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Similar names, different results: Consistency of the associations between prenatal exposure to phthalates and parent-ratings of behavior problems in preschool children

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6. Additional contributions

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105892.

Abstract

Background—Environmental health research has reported mixed findings on the associations between prenatal exposure to phthalates and parent-ratings of child behavioral problems.

Objective—We examined the consistency of the associations between prenatal urinary phthalate concentrations and child behavior scores across two standardized instruments – the Behavior Assessment System for Children-Second Edition (BASC-2) and the Child Behavior Checklist (CBCL) – using two analytical approaches used to correct for urine dilution.

Method—A sample of 351 mother–child pairs were selected from a prospective birth cohort of pregnant women enrolled between 2009 and 2012. Women provided spot urine samples during the second trimester of pregnancy, which were analyzed for levels of nine urinary phthalate metabolites. When their typically developing children were 3–4 years of age, mothers completed the BASC-2 and CBCL on the same day. Adjusted regression analyses examined the associations between maternal prenatal phthalate concentrations and child behavior scores on the BASC-2 and CBCL. To correct for urine dilution, primary regression analyses included urinary creatinine concentration as a separate independent variable (i.e., covariate). In the secondary regression analyses, creatinine-adjusted phthalate concentrations were used.

Results—Primary logistic regression analyses that included urinary creatinine as a covariate showed that higher prenatal phthalate concentrations were related to increased odds of scores falling into the borderline or clinical range on the Hyperactivity, Aggression, Anxiety, Depression, Withdrawal, Externalizing Problems, Internalizing Problems, and Behavioral Symptoms Index scales on the BASC-2 (*ORs* from 1.39 to 2.07), but only the Anxious/Depressed and Externalizing Problems scales on the CBCL (*ORs* from 1.80 to 3.28). Primary linear regression analyses showed that higher prenatal phthalate concentrations were related to higher scores on the Externalizing Problems (β's = 0.16), Internalizing Problems (β's from 0.16 to 0.20), and Behavioral Symptoms Index (β's from 0.18 to 0.21) scales on the BASC-2, but not related to any CBCL scales. Sex-stratified analyses found that many associations were only significant for male children. Secondary analyses using creatinine-adjusted phthalate concentrations revealed that some of the associations from the primary analyses remained significant; however, a number of unique associations were observed.

Conclusion—Prenatal phthalate exposure was associated with preschool behavioral development; however, findings were not consistent for the BASC-2 and CBCL, especially related to the clinical/syndrome scales and Internalizing Problems scale. Further, many findings differed based on the analytical approach used to correct for urine dilution. Future work is needed to delineate the similarities and differences between similarly named child behavior constructs assessed by different neurodevelopmental assessments. Also, research is needed to better understand why and how different analytical approaches influence the reported associations between maternal prenatal phthalate concentrations and children's behavior problems.

Keywords

Phthalates; Behavioral development; Preschool children; Parent-rating scales; APrON Study

1. Introduction

Neurodevelopment is a complex process that begins during the embryonic stage of gestation and continues through adolescence and into adulthood, during which there are periods of vulnerability where nervous system development is sensitive to environmental insults (Rice and Barone, 2000; Rock and Patisaul, 2018). Phthalates are a group of synthetic plasticizers with the potential to alter neurodevelopment. Phthalates are used as solvents and additives in a variety of consumer products, such as food packaging, personal-care products, and children's toys (Lyche et al., 2009). They belong to a group of environmental compounds classified as endocrine-disrupting chemicals (EDCs), and when ingested or absorbed can alter the activity of estrogens, androgens, and thyroid hormones (Schug et al., 2015). Models of developmental neurotoxicity propose that prenatal exposure to phthalates disrupts the hormonal pathways that are crucial for the development of the nervous system (Miodovnik et al., 2014). Further, emerging evidence suggests that prenatal exposure to phthalates is associated with alterations in brain microstructure in preschool children and these alterations are associated with behavioral problems (England-Mason et al., 2020).

The preschool period represents a developmental window during which child behavior problems first emerge (Campbell, 2002; Powell et al., 2006). In preschool-aged children, higher maternal phthalate concentrations during pregnancy have been associated with higher internalizing (i.e., emotionally reactive, anxious/depressed, withdrawal) and externalizing (i.e., aggression, attention) problems (Engel et al., 2010; Philippat et al., 2017; Whyatt et al., 2012). However, there have also been reports of null associations or positive associations between prenatal phthalate concentrations and child behavior outcomes (Jankowska et al., 2019; Kobrosly et al., 2014; Whyatt et al., 2012). Less is known about potential sex-differences in neurobehavioral development following prenatal exposure to phthalates, but some research suggests that prenatal exposure may be associated with different behavioral problems in male children (i.e., aggression, attention, emotionally reactive) compared to female children (i.e., anxious/depressed) (Engel et al., 2010; Kobrosly et al., 2014; Whyatt et al., 2012).

Studies examining the effect of prenatal exposure to phthalates on preschool behavior have frequently utilized one of two gold standard parent-rating scales of child behavior problems – the Behavior Assessment System for Children-Second Edition Parent Report Scales-Preschool (BASC-2; Reynolds & Kamphaus, 2004) or the Child Behavior Checklist for ages 1½–5 (CBCL; Achenbach & Rescorla, 2000). However, findings have varied across these measures. For example, one study reported that higher prenatal phthalate exposure was associated with higher scores on the Aggression, Attention Problems, and Depression scales on the BASC-2 (Engel et al., 2010), whereas another study found that higher prenatal phthalate exposure was associated with higher scores on the Emotionally Reactive, Somatic Complaints, Withdrawn, and Internalizing Problems scales on the CBCL (Whyatt et al., 2012). It is currently unclear whether these dissimilar findings might be due to differences in study design, sample characteristics, and/or analytical approaches, or rather due to or variation in the measurement of child behavior constructs across the BASC-2 and CBCL.

Urine is the most widely used matrix for assessing exposure to nonpersistent chemicals (i.e., chemicals that have a short biological half-live) including phthalates (O'Brien et al., 2017). However, if differences in urinary analyte concentrations due to variability in urine dilution are not adequately corrected for this can directly affect biomarker concentrations and bias associations (Barr et al., 2005; O'Brien et al., 2017). Adjusting for urinary creatinine concentration is a common method of correcting for urine dilution. In environmental research, there are two widely used analytical approaches to correct for urine dilution by adjusting for urinary creatinine. The first approach involves including the analyte concentration and creatinine concentration as separate independent variables (i.e., including creatinine as a covariate) and the second entails dividing the analyte concentration by the creatinine concentration (i.e., creatinine-adjusted analyte concentrations). Although research has indicated that creatinine-adjusted analyte concentrations correlate better with other biological (i.e., blood) concentrations of the parent chemical, creatinine concentrations are predicted by other sample characteristics (e.g., age, sex, ethnicity) (Barr et al., 2005). Therefore, the inclusion of urinary creatinine concentration as a covariate is recommended in order to ensure that the significance of other variables in the model are independent of the effects of creatinine (Barr et al., 2005). Studies examining the associations between prenatal exposure to phthalates and behavior problems in children as measured by the BASC-2 and CBCL have included urinary creatinine concentration as a covariate (e.g., Engel et al., 2010; Kobrosly et al., 2014) or used creatinine-adjusted phthalate concentrations (e.g., Lien et al., 2015; Philippat et al., 2017). However, it is currently unknown whether these two alternative analytical approaches affect reported associations with children's behavior differently.

