter both brain sexual differentiation (Negri-Cesi et al., 2004; Weiss, 2012) and brain aromatase activity (Andrade et al., 2006; Bonefeld-Jorgensen et al., 2007). These disturbances may interfere with estradiol syntheses, critical for hippocampal synaptic plasticity, memory and learning (Garcia-Segura, 2008), thereby affecting motor development and function.

Our study has a number of strengths. First, it is a prospective evaluation of a moderately large birth cohort with assessment of phthalate exposure during late pregnancy as well as during three time points in childhood, ages 3, 5, and 7 years, thereby allowing us to evaluate patterns and timing of associations between phthalate exposure and motor skills. Second, in some analyses, we had sufficient sample size to stratify by child sex, which is crucial as sex can modify the association between phthalate exposure and motor skills. Moreover, as noted above, phthalate exposure may affect neurodevelopment differentially by sex.

Nevertheless, our study contains some limitations. We are unable to identify specific times during pregnancy when phthalates could be related to motor outcomes as phthalate metabolites were measured in a spot urine sample collected during the third trimester. Nevertheless, the sensitivity for correctly classifying a woman as having high phthalate exposure based on a single randomly selected urine sample has been found to be moderately good (Adibi et al., 2008). The restriction of the study sample to healthy inner-city African American and Hispanics reduced the generalizability of our findings, but it likely minimized residual confounding by socioeconomic status and ethnicity. Restricting the study population to healthier women whose children would be at lower risk of impaired psychomotor development would also make finding associations more difficult. There are inconsistent findings regarding validity of short form of BOT-2 in terms of its items' correlation with respective subtest total score. Particularly a study found that individual items in short form of BOT-2 were not strongly associated with total scores in the Balance, Integration, Strength and Precision subtests respectively (Brahler et al., 2012). Nonetheless a subsequent study found a moderate to good correlations between individual items and their respective subscale total scores (Lucas et al., 2013). We lacked data on whether a child received a diagnosis of developmental coordination disorder after they were referred to further evaluation if their BOT-2 scores were below average or well below average according to the descriptive categories corresponding to BOT-2 scores. Because we used the short form of the BOT-2, we could not examine the relationships between phthalate exposure and eight BOT-2 subtests (fine motor precision, fine motor integration, manual dexterity, bilateral coordination, balance, running speed and agility, upper limb coordination, strength). Finally, our results are not corrected for multiple testing and we do not rule out the possibility of Type I error.

Almost 33% of the children in our study had below or well-below average total point-scores measured by short form of BOT-2. Regardless of receipt of a diagnosis of developmental coordination disorder, children with motor problems often face difficulty participating in daily activities of childhood (Dewey et al., 2002; Mandich et al., 2003; Wang et al., 2009; Zwicker et al., 2012). Difficulty with school-related motor skills can negatively affect learning and academic and professional achievement. Beyond the motor domain, children with motor problems can experience far-reaching secondary psychological morbidity including low self-worth and self-esteem, high rates of anxiety and depression, and behavioral disorders, such as Attention Deficit/Hyperactivity Disorder (Lingam et al., 2012; Piek et al., 2010; Piek et al., 2007; Shaffer et al., 1985; Skinner and Piek, 2001). Our findings suggest the necessity for further longitudinal studies to assess the effects of phthalates on motor development.

5. Conclusion

Maternal exposure to phthalates in late pregnancy may have long lasting adverse effects on motor function in children in later childhood, particularly in girls. In contrast, childhood exposure to phthalates may have more harmful effects on motor function in boys. Since children utilize motor skills to navigate their physical and social environment, our findings suggest the need to reduce phthalate exposure. This is a crucial public health challenge given the globally ubiquitous nature of phthalates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We acknowledge Manori Silva, Ella Samandar, Jim Preau, and Tao Jia for technical assistance.

Funding:

National Institute of Environmental Health Sciences (NIEHS) grants [R01ES013543, R01ES014393, R01ES08977 and P30ES009089] and by NIEHS/United States Environmental Protection Agency grant [P50 ES09600/RD 83214101].

