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Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age

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Abstract

Background—Previous studies suggest that prenatal phthalate exposure affects neurodevelopment and behavior during the first years of life.

Objectives—To evaluate the effect of maternal urinary concentrations of phthalate metabolites during pregnancy on mental and psychomotor development in children 24-36 months of age.

Methods—This analysis was conducted on the first three years of life among a subsample of 136 mother-child pairs from the ELEMENT cohort studies conducted in Mexico City. Maternal urine samples collected during the third trimester of pregnancy were analyzed for 9 phthalate metabolites: Mono-ethyl phthalate (MEP), Mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-benzyl phthalate (MBzP), Mono-3-carboxypropyl phthalate (MCPP), and four di-2-ethylhexyl phthalate (DEHP) metabolites [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)]. Among the 136 children, 135 (99.3%) completed the study period. Child neurodevelopment was assessed using mental and psychomotor development indexes (MDI and PDI) from a Bayley (BSID II) test at 24, 30, and 36 months of age. The effect of prenatal phthalate exposure on neurodevelopment was estimated using linear regression models for longitudinal data clustered at the individual level.

Results—No significant associations were observed among all children combined, but differential effects by gender were found. Among girls, there was a negative association between MDI and DEHP metabolites MEHP (β = −2.11 [95% CI: −3.73, −0.49]), MEHHP (β = −1.89 [95% CI: −3.64, −0.15]), MEOHP (β = −1.80 [95% CI: −3.58, −0.03]) MECPP (β = −2.52 [95%

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CI: −4.44, −0.61]), and DEHP (β = −3.41 [95% CI: −5.26, −1.55]); there was no significant effect among boys. Male PDI was positively related to MBzP (β = 1.79 [95% CI: 0.14, 3.45]) and MCPP (β = 1.64 [95% CI: 0.15, 3.12]); there was no significant effect on PDI among girls.

Conclusion—This study demonstrates that sex plays a role of an effect modifier in the association between prenatal phthalate exposure and neurodevelopment.

Keywords

Prenatal Exposure; Biomarkers; Phthalates; Child Development; Longitudinal Study

Introduction

Phthalates are a group of chemicals used in a wide range of industrial applications and consumer products. Higher molecular-weight phthalates, such as di(2-ethylhexyl) phthalate (DEHP), are used in flexible vinyl plastic and other consumer products, while low-molecular-weight phthalates, such as di-n-butyl phthalate (DnBP), diethyl phthalate (DEP), and butyl benzyl phthalate (BBzP) are used in pharmaceuticals and personal care products (Afshari et al., 2004;Schettler, 2006). Due to their widespread and diverse usage, detectable levels of phthalates have been found in a variety of populations worldwide including Mexico(Casas et al., 2011;Romero-Franco et al., 2011;Svensson et al., 2011). During the last decade, there has been growing concern for health risks associated with exposure to phthalates, especially in susceptible populations, such as pregnant women and children(Jurewicz and Hanke, 2011). Phthalates have been shown to cross the fetoplacental barrier with detectable levels found in human amniotic fluid and fetal circulation(Huang et al., 2009;Swan, 2008;Wittassek et al., 2009).

Phthalate metabolites measured in maternal urine during pregnancy have been associated with adverse effects on neurodevelopment and behavior of their offspring(Boas et al., 2006;Jurewicz and Hanke, 2011) and some reports suggest a sex-phthalate interaction affecting neurodevelopment(Cho et al., 2010;Engel et al., 2009;Kim et al., 2009;Kim et al., 2011;Whyatt et al., 2013). Potential mechanisms for these associations remain unclear.

Studies in animals and in vitro have shown that certain phthalates may act as endocrine-disrupting compounds (EDCs) that could lead to adverse reproductive and developmental effects through a number of biological pathways, ranging from effects on hormone receptors to effects on hormone synthesis, secretion, or metabolism(Boas et al., 2006;NRC, 1999). Other mechanisms, such as oxidative stress, may also play a role(Ferguson et al., 2012).

Thus, the aim of our study is to estimate the association between maternal urinary concentrations of phthalate metabolites during the third trimester of pregnancy and child mental and psychomotor development in children 24 to 36 months of age in a subsample of the *Early Life Exposure in Mexico to ENvironmental Toxicants* (ELEMENT) project in Mexico City.