Variation in the measurement of child behaviour constructs across similarly named subscales is an important consideration and could account for some of the dissimilar findings in the literature examining prenatal exposure to phthalates and preschool behavior problems. Previous psychometric research has recognized that although scales from different instruments, such as the BASC-2 and CBCL, share the same or a similar name(s), they may be evaluating different types of behavior (Bradstreet et al., 2017; Myers et al., 2010). Further, although the BASC-2 and CBCL have been stringently evaluated in clinical and nonclinical (i.e., community samples) populations of school-aged children and youth (Bender et al., 2008; McClendon et al., 2011; Pandolfi et al., 2012), limited research is available on the utility of the preschool versions of these scales (Bradstreet et al., 2017). An evaluation of the consistency of BASC-2 and CBCL scale scores in a sample (n = 95) of clinically-referred preschool children provided preliminary evidence that these two parent-rating instruments may provide different results for similarly named scales (Myers et al., 2010). Classification consistency (i.e., population-level and individual-level classification consistency of borderline and clinical ranges of scores) and rank order consistency of scores (i.e., relative rank order of scores in a distribution based on a normative sample) on parent-report scales of child behavioral problems are essential elements of construct reliability and validity. However, the fundamental issue of whether there is consistency across similarly named scales on the BASC-2 and CBCL in typically developing (i.e., not diagnosed with a neurological or neurodevelopmental disorder) children is currently unknown.

The current study sought to elucidate possible contributors to the mixed findings reported in the literature examining the effect of prenatal exposure to phthalates on behavior problems

in preschool children. Specifically, this study examined how different analytical approaches used to correct for urine dilution and variations in the measurement of child behaviour constructs on two parent-rating scales affected the consistency of associations between prenatal exposure to phthalates and child behavior problems in a sample of 351 typically developing children aged 3–4 years. To address these issues, we assessed the consistency of the associations between maternal urinary phthalate concentrations during the second trimester of pregnancy and behavior scores on the BASC-2 and CBCL using two different analytical approaches to correct for urine dilution. The primary regression analyses included unadjusted phthalate concentrations with creatinine concentration included as a covariate; the secondary regression analyses used creatinine-adjusted phthalate concentrations.

2. Methods

2.1. Cohort and study design

The participants were a subset of families (n = 351) recruited between 2009 and 2012 from an ongoing prospective pregnancy cohort, the Alberta Pregnancy Outcomes and Nutrition (APrON) study (Kaplan et al., 2014) (see Table S1 in the Supplementary Materials for maternal and child characteristics). Inclusion criteria for the present study were as follows: (i) a maternal spot urine sample was provided during the second trimester of pregnancy, (ii) two parent-report measures of child behavior problems (i.e., Behavior Assessment System for Children-Second Edition Parent Rating Scales-Preschool/BASC-2 and Child Behavior Checklist for ages 1½−5/CBCL) were completed on the same day when children were age 3–4 years, and (iii) the child was healthy and typically developing (i.e., the child was born at ≥37 weeks gestation at a birth weight ≥2500 g, had not been diagnosed with a neurological or neurodevelopment disorder, and had a Full Scale Intelligence Quotient/FSIQ at age 3–4 years ≥80). Mother-child pairs who did not meet the inclusion criteria were excluded from the analyses (n = 38).

During the second trimester of pregnancy, mothers provided a urine sample from which phthalate metabolite concentrations were quantified (details below). At that time, mothers completed questionnaires on sociodemographic (i.e., ethnicity, education, marital status, household income) and gestational characteristics (i.e., age, parity status, tobacco use, physical and mental illnesses). From 2012 to 2017, when children (50.1% female) were 3–4 years of age (mean years = 4.3, SD = 0.5), mothers completed the BASC-2 and CBCL on the same day. The research protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Written, informed consent was obtained from families prior to the collection of urine samples, and the completion of the questionnaires and the child neurodevelopmental assessments.

2.2. Measures

2.2.1. Urine sample collection and quantification of phthalate metabolites—

Maternal spot urine samples were collected in sterile cups during the second trimester of pregnancy (mean gestational weeks = 17.0, SD =2.1), aliquoted into 9 mL cryovials, and stored at −80 °C. Method validation experiments (i.e., blanks, n = 20) were conducted using liquid chromatography grade water as a surrogate, and checked for potential

contamination that could have occurred during collection, storage, and/or analysis. No phthalate metabolites were detected in any of the blank samples.

At the Alberta Centre for Toxicology, nine monoester phthalate metabolites were quantified using liquid chromatography-tandem mass spectrometry (QTRAP 5500, AB Sciex, Concord, Ontario, Canada) running in negative multiple reaction monitoring (MRM) mode. Using an Agilent 1200 HPLC system (Agilent Technologies, LabX, Mississauga, Ontario, Canada), metabolites were separated on a 100 × 2.1 mm BetaSil Phenyl Column (Thermo Scientific, Burlington, Ontario, Canada), with an injection volume of 10 μL and a constant column temperature of 40 °C. Metabolites were identified based on two MRM transitions at the correct retention time. The limit of detection (LOD) for all metabolites was 0.10 μg/L. All values below the LOD were assigned the value of the LOD divided by the square root of 2 (Hornung and Reed, 1990).

This study considered four metabolites of di(2-ethyl-hexyl) phthalate (DEHP): mono(2-ethyl-hexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxy-hexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP); two metabolites of dibutyl phthalate (DBP): mono-n-butyl phthalate (MBP) and mono-iso-butyl phthalate (MiBP); and three other common metabolites: mono-benzyl phthalate (MBzP), mono-ethyl phthalate (MEP), and mono-methyl phthalate (MMP). Phthalate metabolites were considered both independently (as single chemicals) and grouped into biologically relevant summary measures defined by molecular weight. Molar sums of phthalate metabolites based on molecular weight were computed; groups of metabolites with high (> 250 Da) and low (< 250 Da) molecular weight each have similar molecular compositions, routes of exposure, and levels of biological activity (Engel et al., 2009; Wolff et al., 2008). Based on the recommended practice for computing molar sums (Messerlian et al., 2016; Wolff et al., 2008), five metabolites were grouped in the molar sum of high molecular weight phthalates (ΣHMWP): MEHP, MEHPP, MEOHP, MECPP, and MBzP; and four metabolites were grouped in the molar sum of low molecular weight phthalates (ΣLMWP): MBP, MiBP, MEP, and MMP. Phthalate metabolite concentration quartiles were used for analyses. Specifically, continuous phthalate (i.e., individual phthalate metabolite and molar sums) concentrations were quantified into four ordered intervals (i.e., 0–25%, 25.1–50%, 50.1–75%, 75.1–100%) to create ordered interval variables. To examine the effect of using different analytical approaches of correcting for urine dilution on the associations between prenatal exposure to phthalates and child behavior outcomes, urinary creatinine concentration was included as a covariate in the primary analyses and the creatinine-adjusted phthalate concentration was included in the secondary analyses.

