Published in final edited form as:
Environ Res. 2014 January ; 128: 64–69. doi:10.1016/j.envres.2013.10.004.

Association between phthalates and attention deficit disorder and learning disability in U.S. children, 6–15 years

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Abstract

Objective—This study investigates the association between urinary phthalate metabolite levels and attention deficit disorder (ADD), learning disability (LD), and co-occurrence of ADD and LD in 6–15-year-old children.

Methods—We used cross-sectional data from the National Health and Nutrition Examination Survey (NHANES, 2001–2004). Phthalate metabolites with ≥ 75% detection in urine samples were examined. The study population comprised 1493 children with parent-reported information on ADD or LD diagnosis and phthalate concentrations in urine. Phthalate concentrations were creatinine-adjusted and $\log_{10}$-transformed for analysis. All models controlled for child sex, age, race, household income, blood lead, and maternal smoking during pregnancy.

Results—There were 112 ADD cases, 173 LD cases, and 56 ADD and LD cases in the sample. After adjusting for potential confounders, we found increased odds of ADD with increasing urinary concentration of di-2-ethylhexyl phthalates (OR: 2.1; 95% CI: 1.1, 3.9) and high molecular weight phthalates (OR: 2.7; 95% CI: 1.2, 6.1). In addition, dibutyl phthalates (OR: 3.3; 95% CI: 0.9, 12.7) and high molecular weight phthalates (OR: 3.7; 95% CI: 0.9, 14.8) were marginally associated with increased odds of co-occurring ADD and LD. We did not find associations for any phthalate and LD alone. We observed stronger associations between phthalates and ADD and both ADD and LD in girls than boys in some models.

Conclusions—We found cross-sectional evidence that certain phthalates are associated with increased odds of ADD and both ADD and LD. Further investigations with longitudinal data are needed to confirm these results.

Keywords

Attention deficit disorder; Learning disability; Phthalates; Plasticizers; National Health and Nutrition; Examination Survey

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Disclaimer
The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the funders.

Financial disclosure
The authors have no financial conflict of interest to disclose.

IRB approval
The Committee for Protection of Human Subjects (CPHS) at UC Berkeley determined that our research did not meet the criteria for human research as per federal regulations, and therefore did not require review.

1. Introduction

Phthalates are industrial chemicals often used in personal care products and to soften plastics in toys, household items such as food containers, and medical devices (Barr et al., 2003; Hauser and Calafat, 2005; Sathyanarayana et al., 2008). Because they are not chemically bound to the plastics, they disperse into the environment easily, leading to exposure via inhalation, ingestion, and dermal contact (Afshari et al., 2004; Clark et al., 2003). In the National Health and Nutrition Examination Survey (NHANES) 1999–2000, urinary metabolites of phthalates were detectable in 75–90% of the samples, indicating widespread exposure in the U.S. population (Silva et al., 2004).

Eight different phthalate diesters are in general consumer use. High molecular weight (high M.W.) phthalates, including benzylbutyl phthalate (BzBP), di-2-ethylhexyl phthalate (DEHP), di-isononyl phthalate (DiNP), dimethyl phthalate (DMP), and di-n-octyl phthalate (DOP), are commonly found in vinyl tubing, flooring, and wall covering (NRC, 2008). DEHP, the most commonly used phthalate ester, is the dominant plasticizer in polyvinyl chloride (PVC) due to its low cost (Afshari et al., 2004; Clausen et al., 2004). Low molecular weight (low M.W.) phthalates, such as dibutyl phthalates (DBP), dicylohexyl phthalate (DCHP), diethyl phthalate (DEP), are found in adhesives, printing ink, personal care products, and nail polish (NRC, 2008).

