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Early childhood exposures to phthalates in association with attention-deficit/hyperactivity disorder behaviors in middle childhood and adolescence in the ReCHARGE study

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Declaration of competing interest

Rebecca J. Schmidt consults for the Beasley Law Firm. Rebecca J. Schmidt and Deborah H. Bennett consult for Linus Biotechnology, Inc. Other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114377.

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Abstract

Background: Early-life exposure to phthalates alters behaviors in animals. However, epidemiological evidence on childhood phthalate exposure and attention-deficit/hyperactivity disorder (ADHD) behaviors is limited.

Methods: This study included 243 children from the ReCHARGE (Revisiting Childhood Autism Risks from Genetics and Environment) study, who were previously classified as having autism spectrum disorder (ASD), developmental delay, other early concerns, and typical development in the CHARGE case-control study. Twenty phthalate metabolites were measured in spot urine samples collected from children aged 2–5 years. Parents reported on children's ADHD symptoms at ages 8–18 years using Conners-3 Parent Rating Scale. Covariate-adjusted negative binomial generalized linear models were used to investigate associations between individual phthalate metabolite concentrations and raw scores. Weighted quantile sum (WQS) regression with repeated holdout validation was used to examine mixture effects of phthalate metabolites on behavioral scores. Effect modification by child sex was evaluated.

Results: Among 12 phthalate metabolites detected in >75% of the samples, higher mono-2-heptyl phthalate (MHPP) was associated with higher scores on Inattentive (β per doubling = 0.05, 95% confidence interval [CI]: 0.02, 0.08) and Hyperactive/Impulsive scales (β = 0.04, 95% CI: 0.00, 0.07), especially among children with ASD. Higher mono-carboxy isooctyl phthalate (MCiOP) was associated with higher Hyperactivity/Impulsivity scores (β = 0.07, 95% CI: −0.01, 0.15), especially among typically developing children. The associations of the molar sum of high molecular weight (HMW) phthalate metabolites and a phthalate metabolite mixture with Hyperactivity/Impulsivity scores were modified by sex, showing more pronounced adverse associations among females.

Conclusion: Exposure to phthalates during early childhood may impact ADHD behaviors in middle childhood and adolescence, particularly among females. Although our findings may not be broadly generalizable due to the diverse diagnostic profiles within our study population, our robust findings on sex-specific associations warrant further investigations.

Keywords

Phthalates; Mixture effect; ADHD; ASD; Childhood; Adolescence

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neuro-developmental disorder, characterized by a persistent pattern of inattentiveness and/or hyperactivity-impulsivity (American Psychiatric Association 2013). ADHD is a significant concern, with prevalence rates indicating it to be one of the leading childhood behavioral disorders in the United States (U.S.), regardless of the diagnostic approach used. Prevalence within the U.S. varies

depending on data ascertainment methods, with parent reports of ADHD diagnosis ranging from 5.9% (Willcutt 2012) to 9.4% (Danielson et al., 2018), and symptom impairment persists into adulthood in about 70% of ADHD cases (Faraone et al. 2006, 2015). Furthermore, the diagnosis of ADHD continues to rise in the U.S. (Cortese et al., 2023; Rydell et al., 2018; Song et al., 2019; Xu et al., 2018). Children with autism spectrum disorder (ASD) have shown higher prevalence of comorbid ADHD (Rau et al., 2020) and more frequent ADHD-related behaviors compared to typically developing children (Lyall et al., 2017). The development of ADHD involves a combination of genetic and environmental risk factors (Faraone et al., 2021). Environmental risks during pregnancy and early-life stages include but are not limited to exposure to lead, acetaminophen, alcohol, cigarette smoking, nutrient deficiencies, and maternal and child trauma (Banerjee et al., 2007; Masarwa et al., 2018; Moore et al., 2022; Schantz et al., 2020; Thapar et al., 2013).

Phthalates are high-production-volume chemicals that have been extensively used in a wide range of consumer products, such as food production materials and packaging, flooring, wall coverings, building supplies, medicine coatings, medical supplies, cosmetics, and other personal care products (Engel et al., 2021; Hauser and Calafat 2005; Heudorf et al., 2007; Meeker et al., 2009; Schettler 2006; Wang et al., 2019). Children are exposed to phthalates not only through the ingestion of contaminated food and dermal uptake from personal care products but also through the ingestion of dust, mouthing, and inhalation of indoor and outdoor air (Wormuth et al., 2006). Young children have shown higher phthalate exposure levels than adults, potentially due to their higher ingestion rates as well as frequent hand-to-mouth activity and skin contact with surfaces (Huang et al., 2021; Wang et al., 2019; Wittassek et al., 2011). Given the ubiquitous and continuous exposure to phthalates (Buckley et al., 2020) and their endocrine disrupting properties (Hauser and Calafat 2005; Wang and Qian 2021), the importance of investigating their broad health impacts as well as the specific need to evaluate their influence on neurodevelopment have been emphasized (Engel et al., 2021; Schantz et al., 2020). While the prenatal period is widely considered the most vulnerable window for exposure to environmental neurotoxicants (Lanphear 2015), brain development continues in the first few years of life (Stiles and Jernigan 2010). Critical processes, such as cell proliferation, migration, myelination, and pruning, continue during this time (Brown and Jernigan 2012; Gilmore et al., 2018; Safarpour et al., 2022). These processes, especially myelination, are closely regulated by the endocrine system, such as thyroid hormones (Bernal 2005; Calza et al., 2015). Animal studies suggest that phthalate exposure, especially during pregnancy and early-life stages, has adverse effects on the nervous system (Holahan and Smith 2015; Safarpour et al., 2022). Early postnatal exposure of laboratory animals to phthalates induced behavioral changes, particularly motor hyperactivity (Ishido et al. 2004, 2005; Masuo et al. 2004a, 2004b).