Methods

The present study was conducted in a subsample of the ELEMENT birth cohort studies developed in Mexico City. The study comprises 1,710 mother and child pair from which 646 women were recruited during prenatal visits in the first trimester of pregnancy and with the same inclusion criteria at the Mexican Institute of Social Security (1997-2003) and have been describe elsewhere(Ettinger et al., 2009). Archived third trimester urine sample were available for 136 women and their children were followed at 24, 30 and 36 months of age. One girl was excluded due to a diagnosis of Down's syndrome, resulting in a final sample of

135 children (64 boys and 71 girls). Questionnaires were administered to collect sociodemographic information such as mother's age, maternal education and marital status. Study personnel were trained to measure children's weight and height during all visits.

The research protocol was approved by the Ethics and Research Committees of all participating institutions. The study was described in detail to all participating mothers, and all study participants signed an informed consent.

Measurement of Child Development

All children were assessed for the infant's mental and psychomotor development indexes (MDI and PDI) using the Bayley Scales of Infant Development II (BSID II) at 24, 30, and 36 months of age(Bayley, 1993): from the 135 children participating in the study, we had 127, 120 and 113 kids with MDI and PDI assessments at 24, 30 and 36 months that entered in the analyses, respectively. The instructions and prompts were translated into Spanish by L.S.A., the psychologist personnel coordinator, who administered the BSID II and was also responsible for personnel standardization, training and supervision. Quality control checks were conducted by reviewing videotaped evaluations.

Measure of Phthalate in Urine

A spot (second morning void) urine sample was collected from each woman during her third-trimester visit to the project's research center and frozen at −80°C. Samples were shipped on dry ice overnight to either the U.S. Centers for Disease Control and Prevention (CDC; n = 36) or the University of Michigan (n = 99), where samples were analyzed for nine phthalate metabolites: Mono-ethyl phthalate (MEP), Mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-benzyl phthalate (MBzP), Mono-3-carboxypropyl phthalate (MCPP), and four di-2-ethylhexyl phthalate (DEHP) metabolites [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)]. Both laboratories utilized previously published methods involving enzymatic deconjugation of the metabolites from their glucuronidated form, solid-phase extraction, separation with high-performance liquid chromatography, and detection by isotope-dilution tandem mass spectrometry using methods developed at CDC (Silva et al., 2007). The limits of detection (LODs) were similar for both laboratories and in the low nanogram per milliliter range for each phthalate metabolite. There was also good agreement in phthalate concentrations between laboratories among a small subset of samples that were analyzed by both labs. Isotopically labeled internal standards and conjugated internal standards were used to increase precision of measurements. Along with the unknown samples, each analytical run included calibration standards, reagent blanks, and quality control materials of high and low concentration to monitor for accuracy and precision. Analysts were blind to all information concerning subjects.

Urinary phthalate metabolite concentrations were corrected for urine dilution by specific gravity (SG) using the formula $Pc = P[(1.014 - 1)/SG - 1)]$, where Pc is the SG-corrected phthalate metabolite concentration (micrograms per liter), P is the observed phthalate metabolite concentration, 1.014 is the median SG value among the present study population, and SG is the specific gravity of the individual urine sample. SG was measured using a handheld digital refractometer (ATAGO Company Ltd., Tokyo, Japan). Finally, we calculated (in nanomoles per milliliter) the sum of concentrations of DEHP metabolites that were measured (i.e., MEHP, MEHHP, MEOHP, and MECPP).

Statistical analysis

Since the distributions of phthalate metabolite concentrations were right-skewed, these variables were transformed by the natural logarithm (ln) to improve their linear relation with the outcome variables (MDI and PDI scores). Phthalate metabolite values below their respective LODs were assigned the value of one-half of the LOD. Descriptive statistics from mothers and kids were compared by sex of the offspring using either parametrical tests for comparison of proportions or the nonparametric Wilcoxon test when the assumptions of normality were not achieved.

To examine the relation between prenatal phthalate exposures on the overall neurodevelopment along 2-3 years of age, we performed linear regression models for longitudinal data that allowed us to deal with an unbalanced panel design using the individual as the unit of analysis for clustering. We then generated models stratified by sex. Models were adjusted by birth weight, breastfeeding practices, Z-scores for weight-for-age, child's current age, mother's age, mother's educational level, and laboratory where urine phthalate analysis took place.

All data analyses were performed with Stata 10.0 (StataCorp, College Station, TX).

Results

Maternal and children characteristics are shown in Table 1. The mother participants of our study had a mean age of 27.2 years and 10.8 years of school education. More than half were married (71.9%). Among the children, the average birth weight was 3.11 kg, and the average height at birth was 49.96 cm. Average gestational age was 38.5 weeks, and 33% if children were breastfeeding until 12 months of age. Our primary statistical analyses were stratified by sex, so we first compared main characteristics between sexes. No significant differences in relevant covariants between sexes were observed. A sociodemographic comparison between participants of this pilot study and the remaining cohort participants was conducted on variables such as gestational age, birth weight, maternal age and maternal educational level to support the representativeness of the subsample in comparison with the remaining cohort; no statistical difference was found (data not shown).