In animal studies, phthalates have been demonstrated to be endocrine disruptors that exhibit weak estrogenic activity, impair thyroid function, and affect neurodevelopment (Boas et al., 2010; Colborn, 2004; Crofton, 2008; Kavlock et al., 1996). In rats, prenatal and neonatal exposure to DEHP or DBP results in impaired neuronal growth and activity (Arcadi et al., 1998; Chen et al., 2011; Li et al., 2009; Tanaka, 2005; Tanida et al., 2009). Neonatal dosing of rats with 87 nmol (29 μg) of DCHP, DBP and DEHP via intracisternal injection was associated with increased motor hyperactivity at 4–5 weeks of age (Ishido et al., 2004; Masuo et al., 2004). Exposure to higher levels (10 mg/kg) of DEHP during the third week after birth was associated with reduced hippocampal development in male, but not female, rats (Smith et al., 2011).

A small number of studies have assessed the association of prenatal or postnatal phthalate exposure and neurobehavioral development in humans (Engel et al., 2010, 2009; Kimet al., 2009; Whyatt et al., 2012). In a study from New York City (NYC), higher concentrations of prenatal urinary metabolites of low and high M.W. phthalates were linked to decrements in motor and mental development and increased odds of internalizing behavior problems in 3-year-olds (N = 319) (Whyatt et al., 2012). In another birth cohort from NYC (N = 188), prenatal urinary levels of low M.W. phthalates were associated with increased odds of externalizing behaviors such as aggression, conduct problems, and attention problems in 4–9-year-old children (Engel et al., 2010). Postnatal exposure to phthalates has been assessed in one previous study; child urinary concentrations of DEHP metabolites were found to be related to attention-deficit/hyperactivity disorder (ADHD) in 8–11-year-old Korean children (N = 261) (Kim et al., 2009). Thus, there is growing evidence that phthalate exposure may be related to attention and behavioral problems.

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) categorizes ADD into three subtypes: predominantly inattentive, predominantly hyperactive/impulsive, or combined (APA, 1994). ADD and learning disability (LD) are the most frequent neurobehavioral disorders diagnosed in children. These disorders affect 5–12% of school-age children in the United States (Vakil et al., 2012). The co-occurrence of ADD and LD is of concern due to its association with worse executive functioning in children than either alone (Mattison and Mayes, 2012). This study investigates the association between

urinary phthalate metabolite levels and ADD, LD, and the co-occurrence of ADD and LD in 6–15-year-old children in NHANES (2001–2004).

2. Methods

2.1. Study design and participants

The study sample was 6–15-year-old children who participated in the 2001–2004 cycles of the National Health and Nutrition Examination Survey (NHANES), a population-based, annual health survey of the United States (U.S.). NHANES data were collected using a complex, multistage, probability sampling design of the civilian non-institutionalized U.S. population, and certain subgroups were over-sampled. Details of the NHANES study have been published elsewhere (CDC, 2012). Participant's parents or guardians completed home interviews about their demographic, socioeconomic, and health information. Urine samples were collected during physical examinations in mobile units (NHANES, 2004).

NHANES data from the 2001–2002 and 2003–2004 cycles were combined, as these cycles provided both information on parent/guardian report of ADD and LD and measures of urinary phthalate metabolite concentrations in a subsample of 1494 participants aged 6–15 years. We excluded individuals missing ADD ($N = 3$) or LD ($N = 1$) data, for final sample sizes of 1491 for ADD analyses and 1493 for LD analyses. For analyses of individuals diagnosed with co-occurrence of ADD and LD, the comparison group were those who were diagnosed with neither; therefore, we excluded 172 individuals who had answered “yes” to having only ADD or LD, for a total of $N = 1318$ for these analyses.

2.2. ADD and/or LD diagnoses

Information about the child’s ADD or LD diagnosis was based on the parent or guardian’s response to the questions “Has a doctor or health professional ever told you that your child had attention deficit disorder?” and “Has a representative from a school or a health professional ever told you that your child had a learning disability?” In our study population of 6–15-year-olds, there were 112 ADD cases, 173 LD cases, and 56 cases with co-occurring ADD and LD. The 56 participants with ADD and LD were a subset of those who had ADD or LD.