A fairly consistent pattern has emerged across multiple epidemiological studies, showing associations of prenatal phthalate exposures with elevated risks of ADHD clinical diagnosis (Engel et al., 2018; Kamai et al., 2021; Radke et al., 2020) or greater ADHD-related behaviors (Chen et al., 2019; Engel et al., 2010; Huang et al., 2019; Hyland et al., 2019; Jedynak et al., 2021; Kobrosly et al., 2014; Ku et al., 2020; Li et al., 2020; Lien et al., 2015; Philippat et al., 2017; Radke et al., 2020; Watkins et al., 2021; Whyatt et al., 2012). Postnatal exposure to phthalates also has shown adverse associations with ADHD diagnosis

or related behaviors (Arbuckle et al., 2016; Chopra et al., 2014; Hu et al., 2017; Jankowska et al., 2019b; Kim et al. 2009, 2017; Park et al. 2014, 2015; Shoaff et al., 2020; Tsai et al., 2020; Watkins et al., 2021; Won et al., 2016), although these findings were based on cross-sectional study designs. Only a limited number of prospective studies have examined the association between phthalate exposures during early childhood and ADHD behaviors in middle childhood or adolescence, reporting adverse (Daniel et al., 2020; Li et al., 2020) or null associations (Huang et al., 2019; Jankowska et al., 2019a). The two studies that reported adverse associations observed sex-specific patterns, with more pronounced adverse associations in females compared to males (Daniel et al., 2020; Li et al., 2020).

The present study aimed to investigate whether exposure to phthalates or their mixtures in children at ages 2–5 years was associated with ADHD symptoms at ages 8–18 years within a study population including children who had been classified as having autism spectrum disorder (ASD), developmental delays (DD), and typical development (TD). We further examined if these associations were modified by child sex.

2. Methods

2.1 Study population

The University of California (UC) Davis ReCHARGE study revisits a subset of children from the Childhood Autism Risks from Genetics and Environment (CHARGE) case-control study, which began in 2002. In the CHARGE study, children aged 2–5 years with ASD or DD concerns were referred primarily through the California Department of Developmental Services/Regional Centers system. General population controls, identified through state birth files, were frequency-matched to ASD cases in terms of sex, age, and catchment area, with the goal of attaining a 4:1 male-to-female ratio. Other eligibility criteria include: a) children living with at least one biological parent who speaks English or Spanish; b) children residing in the study catchment areas; and c) children born in California. After enrollment, the CHARGE children recruited with ASD or DD concerns were administered multiple standardized assessments to confirm their diagnoses, and those with DD concerns were screened for ASD. The general population controls were screened for ASD and evaluated for DD, and if needed, received further assessments for ASD. Children who did not meet the criteria for ASD or DD, respectively, were divided into two groups: those with previous concerns for these conditions were classified as other early concerns (OEC), while those recruited as general population controls were classified as TD. Detailed information regarding the CHARGE study's design, recruitment, data/sample collection, and diagnostic tools is described elsewhere (Hertz-Picciotto et al., 2006). In 2017, the ReCHARGE study started recruiting the CHARGE children aged 8–19 years to explore the environmental factors associated with neurodevelopmental outcomes during pre-, mid-, and late-adolescence. The outcomes of interest included longitudinal changes in diagnosis, cognitive and adaptive function, and symptoms of ADHD, anxiety, or depression. The children enrolled in the ReCHARGE study received additional developmental and behavioral assessments, including an evaluation of ADHD at the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute. The study protocol was approved by the UC Davis Institutional Review Boards and the State of California Committee for

the Protection of Human Subjects. The CHARGE/ReCHARGE study obtained children's written consent or parental/guardian permission prior to any data collection.

Among 1287 CHARGE children who were enrolled, had a visit at the MIND Institute, and received a final diagnosis during 2006–2017, 656 children provided a sufficient volume of spot urine samples at ages 2–5 years for phthalate metabolite quantification. After excluding those who were lost to contact, not eligible for, or chose not to participate in the ReCHARGE study, and those not assessed for ADHD symptoms during middle childhood or adolescence, a total of 243 children participated in the current study (Fig. S1).

2.2 Behavior assessment

The parents of ReCHARGE children, aged 8–18 years, used the Conners-3 Parent Rating Scale (Conners 3-P) (Conners 2008) to assess their child's ADHD-related behaviors. This widely used behavior rating scale system assesses behavior problems, particularly externalizing behaviors, in children aged 6–18 years (Conners et al., 1998). The parents' responses to 110 items, rated on a 0–3 scale (never/seldom, occasionally, often, very often), were aggregated to calculate raw scores for each specific scale, where higher scores indicated more behavioral problems. This study focused on two ADHD-related Diagnostic and Statistical Manual of Mental Disorders, 5^{h} edition (DSM-5) Symptom Scales: ADHD Predominantly Inattentive and Hyperactive-Impulsive Presentation (Conners 2014). Additionally, outcomes included the Executive Functioning scale, one of the empirically derived Content Scales, and the Global Emotional Lability Index, both of which are clinically related to ADHD symptoms (Corbett et al., 2009; Sobanski et al., 2010). Raw scores were standardized based on sex and age into T-scores, having a mean of 50 and a standard deviation (SD) of 10. However, raw scores were analyzed as counts in the primary statistical analysis because they reflect all differences among scores, enabling the detection of subtle behavioral changes in association with chemical exposures (Kobrosly et al., 2014; Quaak et al., 2016).

2.3 Exposure assessment

Urine samples from children collected at ages 2–5 years were stored at − 20 °C. Aliquots were transferred and shipped to the New York State Department of Health's Wadsworth Center's Human Health Exposure Analysis Resource (HHEAR) Targeted Analysis Laboratory. Twenty phthalate metabolites were analyzed in the children's urine samples: mono-benzyl phthalate (MBzP), monocyclohexyl phthalate (MCHP), mono(7-carboxyheptyl)phthalate (MCHPP), mono-carboxy isononyl phthalate (MCiNP), mono-carboxy isooctyl phthalate (MCiOP), mono-2-(carboxymethyl) hexyl phthalate (MCMHP), mono (3-carboxypropyl) phthalate (MCPP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), monoethyl phthalate (MEP), mono-2-heptyl phthalate (MHPP), mono-hexyl phthalate (MHxP), mono-isobutyl phthalate (MiBP), mono-isononyl phthalate (MiNP), mono-isopropyl phthalate (MiPP), mono-methyl phthalate (MMP), mono-n-butyl phthalate (MnBP), mono-n-octyl phthalate (MOP), and mono-pentyl phthalate (MPeP). The urine samples were processed using enzymatic deconjugation and solid-phase extraction,

and then analyzed by high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) as previously described (Li et al., 2019; Rocha et al., 2018).