2.2.2. Behavior Assessment System for Children–Second Edition Parent Rating Scales Preschool (BASC-2)—When children were 3–4 years of age, mothers completed the preschool version of the BASC-2 (Reynolds & Kamphaus, 2004). The BASC-2 asked parents to rate the occurrence of 134 different problems on a four-point rating scale (*0 = never, 1 = sometimes, 2 = often, 3 = almost always*) (Reynolds and Kamphaus, 2004). The BASC-2 groups problems into eight “clinical” scales (i.e., Hyperactivity, Aggression, Anxiety, Depression, Somatization, Atypicality, Withdrawal, and Attention Problems) and four “adaptive” scales (i.e., Adaptability, Social Skills, Activities of

Daily Living, and Functional Communication). Problems are also scored for four composites scales: Internalizing Problems, Externalizing Problems, Adaptive Skills, and the Behavioral Symptoms Index (BSI). Scores from the BASC-2 adaptive scales and the Adaptive Skills composite scale were not included in the current study as the CBCL does not have an adaptive scale. Results from the BASC-2 scales are provided in the form of *T* scores (M = 50, SD = 10); higher scores indicated more behavior problems. Based on the borderline and clinical cut-offs from the manual (Reynolds & Kamphaus, 2004), scale scores were classified as falling in the borderline or clinical range or as falling below these cut-offs (for further information on the BASC-2 scales and scoring please see Section 1 in the Supplementary Materials). In the current sample, *T* scores on the Internalizing Problems scale (Cronbach's α = 0.70), Externalizing Problems scale (Cronbach's α = 0.74), and BSI scale (Cronbach's α = 0.80) demonstrated acceptable internal consistency.

2.2.3. Child Behavior Checklist for ages 1½–5 (CBCL)—Mothers also completed the parent version of the CBCL (Achenbach & Rescorla, 2000). The CBCL asked parents to rate the occurrence of 99 different problems on a three-point rating scale (*0 = not true, 1 = somewhat/sometimes true, 2 = very/often true*) (Rescorla, 2005). The CBCL groups problems into seven "syndrome" scales (i.e., Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behavior) and five "DSM-oriented" scales (i.e., Affective Problems, Anxiety Problems, Pervasive Developmental (PD) Problems, Attention-Deficit/Hyperactivity (ADH) Problems, and Oppositional Defiant Problems). Two broad groupings of syndromes are scored based on children's scores on the syndrome scales: Internalizing Problems and Externalizing Problems. Additionally, a Total Problems score is computed. For all the scales, *T* scores (M = 50, SD = 10) were computed. As with the BASC-2, higher scores on the CBCL scales indicated more behavior problems. Based on the borderline and clinical cut-offs from the manual (Achenbach & Rescorla, 2000), scale scores were classified as falling in the borderline or clinical range or as falling below these cut-offs (for further information on the CBCL scales and scoring please see Section 2 in the Supplementary Materials). In the current sample, *T* scores on the Internalizing Problems scale (Cronbach's α = 0.75), Externalizing Problems scale (Cronbach's α = 0.72), and Total Problems scale (Cronbach's α = 0.82) demonstrated acceptable internal consistency.

2.3. Statistical analyses

All statistical analyses were performed in version 26.0 of SPSS (IBM Corp., 2019). Based on previous research with preschool children, 15 pairs of scales from the BASC-2 and CBCL were compared (see Table S2 in the Supplementary Materials) (Bour, 2008; Myers et al., 2010; Reynolds and Kamphaus, 2004). Most of the child behavior scale *T* scores were skewed, which is common in typically developing samples of preschool children with relatively few behavior problems (Basten et al., 2016; Chen, 2010). Following a log-transformation, the CBCL broad groupings of syndromes (i.e., Internalizing Problems scale, Externalizing Problems scale) and the Total Problems scale, and the BASC-2 composite scales (i.e., Internalizing Problems, Externalizing Problems, BSI) did not violate the assumptions of normality; however, most of the CBCL syndrome and DSM-oriented scales and most of the BASC-2 clinical scales remained skewed.

In line with previous research examining odds ratios (ORs) for prenatal exposure to phthalates and child behavior problems (Lien et al., 2015) and to improve statistical power, we merged the small number of children who fell in the borderline and clinical ranges of scores into a single group, which we refer to as 'borderline or clinical'. Binomial logistic regressions were performed to estimate the odds of child behavior scale scores falling into the borderline or clinical range for each 1-unit increase in prenatal phthalate concentration quartile, whilst adjusting for covariates. Adjusted linear regressions were used to investigate the associations between phthalate concentration quartiles and log-transformed *T* scores on the Internalizing Problems, Externalizing Problems, BSI, and Total Problems scales. Sex-stratified analyses examined the associations between phthalate concentration quartiles and child behavior scores on these scales for female and male children, and moderation models examined whether child sex modified the associations.

All regression analyses were adjusted for the following covariates: family income, child sex, and child FSIQ. These covariates were selected as previous research has reported that they were associated with the exposure (i.e., prenatal exposure to phthalates), associated with the outcomes (i.e., child behavior scores), were not an intermediate variable between the exposure and outcomes, and/or had at least a 10% change in the estimate of the main effect (Engel et al., 2010; Huang et al., 2019; Lien et al., 2015). As the BASC-2 and CBCL *T* scores are standardized by age, no adjustments were made for child age (Engel et al., 2010). To correct for urine dilution, the primary analyses included urinary creatinine concentration as a covariate and the secondary analyses included creatinine-adjusted phthalate concentrations.

To correct for multiple comparisons in the primary regression analyses, the Benjamini-Hochberg procedure was used to control the false discovery rate (FDR) (Benjamini and Hochberg, 1995). We adopted an approach consistent with prior research examining the associations between prenatal exposure to phthalates and behavior problems in preschool-aged children (England-Mason et al., 2020; Philippat et al., 2017), and consider adjusted *p*-values (i.e., *q*-values) from 0.05 to 0.10 as significant. In the results section, we report all associations ($p < 0.05$) and associations that survived the FDR correction ($q < 0.10$). Unless otherwise stated in the results, the reported associations survived the FDR correction for multiple comparisons ($q < 0.10$).