2.3. Urinary phthalate metabolite measurements

After collection, urine samples were stored at −20 °C until shipment to the centers for Disease Control and Prevention (CDC) for testing. Details on the laboratory procedures have been published elsewhere (CDC, 2006). Briefly, high performance liquid chromatography–electrospray ionization–tandem mass spectrometry (HPLC–ESI–MS/MS) was used to detect concentrations of phthalate metabolites in urine. The samples were processed by the enzymatic deconjugation of the glucuronidated phthalate monoesters, which was followed by solid phase extraction (NHANES, 2004). Concentrations below the limit of detection (LOD) were assigned the value of the detection limit divided by √2 (Hornung and Reed, 1990). Eight phthalate groups were measured in the 2001–2004 NHANES data sets.

We limited our analyses on those phthalates whose metabolites were detected in ≥ 75% of samples, namely sum (Σ) DEHP, ΣDBP, BzBP, DEP, and DOP. DEHP exposure was estimated by summing the values of three DEHP metabolites, mono- (2-ethyl)-hexyl phthalate (MEHP), mono- (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono- (2-ethyl-5-oxohexyl) phthalate (MEOHP). DBP devolves to two metabolites, mono-n-butyl phthalate (MnBP) and mono-isobutyl phthalate (MiBP), which were summed to obtain the ΣDBP variable. Three phthalates were estimated using a single metabolite: DOP devolves to

mono- (3-carboxypropyl) phthalate (MCPP), BzBP to mono-benzyl phthalate (MBzP), and DEP to mono-ethyl phthalate (MEP) (CDC, 2009).

Additionally, we created variables for the sum of the high M.W. (> 250 Da) and low M.W. (< 250 Da) phthalates, as they come from similar sources and have similar biological activity (Engel et al., 2010; NRC, 2008; Wolff et al., 2008). The Σhigh M.W. variable comprised MBzP + MCPP + MEHP + MEHHP + MEOHP, the Σlow M.W. variable was MEP + MMP + MiBP + MnBP.

2.4. Statistical analysis

All statistical analyses were performed using STATA/IC (version 11.1; StataCorp LP, College Station, TX, USA). Since NHANES is a multi-stage probability design, appropriate weights, primary sampling units, and strata were applied to the data to obtain robust standard errors and unbiased point estimates (CDC, 2011).

Potential confounders considered *a priori* were: age, sex, race, household income (poverty–income ratio (PIR)), low birth weight, health insurance coverage, routine source of healthcare, mental health professional use in past year, child blood lead concentration ($\log_{10}$ transformed), maternal age at birth, and maternal smoking during pregnancy. Variables were kept in the models if they were associated with any of the exposure and outcome variables at $p < 0.10$ or if their exclusion changed the main effect by > 10%. Covariates included in the final models were: child sex (M/F), age (continuous), race (White/Black/Mexican American/Other Hispanic/Other), household income (< 1 PIR/1–2.99 PIR/3–4.99 PIR/≥ 5 PIR), blood lead (continuous), and maternal smoking during pregnancy (Y/N).

All phthalate concentrations were adjusted for creatinine to account for urine dilution (Jackson, 1966), summed, and $\log_{10}$ transformed to approximate a normal distribution and minimize the effects of outliers. In sensitivity analyses, we examined non-creatinine-adjusted phthalate concentrations or included $\log_{10}$ transformed urinary creatinine in the model (Silva et al., 2004).

Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for ADD, LD, and both ADD and LD, per 10-fold increase in ΣDEHP, ΣDBP, MBzP, MEP, MCPP, Σhigh M.W. and Σlow M.W. phthalate concentrations (μg/g creatinine). Statistical interactions of phthalate variables with lead and sex were investigated in the multivariate models using cross-product terms. Interaction terms with $p < 0.10$ in the model were considered statistically significant.