For quality assurance and quality control, three aliquots of two urine pools were analyzed per batch, and fifteen duplicate pairs were analyzed across the batches. Median relative percentage differences calculated for each valid duplicate pair, in which both sample concentrations were above the limit of detection (LOD), ranged from 5% to 38% depending on the analyte. The LODs for the urinary phthalate metabolites ranged from 0.01 to 5 ng/mL. For phthalate metabolite concentrations below the LOD, machine-read values were used rather than imputing them with a single value. Zero or negative machine-read values, legitimately arisen during the process of blank correction, were replaced with a small value (i.e., 0.0001) (Buckley et al., 2022).

2.4 Statistical analysis

Raw scores from two ADHD-related DSM-5 Symptom Scales (i.e., Inattentive and Hyperactive/Impulsive) were summarized and compared across participant characteristics using the Wilcoxon rank-sum test for binary variables or the Kruskal-Wallis test for categorical variables (with >2 levels) and the significance test of Spearman correlation coefficient for continuous variables.

Twelve phthalate metabolites detected in >75% of the urine samples were included in the statistical analysis (Hornung and Reed 1990). However, due to the common exposure source and high correlations among di-2-ethylhexyl phthalate (DEHP) metabolites (i.e., MCMHP, MECPP, MEHHP, and MEOHP), their molar sums (∑DEHP; nmol/mL) were calculated and included in the analysis instead of individual compounds. In addition, two molar sums were computed based on structural similarity, biological activity, and exposure sources: low molecular weight phthalate metabolites (∑LMW: MEP, MiBP, and MnBP) and high molecular weight phthalate metabolites (∑HMW: MBzP, MCiNP, MCiOP, MCPP, MHPP, MCMHP, MECPP, MEHHP, and MEOHP) (Teitelbaum et al., 2012; Wolff et al., 2008). To account for urinary dilution, phthalate metabolite concentrations and molar sums were corrected for specific gravity (SG) using the Boeniger method: $C_{sg} = C \times [(SG_{median} - 1)/(SG - 1)$, where C_{sg} is the SG-corrected concentration, C is the measured concentration, SG_{median} (1.022) is the median SG values in this study samples, and SG is the SG value measured in each sample (Boeniger et al., 1993; Kuiper et al., 2021). Descriptive statistics and Spearman correlation coefficients of the SG-corrected concentrations were computed. SG-corrected phthalate metabolite concentrations between females and males were compared using the Wilcoxon rank-sum test. For regression analysis, the SG-corrected concentrations were log 2-transformed due to their skewed distributions.

Negative binomial generalized liner models, adjusted for covariates, were used to examine the associations between SG-corrected phthalate metabolite concentrations and raw scores of four Conners 3-P scales. Potential covariates were identified *a priori* from a directed acyclic graph, established through a literature review (Textor et al., 2016) (Fig. S2). The final adjustment set included CHARGE case-control study frequency matching factors, confounders, and risk factors of ADHD: child sex (female, male) and age at behavior assessment (in years), recruitment regional center (Alta, North Bay, East Bay, Valley

Mountain), preterm birth (<37, ≥37 completed weeks), maternal metabolic conditions (healthy weight/overweight and no pregnancy conditions, obese or hypertensive disorder/gestational diabetes), maternal age at delivery (<30, 30–34, ≥35 years), parity (1, ≥2), homeownership (owner, non-owner) as a proxy for socioeconomic status (SES), and diagnostic groups (ASD, DD, OEC, TD). Child race/ethnicity as a proxy for structural racism (non-Hispanic White or other race/ethnicity, non-Hispanic Black, Hispanic) was considered but not included in the models because it was not associated with ADHD behaviors in our sample (p-values>0.2) (Table 1). Highest education in household (high school or less, some college credit or higher), another proxy for SES, was also excluded to minimize multicollinearity and overfitting as homeownership showed the stronger bivariate associations with ADHD behaviors. Instead, these two variables were additionally adjusted for in the sensitivity analysis. The generalized variance inflation factors for the models (range = 1.04–1.37) indicated weak correlations among covariates (Daoud 2017). The missing covariates were imputed using multiple imputation by chained equations that included all exposures, outcomes, and covariates (White et al., 2011). Twenty imputed datasets were generated to estimate pooled regression coefficients (βs) and 95% confidence intervals (CIs) (Graham et al., 2007; Rubin 2004). To correct for multiple comparisons, a false discovery rate (FDR) was applied to p-values per each scale (Benjamini and Hochberg 1995). Furthermore, in an exploratory analysis, negative binomial regression analyses were restricted to children with ASD (n=94) or TD (n=98). As an additional sensitivity analysis, T-scores of Conners 3-P were used in multiple linear regression models, adjusting for the same covariate set. To enhance the normality of residuals, T-scores were square root transformed prior to the regression analyses.

To investigate the overall mixture effects of 12 phthalate metabolites on Conners 3-P raw scores, weighted quantile sum (WQS) regression for negative binomial outcomes was conducted across 100 repeated holdout datasets (Tanner et al., 2019). Within each iteration, children were randomly divided into training (40%) and testing (60%) sets (Carrico et al., 2015), estimating empirical weights for each metabolite and the WQS index from 100 bootstrap samples. The WQS index, representing the overall body burden, was then used as the exposure variable in the multiple regression models, adjusted for the same covariate set as before. After 100 repeated holdouts, weight distributions were interpreted only when the regression coefficients within the 2.5th and 97.5th percentile range indicated significant associations (i.e., $\beta > 0$ or $\beta < 0$). Metabolites for which 50% of the iterations exceeded a threshold of 0.083 (equivalent to 1/12 metabolites in the mixture) were identified as possible contributors (Bennett et al., 2022). Given that higher Conners 3-P scores indicate greater behavioral problems, the WQS regression was constrained to a positive direction. As a complementary approach to estimate the overall mixture effects, quantile-based g-computation was used, which is similar to WQS regression in terms of simplicity of interpretation while incorporating the flexibility of g-computation (Keil et al., 2020). While WQS regression estimates associations in only one direction, quantile-based g-computation allows the estimation of mixture effects in both directions. The estimated effect per simultaneous quartile increase in all phthalate metabolites was presented using psi (ψ).

As previous prospective studies suggested evidence of sex-specific associations between phthalate exposures and ADHD-related behaviors (Daniel et al., 2020; Li et al., 2020), effect modification by child sex was examined. For individual phthalate metabolites, sex-stratified estimates in multiple regression models were calculated, and the interaction term between each metabolite and sex was evaluated. For metabolite mixtures, the sex-stratified interaction WQS regression models were used by additionally including the interaction term between the WQS index and sex in the main WQS regression models (Busgang et al., 2022; Gennings et al., 2022). The distributions of sex-specific metabolite weights and regression coefficients across 100 repeated holdout datasets were generated.