Abbreviations:

BOT-2)	Bruininks-Oseretsky Test of Motor Proficiency-2
BSID-II	Bayley Scales of Infant Development II
BMI	Body Mass Index
BbZP	Butylbenzyl Phthalate
CCCEH	Columbia Center for Children's Environmental Health
CDC	Center for Disease Control
DAG	Directed Acyclic Graph
DEHP	Di-2-Ethylhexyl Phthalate
DEP	Diethyl Phthalate
DnBP	Di(<i>N</i> -Butyl, Phthalate
DiBP	Di-Isobutyl Phthalate
DiNP	Diisononyl Phthalate
HOME	Home Observation for Measurement of The Environment
ICC	Intraclass Correlation Coefficients
IQ	Intelligence Quotient

LOD	Limit of Detection
MBzP	Monobenzyl Phthalate
MnBP	Mono- <i>N</i> -Butyl Phthalate
MiBP	Monoisobutyl Phthalate
MEP	Monoethyl Phthalate
MCOP	Mono-Carboxy-Isooctyl Phthalate
MDI	Mental Development Index
PDI	Psychomotor Development Scale
SG	Specific Gravity
WISC-IV	Wechsler Intelligence Scale for Children, 4th Edition

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Highlights

Prenatal exposure to certain phthalates was associated with lower motor BOT-2 scores measured at 11 years of age among girls.

Postnatal exposure to certain phthalates was associated with lower motor proficiency among boys measured at 11 years of age.

The association between MEP measured at age 3 and motor performance at age 11 was different among girls and boys.

Figure 1. Adjusted estimated regression coefficients of prenatal phthalate metabolites and BOT-2 Total, Fine, and Gross motor composite score at age 11 in boys (squares) and girls (diamonds). The x-axis represents the change in BOT-2 motor associated with a $\log_e$ unit increase in phthalate metabolite. Adjusted for prenatal specific gravity, maternal ethnicity, prenatal maternal demoralization, prenatal maternal alcohol consumption, quality of the home environment (HOME score), child BMI z-score at age 11, and child's age in months at BOT-2 administration. Bars represent 95% confidence intervals.

Figure 2. Adjusted estimated regression coefficients of age 3 phthalate metabolites and BOT-2 Total, Fine, and Gross composite motor score at age 11 in boys (squares) and girls (diamonds). The x-axis represents the change in BOT-2 motor score associated with a $\log_e$ unit increase in phthalate metabolite. Adjusted for age 3 specific gravity, maternal ethnicity, prenatal maternal demoralization, prenatal maternal alcohol consumption, quality of the home environment (HOME score), child BMI z-score at age 11, and child's age in months at BOT-2 administration. Bars represent 95% confidence intervals.

Figure 3. Adjusted estimated regression coefficients of age 5 phthalate metabolites and BOT-2 Total, Fine, and Gross composite motor score at age 11 in boys (squares) and girls (diamonds). The x-axis represents the change in BOT-2 motor score associated with a log_e unit increase in phthalate metabolite. Adjusted for age 5 specific gravity, maternal ethnicity, prenatal maternal demoralization, prenatal maternal alcohol consumption, quality of the home environment (HOME score), child BMI z-score at age 11, and child's age in months at BOT-2 administration. Bars represent 95% confidence intervals. *For MCOP metabolite at age 5, data were available for 116 women corresponding to 62 girls and 54 boys.

Figure 4. Adjusted estimated regression coefficients of age 7 phthalate metabolites and BOT-2 Total, Fine, and Gross composite motor score at age 11 in boys (squares) and girls (diamonds). The x-axis represents the change in BOT-2 motor score associated with a $\log_e$ unit increase in phthalate metabolite. Adjusted for age 7 specific gravity, maternal ethnicity, prenatal maternal demoralization, prenatal maternal alcohol consumption, quality of the home environment (HOME score), child BMI z-score at age 11, and child's age in months at BOT-2 administration. Bars represent 95% confidence intervals.