To enhance the comparability of the results obtained from the BASC-2 and CBCL, consistency analyses examined the intercorrelations, classification consistency, and rank order consistency between pairs of similarly named scales. Nonparametric correlations were used to assess the strength and direction of relationships between the untransformed comparable child behavior scale *T* scores. Classification consistency was evaluated by calculating the percentages of *T* scores (i.e., population-level consistency) and the percentages of individuals whose *T* scores (i.e., individual-level consistency) fell into the borderline and clinical ranges of child behavior problems based on cut-offs from the manuals and the 'clinically significant' range based on cut-offs (i.e., ≥ 65) from previous research (Bour, 2008; Myers et al., 2010). Rank order consistency (i.e., differences in mean ranks of *T* scores) was also examined. Notably, the CBCL truncates its "syndrome" and "DSM-oriented" scales at a *T* score of 50, but the BASC-2 does not. To determine if

mean rank differences were due to the CBCL's truncations of these scale scores, Wilcoxon signed-rank tests compared the mean ranks of untruncated (i.e., original) and truncated BASC-2 *T* scores with the truncated CBCL *T* scores.

Finally, sensitivity analyses were conducted to assess the robustness of results from our regression analyses. Specifically, we examined the influence of maternal depression as a potential confounder in the primary analyses among participants for whom data was available (n = 341; 97.2%). Maternal depression was assessed using the total score from the Edinburg Postnatal Depression Scale (EPDS) (Cox et al., 1987).

3. Results

3.1. Sample demographics

At the time of the prenatal urine sample collection, mothers were between the ages of 20–42 years (M = 32.3, SD = 3.8 years), predominantly Caucasian (87.3%), university-educated (77.5%), married (89.3%), and had a median household income of greater than $100,000. For approximately half of the women this was their first pregnancy (52.7% = primiparous, 47.3% = multiparous). None of the women reported smoking during pregnancy and few women reported physical (7.5% reported a thyroid condition, 5.0% reported irritable bowel syndrome, 14.3% reported another physical condition) or mental health problems (4.2% reported anxiety and 2.5% reported depression). Information on birth outcomes was obtained from medical records (i.e., birth weight, gestational age, sex). Children were born between 37 and 42 weeks of gestation (M = 39.5, SD = 1.1 weeks) and weighed between 2510 and 5210 g (M = 3445.3, SD = 445.8 g).

3.2. Phthalate concentrations

Geometric means (GMs) and distribution percentiles for concentrations of unadjusted individual phthalate metabolites and for the molar sums based on molecular weight categories are presented in Table 1 (see Table S3 for this information with regard to the creatinine-adjusted phthalate concentrations). The GMs of the phthalate metabolites ranged from 3.31 μg/L (mono-methyl phthalate; MMP) to 50.41 μg/L (mono-ethyl phthalate; MEP). The ΣHMWP and ΣLMWP had GMs of 0.18 μmol/L creatinine and 0.49 μmol/L creatinine, respectively.

3.3. Logistic regressions: Phthalates and borderline or clinical child behavior scores

Adjusted binomial logistic regressions that included urinary creatinine as a covariate estimated the odds that child behavior scale scores would fall into the borderline or clinical range for each 1-unit increase in prenatal phthalate concentration quartile (see Tables 2 and 3). Most of the high molecular weight phthalate metabolites (i.e., MEHP, MEOHP, MECPP, MBzP) and the molar sum of high molecular weight phthalates (ΣHMWP) were associated with increased odds of child behavior scores falling into the borderline or clinical range of scores on some scales on the BASC-2 and CBCL (see Table 2). Higher maternal prenatal MEOHP was associated with increased odds of scores falling into the borderline or clinical range of the Internalizing Problems scale on the BASC-2 ($OR = 1.50$, $CI_{95} = 1.01, 2.23$); however, this association did not survive the correction for multiple comparisons ($q > 0.10$).

Higher maternal prenatal MEOHP, MECPP, and MBzP were associated with increased odds of scores falling into the borderline or clinical range of the Anxiety scale on the BASC-2 (*OR* = 1.50, CI_{95} = 1.08, 2.08 for MEOHP; *OR* = 1.39, CI_{95} = 1.00, 1.93 for MECPP; *OR* = 1.66, CI_{95} = 1.22, 2.24 for MBzP). Further, higher maternal prenatal MBzP was associated with increased odds of scores falling into the borderline or clinical range of the Externalizing Problems (*OR* = 2.07, CI_{95} = 1.27, 3.38), BSI (*OR* = 2.02, CI_{95} = 1.31, 3.13), Hyperactivity (*OR* = 1.60, CI_{95} = 1.09, 2.35), Aggression (*OR* = 1.61, CI_{95} = 1.05, 2.47), and Withdrawal scales on the BASC-2 (*OR* = 1.67, CI_{95} = 1.13, 2.45). However, the association between MBzP and the Aggression scale did not survive the correction for multiple comparisons ($q > 0.10$). Thus, for each 1-unit increase in high molecular weight phthalate metabolite (i.e., MEOHP, MECPP, MBzP) concentration quartile, the odds of child behavior scores falling into the borderline or clinical range of the Externalizing Problems, BSI, Hyperactivity, Anxiety, and Withdrawal scales on the BASC-2 increased by 1.39 to 2.07. On the CBCL, higher maternal prenatal MBzP was associated with increased odds of scores falling into the borderline or clinical range of the Externalizing Problems scale (*OR* = 1.80, CI_{95} = 1.19, 2.72). Higher maternal prenatal MEHP, MECPP, and ΣHMWP were associated with increased odds of scores falling into the borderline or clinical range of the Anxious/Depressed scale (*OR* = 3.28, CI_{95} = 1.09, 9.88 for MEHP; *OR* = 3.21, CI_{95} = 1.11, 9.25 for MECPP; *OR* = 3.00, CI_{95} = 1.09, 8.24 for ΣHMWP). Thus, for each 1-unit increase in MBzP, MEHP, MECPP or ΣHMWP quartile, the odds of child behavior scores falling into the borderline or clinical range of the Externalizing Problems and Anxious/Depressed scales on the CBCL increased by 1.80 to–3.28.

Various low molecular weight phthalate metabolites (i.e., MBP, MiBP, MEP), but not the ΣLMWP, were associated with increased odds of child behavior scores falling into the borderline or clinical range of scores on some BASC-2 scales and one CBCL scale (see Table 3). Higher maternal prenatal MBP (*OR* = 1.37, CI_{95} = 1.00, 1.88) and MiBP concentrations (*OR* = 1.47, CI_{95} = 1.03, 2.11) were associated with increased odds of scores falling into the borderline or clinical range of the Anxiety scale on the BASC-2. However, these associations did not survive the correction for multiple comparisons ($q > 0.10$). Higher maternal prenatal MiBP concentrations were also associated with increased odds of scores falling into the borderline or clinical range of the Internalizing Problems (*OR* = 1.93, CI_{95} = 1.25, 3.00), Aggression (*OR* = 1.78, CI_{95} = 1.10, 2.88), and Depression scales on the BASC-2 (*OR* = 1.78, CI_{95} = 1.14, 2.79). Thus, for each 1-unit increase in MiBP concentration quartile, the odds of child behavior scores falling into the borderline or clinical range of the Internalizing Problems, Aggression, or Depression scales on the BASC-2 increased by 1.78 to 1.93. On the CBCL, higher maternal prenatal MEP was associated with increased odds of scores falling into the borderline or clinical range of the Anxious/Depressed scale (*OR* = 2.56, CI_{95} = 1.00, 6.57); however, this association did not survive the correction for multiple comparisons ($q > 0.10$).