Median phthalate biomarker concentrations were also compared between boys and girls (see Table 2), and there were no statistical differences between sexes. Most of the metabolites were detected in greater than 95% of the samples. Correlations among phthalate metabolites (log-transformed) were statistically significant (<0.01); however, high molecular weight metabolites were more strongly correlated with one another than low molecular weight metabolites (mean correlation coefficient 0.80 vs 0.44, respectively).

There were no significant effects of prenatal phthalates exposure on MDI nor PDI in the whole sample. In the stratified analyses, there was a significant inverse effect on MDI in girls associated with a natural log-unit increases of DEHP metabolites MEHP ($\beta = -2.11$ [95% CI: −3.73, −0.49]), MECPP ($\beta = -2.52$ [95% CI: −4.44, −0.61]), MEHHP ($\beta = -1.89$ [95% CI: −3.64, −0.15]), MEOHP ($\beta = -1.80$ [95% CI: −3.58, −0.03]) and DEHP ($\beta = -3.41$ [95% CI: −5.26, −1.55]). In boys, PDI was positively associated with a natural log-unit increase of MBzP ($\beta = 1.79$ [95% CI: 0.14, 3.45]) and MCPP ($\beta = 1.64$ [95% CI: 0.15, 3.12]). (Tables 3 and 4).

Discussion

No significant association between prenatal phthalate exposure and neurodevelopment was found among all children in the study. However, some evidence for sex-specific effects was

observed. We found an inverse association between prenatal exposure to metabolites of the high molecular weight phthalate DEHP (MEHP, MECPP, MEHHP, MEOHP and ΣDEHP) and overall MDI scores in female infants between two and three years of age. We also found a positive association between prenatal exposure to LMWP (MBzP and MCPP) and PDI scores in boys. Levels of urinary phthalates from different studies vary across countries, and there were no clear trends between values reported in this study population and other populations of pregnant women for most metabolites except MnBP, which appeared to be higher in this population compared to most others(Casas et al., 2011;Casas et al., 2013;Woodruff et al., 2011).

Some epidemiological studies have investigated associations between prenatal phthalate exposure and infant neurodevelopment, though demographic makeup, outcomes assessed, timing of exposure and outcome measures, and other factors have differed between studies. Those studies also reported sex-phthalate metabolite interactions, and some of them also found that girls are more vulnerable to the neurotoxic effects of phthalates than boys. In a U.S. study, Engel et al. evaluated associations between prenatal maternal urinary concentrations of phthalate metabolites and neonatal behavior using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) administered to children within five days of delivery, and observed a linear decline in adjusted mean orientation score with increasing urinary concentrations of high molecular weight phthalates among girls (n=295)(Engel et al., 2009). These results among girls may be consistent with those obtained in our study. In the same study, the researchers reported some indication of improved motor performance with increasing concentration of low molecular weight phthalates among boys. A second U.S. study by Whyatt et al. reported that prenatal maternal urinary concentrations of MnBP, but not DEHP metabolites, were associated with a significant decrease in mental development at three years of age in girls (n= 319)(Whyatt et al., 2013). A third U.S. study by Yolton et al. measured maternal urinary phthalate metabolites at two points during pregnancy (16w, 26w) and related them to neurobehavior at 5 weeks of age. They found associations only with phthalate levels at 26 weeks, and reported that prenatal exposure to DEHP was associated with nonoptimal reflexes in male infants (n=350, U.S.)(Yolton et al., 2011). Finally, a recent Korean study by Kim et al. also did not report stronger inverse associations among girls as reported here in their study of phthalate exposure characterized by the Mental and Psychomotor Developmental Indices of Bayley Scale at six months of age. Conversely, their results suggested an inverse association between prenatal MnBP or DEHP metabolites and both MDI and PDI among boys (n= 460)(Kim et al., 2011).

One primary limitation of our study is the modest sample size and therefore limited statistical power to detect subtle effects. However, a major strength, compared to previous studies, is the longitudinal design of the study that allows us to relate prenatal exposures to repeated measurements of neurodevelopment during infancy. However, more research is needed to confirm the adverse effects of these chemicals on neurodevelopment and to clarify the particular biological mechanisms that produce differential effects across sex. In conclusion, we found that girls' MDI was negatively associated with HMWP while boys' PDI was positively associated with LMWP. However, no significant relationships were observed when assessing all children combined, even when adjusting for sex as a covariate in the analysis. These findings, in addition to those reported by others, stress the need for exploring sex-specific associations when analyzing effects of prenatal phthalate exposure on neurodevelopment.