The statistical analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria), implementing publicly available packages such as "*mice*" for multiple imputation by chained equations (Van Buuren and Groothuis-Oudshoorn 2011), "*MASS*" for negative binomial generalized linear regression (Ripley et al., 2013), "*gWQS*" for WQS regression with repeated holdout validation (Renzetti et al., 2021), and "*qgcomp*" for quantile-based g-computation (Keil et al., 2020).

3. Results

The 243 ReCHARGE children had diverse diagnostic profiles, with approximately 40% classified as TD, 39% as ASD, 12% as DD, and 9% as OEC (Table 1). As children with ASD and TD were frequency-matched by sex, the majority of this study population were male (74%). Most children were born to mothers without pre-pregnancy obesity, hypertensive disorders of pregnancy, or gestational diabetes (67%), in families that owned a home (71%), and where the highest education attained in the household was some college credit, a bachelor's, or a higher degree (64%). Many of the participant characteristics in this study population were similar to those in the 1044 CHARGE children who were excluded from this study (Table S1). However, our study population included fewer Hispanic children and more children from families who owned a home, had higher levels of education, and were enrolled in later years compared to those excluded from this study.

Conners 3-P raw scores were higher among children classified as ASD, DD, and OEC compared to children classified as TD (Table 1 and Fig. S3). Males had higher scores of two ADHD-related DSM-5 Symptom Scales than females. Inattentive scores were higher among children born to primiparous mothers than those born to multiparous mothers. Furthermore, children born to mothers aged 30–34 years at delivery had lower scores on both scales compared to those born to mothers either younger or older. Children born to mothers who had pre-pregnancy obesity, hypertensive disorder of pregnancy, or gestational diabetes had higher scores than those born to mothers without these conditions. Children from families that did not own a home or attained lower education had higher scores than those from families that owned a home or attained higher education.

Three LMW phthalate metabolites (MEP, MiBP, and MnBP) and eight HMW phthalate metabolites (MBzP, MCiNP, MCiOP, MCPP, MCMHP, MECPP, MEHHP, and MEOHP), including all DEHP metabolites, were detected in >98% of the samples (Table 2). MHPP was less frequently detected (77%) with a median SG-corrected concentration of 1.4

ng/mL. The highest median concentration was observed for MEHHP (43 ng/mL), a DEHP metabolite, followed by MnBP (42 ng/mL), MEP (40 ng/mL), MECPP (32 ng/mL), and MBzP (32 ng/mL). Males had higher SG-corrected concentrations of MnBP, MBzP, MCPP, MHPP, ∑DEHP, and ∑HMW compared to females (Fig. S4). Four DEHP metabolites showed strong correlations with each other (Spearman correlation coefficients [r_{sp}] = 0.68–0.97) (Fig. S5). Other HMW phthalate metabolites were moderately correlated with each other (r_{sp} = 0.35–0.65), except for MBzP (r_{sp} = 0.25–0.48), and were relatively weakly correlated with LMW phthalate metabolites (r_{sp} = 0.16–0.58).

Most phthalate metabolites and molar sums were not associated with any of the four Conners 3-P scales (Fig. 1 and Table S2). Higher MHPP concentrations in early childhood urine were associated with higher raw scores on Inattentive (β per doubling = 0.05, 95% CI: 0.02, 0.08), Hyperactive/Impulsive (β = 0.04, 95% CI: 0.00, 0.07), Executive Functioning (β = 0.03, 95% CI: 0.01, 0.06), and Emotional Lability scales (β = 0.09, 95% CI: 0.04, 0.14). These associations remained statistically significant after FDR correction, except for the Hyperactive/Impulsive scale. Higher MCiNP (β = 0.05, 95% CI: 0.00, 0.09) and MCiOP (β = 0.07, 95% CI: − 0.01, 0.15) were associated with higher Hyperactive/Impulsive scores, although they were not statistically significant after FDR correction. These results remained similar when using normalized T-scores (Fig. S6) or additionally adjusting for highest education in household and child race/ethnicity (Fig. S7). The adverse associations between MHPP and all four scales persisted when restricted to children with ASD or to males, respectively (Fig. 2 and Fig. S8). When limited to children with TD, higher MCiOP was associated with higher Hyperactive/Impulsive scores (β = 0.21, 95% CI: 0.04, 0.37).

Child sex modified the associations of MCPP with all four scales (p-value for interaction [p_{int}]<0.04) with more pronounced adverse associations among females (Fig. 2 and Table S3). Similarly, the associations of MCiOP, ΣDEHP, and ΣHMW with the Hyperactive/Impulsive scale were modified by child sex (p_{int}<0.04), consistently showing associations with higher scores among females and non-significant associations with lower scores among males. Furthermore, sex-modified associations showed adverse associations among females only for MiBP and MnBP with respect to Inattentive and Executive Functioning, whereas MCiNP and Emotional Lability showed adverse associations among males only.

The repeated holdout WQS regression revealed null associations between the phthalate metabolite WQS index and the four scales (Fig. S9). However, in the sex-stratified interaction WQS regression models, the WQS index was associated with higher scores of Inattentive (median β = 0.50, 2.5th and 97.5th percentile: 0.20, 1.11) and Hyperactive/Impulsive (median β = 0.42, 2.5th and 97.5th percentile: 0.05, 0.84) among females only. Possible contributors were MiBP, MnBP, and MHPP for the Inattentive scale and MCiNP, MCiOP, MCPP, and MHPP for the Hyperactive/Impulsive scale (Fig. S10). Similarly, when using quantile-based g-computation, no significant associations were observed in 243 children (Table S4). When stratified by child sex, the phthalate metabolite mixture was associated with higher Hyperactive/Impulsive scores among females (ψ per simultaneous quartile increase in all phthalate metabolites = 0.28, 95% CI: − 0.01, 0.58), contributed by ∑DEHP, MEP, and MiBP for positive scaled effects. In contrast, the phthalate metabolite

mixture was associated with lower Hyperactive/Impulsive scores among males ($\psi = -0.16$, 95% CI: − 0.31, 0.00), contributed by MiBP and ∑DEHP for negative scaled effects.