3.4. Linear regressions: Phthalates and continuous child behavior scores

Adjusted linear regressions that included urinary creatinine concentration as a covariate examined the associations between maternal prenatal phthalate concentration quartiles and log-transformed *T* scores from the Internalizing Problems, Externalizing Problems,

BSI, and Total Problems scales (see Tables 4 and 5). Two of the phthalate metabolites were significantly associated with scores on the BASC-2 composite scales (see Table 4). Specifically, higher prenatal concentrations of MBzP were related to higher scores on the Externalizing Problems (β = 0.16, CI_{95} = 0.04, 0.28), Internalizing Problems (β = 0.16, CI_{95} = 0.04, 0.29), and BSI (β = 0.18, CI_{95} = 0.05, 0.30) scales. Further, higher prenatal concentrations of MiBP were related to higher scores on the Externalizing Problems (β = 0.16, CI_{95} = 0.01, 0.31), Internalizing Problems (β = 0.20, CI_{95} = 0.05, 0.36), and BSI (β = 0.21, CI_{95} = 0.06, 0.36) scales. However, the associations between MiBP and Externalizing Problems and Internalizing Problems did not survive the correction for multiple comparisons (q > 0.10). No associations were found between any of the phthalate metabolites or molar sums and the CBCL composite scales (see Table 5).

Sex-stratified analyses revealed that for the BASC-2, higher prenatal concentrations of MBzP were related to higher scores on the Externalizing Problems (β = 0.26, CI_{95} = 0.08, 0.44), Internalizing Problems (β = 0.24, CI_{95} = 0.06, 0.42), and BSI (β = 0.26, CI_{95} = 0.09, 0.43) scales in male children. Higher maternal concentrations of MiBP were also related to higher scores on the Internalizing Problems (β = 0.21, CI_{95} = 0.01, 0.41) and BSI (β = 0.22, CI_{95} = 0.03, 0.42) scales in male children. Also, in male children, higher maternal concentrations of ΣLMWP were related to higher scores on the Internalizing Problems (β = 0.17, CI_{95} = 0.01, 0.33) and BSI (β = 0.17, CI_{95} = 0.02, 0.33) scales. However, the association between ΣLMWP and Internalizing Problems in male children did not survive the correction for multiple comparisons (q > 0.10) (Table 4). On the CBCL, higher maternal concentrations of MBzP (β = 0.19, CI_{95} = 0.01, 0.37) were related to higher scores on the Externalizing Problems scale in male children; however, this association did not survive the correction for multiple comparisons (q > 0.10). Also, for male children, higher prenatal concentrations of ΣLMWP were related to higher scores on the Externalizing Problems (β = 0.16, CI_{95} = 0.01, 0.32) and Total Problems (β = 0.16, CI_{95} = 0.01, 0.31) scales. Again, these associations did not survive the corrections for multiple comparisons (q > 0.10). For female children, higher prenatal concentrations of MMP were associated with lower scores on the Total Problems scale on the CBCL (β = −0.19, CI_{95} = −0.36, −0.02); however, this association did not survive the correction for multiple comparisons (q > 0.10) (Table 5).

Moderation models examined whether there were significant interactions between prenatal phthalate concentrations and child sex on child behavior scores (see interaction p-values in Tables 4 and 5). For most of the significant associations found, we did not find evidence for interaction effects (p > 0.05) in the moderation models, with the exception of the regression model examining the association between MMP and Total Problems on the CBCL in female children. However, this interaction effect dropped from significance after correcting for multiple comparisons (q > 0.10). Cumulatively, the sex-stratified and moderation analyses suggest that for the associations between MBzP and the BASC-2 composite scales, and MiBP and the BASC-2 BSI scale, the strength of the associations for male children was what was driving the associations for the overall sample. Further, the associations between MBP and the BASC-2 BSI scale, MiBP and the BASC-2 Internalizing Problems scale, and ΣLMWP and the BASC-2 BSI scale, were only significant for male children.

3.5. Creatinine-adjusted analyses

Binomial logistic and linear regression models using creatinine-adjusted phthalate concentration quartiles revealed many of the same significant associations reported in the primary analytical models (see Tables S4–S7). However, some unique significant associations were also identified. Specifically, higher maternal prenatal ΣHMWP (*OR* = 1.32, CI_{95} = 1.02, 1.71) and MMP concentrations (*OR* = 1.31, CI_{95} = 1.01, 1.68) were associated with increased odds of scores falling in the borderline or clinical range of the Anxiety scale on the BASC-2. Similarly, higher maternal prenatal MBP concentrations were associated with increased odds of scores falling into the borderline or clinical range of the Internalizing Problems scale on the CBCL (*OR* = 1.43, CI_{95} = 1.03, 1.99) (see Tables S4 and S5).

Linear regression analyses revealed unique associations between multiple phthalate metabolites concentration quartiles and the BASC-2 composite scales (see Table S6). Specifically, significant positive associations were found between MEOHP and Internalizing Problems scores in males (β = 0.17, CI_{95} = 0.02, 0.32), MBP and Internalizing Problems scores in the overall sample (β = 0.11, CI_{95} = 0.01, 0.22) and in males (β = 0.19, CI_{95} = 0.04, 0.34), MiBP and Internalizing Problems scores in females (β = 0.16, CI_{95} = 0.01, 0.31), and MiBP and BSI scores in females (β = 0.15, CI_{95} = 0.01, 0.30). Further, the interaction (i.e., interaction between phthalate concentration and child sex) *p*-values in the regression models examining MEOHP and Internalizing Problems scores (p = 0.03), ΣLMWP and Internalizing Problems scores (p = 0.02), and ΣLMWP and BSI scores on the BASC-2 (p = 0.04) were significant. On the CBCL, significant positive associations were found between MiBP and Internalizing Problems scores in the overall sample (β = 0.11, CI_{95} = 0.01, 0.22) and in males (β = 0.16, CI_{95} = 0.01, 0.31), ΣLMWP and Internalizing Problems scores in males (β = 0.15, CI_{95} = 0.01, 0.29), and ΣLMWP and Total Problems scores in the overall sample (β = 0.11, CI_{95} = 0.01, 0.21) and in males (β = 0.18, CI_{95} = 0.03, 0.31) (see Table S7).