3. Results

The weighted prevalence of ADD was 9.1%, LD was 12.1%, and co-occurrence of ADD and LD was 5.9%. The demographic characteristics of the study population are listed in Table 1. Most participants had health insurance (87%) and a routine source of medical care (94%). The mean child age was 10.5 years (95% CI: 10.3, 10.8) and mean child blood lead levels were 1.3 μg/dL (95% CI: 1.2, 1.4). Metabolites of ΣDEHP, ΣDBP, MBzP, MEP and MCPP were detected in almost all individuals, with the highest concentrations seen for MEP (Table 2). When comparing geometric mean (GM) phthalate metabolite concentrations by diagnosis of ADD only, LD only, both ADD and LD, or neither, significant differences were seen for ΣDEHP and Σhigh M.W. phthalates, with the highest concentrations in those with both ADD and LD (Table 3).

The association of the various phthalate metabolites with diagnosis of ADD and/or LD is shown in Table 4. Each 10-fold increase in ΣDEHP concentrations was associated with a 2-

fold increase in odds of ADD (odds ratio (OR)=2.1, 95% Confidence Interval (CI): 1.1, 3.9). Each 10-fold increase in Σhigh M.W. phthalate concentrations was associated with an adjusted odds ratio for ADD of 2.7 (95% CI: 1.2, 6.1). No other urinary phthalate metabolite concentrations were associated with ADD. Sex of the child modified the association between MEP and ADD (interaction $p = 0.04$); however, the association included 1 for both sexes (Table 5).

We found no significant associations of urinary phthalate metabolites with LD. Although ΣDEHP and Σhigh M.W. phthalate concentrations were marginally associated with LD in unadjusted models (OR=1.6; 95% CI: 0.9, 2.8 and OR: 2.0; 95% CI: 1.0, 3.9, respectively), upon adjusting for potential confounders, these associations were no longer observed. We found no effect modification by sex (data not shown).

In models of co-occurring ADD and LD, the adjusted odds ratio for each 10-fold increase in ΣDBP and Σhigh M.W. phthalates was 3.3 (95% CI: 0.9, 12.7) and 3.7 (95% CI: 0.9, 14.8) (Table 4), respectively, albeit not statistically significant. Although no other metabolites were significantly related to ADD and LD in the overall models, we found significant effect modification by sex in the association of ΣDEHP and co-occurrence of ADD and LD ($p = 0.003$). The odds ratio associated with each 10-fold increase in ΣDEHP levels was 6.2 for females (95% CI: 1.7, 22.7) but 0.9 in males (95% CI: 0.3, 2.7). There was evidence that the ORs for MCPP and both ADD and LD ($p = 0.05$) differed for males and females, but confidence intervals included 1 for both sexes (Table 5).

No significant interaction was found between child's blood lead and phthalate concentrations. Models using the $\log_{10}$ of phthalate concentrations without creatinine adjustment gave similar results.

4. Discussion

In NHANES, a nationally representative survey of the U.S. population, we found that children's urinary concentrations of metabolites of certain phthalates, commonly used as plasticizers, were related to diagnoses of ADD in school-age children 6–15 years old. Children had twice the odds of having ADD with every 10-fold increase in ΣDEHP concentrations, and three times the odds of having both ADD and LD for every 10-fold increase in Σhigh M.W. phthalates. Effect modification by sex was statistically significant in some models with phthalate concentrations to be more likely associated with ADD or ADD and LD in girls than in boys; however, stratum-specific ORs usually included 1 for both sexes. Only in the association between ΣDEHP and co-occurrence of ADD and LD was the association significant for girls. A main strength of our study is that our results are highly generalizable to the U.S. population, unlike previous studies (Engel et al., 2010, 2009; Kim et al., 2009; Whyatt et al., 2012). In addition, to the best of our knowledge, this is the first study to investigate LD as well as both ADD and LD as an outcome for phthalate exposures.

Since NHANES does not provide longitudinal data, we did not have data on *in utero* exposure and could not control for it in our analyses. This may be the time of greatest vulnerability. In addition, due to the cross-sectional design, we could not establish causality in the relationship between phthalates and ADD or LD and reverse causality remains a possibility. This study is also limited by the fact that phthalate exposure is estimated by metabolite concentrations in a single urine sample. Phthalate diesters are broken down into monoester metabolites in the body and excreted in urine within 24 h, suggesting that urinary measurements represent short-term exposure (Anderson et al., 2001; CDC, 2009; Wittassek and Angerer, 2008). However, urinary metabolite concentrations have been shown to be

fairly stable over six months, likely due to regular, ongoing human exposure to phthalate-containing products (Teitelbaum et al., 2008).