4. Discussion

In the ReCHARGE study of children previously classified as ASD, DD, OEC, and TD, urinary concentrations of most phthalate metabolites at ages 2–5 years were not associated with ADHD-related behaviors at ages 8–18 years. However, higher urinary MHPP was associated with more ADHD behaviors, particularly evident among children classified as ASD or among males. MCiOP was associated with more hyperactive/impulsive behaviors, notably observed among typically developing children. Furthermore, child sex modified associations of MCPP with all the ADHD-related behaviors, those of MCiOP, ∑DEHP, and ∑HMW with hyperactivity/impulsivity, and those of MiBP and MnBP with inattentiveness and executive functioning problems. Consistently, females showed stronger associations with higher scores, whereas males showed relatively null associations or in the opposite direction (with lower scores). These trends were also observed for phthalate metabolite mixtures in association with hyperactivity/impulsivity, confirmed through two mixture approaches. Although both approaches indicated adverse associations, the contributors driving the mixture effects differed between WQS regression and quantile-based g-computation, possibly due to differences in directional homogeneity assumptions. Additionally, given the limited sample size, interpreting these findings requires caution because outliers might have influenced the results. However, the consistent adverse associations among females underscore the need for further studies investigating sex-specific associations.

In our previous cross-sectional study, which examined early childhood phthalate exposures and ADHD symptoms assessed using the Aberrant Behavior Checklist in a larger sample of CHARGE children ($n = 574$), we observed associations of greater hyperactivity/impulsivity with DEHP metabolites and a phthalate mixture, with DEHP metabolites, MHPP, MCiNP, and MnBP possibly contributing to the mixture effect (Oh et al., 2024). Considering both studies, MHPP and MCiNP showed adverse associations with hyperactivity/impulsivity in both early childhood and middle childhood/adolescence. Di-n-heptyl phthalate (DHPP) and di-iso-decyl phthalate (DIDP), the parent compounds of MHPP and MCiNP, respectively, are high-production-volume chemicals primarily used as plasticizers in polyvinyl chloride (U.S. EPA, 2021). While DIDP and MCiNP have been relatively well-studied for adverse health effects, including developmental toxicity (Center for the Evaluation of Risks to Human Reproduction, 2003; Kamrin 2009), DHPP and MHPP have received less attention regarding their association with neurodevelopment. However, given that DHPP exposure led to developmental toxicity and behavior changes in animal models (Poopal et al., 2020; Saillenfait et al., 2011), this compound warrants further investigation.

Several prior studies investigated early childhood exposure to phthalates in association with ADHD behaviors in prospective study settings. Jankowska et al. did not observe convincing associations between phthalate exposures at age 2 years and ADHD-related behavioral problems at age 7 years among Polish children (Jankowska et al., 2019a). However, they found associations of urinary MEP with lower fluid intelligence and MnBP with lower

cognition. Huang et al. observed null associations between urinary phthalate metabolite concentrations in Taiwanese children aged 2–8 years and ADHD-related behaviors at ages 8–14 years, except for an association between MBzP and greater social problems (Huang et al., 2019). It is noteworthy that Jankowska et al. and Huang et al. mutually adjusted for prenatal maternal and childhood phthalate metabolite concentrations in a single model and did not examine prenatal and childhood exposure separately. Although Huang et al. reported no correlations between prenatal and childhood concentrations of the same phthalate metabolite, our findings cannot be directly compared to those of these two studies. On the other hand, Li et al. observed adverse associations for several phthalate metabolites in U.S. children: MEP, MnBP, MCiNP, and the phthalate metabolite mixture at ages 1–5 years with greater externalizing problems at ages 2–8 years and MEP, MBzP, MCiNP, MCiOP, MCPP, and the phthalate metabolite mixture with greater overall behavioral problems (Li et al., 2020). These results remained similar after mutually adjusting for prenatal maternal phthalate metabolite concentrations. When examining the clinical subscales, childhood MCiNP was associated with hyperactivity and inattention. Their wider range of adverse associations could be attributed to their more comprehensive approach, capturing phthalate exposure and behavioral outcomes through multiple measurements at six age points (i.e., 1–5 and 8 years) for phthalate metabolite concentrations and at five age points (i.e., 2–5 and 8 years) for behavioral assessments.

Consistent with our findings, some of these prior studies reported sex-specific associations, mostly showing stronger adverse associations between certain phthalate metabolites and behavioral problems among females than males. Li et al. reported effect modification by sex, with MEP, MiBP, and MBzP showing more pronounced associations with greater externalizing problems among females (Li et al., 2020). Furthermore, Daniel et al. examined sex-stratified associations of phthalate exposure at ages 3 and 5 years, separately, with ADHD-related behaviors at age 7 years (Daniel et al., 2020). They found that urinary MBzP concentrations at age 3 years were associated with greater ADHD symptoms only in females, whereas MEP was associated with more ADHD symptoms in males only. Phthalate metabolite concentrations at age 5 years showed no associations with ADHD-related behaviors, but DEHP metabolites were associated with greater social problems and emotional lability among females only. This is in line with our results for MCiOP, MCPP, and MHPP in association with emotional lability observed in females only. Collectively, these findings support the increasingly recognized role of emotional lability and irritability (a form of negative symptoms of lability) appear in association with ADHD symptoms in youth, particularly in females (De Ronda et al., 2023; Elahi et al., 2023; Kahle et al., 2021). Moreover, these findings underscore the importance of further research to investigate a potential relationship between phthalate exposure and the rising prevalence of ADHD diagnosis among females (Castle et al., 2007; Fairman et al., 2020; Jensen and Steinhausen 2015), which has primarily been considered due to improved recognition of ADHD in females (Chronis-Tuscano 2022; Hinshaw et al., 2022). On the other hand, Huang et al. did not observe any sex-specific associations possibly due to the small sample size ($n = 153$) (Huang et al., 2019). Therefore, further studies in larger populations are needed to confirm the sex-specific effects of early childhood exposure to phthalates on child behaviors.