Table 1:

Comparison of Participants with and without Prenatal Phthalate Concentrations

Characteristic	All (n=356)	With Prenatal Measures (n=209) ^a	Without Prenatal Measures (n=147)	P-value ^b
Maternal age at prenatal interview (yr.)	25.3 ± 5.1	25.3 ± 4.9	25.3 ± 5.3	0.92
Ethnicity				
African American	127 (35.7)	69 (33.0)	58(39.46)	0.21
Dominican or other Hispanic	229 (64.3)	140 (67.0)	89 (60.54)	
Maternal education (n=410)				
<High school degree	126 (36.2)	77 (36.8)	49(35.25)	0.76
High school diploma or GED	222 (63.8)	132 (63.2)	90 (64.75)	
Marital status (n=409)				
Ever Married ^c	123 (34.8)	69 (33.0)	54 (37.2)	0.41
Never Married	231 (65.2)	140 (67.0)	91 (62.8)	
Missing	2	0	2	
Prenatal alcohol consumption				
Yes	80 (23.3)	48 (23.8)	32 (22.5)	0.79
No	264 (76.7)	154 (76.2)	110 (77.5)	
Missing	14	7	7	
Maternal demoralization	1.1 ± 0.6	1.1 ± 0.6	1.2 ± 0.6	0.59
Missing	27	3	24	
HOME scale	39.6 ± 6.0	39.9 ± 5.8	39.2 ± 6.1	0.31
Missing	21	9	12	
Maternal IQ	85.0 ± 13.2	84.4 ± 12.9	86.0 ± 13.53	0.30
Missing	6	2	4	
Child Sex				
Male	165 (46.35)	93(44.5)	107 (53.0)	0.40
Female	191 (53.65)	116 (55.5)	95 (47.0)	
Birth weight (gm)	3397.9±476.9	3399.8 ±481.1	3395.3 ±472.6	0.93
Missing	4	3	1	
Gestational age (weeks)	39.3 ± 1.3	39.3 ± 1.3	39.4 ± 1.3	0.85
Missing	2	2	0	
Bayley Scales of Infant Development-II				
Psychomotor Development Index	100.7 ±12.6	102.1 ±11.8	98.6 ±13.4	0.01
Missing	34	18	16	
Mental Development Index	90.5 ± 11.8	92.0 ± 11.2	88.5 ±12.3	0.01
Missing	34	18	16	
WISC-IV at age 7				
Missing	12	3	9	
Full Scale Composite Score	99.3 ± 12.44*	98.7 ± 12.4	100.2 ± 12.5	0.29
Perceptual Reasoning Composite	100.4 ± 13.6	100.2 ± 13.7	100.7 ± 13.5	0.77

Characteristic	All (n=356)	With Prenatal Measures (n=209) ^a	Without Prenatal Measures (n=147)	P-value ^b
Processing Speed Composite Score	101.8 ± 15.9	99.5 ± 15.2	105.1 ± 16.5	0.001
Verbal Comprehension Composite	97.2 ± 11.3	96.5 ± 11.5	98.4 ± 11.0	0.11
Working Memory Composite Score	98.4 ± 14.1	99.7 ± 14.7	96.5 ± 12.9	0.04
Bruininks-Oseretsky Test of Motor Proficiency-2				
Child age at BOT-2 (yr.)	11.27 ± 0.6	11.0 ± 0.39	11.6 ± 0.6	0.001
Child BMI z-score ^d	0.99 ± 1.1	1.0 ± 1.10	0.9 ± 1.0	0.73
BOT-2 ^e Outcomes				
Gross Motor Composite Score	29.5 ± 3.1	29.1 ± 2.9	30.1 ± 3.2	0.003
Fine Motor Composite Score	38.8 ± 3.6	38.6 ± 3.9	39.2 ± 3.1	0.15
Total Composite Score	68.4 ± 5.7	67.7 ± 5.7	69.3 ± 0.5	0.01
BOT-2 Development Clinical Category				
Above Average	4 (1.12)	2 (0.96)	2 (1.36)	0.04
Average	251 (70.51)	137 (65.55)	114 (77.55)	
Below Average	98 (27.53)	68 (32.54)	30 (20.40)	
Well Below Average	3 (0.84)	2 (0.96)	1 (0.68)	

Abbreviations: BOT-2, Bruininks-Oseretsky Test of Motor Proficiency, version II; GED, General Educational Development.; WISC-IV, Wechsler Intelligence Scale for Children, 4th ed; BMI, Body mass index

^aValues are mean ± SD or No. (percent). Unless noted, n = 209 for the subjects with BOT-2 and for n=356 for subjects with prenatal phthalates.