3.6. Consistency of similarly named child behavior BASC-2 and CBCL scales

Nonparametric correlations showed that *T* scores from comparable scales on the BASC-2 and CBCL were significantly and positively correlated (*Spearman's rho* range from 0.24 to 0.72; see Table S8). Examination of the percentage of *T* scores (i.e., population-level consistency; see Table S9) that met the classification criteria (i.e., cut-off score) of borderline or clinical as defined by the manuals revealed that for all comparable scales a higher percentage of *T* scores fell into the borderline range on the BASC-2 compared to the CBCL. In contrast, when comparing the BASC-2 composite scales to the comparable CBCL scales (i.e., Internalizing Problems, Externalizing Problems, BSI – Total Problems), a higher percentage of children fell into the clinical range on the CBCL compared to the BASC-2. Based on the 'clinically significant' cut-off (i.e., ≥ 65) (Bour, 2008; Myers et al., 2010), seven comparable scales had a higher percentage of *T* scores that met this classification cut-off on the BASC-2; whereas, three comparable scales had a higher percentage of *T* scores that met this cut-off on the CBCL. Examination of the percentages of individuals whose *T* scores (i.e., individual-level consistency) met the classification criteria defined by the manuals, showed that across comparable scales, 78.3–90.6% of individuals had *T*

scores that were classified as falling below the borderline or clinical range cut-offs on both the BASC-2 and CBCL (see Table S10) and 88.0–95.3% were classified as falling below the 'clinically significant' cut-off on both of these measures (see Table S11). Wilcoxon signed-rank tests compared the means ranks of BASC-2 *T* scores with the CBCL *T* scores. Significant differences were found for 14 of the 15 comparable scales when untruncated BASC-2 scores were compared with truncated CBCL scales (see Table S12) and for 9 of the 15 comparable scales when truncated BASC-2 scores were compared with truncated CBCL scores (see Table S13).

3.7. Sensitivity analyses

In general, the point estimates did not change appreciably after adjusting for maternal depression score (M = 5.28, SD = 4.09) as a potential confounder in the primary analyses (see Tables S14–S17). All the significant associations reported in the primary logistic regressions remained significant. However, the point estimates for the associations between some phthalates (i.e., MEHP, MECPP, ΣHMPW, MEP) and odds of scores falling into the borderline or clinical range on the Anxious/Depression scale on the CBCL were reduced (Tables S14 and S15). Most of the significant associations reported in the primary linear regressions remained significant (Tables S16 and S17). However, the associations between MiBP and BSI scores on the BASC-2, ΣLMWP and Internalizing Problems and BSI scores on the BASC-2, and ΣLMWP and Externalizing Problems scores on the CBCL in males, were attenuated in models adjusted for maternal depression.

4. Discussion

In this prospective pregnancy cohort, we found that maternal urinary phthalate concentrations during pregnancy were associated with parent-ratings of behavior problems in children aged 3–4 years. However, many of these associations differed based on the specific parent-rating instrument used. Associations between maternal urinary phthalate concentrations during pregnancy and parent-ratings of behavior problems in children were also found to differ based on the analytical approach used to correct for urine dilution by adjusting for urinary creatinine. Our findings suggest that some of the inconsistencies in the associations reported in the research literature that has examined the effects of prenatal phthalate exposure on child behavior problems are likely due to the differences in analytical approaches used to correct for urine dilution and variations in the behaviors that are measured by similarly named scales on standardized measures. In other words, our analyses provided evidence that preschool behavior problems are differently operationalized and evaluated on multiple scales from the BASC-2 and CBCL, especially for the clinical/syndrome scales and the Internalizing Problems scale.

Our primary regression analyses revealed that higher prenatal exposure to phthalates was associated with increased odds of scores falling into the borderline or clinical range of scores on the Hyperactivity, Aggression, Anxiety, Depression, Withdrawal, Externalizing Problems, Internalizing Problems, and BSI scales on the BASC-2. In contrast, on the CBCL, higher prenatal exposure to phthalates was only related to increased odds of scores falling into the borderline or clinical range of scores on the Anxious/Depressed

and Externalizing Problems scales. Regression analyses examining the associations between maternal prenatal phthalate concentrations and continuous *T* scores on the Internalizing Problems, Externalizing Problems, BSI, and Total Problems scales also found differing results for the BASC-2 and the CBCL. However, sex-stratified analyses using these scales revealed some similarities between the BASC-2 and CBCL for male children. Specifically, for male children, higher prenatal exposure to phthalates was associated with higher scores on the Externalizing Problems, Internalizing Problems, and BSI scales on the BASC-2, and higher scores on the Externalizing Problems and Total Problems scales on the CBCL. These findings are consistent with previous research showing that higher prenatal exposure to phthalates was associated with higher scores on the Aggression, Attention Problems, Depression, Externalizing Problems, and BSI scales of the BASC-2 in preschool children (Engel et al., 2010), and that higher prenatal exposure to phthalates was related to increased odds of scores falling into the borderline or clinical range on the Externalizing Problems scale on the CBCL in 8-year old children (Lien et al., 2015).

The differing effects of the two analytical approaches used to correct for urine dilution on associations between maternal urinary phthalate concentrations during pregnancy and parent-ratings of behavior problems provides some insight regarding the mixed findings reported in the literature. Prior research that corrected for urine dilution by including urinary creatinine concentration as a covariate in their models found that higher ΣLMWP concentrations were associated with higher scores on the Aggression, Attention Problems, Depression, Externalizing Problems, and BSI scales on the BASC-2 in preschool children (Engel, et al., 2010). Further, in sex-stratified analyses, they found that ΣLMWP and other individual metabolite (i.e., MBP, MEP, MMP) concentrations were positively associated with scores on one or more of the clinical and/or composite scales in male children (Engel, et al., 2010). These findings are similar to the results of the present study, which showed that higher phthalate metabolite (i.e., MBzP, MiBP) concentrations were associated with increased odds of scores falling into the borderline or clinical range of the Aggression and Depression scales of the BASC-2 and with higher scores on the BASC-2 composite scales. Further, the results of sex-stratified analyses conducted by Engel et al (2010) are comparable to our results showing that multiple phthalate metabolites (i.e., MBzP, MBP, MiBP) and ΣLMWP concentrations were positively associated scores on the BASC-2 composite scales in male children. In another study, Kobrosly et al. (2014) found that higher MiBP concentrations were associated with higher scores on the Aggressive Behavior and Attention Problems scales on the CBCL in children 6–10 years of age. Additionally, in sex-stratified analyses, they found that higher MiBP concentrations were associated with higher scores on the Aggressive Behavior, Attention Problems, Externalizing Problems, and Total Problems scales on the CBCL in males; whereas, higher MBzP and DEHP concentrations were associated with lower Anxious/Depressed scores in females (Kobrosly et al., 2014). Some of our findings from the sex-stratified analyses were similar; specifically, higher prental exposure to phthalates was positively associated with scores on the Externalizing Problems and Total Problems scales on the CBCL in males.

Previous research examining the associations between prenatal exposure to phthalates and behavior problems in children using creatinine-adjusted concentrations found that individual phthalate concentrations (i.e., MEHP, MEHHP, MEOHP, MBP) were associated

with increased odds of scores falling in the borderline or clinical range on the Aggressive Behavior and Externalizing Problems scales on the CBCL in 8-year-old children (Lien et al, 2015). They also found that individual phthalate metabolite concentrations (i.e., MEHP, MEOHP, MBP) were positively associated with scores on the Externalizing Problems scale (Lien et al, 2015). These findings are not consistent with the results from our creatinine-adjusted analyses; however, this could be due to differences in sociodemographic characteristics or level of phthalate exposure. Overall, the results of the present study and prior research examining maternal urinary phthalate concentrations during pregnancy and behavior problems in young children suggest that the analytical approach that is used to correct for urine dilution by adjusting for urinary creatinine can affect results. Further research is needed using diverse samples to better understand how theses different analytical approaches influence the reported associations between maternal prenatal phthalate concentrations and children's behavior problems on the BASC-2 and CBCL.