Although biological mechanisms underlying these associations remain largely unknown, disruption of thyroid and sex steroid hormones have been proposed as potential mechanisms (Boas et al., 2012; Cowell and Wright 2017; Miodovnik et al., 2014). Thyroid hormones play essential roles in both prenatal and early postnatal neurodevelopment (Ahmed et al., 2008; Porterfield and Hendrich 1993). Disrupted thyroid hormone homeostasis in children has been associated with ADHD diagnosis or symptoms (Albrecht et al., 2020; Álvarez-Pedrerol et al., 2007; Lain et al., 2021; Villanger et al., 2020). Early-life exposure to phthalates, as endocrine disrupting chemicals, could perturb thyroid hormone levels in young children (Boas et al. 2010, 2012; Huang et al., 2017; Kim et al., 2020; Morgenstern et al., 2017; Wu et al., 2017), potentially influencing ADHD behaviors in later childhood or adolescence. Sex steroid hormones are also crucial for sexual differentiation of the brain and behaviors (Waddell and McCarthy 2012), and children are highly sensitive to the actions of these hormones (Aksglaede et al., 2006). Childhood phthalate exposure was associated with altered sex steroid hormone levels in sex-dimorphic manners (Hu et al., 2022; Su et al., 2014; Wen et al. 2017a, 2017b). Among females, increased sex hormone-binding globulin levels were associated with a mixture of phthalates and phenols, primarily contributed by MBzP, during puberty (Hu et al., 2022) and daily intake of DEHP exposure during prepuberty (Wen et al., 2017a). Several phthalate metabolites were associated with increased progesterone and follicle-stimulating hormones among prepubertal females only (Su et al., 2014; Wen et al., 2017a). In a longitudinal study that repeatedly measured phthalate metabolites and sex hormone levels from birth to 11 years, DEHP metabolites were associated with decreased estradiol and progesterone levels in females and decreased free testosterone levels in males (Wen et al., 2017b). These findings may support sex-specific associations between phthalate exposure and ADHD behaviors.

A major strength of this study is the prospective design that allowed us to examine associations between early childhood phthalate exposure and ADHD behaviors in middle childhood and adolescence. Twelve out of 20 phthalate metabolites were detected in >75% the child urine samples, allowing us to investigate the mixture effects on ADHD behaviors. However, several limitations should be noted. First, phthalate metabolite concentrations were measured in spot urine samples collected at ages 2–5 years. Due to the weak to moderate reproducibility of phthalates in young children, attributed to their short half-lives and episodic exposure (Sjöström et al., 2023; Teitelbaum et al., 2008; Watkins et al., 2014), our findings based on phthalate metabolite concentrations in a single urine sample might have caused exposure misclassification. Second, while prenatal phthalate exposure has been associated with greater ADHD behaviors, this study could not account for prenatal maternal or early postnatal phthalate exposure because the CHARGE case-control study enrolls the children aged 2–5 years. Third, our study children had diverse diagnostic profiles, including approximately 60% who had ever had neurodevelopmental concerns. Consequently, ADHD-related behavior scores in our children were higher than those in the general population, thereby limiting the generalizability of our findings, while also increasing our ability to study the relationship between these comorbid symptoms and phthalate exposure. Fourth, although Conners 3-P is a valid and reliable instrument for assessing children's behaviors, assessment based only on the questionnaire completed by the parents may have introduced reporting bias (Gianarris et al., 2001). Fifth, this study assessed the behavior of children

over a wide age range. Despite adjusting for age at behavior assessment in our models, the results should be interpreted cautiously. Lastly, the sex distribution in our study consisted of approximately three times as many males as females, due to the recruitment strategy aiming for a 4:1 male-to-female ratio among children in the general population to match the ratio observed in the children with ASD. Although our overall sample size was not small, the limited number of females might have constrained the statistical power in analyses of modification by sex. Moreover, this could potentially limit future replication because outliers might have driven the associations.

5. Conclusion

In the ReCHARGE study that followed up children having been classified as ASD, DD, OEC, TD, early childhood exposure to several phthalates may be associated with more ADHD behaviors in middle childhood and adolescence. This study also provided evidence of sex-specific associations of exposure to HMW phthalates and a phthalate mixture with higher hyperactivity/impulsivity scores, with stronger associations among females. These findings should be interpreted cautiously and not generalized due to the diverse diagnostic profiles and the small number of female children. Given the growing evidence associating early childhood phthalate exposure with ADHD behaviors in later life, further studies with repeated measurements of both phthalate exposure and behaviors are needed to better elucidate the exposure-outcome relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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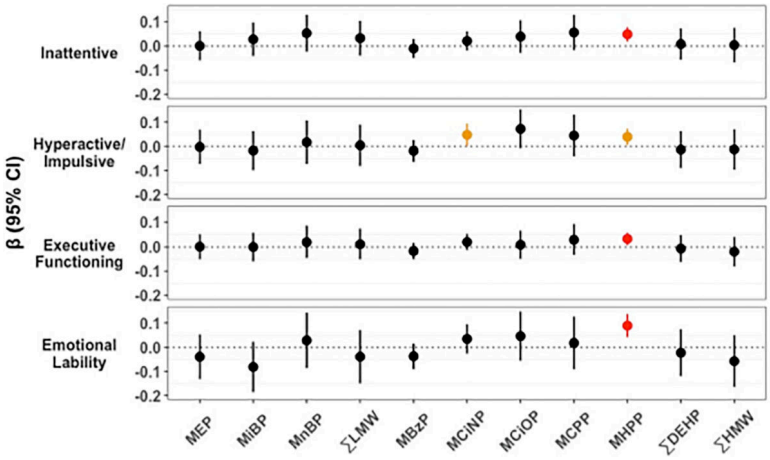

Fig. 1.

Adjusted associations between log2-transformed SG-corrected phthalate metabolite concentrations in early childhood urine samples and Conners 3-P raw scores in middle childhood and adolescence in 243 ReCHARGE children. Point estimates indicate regression coefficients, and error bars indicate their 95% CIs. Red color indicates associations with an unadjusted $p < 0.05$ and an FDR-corrected $p < 0.10$, and orange color indicates associations with an unadjusted $p < 0.05$ but an FDR-corrected $p \geq 0.10$. Negative binomial regression models were adjusted for CHARGE case-control study frequency matching factors (child sex, age at behavior assessment, and recruitment regional center), preterm birth, maternal metabolic conditions, maternal age at delivery, parity, homeownership, and diagnostic groups. CHARGE, Childhood Autism Risks from Genetics and Environment; CI, confidence interval; Conners 3-P, Conners-3 Parent Rating Scale; DEHP, di-2-ethylhexyl phthalate; HMW, high molecular weight; LMW, low molecular weight; MBzP, mono-benzyl phthalate; MCiNP, mono-carboxy isononyl phthalate; MCiOP, mono-carboxy isooctyl phthalate; MCPP, mono (3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MHPP, mono-2-heptyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-n-butyl phthalate; ReCHARGE, Revisiting Childhood Autism Risks from Genetics and Environment; SG, specific gravity. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