^bp values are derived from chi-square test of equality of proportions for categorical variables and t-test for equality of means for numeric variables between the groups with and without prenatal measures

^cIncludes living with same partner for >7 years.

^dBMI z-score is measure of relative weight adjusted for child age and sex.

^eBOT-2 is the Bruininks-Oseretsky Test of Motor Proficiency, version II.

Table 2:

Distribution of Phthalate metabolites (ng/ml) in maternal spot urine during the third trimester of pregnancy (n=209).

Metabolite	Geometric Mean	95% CI	No Available	LOD*	% <LOD	Range	25%	Median	75%
Prenatal Exposures (n=209)									
Non DEHP									
MnBP	35.7	(30.8, 41.4)	209	0.6	0	1.2 to 1,110	18.7	37.1	74.5
MBzP	12.3	(10.3, 14.8)	209	0.2	0.5	<LOD to 390.2	5.0	13.2	26.7
MiBP	7.5	(6.5, 8.7)	208	0.3	0.5	<LOD to 118	4.1	7.6	16.4
MCOP ^a	2.1	(1.7, 2.7)	72	0.7	13.9	<LOD to 18.3	1.2	2.3	4.1
MEP	148.7	(126.6, 174.7)	209	0.5	0	7.8 – 3663.8	66.7	131.1	302.3
DEHP									
DEHP ^b	281.9	(241.4, 329.4)	N/A	N/A	N/A	<LOD to 9937.5	137.1	264.5	577.7
MEHHP	21.2	(17.9, 25.1)	209	0.7	0	1.1 – 1,380	10.0	21.0	44.1
MEHP	4.8	(3.7, 5.4)	174	1.2	16.7	<LOD to 213	2.0	4.4	10.5
MECPP	37.7	(32.5, 43.7)	209	0.6	0	3.0 – 1,210	19.4	35.2	75.8
MEOHP	17.6	(14.4, 20.8)	209	0.7	0	0.7 – 795	8.2	17.9	37.5
Exposures at age 3 (n=166)									
Non DEHP									
MnBP	44.8	(37.2, 53.9)	166	0.6	0	1.90 – 2,020	22	48.2	103
MBzP	23.1	(18.1, 29.5)	166	0.216	0	0.29 – 2, 253	8.5	25.59	67.45
MiBP	12.1	(10, 14.6)	165	0.3	0.6	<LOD to 260	5.09	14.55	30.80
MCOP	8.8	(7, 11)	113	0.7	0.9	<LOD to 235	3.7	9.20	20.5
MEP	149.6	(122.1, 183.3)	166	0.528	0	7.98 – 5847.60	57.55	135.3	304.9
DEHP									
DEHP	400.6	(336.4, 477.1)	N/A	N/A	N/A	<LOD to 6568.44	186.80	410.3	919.3
MEHHP	32.8	(26.9, 40)	165	0.7	0.6	<LOD to 646	15.5	32	87.5
MEHP	3.2	(2.7, 3.8)	131	1.2	21.08	<LOD to 60	1.2	3.2	7.1
MECPP	61.6	(52.0, 72.9)	166	0.6	0	1.2 – 933	27.6	58.75	133.0
MEOHP	19.3	(15.9, 23.4)	165	0.7	0.6	<LOD to 345	8.90	20.45	47.70
Exposures at age 5 (n=199)									
Non DEHP									
MnBP	41.1	(35, 48.2)	199	0.6	0	1.90 – 549	18.90	43.7	103
MBzP	22.0	(18.3, 26.5)	199	0.216	0	0.29 – 2253	8.5	25.6	67.4
MiBP	17.8	(15.1, 20.9)	199	0.3	0	0.80 – 1770	7.5	18.8	41
MCOP	11.0	(9, 13.3)	199	0.7	0	1.10 – 293	5.85	11.1	21.20
MEP	140.6	(117.5, 168.2)	199	0.528	0	6.20 – 7920	61.5	131.3	319.4
DEHP									
DEHP	422.2	(362.7, 491.9)	N/A	N/A	N/A	15.52 – 7312.15	203.53	462.9	852.9
MEHHP	36.4	(30.9, 43)	198	0.7	0.29	<LOD to 817	16.30	35.8	81.8
MEHP	3.2	(2.7, 3.7)		1.2	20.82	<LOD to 146	0.85	3.1	6