Additionally, our analyses are potentially limited by reliance on parent-reported ADD and LD as outcome measures rather than diagnostic data based on DSM-IV criteria in NHANES. However, it is important to note that the DSM-IV restricted data is not free of bias as it is collected by interviewers with no clinical training and relies on parent reported symptoms, ultimately sharing the same limitation of parent recall bias as the public data. Questions about current ADD or LD were not added to NHANES until 2007, which would minimize such a bias (CDC, 2010). Research suggests that parent-reported ADHD is fairly reliable and accurate, with 94% sensitivity and 97% specificity for maternal recall of ADHD diagnosis over a one-year period (Faraone et al., 1995). Further, it has been shown that parent-reported ADHD is as sensitive as teacher-reported ADHD in a clinical trial setting (Biederman et al., 2004), with a 90% likelihood of corroboration leading to clinical diagnosis (Biederman et al., 1990).

Another limitation of this study is that we could not include one metabolite (MECPP) in our ΣDEHP and Σhigh M.W. phthalate variables, since NHANES did not measure this in 2001–2002. It has been shown that MECPP and other oxidative metabolites of DEHP are better biomarkers for exposure assessment in the US population than MEHP, a non-oxidative metabolite (Silva et al., 2006).

Our results corroborate some of the findings from previous studies. The only other cross-sectional study to date found that DEHP, but not DBP, was associated with increased odds of ADHD in Korean children (Kim et al., 2009). We confirmed these results with ADD as well as co-occurring ADD and LD. Although the Korean study did not examine effect modification by sex, a study investigating prenatal exposure to phthalates confirmed our report that higher concentrations of some high M.W. phthalate metabolites (including DEHP) are associated with decreased attention and alertness primarily in females (Engel et al., 2009). However, in contrast to our findings, a cross sectional study found a negative association between DEHP metabolites and IQ scores among boys but not girls (Cho et al., 2010).

In part, the stronger association between some phthalates and ADD and LD in females than males may derive from the higher likelihood that they use phthalate-containing personal care products, such as body lotions, perfumes, and deodorants (Romero-Franco et al., 2011). For example, in NHANES, girls had significantly higher urinary concentrations of MEP, ΣDBP, and Σlow M.W. phthalates than boys. However, females did not have higher levels of Σhigh M.W. phthalates including MBzP, MCPP and ΣDEHP. Thus, this hypothesis cannot explain why ΣDEHP were associated with ADD and LD in girls but not boys.

Biological mechanisms underlying the association between certain phthalates and childhood developmental disorders are uncertain. Peroxisome proliferator-activated receptors (PPARs) have been detected in neural tubes of rat embryos (Braissant and Wahli, 1998) and phthalates have been shown to activate these receptors (Roberts et al., 1997). PPAR signal transduction pathways have been linked to neurodegenerative diseases and cognitive functioning by mechanisms of inflammation and lipid metabolism (van Neerven et al., 2008). *In utero* exposure to DEHP has been shown to decrease lipid concentration and composition in the fetal rat brain (Innis, 2003; Xu et al., 2007).

An alternative biological explanation is that phthalates impact brain development through their effects on thyroid function (Hinton et al., 1986; Price et al., 1988). Thyroid hormones play a key role in neurodevelopment and hippocampal function, and delayed or impaired

brain differentiation and hippocampal dysfunction often result in deficits in learning and memory in rats such as impaired spatial maze memory (Akaike et al., 1991; Nunez, 1984; Porterfield and Hendry, 1998; Stein et al., 1991; Vaccari, 1988). Exposure to low levels of phthalates can result in loss of midbrain dopaminergic nuclei (Tanida et al., 2009). Research suggests that aberrations in the dopamine system play a major role in the pathophysiology of ADD and other neuropsychiatric disorders (Krause, 2008; Krause et al., 2003; Shen et al., 2012; Spencer et al., 2005).