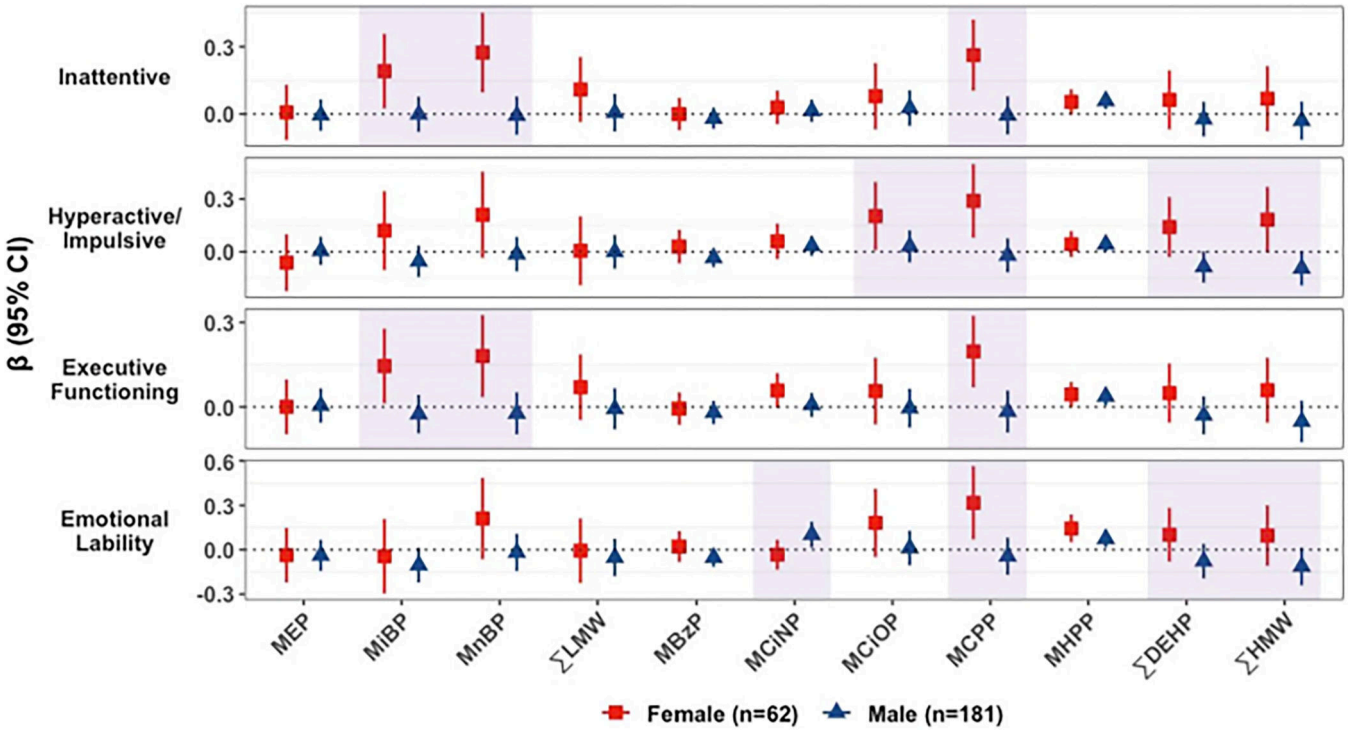

Fig. 2.

Adjusted associations between log2-transformed SG-corrected phthalate metabolite concentrations in early childhood urine samples and Conners 3-P raw scores in middle childhood and adolescence, stratified by child sex. Point estimates indicate regression coefficients, and error bars indicate their 95% confidence intervals. Shaded areas indicate *p*-value for interaction term for phthalate metabolites and sex is less than 0.10. Negative binomial regression models were adjusted for CHARGE case-control study frequency matching factors (child age at behavior assessment, and recruitment regional center), preterm birth, maternal metabolic conditions, maternal age at delivery, parity, homeownership, and diagnostic groups. The interaction term model was additionally adjusted for the main effect for child sex and the interaction term for phthalate metabolites and sex. CHARGE, Childhood Autism Risks from Genetics and Environment; CI, confidence interval; Conners 3-P, Conners-3 Parent Rating Scale; DEHP, di-2-ethylhexyl phthalate; HMW, high molecular weight; LMW, low molecular weight; MBzP, mono-benzyl phthalate; MCiNP, mono-carboxy isononyl phthalate; MCiOP, mono-carboxy isooctyl phthalate; MCPP, mono (3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MHPP, mono-2-heptyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-n-butyl phthalate; SG, specific gravity.

Table 1

ADHD-related Conners 3-P DSM-5 Symptom Scales raw scores by participant characteristics of 243 ReCHARGE children.

Characteristics[a]	All children	Inattentive[b]		Hyperactive-Impulsive[b]	
	Freq (%)[c]	Median (IQR)	*p*-value[d]	Median (IQR)	*p*-value[d]
Child sex			0.07		<0.01
Female	62 (26%)	8 (4, 15)		4 (1, 11)	
Male	181 (74%)	10 (6, 16)		7 (3, 13)	
Child race/ethnicity			0.84		0.77
Non-Hispanic White or other races/ethnicities[e]	122 (51%)	9 (4, 15)		7 (3, 13)	
Non-Hispanic Black	60 (25%)	9 (6, 14)		6 (2, 12)	
Hispanic	58 (24%)	11 (5, 16)		8 (2, 13)	
Preterm birth			0.50		0.19
Yes (<37 completed weeks)	30 (12%)	9 (5, 13)		6 (2, 10)	
No (≥37 completed weeks)	211 (88%)	9 (5, 16)		6 (3, 13)	
Maternal age at delivery			0.06		0.02
<30 years	102 (42%)	11 (5, 18)		9 (3, 17)	
30–34 years	77 (32%)	8 (4, 13)		6 (1, 11)	
≥35 years	64 (26%)	10 (7, 14)		6 (3, 12)	
Maternal metabolic conditions			0.03		0.01
Healthy weight/overweight and no pregnancy conditions	157 (67%)	8 (4, 16)		6 (2, 12)	
Obese or hypertensive disorder/gestational diabetes	77 (33%)	11 (8, 16)		8 (4, 14)	
Parity			<0.01		0.11
1	109 (46%)	11 (7, 17)		7 (3, 15)	
>2	128 (54%)	8 (3, 14)		6 (2, 12)	
Homeownership			0.04		0.03
Yes	169 (71%)	9 (4, 15)		6 (2, 12)	
No	68 (29%)	12 (8, 17)		8 (4, 14)	
Highest education in household			0.13		0.06
High school/GED or less	87 (36%)	10 (6, 17)		8 (4, 12)	
Some college credit, bachelor's or higher degree	156 (64%)	9 (4, 15)		5 (2, 13)	