Metabolite	Geometric Mean	95% CI	No Available	LOD*	% <LOD	Range	25%	Median	75%
MECPP	62.3	(53.9, 72.1)	199	0.6	0	2.80 – 924	29.1	68.7	123
MEOHP	21.7	(18.5, 26.5)	198	0.7	0.52	<LOD to 512	9.9	22.9	48.5
Exposures at age 7 (n=156)									
Non DEHP									
MnBP	41.7	(35.3, 49.3)	156	0.6	0	2.7 – 852	21.3	43.5	87.4
MBzP	23.2	(18.7, 29)	156	0.2	0.35	<LOD to 1497.6	8.96	22.7	61.3
MiBP	20.5	(17.5, 24.1)	156	0.3	0	1.10 – 558	9.8	22.4	37.9
MCOP	13.4	(11.2, 15.9)	156	0.7	0.71	<LOD to 278.0	6.35	12.2	24.9
MEP	121.7	(100.2, 147.8)	156	0.528	0	8.12 – 8250	58.2	100.6	231
DEHP									
DEHP	493.1	(414.3, 586.8)	N/A	N/A	N/A	38.45 – 12121.65	245.7	452.2	865.4
MEHHP	43	(35.6, 52.1)	156	0.7	0	2.7 – 1370	18.5	41.1	79
MEHP	4.1	(3.4, 5.0)	156	1.2	7.77	<LOD to 218	1.7	3.6	8.55
MECPP	70.1	(59.6, 82.5)	156	0.6	0	6.60 – 1490	37.7	65	119
MEOHP	27.5	(22.8, 33.0)	156	0.7	0	1.49 - 636	12	28.8	51.7

Abbreviations: LOD, below the limit of detection; ND, not detected; N/A, not applicable

^aFor MCOP: n=72.

^b DEHP is the total molar sum of all four DEHP metabolites (MEHP, MEHHP, MECPP, and MEOHP). Therefore LOD and n available would not be applicable to DEHP.

MEHP=mono-2-ethylhexyl phthalate, MEHHP=mono-2-ethyl-5-hydroxyhexyl phthalate, MECPP=mono-2-ethyl-5-carboxypentyl phthalate, MEOHP= mono-(2-ethyl-5-oxohexyl) phthalate, MCOP= mono-carboxy-isooctyl phthalate

Table 3.

Estimated adjusted coefficients of maternal urinary phthalate metabolite concentrations in linear model for Bruininks-Oseretsky Test of Motor Proficiency-2 scores at 11 years of age.