5. Conclusion

Our study using representative data from the general U.S. population adds to the body of evidence suggesting an association between phthalate exposure and childhood developmental disorders, specifically ADD and LD. We found that ΣDEHP and Σhigh M.W. phthalates were associated with increased odds for ADD as well as both ADD and LD, especially in girls.

Acknowledgments

Funding source

This work was supported by Grants PO1 ES009605 from the National Institute of Environmental Health Sciences and RD83451301 from the United States Environmental Protection Agency.

Abbreviations

High M.W	high molecular weight
Low M.W	low molecular weight
DEHP	di-2-ethylhexyl phthalate
DBP	dibutyl phthalate
MBzP	mono-benzyl phthalate
MEP	mono-ethyl phthalate
MCPP	mono-(3-carboxypropyl) phthalate
ADHD	attention-deficit/hyperactivity disorder
ADD	attention deficit disorder
LD	learning disability
OR	odds ratio
CI	confidence interval
NHANES	National Health and Nutrition Examination Survey
CDC	Centers for Disease Control and Prevention
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition
PIR	poverty income ratio
LOD	limit of detection

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Table 1

Demographic characteristics of 6–15 year old children in our study population, NHANES (2001–2004).

Population characteristics	N[a]	Weighted (%)
Sex (*N* = 1493)		
Male	726	51.5
Female	767	48.5
Race (*N* = 1493)		
White	399	61.1
Black	532	15.5
Mexican American	461	11.5
Other hispanic	50	6.5
Other	51	5.4
Household income (*N* = 1428)		
< 1.00 PIR[b]	473	23.6
1.00–2.99 PIR	585	38.7
3.00–4.99 PIR	239	23.0
≥ 5.00 PIR	131	14.7
Low birth weight (< 2500 g) (*N* = 1422)		
Yes	196	13.2
No	1226	86.8
Health insurance coverage (*N* = 1483)		
Yes	1244	87.2
No	239	12.8
Routine place for healthcare (*N* = 1493)		
Yes	1370	93.9
No	123	6.1
Seen mental health professional in past year (*N* = 1493)		
Yes	121	9.8
No	1372	90.2
Maternal age at birth (years) (*N* = 1473)		
< 20	246	12.4
20–29	845	56.5
30–39	369	29.7
≥ 40	13	1.4
Maternal Smoking during pregnancy (*N* = 1478)		
Yes	233	20.0
No	1245	80.0

[a] N: unweighted *N*.

[b] PIR: family poverty income ratio as defined by NHANES.

Table 2

Concentrations of urinary phthalate metabolites (N = 1493), NHANES (2001–2004).