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Diagnostic groups			<0.01		<0.01
TD	98 (40%)	5 (1, 9)		3 (1, 6)	
ASD	94 (39%)	14 (9, 18)		12 (6, 19)	
DD	30 (12%)	10 (7, 18)		8 (4, 13)	
OEC	21 (9%)	12 (8, 18)		4 (2, 12)	
Enrollment year			0.76		<0.01
2006–2009	85 (35%)	10 (4, 15)		4 (1, 10)	
2010–2013	97 (39%)	9 (6, 15)		7 (3, 14)	
2014–2017	61 (25%)	10 (6, 16)		9 (3, 18)	
Recruitment regional center			0.97		0.16
Alta, Far Northern, Redwood Coast	124 (51%)	9 (5, 15)		7 (3, 12)	
North Bay, East Bay, San Andreas, Golden Gate	74 (30%)	11 (5, 16)		4 (1, 12)	
Valley Mt, Central Valley, Kern	45 (19%)	9 (5, 15)		8 (3, 14)	
	Median (IQR)	r_{sp} [f]	***p*-value [g]**	r_{sp} [f]	***p*-value [g]**
Age (year) at sample collection	4 (3, 5)	0.05	0.39	0.02	0.72
Age (year) at behavior assessment	11 (9, 15)	—0.12	0.07	—0.31	<0.01

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; DD, developmental delay; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5h edition; Freq, frequency; GED, general educational development; IQR, interquartile range; OEC, other early concerns; ReCHARGE, Revisiting Childhood Autism Risks from Genetics and Environment; r_{sp}, Spearman correlation coefficient; TD, typical development.

[a] Missing observations (*n*): child race/ethnicity (3), preterm birth (2), pregnancy condition (9), parity (6), homeownership (6).

[b] Median (IQR) for each scale score in all children: 9 (5, 16) for Inattention, 6 (2, 13) for Hyperactivity-Impulsivity.

[C] Percentage was calculated without missing observations.

[d] P-values from the Wilcoxon rank-sum test or the Kruskal-Wallis test.

[e] Other races/ethnicities include Asian and multiple races.

[f] Spearman correlation coefficients between child age and Inattention or Hyperactivity-Impulsivity scale scores.

[g] P-values from the significance test of Spearman correlation coefficient.

Table 2

Distribution of SG-corrected phthalate metabolite concentrations in early childhood urine samples of 243 ReCHARGE children.

Phthalate metabolites [a]	LOD	%>LOD	Percentiles				
			5th	25th	50th	75th	95th
MEP	0.10	100	13.7	24.2	39.0	79.0	299.6
MiBP	0.01	100	6.0	11.7	20.7	35.2	115.9
MnBP	0.20	100	11.6	25.4	43.0	68.7	201.6
MMP	5.00	40	<LOD	<LOD	<LOD	7.8	24.3
∑LMW [b]			0.2	0.4	0.6	1.1	2.4
MBzP	0.02	99	3.6	15.4	32.1	70.6	236.8
MCiNP	0.01	98	1.7	3.6	6.0	10.0	24.3
MCiOP	0.01	100	4.9	12.0	20.3	40.4	112.8
MCPP	0.05	100	1.4	3.1	5.8	9.7	24.0
MCHPP	0.10	27	<LOD	<LOD	<LOD	0.1	19.6
MHPP	0.50	77	<LOD	0.6	1.4	3.7	16.1
MHxP	0.50	56	<LOD	<LOD	0.8	19.7	149.9
MCMHP	0.02	98	3.0	9.0	15.5	32.2	84.4
MECPP	0.02	100	8.2	19.1	32.3	74.5	197.8
MEHHP	0.20	100	10.5	23.1	43.0	91.0	249.1
MEOHP	0.01	100	3.6	9.7	18.0	41.9	98.2
∑DEHP [c]			0.1	0.2	0.4	0.8	2.1
∑HMW [d]			0.2	0.4	0.7	1.5	3.5

Abbreviations: DEHP, di-2-ethylhexyl phthalate; HMW, high molecular weight; LMW, low molecular weight; LOD, limit of detection; MBzP, mono-benzyl phthalate; MCHP, monocyclohexyl phthalate; MCHPP, mono(7-carboxyheptyl) phthalate; MCiNP, mono-carboxy isononyl phthalate; MCiOP, mono-carboxy isooctyl phthalate; MCMHP, mono-2-(carboxymethyl) hexyl phthalate; MCPP, mono (3-carboxypropyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono (2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MHPP, mono-2-heptyl phthalate; MHxP, mono-hexyl phthalate; MiBP, mono-isobutyl phthalate; MiNP, mono-isononyl phthalate; MiPP, mono-isopropyl phthalate; MMP, mono-methyl phthalate; MnBP, mono-n-butyl phthalate; MOP, mono-n-octyl phthalate; MPeP, mono-pentyl phthalate; ReCHARGE, Revisiting Childhood Autism Risks from Genetics and Environment; SG, specific gravity.

[a] Units are ng/mL for phthalate metabolites and nmol/mL for molar sum of phthalate metabolites (∑LMW, ∑DEHP, ∑HMW). Phthalate metabolites detected in <10% of samples (i.e., MCHP, MPeP, MiNP, MiPP, and MOP) were not presented.

[b] Molar sum of LMW phthalate metabolites detected in >75% of samples (MEP, MiBP, MnBP).

[c] Molar sum of DEHP metabolites detected in >75% of samples (MCMHP, MECPP, MEHHP, MEOHP).

[d] Molar sum of HMW phthalate metabolites detected in >75% of samples (MBzP, MCiNP, MCiOP, MCPP, MHPP, MCMHP, MECPP, MEHHP, MEOHP).