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Abbreviations

BSID II	The Bayley Scales of Infant Development II
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DEHP	di-2-ethylhexyl phthalate
HMWP	high molecular weight phthalates
LMWP	low molecular weight phthalates
LOD	limit of detection
MDI	Mental Development Index
PDI	Psychomotor Development Index
MBzP	mono-benzyl phthalate
MEP	monoethyl phthalate
MCPP	mono-(3-carboxypropyl) phthalate
MnBP	mono-n-butyl phthalate
MiBP	mono-isobutyl phthalate
MEHP	mono-2-ethylhexyl phthalate
MEHHP	mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	mono-(2-ethyl-5-oxohexyl) phthalate
MECPP	mono-(2-ethyl-5-carboxypentyl) phthalate
ΣDEHP	sum of di-2-ethylhexyl phthalate metabolites
SG	specific gravity

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Highlights

- In a cohort study, a differential effect of prenatal phthalate exposure by gender was found.
- A negative effect among girls between MDI and HMWP was estimated.
- There was no effect between MDI and Phthalates among boys.
- A positive effect between prenatal LMWP exposure and PDI was estimated for boys.

Table 1

Summary statistics of the study sample.

Study Sample (n=135)		**Boys (n=64)**	**Girls (n=71)**	***P*-value**
Mothers characteristics				
Maternal age (years)[§]	27.2 (5.4)	26.9 (4.6)	27.5 (6.1)	0.53
Maternal education (years)[§]	10.8 (3.3)	11.1 (3.1)	10.5 (3.5)	0.24
Marital status (1=Married)[£]	71.9%	79.7%	64.8%	0.05
Children characteritics				
Weight at birth (kg)[§]	3.1 (0.4)	3.2 (0.4)	3.0 (0.4)	0.02
Height at birth (cm)[§]	50.0 (2.0)	50.3 (1.8)	49.7 (2.2)	0.19
Gestational age (weeks)[§]	38.5 (1.7)	38.8 (1.5)	38.2(1.9)	0.20
Breast feeding for at least 1 month[£]	93.3%	95.3%	91.6%	0.38
Breast feeding (any type)	6.49 (4.72)	6.66 (4.73)	6.33 (4.74)	0.51
Never	8.33%	6.25%	10.29%	
1 month	28.03%	29.69%	26.47%	
7 months	30.30%	29.69%	30.88%	
12 months	33.33%	34.38%	32.35%	
Mental Development Index				
24 months	86.74 (18.81)	84.36 (10.88)	88.93(10.35)	0.01
30 months	89.60 (9.19)	87.42 (8.86)	91.39 (9.12)	0.01
36 months	91.23 (9.21)	90.62(9.30)	91.78 (9.18)	0.5
Psychomotor Development Index				
24 months	93.25 (9.63)	93.65 (8.94)	92.81 (10.39)	0.62
30 months	92.93 (11.08)	95.18 (11.98)	90.18 (9.24)	0.01
36 months	94.73 (10.69)	96.9 (11.60)	92.28 (9.05)	0.02

[§]Sample mean and interquartile range, Wilcoxon test

[£]Proportion, Test of equal proportions

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Table 2

Distribution of SG-corrected phthalate metabolite concentrations (ng/ml) in maternal urine samples collected during the third trimester of pregnancy by sex of child.

			ALL (n=135)	BOYS (n=64)	GIRLS (n=71)	*P*-value*
Metabolite	**LOD**	**% below LOD**	**Geometric mean (95% CI)**	**Geometric mean (95% CI)**	**Geometric mean (95% CI)**	
MEP	0.8	0	138 (108, 176)	140.5 (99,199)	136 (96, 191)	0.95
MnBP	0.6	0	85.61 (71.55, 102.42)	86.95 (65.48, 115)	84.41 (66.9, 106)	0.86
MIBP	0.2	2.2	2.30 (1.92, 2.76)	2.15 (1.63, 2.82)	2.45 (1.92, 3.12)	0.24
MBzP	0.3	1.5	3.54 (2.94, 4.26)	3.66 (2.76, 4.85)	3.44 (2.68, 4.40)	0.74
MCPP	0.2	0.7	1.75 (1.49, 2.06)	1.67 (1.28, 2.18)	1.83 (1.49, 2.23)	0.52
MEHP	1.2	4.4	6.56 (5.72, 7.53)	6.21 (5.09, 7.58)	6.89 (5.67, 8.36)	0.31
MEHHP	0.1	0	22.08 (18.77, 25.96)	21.19 (17.03, 26.37)	22.90 (17.98, 29.17)	0.39
MEOHP	0.1	0	14.23 (12.05, 16.80)	13.71 (10.96, 17.15)	14.72 (11.48, 18.86)	0.40
MECPP	0.2	0	39.65 (34.32, 45.81)	36.99 (30.35, 45.08)	42.22 (34.14, 52.20)	0.32
Σ DEHP (nmol/ml)	--		0.35 (0.30, 0.40)	0.32 (0.28, 0.36)	0.38 (0.32, 0.45)	0.06

*Wilcoxon test comparing metabolite concentrations by sex.