Phthalate (μg/g creatinine)	LOD[a]	> LOD (%)	GM[b] (95% CI[c])	Percentile						
				0	10	25	50	75	90	100
ΣDEHP[d]			56.9 (52.0, 62.2)	1.5	17.6	29.2	50.7	94.8	181.3	3613.5
MEHP	0.9	75.4	3.4 (3.0, 3.8)	< LOD	< LOD	1.6	3.5	7.5	16.4	294.2
MEHHP	0.3	99.7	30.6 (27.9, 33.6)	< LOD	9.3	15.4	27.1	52.1	102.2	2062.7
MEOHP	0.5	99.7	21.2 (19.4, 23.1)	< LOD	6.7	10.8	18.6	35.2	69.6	1301.8
ΣDBP			36.1 (33.6, 38.9)	0.51	13.3	21.7	36.3	62.0	97.8	1924.7
MiBP	0.3	99.5	4.6 (4.1, 5.2)	< LOD	1.5	2.7	4.9	8.9	15.3	140.1
MnBP	0.4	99.9	30.2 (28.2, 32.2)	< LOD	10.8	17.6	30.3	50.9	84.3	1912.9
MBzP	0.1	100.0	29.4 (27.3, 31.6)	0.1	7.8	13.0	24.7	48.7	96.3	917.0
MCHP	0.2	15.5	0.2 (0.2, 0.2)	< LOD	< LOD	< LOD	< LOD	< LOD	0.5	15.4
MEP	0.4	100.0	114.1 (104.6, 124.5)	2.7	40.9	65.3	131.8	296.4	687.8	13187.5
MiNP	1.0	9.1	0.7 (0.6, 0.7)	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD	23.0
MMP	1.0	62.4	1.7 (1.5, 2.0)	< LOD	< LOD	< LOD	1.8	3.6	7.7	431.8
ΣDOP			6.4 (6.0, 6.8)	0.5	2.3	3.4	5.3	8.8	14.7	77.8
MCPP	0.2	99.9	5.3 (5.0, 5.7)	< LOD	1.7	2.7	4.5	7.7	13.7	76.4
MOP	1.0	8.4	0.7 (0.7, 0.8)	< LOD	< LOD	< LOD	< LOD	< LOD	1.6	14.0
ΣHigh M.W.[e]			105.0 (98.9, 111.6)	3.3	35.3	55.2	92.3	161.6	292.3	3741.3
ΣLow M.W.[f]			177.0 (163.4, 191.8)	10.8	73.9	108.7	191.5	371.4	756.5	13262.4

[a] LOD: limit of detection.

[b] GM: geometric mean.

[c] CI: confidence interval.

[d] Sum of DEHP does not include MECPP because it was measured only in NHANES (2003–2004).

[e] ΣHigh M.W.: sum of high molecular weight phthalates = MBzP + MCPP + ΣDEHP [MEHP + MEHHP + MEOHP].

[f] ΣLow M.W.: sum of low molecular weight phthalates = MEP + MMP + ΣDBP [MiBP + MnBP].

Table 3

Geometric means of urinary phthalate metabolites (μg/g creatinine) by diagnosis in study population (*N* = 1490).

	Neither (*N* 1262) GM (95% CI)	ADD only[a] (*N* = 56) GM (95% CI)	LD only[b] (*N* = 116) GM (95% CI)	ADD + LD (*N* = 56) GM (95% CI)	*p* Value[c]
ΣDEHP	55.1 (50.3, 60.4)	66.8 (52.7, 84.7)	58.6 (45.6, 75.4)	81.0 (55.6, 118.0)	0.04
ΣDBP	35.9 (33.4, 38.6)	31.7 (24.3, 41.3)	33.3 (27.5, 40.5)	49.3 (36.4, 66.8)	0.28
MBzP	28.7 (26.6, 31.0)	25.8 (17.6, 38.0)	28.8 (22.3, 37.3)	46.6 (29.0, 75.1)	0.14
MEP	116.4 (105.4, 128.5)	90.5 (61.4, 133.4)	106.1 (91.6, 123.0)	108.5 (71.9, 164.0)	0.45
MCPP	5.3 (4.9, 5.7)	5.4 (4.0, 7.4)	5.2 (4.4, 6.3)	6.2 (4.9, 7.7)	0.36
ΣHigh M.W.	101.6 (95.6, 107.9)	111.7 (87.5, 142.6)	105.1 (84.4, 131.0)	171.8 (116.8, 252.7)	0.02
ΣLow M.W.	179.5 (163.6, 196.9)	141.4 (102.5, 195.0)	157.6 (138.3, 179.7)	193.6 (137.2, 273.1)	0.75

[a] ADD only: children with a diagnosis of ADD but not LD.

[b] LD only: children with a diagnosis of LD but not ADD.

[c] Test of trend *p*-value.

Table 4

Odds ratios for ADD (*N* = 1491), LD (*N* = 1493), and ADD + LD (*N* = 1318) for 10-fold increases in urinary phthalate metabolite levels.