Prenatal	B (95% CI)^a				Sex Difference
Metabolite	Girls (n=116)		Boys (n=93)		P value
BOT-2 Total Composite Score					
MnBP	-2.09	(-3.43, -0.75)	-0.63	(-1.96, 0.69)	0.13
MBzP	-1.14	(-2.13, -0.14)	-0.87	(-1.82, 0.07)	0.70
MiBP	-1.36	(-2.51, -0.21)	-0.58	(-1.93, 0.77)	0.38
MEP	-1.23	(-2.36, -0.11)	0.50	(-0.52, 1.52)	0.02
MCOP ^b	-4.34	(-9.06, 0.37)	-0.92	(-3.17, 1.32)	0.18
DEHP ^c	-0.21	(-1.27, 0.85)	-0.31	(-1.88, 1.25)	0.91
BOT-2 Fine Motor Composite Score					
MnBP	-1.43	(-2.44, -0.42)	-0.78	(-1.63, 0.07)	0.33
MBzP	-0.70	(-1.45, 0.04)	-0.79	(-1.40, -0.19)	0.85
MiBP	-0.80	(-1.66, 0.07)	-0.54	(-1.42, 0.33)	0.68
MEP	-0.63	(-1.48, 0.22)	0.25	(-0.42, 0.91)	0.11
MCOP ^b	-3.27	(-7.00, 0.45)	-0.84	(-3.17, 1.32)	0.21
DEHP ^c	-0.26	(-1.05, 0.54)	-0.26	(-1.28, 0.76)	1.00
BOT-2 Gross Motor Composite Score					
MnBP	-0.66	(-1.33, 0.002)	0.15	(-0.56, 0.86)	0.10
MBzP	-0.44	(-0.92, 0.05)	-0.08	(-0.59, 0.44)	0.32
MiBP	-0.56	(-1.12, -0.01)	-0.03	(-0.76, 0.69)	0.25
MEP	-0.60	(-1.14, -0.06)	0.25	(-0.29, 0.80)	0.03
MCOP ^b	-1.07	(-2.98, 0.81)	-0.08	(-1.32, 1.16)	0.36
DEHP ^c	0.04	(-0.47, 0.56)	-0.06	(-0.90, 0.79)	0.84

Abbreviations: CI, Confidence Interval

^aControlling for specific gravity, maternal ethnicity, prenatal maternal demoralization, prenatal maternal alcohol exposure, quality of the home environment (HOME score), child BMI z-score at age 11, and child's age in months at administration.

^bFor prenatal MCOP metabolite, data were available for 72 women corresponding to 34 girls and 38 boys.

^cEstimated coefficients of maternal urinary concentrations of individual DEHP metabolites in linear model for Bruininks-Oseretsky Test of Motor Proficiency-2 scores at 11 years of age is presented Table S3a.

Table 4.

Estimated adjusted coefficients of child age 3, 5, and 7 years urinary phthalate metabolite concentrations in linear models for Bruininks-Oseretsky Test of Motor Proficiency-2 scores at 11 years of age.