Table 3

Adjusted regression coefficients for change in Mental Development Index associated with a ln-unit increase in urinary phthalate metabolite concentration, both overall and stratified by sex.

Metabolite	All (n=135)	Boys (n=64)	Girls (n=71)
	β (95%CI)	β (95%CI)	β (95%CI)
MEP	0.22 (−0.76, 1.21)	−0.64 (−2.31, 1.02)	1.05 (−0.13, 2.23)
MnBP	0.30 (−1.04, 1.65)	0.54 (−1.28, 2.37)	−0.15 (−2.16, 1.84)
MIBP	0.53 (−0.85, 1.91)	0.32 (−1.62, 2.28)	−0.12 (−1.94, 1.69)
MBzP	0.30 (−1.11, 1.73)	1.30 (−0.37, 2.97)	−0.72 (−2.45, 1.01)
MCPP	0.73 (−0.87, 2.33)	1.21 (−0.94, 3.36)	−0.52 (−2.83, 1.78)
MEHP	−0.16 (−1.89, 1.55)	1.72 (−0.89, 4.34)	−2.11 (−3.73, −0.49) *
MEHHP	−0.61 (−2.02, 0.79)	0.66 (−1.39, 2.72)	−1.89 (−3.64, −0.15) *
MEOHP	−0.54 (−1.91, 0.82)	0.85 (−1.11, 2.81)	−1.80 (−3.58, −0.03) *
MECPP	−0.80 (−2.38, 0.77)	0.91 (−1.18, 3.01)	−2.52 (−4.44, −0.61) *
Σ DEHP	−0.48 (−2.30,1.34)	1.45 (−0.75, 3.66)	−3.41 (−5.26, −1.55) **

Models were adjusted by mother's age, mother's educational level (total years of school), birth weight, breastfeeding practices (0=never, 1= at least one month, 2= 7 months, 3= 12 months), Z-score for weight-for-age, child's current age (24, 30 or 36 months), and laboratory.

* p value<0.05

** p value<0.01

Table 4

Adjusted regression coefficients for change in Psychomotor Development Index associated with a ln-unit increase in urinary phthalate metabolite concentration, both overall and stratified by sex.

Metabolite	All (n=135)	Boys (n=64)	Girls (n=71)
	β (95%CI)	β (95%CI)	β (95%CI)
MEP	0.02 (−0.96, 1.01)	0.06 (−1.33, 1.47)	0.29 (−1.06, 1.66)
MnBP	0.49 (−0.66, 1.64)	0.86 (−0.54, 2.27)	0.52 (−1.68, 2.73)
MIBP	0.57 (−0.67, 1.82)	0.63 (−0.68, 1.95)	0.37 (−1.67, 2.43)
MBzP	0.10 (−1.16, 1.37)	1.79 (0.14, 3.45) *	−1.21 (−3.31, 0.88)
MCPP	0.86 (−0.41, 2.15)	1.64 (0.15, 3.12) *	−0.26 (−2.83, 2.30)
MEHP	0.02 (−1.62, 1.66)	0.34 (−1.47, 2.16)	−0.07 (−2.49, 2.34)
MEHHP	−0.11 (−1.45, 1.22)	0.68 (−0.76, 2.13)	−0.48 (−2.75, 1.79)
MEOHP	0.03 (−1.26, 1.33)	0.80 (−0.62, 2.22)	−0.18 (−2.38, 2.01)
MECPP	−0.19 (−1.77, 1.38)	0.89 (−0.90, 2.68)	−0.90 (−3.48, 1.66)
Σ DEHP	0.01 (−1.46, 1.49)	1.05 (−0.72,2.83)	−1.22 (−3.92, 1.48)

Models were adjusted by mother's age, mother's educational level (total years of school), birth weight, breastfeeding practices (0=never, 1= at least one month, 2= 7 months, 3= 12 months), Z-score for weight-for-age, child's current age (24, 30 or 36 months), and laboratory.

* p value<0.05