	ADD (*N* = 112)		LD (*N* = 173)		ADD + LD (*N* = 56)	
	Unadjusted OR[a] (95% CI)	Adjusted[b] OR[a] (95% CI)	Unadjusted OR[a] (95% CI)	Adjusted[b] OR[a] (95% CI)	Unadjusted OR[a] (95% CI)	Adjusted[b] OR[a] (95% CI)
ΣDEHP	2.0 (1.2, 2.3)*	2.1 (1.1, 3.9)*	1.6 (0.9, 2.8)***	1.5 (0.7, 3.0)	2.4 (1.1, 5.3)*	2.2 (0.6, 7.4)
ΣDBP	1.5 (0.8, 2.9)	1.8 (0.6, 4.8)	1.4 (0.7, 2.7)	1.3 (0.6, 2.9)	2.5 (1.1, 5.6)*	3.3 (0.9, 12.7)***
MBzP	1.7 (0.9, 3.2)	1.5 (0.7, 3.4)	1.6 (0.8, 3.0)	1.2 (0.6, 2.5)	2.7 (1.1, 6.4)*	2.0 (0.6, 6.3)
MEP	0.8 (0.4, 1.4)	1.0 (0.6, 1.8)	0.9 (0.6, 1.4)	1.0 (0.6, 1.6)	0.9 (0.4, 2.0)	1.7 (0.9, 3.3)
MCPP	1.4 (0.7, 2.8)	1.2 (0.4, 4.0)	1.2 (0.7, 2.1)	0.9 (0.4, 1.9)	1.7 (0.8, 3.8)	1.0 (0.2, 4.7)
ΣHigh M.W.	2.7 (1.4, 5.1)**	2.7 (1.2, 6.1)*	2.0 (1.0, 3.9)*	1.6 (0.7, 3.6)	4.3 (1.6, 11.8)**	3.7 (0.9, 14.8)***
ΣLow M.W.	0.9 (0.4, 1.9)	1.1 (0.5, 2.4)	0.9 (0.5, 1.7)	1.0 (0.5, 1.9)	1.2 (0.5, 3.1)	2.2 (0.8, 6.2)

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.10$.

[a]OR: odds ratio.

[b]Adjusted for child sex, age, race, household income, blood lead, and maternal smoking during pregnancy.

Table 5

Odds ratios for ADD and ADD + LD for 10-fold increases in urinary phthalate metabolite levels, stratified by sex.

	ADD			ADD + LD		
	Male OR[a] (95% CI) (*N* = 726)	**Female OR[a] (95% CI) (*N* = 765)**	**Interaction term *p* value (*N* = 1491)**	**Male OR[a] (95% CI) (*N* = 613)**	**Female OR[a] (95% CI) (*N* = 705)**	**Interaction term *p* value (*N* = 1318)**
ΣDEHP	1.5 (0.7, 3.1)	3.5 (1.0, 11.8)*	0.26	0.9 (0.3, 2.7)	6.2 (1.7, 22.7)**	0.003
ΣDBP	1.7 (0.5, 5.4)	2.0 (0.4, 8.8)	0.85	2.1 (0.3, 17.0)	6.4 (1.4, 28.7)*	0.36
MBzP	1.4 (0.5, 3.6)	2.1 (0.8, 5.5)	0.48	1.9 (0.5, 7.1)	2.5 (0.7, 9.6)	0.68
MEP	1.3 (0.7, 2.4)	0.5 (0.2, 1.1)***	0.04	2.2 (0.8, 5.7)	0.8 (0.3, 1.9)	0.21
MCPP	1.1 (0.3, 4.3)	1.7 (0.5, 5.8)	0.53	0.6 (0.1, 3.8)	2.8 (0.6, 13.5)	0.05
ΣHigh M.W.	2.1 (0.8, 6.1)	4.1 (0.9, 19.3)***	0.51	2.1 (0.3, 12.9)	8.6 (1.7, 43.1)*	0.20
ΣLow M.W.	1.4 (0.6, 3.2)	0.7 (0.2, 2.0)	0.26	2.4 (0.6, 10.2)	1.7 (0.5, 5.3)	0.73

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.10$.

[a] Adjusted for child age, race, household income, blood lead, and maternal smoking during pregnancy.