Child Phthalate Metabolite	Girls B (95% CI) ^a			Boys B (95% CI) ^a		
	Age 3 (n=96)	Age 5 (n=112)	Age 7 (n=82)	Age 3 (n=70)	Age 5 (n=87)	Age 7 (n=74)
MnBP	0.35 (−1.11, 1.80)	−0.64 (−1.90, 0.63)	0.58 (−1.11, 2.26)	−0.08 (−1.90, 1.75)	−0.20 (−1.62, 1.23)	−0.73 (−2.11, 0.65)
MBzP	0.02 (−1.01, 1.06)	−0.10 (−1.01, 0.80)	0.28 (−0.87, 1.42)	−0.72 (−1.80, 0.36)	−0.77 (−1.86, 0.33)	0.14 (−0.87, 1.14)
MiBP	−0.47 (−1.88, 0.94)	−0.74 (−1.86, 0.39)	0.21 (−1.54, 1.96)	−0.99 (−2.42, 0.44)	−0.81 (−2.20, 0.58)	−0.52 (−1.90, 0.85)
MEP	1.21 (0.13, 2.28)	−0.58 (−1.60, 0.45)	−1.12 (−2.23, −0.02)	−1.68 (−2.76, −0.60)	0.78 (−0.22, 1.78)	0.64 (−0.40, 1.68)
MCOP	−0.64 (−2.57, 1.28)	−1.58 (−4.04, 0.87)	−0.26 (−1.78, 1.26)	−3.08 (−5.35, −0.80)	−0.49 (−2.61, 1.62)	−0.56 (−1.77, 0.64)
DEHP ^b	−1.05 (−2.68, 0.58)	−0.71 (−1.97, 0.55)	0.60 (−0.84, 2.04)	−1.55 (−3.16, 0.06)	0.37 (−1.02, 1.75)	−1.30 (−2.56, −0.03)
BOT-2 Fine Motor Composite Score						
MnBP	0.37 (−0.72, 1.47)	−0.80 (−1.73, 0.14)	0.28 (−0.98, 1.55)	0.48 (−0.71, 1.68)	−0.24 (−1.17, 0.69)	−0.13 (−1.04, 0.79)
MBzP	−0.17 (−0.95, 0.60)	−0.25 (−0.93, 0.42)	0.20 (−0.65, 1.06)	−0.23 (−0.95, 0.49)	−0.55 (−1.27, 0.16)	0.19 (−0.47, 0.85)
MiBP	−0.16 (−1.22, 0.90)	−0.60 (−1.44, 0.24)	−0.17 (−1.48, 1.14)	−0.30 (−1.26, 0.65)	−0.74 (−1.64, 0.16)	−0.26 (−1.17, 0.65)
MEP	0.66 (−0.16, 1.48)	−0.47 (−1.24, 0.30)	−0.81 (−1.64, 0.02)	−0.83 (−1.57, −0.09)	0.19 (−0.47, 0.85)	0.24 (−0.46, 0.93)
MCOP	−0.30 (−1.80, 1.19)	−0.98 (−2.85, 0.88)	−0.42 (−1.56, 0.71)	−1.64 (−3.16, −0.12)	−0.56 (−1.89, 0.78)	−0.45 (−1.24, 0.34)
DEHP ^b	−0.99 (−2.21, 0.23)	−0.34 (−1.28, 0.61)	0.53 (−0.55, 1.61)	−1.30 (−2.34, −0.26)	0.11 (−0.80, 1.02)	−0.96 (−1.79, −0.13)
BOT-2 Gross Motor Composite Score						
MnBP	−0.03 (−0.72, 0.67)	0.16 (−0.45, 0.77)	0.30 (−0.45, 1.05)	−0.56 (−1.52, 0.40)	0.04 (−0.71, 0.80)	−0.60 (−1.35, 0.15)
MBzP	0.20 (−0.29, 0.69)	−0.15 (−0.29, 0.59)	0.07 (−0.44, 0.58)	−0.49 (−1.06, 0.08)	−0.21 (−0.80, 0.37)	−0.05 (−0.61, 0.50)
MiBP	−0.32 (−0.99, 0.35)	−0.14 (−0.69, 0.41)	0.38 (−0.39, 1.16)	−0.69 (−1.44, 0.06)	−0.07 (−0.81, 0.67)	−0.26 (−1.02, 0.50)
MEP	0.55 (0.03, 1.06)	−0.11 (−0.60, 0.39)	−0.31 (−0.82, 0.19)	−0.85 (−1.43, −0.27)	0.59 (0.07, 1.11)	0.40 (−0.17, 0.98)
MCOP	−0.34 (−1.24, 0.57)	−0.60 (−1.80, 0.60)	0.16 (−0.52, 0.84)	−1.44 (−2.60, −0.28)	0.06 (−0.95, 1.08)	−0.11 (−0.78, 0.56)
DEHP ^b	−0.06 (−0.85, 0.73)	−0.37 (−0.98, 0.24)	0.07 (−0.58, 0.71)	−0.25 (−1.13, 0.62)	0.26 (−0.47, 0.99)	−0.34 (−1.05, 0.38)

^aControlling for specific gravity (prenatal, age 3, age 5, and or age 7, as appropriate) maternal ethnicity, prenatal maternal demoralization, prenatal maternal alcohol exposure, quality of the home environment (HOME score), child BMI z-score at age 11, and child's age in months at administration.

^bEstimated coefficients of individual DEHP urinary metabolite concentrations in linear models for Bruininks-Oseretsky Test of Motor Proficiency-2 scores at 11 years of age is presented in Table S4a.

Significant child sex differences were seen in associations between MEP at age 3 and BOT-2 Total and Gross Motor Composite Scores; DEHP at age 7 was associated with decrease in both BOT-2 Total and Fine Motor Composite Scores.