Relatedly, the results of our primary and secondary analyses showed that the different analytical approaches for correcting for urine dilution revealed a number of unique results for multiple phthalates. For example, when urinary creatinine was included as a covariate, significant associations were found between prenatal MBzP concentrations and odds of scores falling into the borderline or clinical range of scores on a number of scales on the BASC-2 (i.e., Externalizing Problems, BSI, Hyperactivity, Aggression) and one CBCL subscale (i.e., Externalizing Problems). However, when creatinine-adjusted concentrations were used none of these associations were significant. Additionally, the significant associations found between multiple phthalate metabolites (i.e., MEHP, MECPP, MEP) and the ΣHMWP and the odds of scores falling in the borderline or clinical range of scores on the Anxious/Depressed subscale of the CBCL when urinary creatinine was included as a covariate, were not replicated when creatine-adjusted phthalate concentrations were used. Consequently, further investigation is needed to better understand why and how different analytical approaches that correct for urine dilution may bias the associations between phthalates, possibly for certain metabolites and molar sums based on molecular weight, and child behavior outcomes.

The results of our consistency analyses may also help to potentially explain some of the different associations found for the BASC-2 and CBCL. Similar to Reynolds and Kamphaus (2004), we found that the 15 corresponding child behavior scales on these measures were positively correlated with each other, but some scales showed low-moderate correlations. However, we found inconsistencies in the population-level and individual-level classifications for many of the corresponding scales. Specifically, a higher percentage of scale scores (i.e., population-level inconsistency) met the borderline classification criteria on the BASC-2 and a higher percentage of individuals (i.e., individual-level inconsistency) met the borderline or clinical classification criteria on one, but not both, scales. Further, although previous research has utilized the same 'clinically significant' cut-off (i.e., *T* scores ≥ 65) (Bour, 2008; Myers et al., 2010) to compare scores on the BASC-2 and CBCL, neither this cut-off nor those from the manuals classified children consistently at the population- or individual-level. Our analyses examining the consistency of mean ranks also found significant differences between most of the comparable scales, with the exception

of one scale (i.e., Internalizing Problems). Thus, these findings provide evidence that there are notable variations across many of the similarly named child behavior constructs on the BASC-2 and CBCL, and this is likely to result in inconsistencies in the associations reported between phthalates and these two standardized parent-report measures of child behavior.

Unfortunately, the findings of the present study do not provide any insight as to which parent-rating measure provides the most accurate assessment of these behavioral constructs in preschool-age children. The differences in associations between prenatal phthalate exposure and child behavior outcomes on the BASC-2 and CBCL could be due to several factors (e.g., use of different normative samples, differences in items for similarly named constructs, differences in definitions for similarly named constructs), but this provides little practical assistance in determining which instrument is superior for evaluating preschool behavior. It is possible that: (i) the BASC-2 gives inflated scores in the borderline and 'clinically significant' range, (ii) the CBCL underestimates children's behavior problems in the borderline and 'clinically significant' range, (iii) each instrument measures certain behavior constructs more accurately than the other, or (iv) the underlying constructs measured are different and thus the scales are actually assessing different behaviors despite having similar names. Previous research has suggested that the CBCL may result in higher scores than the BASC-2 for clinically-referred preschool children (Myers et al., 2010). Considering this and the present results, it is possible that CBCL may underestimate behavior problems in preschool children unless they fall into the clinical range; whereas, the BASC-2 may be more sensitive to detecting sub-clinical alterations in preschool children's behavior following prenatal exposure to phthalates. In light of the present findings, it is important to consider these differences and similarities when interpreting the results of developmental research and to not equate the findings from studies that have utilized these two different child behavior instruments.

Developmental theories posit that prenatal exposure to phthalates may disrupt the organization of neurochemical and neuroendocrine systems and potentially have a lasting impact on neurobehavioral development, which could explain the associations between prenatal phthalate concentrations and behavior problems in young children (Gore et al., 2019; Walker and Gore, 2011). During early childhood, internalizing and externalizing behaviors have a high rate of comorbidity, and the diversity of methods used to evaluate these behavior problems poses a challenge for child development research (Achenbach et al., 2016). Although previous research reports sex differences in the prevalence of internalizing and externalizing problems in young children (Basten et al., 2016; Mesman et al., 2001), and prenatal phthalate exposure is thought to influence sex-specific neurobehavioral development (Schug et al., 2015), only limited evidence suggests that prenatal phthalate concentrations may be associated with different behavior problems in male children (i.e., aggression, attention, emotionally reactive) compared to female children (i.e., anxious/depressed) (Engel et al., 2010; Whyatt et al., 2012). In the present study, we found that higher prenatal phthalate levels were associated with higher scores on the Externalizing Problems, Internalizing Problems, and BSI/Total Problems scales in male children; we also found limited evidence that higher phthalate levels may be associated with lower BSI scale scores in females. The current findings support the model of developmental neurotoxicity proposed by Miodovnik et al., (2014), and suggest that prenatal exposure to phthalates may

disrupt development of the nervous system during gestation and have lasting effects on sexually-dimorphic behavioral development of young children.

4.1. Strengths and limitations

It is important to consider the characteristics of the current sample when interpreting and determining the generalizability of our findings. The findings from this study are strengthened by the large sample of typically developing preschool children who participated in our investigation of the consistency of two parent-report measures, considered the gold standards for assessing child behavior. However, as the sample was a relatively homogeneous group of typically developing children of high socioeconomic status (i.e., mothers were predominantly Caucasian, university-educated, married, and had high household incomes), it is unknown if these results would be generalizable to samples with greater ethnic diversity, more variability in socioeconomic status, or children referred for specific clinical issues or diagnoses.

There are some additional potential limitations imposed by constraints of the study design and the assessments utilized. Prenatal phthalate concentrations were only assessed via a single maternal spot urine sample; however, research suggests that single spot-sampling reflects average exposure and exhibits moderate sensitivity (Mahalingaiah et al., 2008; Ye et al., 2011). Given the nonpersistent nature of phthalates in the body and corresponding variation in phthalate exposure levels, future research is encouraged to examine phthalate concentrations across multiple sampling timepoints during pregnancy in relation to child behavior outcomes. Further, we assessed maternal prenatal phthalate concentrations during the second trimester of pregnancy, which contrasts with some previous work that assessed phthalate concentrations during the third trimester (i.e., Engel et al., 2010; Whyatt et al., 2012). Childhood exposure to EDCs, such as phthalates and bisphenol A (BPA) could also impact child neurodevelopment (Schug et al., 2015). However, we do not have any assessments of phthalate exposure during the postnatal period or early childhood, and future research is encouraged that examines how exposure to EDCs in early childhood impacts behavior. Relatedly, although one of our objectives was to investigate the effects of different analytical approaches for correcting for urine dilution on the consistency of results from two child behavior instruments, it is also possible that other methods of analyzing phthalate concentrations (e.g., correcting for urine dilution by adjusting for specific gravity) may influence outcomes. Finally, although the current study investigated two gold standard parent-rating instruments of child behavior, other research examining the associations between maternal phthalate concentrations during pregnancy and behavior outcomes in young children have used other instruments with similarly named scales (e.g., Externalizing Behaviour, Internalizing Behavior, etc.) – such as the Strengths and Difficulties Questionnaire/SDQ (i.e., in Philippat et al., 2017). Future research using multi-method assessments of children's behavior is needed to help clarify the associations between exposure to phthalates during fetal development and early childhood and behavior outcomes.

4.2. Conclusions

The current study provides preliminary, but important evidence that variations in the behavioral constructs measured by the BASC-2 and CBCL scales and different analytical

approaches used to correct for urine dilution could account for some of the discrepancies in the environmental health literature regarding the associations between prenatal phthalate exposure and child behavioral outcomes. Although the BASC-2 and CBCL purport to assess similar behavior constructs, divergent results were found for the associations between prenatal exposure to phthalates and behavioral outcomes on comparative scales (i.e., scales with the same or a similar name(s)) on these measures. This suggests that how comparative behavior constructs are operationalized and evaluated in preschool children may differ between these two instruments. Our findings also suggest that the CBCL may underestimate child behavior problems unless they fall into the clinical range and the BASC-2 may be more sensitive in detecting sub-clinical variations in child behavior following prenatal exposure to phthalates. Additionally, we found unique associations between phthalate concentrations and child behavior scores in models that considered creatinine as a covariate and in models that considered creatinine-adjusted phthalate concentrations. Future investigations to further delineate the similarities and differences between the child behavior constructs assessed by the BASC-2, CBCL, and other parent-rating scales (i.e., SDQ), as well as how analytical approaches used to correct for urine dilution may bias associations, are required to better understand how prenatal exposure to phthalates impacts children's neurobehavioral development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EDCs	endocrine-disrupting chemicals
CBCL	Child Behavior Checklist for ages 1½–5
BASC-2	Behavior Assessment System for Children-Second Edition Parent Rating Scales-Preschool
FSIQ	Full-Scale Intelligence Quotient
DEHP	di(2-ethyl-hexyl) phthalate
MEHP	mono(2-ethylhexyl) phthalate
MEHHP	mono(2-ethyl-5-hydroxy-hexyl) phthalate

MEOHP	mono(2-ethyl-5-oxohexyl) phthalate
MECPP	mono(2-ethyl-5-carboxypentyl) phthalate
DBP	dibutyl phthalate
MBP	mono-n-butyl phthalate
MiBP	mono-iso-butyl phthalate
MBzP	mono-benzyl phthalate
MEP	mono-ethyl phthalate
MMP	mono-methyl phthalate
ΣHMWP	molar sum of high molecular weight phthalates
ΣLMWP	molar sum of low molecular weight phthalates
LOD	limit of detection
GMs	geometric means
ADH	Attention-Deficit/Hyperactivity
PD	Pervasive Developmental
BSI	Behavioral Symptoms Index
ORs	odds ratios

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Table 1

Unadjusted phthalate metabolite concentrations (μg/L) in maternal second trimester urine.

Metabolite	% > LOD	Range	GM	25th Percentile	50th Percentile	75th Percentile
MEHP[a]	99.1	< LOD–120.13	3.31	1.59	3.31	6.68
MEHHP[a]	100	0.61–250.47	10.38	5.31	10.74	19.36
MEOHP[a]	100	0.60–192.35	8.45	4.50	8.73	16.12
MECPP[a]	100	0.87–336.18	14.81	7.88	15.51	27.80
MBzP[a]	99.2	< LOD–515.52	8.13	3.55	8.56	17.66
ΣHMWP[b]	99.1	< LOD–17.03	0.18	0.10	0.19	0.33
MBP[a]	99.1	< LOD–1129.72	16.66	8.82	16.96	32.09
MiBP[a]	98.9	< LOD–374.22	9.71	5.49	10.30	17.90
MEP[a]	100	1.39–22520.68	50.41	17.29	46.00	144.17
MMP[a]	99.4	< LOD–86.09	2.35	1.29	2.36	4.28
ΣLMWP[b]	99.1	< LOD–116.30	0.49	0.22	0.43	1.07

LOD = limit of detection; GM = geometric mean.

[a] LOD = 0.10 μg/L.

[b] μmol/L.

Table 2

Adjusted ORs for BASC-2 and CBCL scores in the borderline or clinical range for each 1-unit increase in unadjusted prenatal phthalate concentration quartiles for high molecular weight phthalates (i.e., MEHP, MEHPP, MEOHP, MECPP, MBzP, ΣHMWP).

	MEHP[a] OR (95% CI)	**MEHHP[a] OR (95% CI)**	**MEOHP[a] OR (95% CI)**	**MECPP[a] OR (95% CI)**	**MBzP[a] OR (95% CI)**	**ΣHMWP[b] OR (95% CI)**
BASC-2						
Externalizing Problems	1.09 (0.72, 1.65)	1.02 (0.63, 1.65)	1.01 (0.62, 1.65)	0.87 (0.59, 1.56)	2.07*** (1.27, 3.38)	1.32 (0.82, 2.13)
Internalizing Problems	1.38 (0.98, 1.94)	1.33 (0.91, 1.95)	1.50* (1.01, 2.23)	1.34 (0.91, 1.97)	1.41 (0.99, 2.03)	1.37 (0.94, 2.01)
BSI	1.18 (0.80, 1.72)	1.03 (0.67, 1.59)	1.13 (0.73, 1.76)	1.08 (0.70, 1.68)	2.02*** (1.31, 3.13)	1.38 (0.90, 2.13)
Hyperactivity	1.00 (0.71, 1.42)	0.81 (0.54, 1.23)	0.80 (0.52, 1.22)	0.79 (0.52, 1.20)	1.60** (1.09, 2.35)	1.01 (0.68, 1.51)
Aggression	1.06 (0.72, 1.56)	0.92 (0.59, 1.45)	1.07 (0.68, 1.67)	0.95 (0.61, 1.49)	1.61* (1.05, 2.47)	1.16 (0.75, 1.80)
Anxiety	1.08 (0.81, 1.42)	1.26 (0.92, 1.73)	1.50** (1.08, 2.08)	1.39** (1.00, 1.93)	1.66** (1.22, 2.24)	1.31 (0.96, 1.80)
Depression	0.97 (0.68, 1.37)	1.15 (0.77, 1.70)	1.10 (0.73, 1.64)	1.16 (0.78, 1.74)	1.33 (0.92, 1.92)	1.06 (0.71, 1.58)
Somatization	1.16 (0.73, 1.83)	1.00 (0.60, 1.69)	0.99 (0.58, 1.70)	0.90 (0.53, 1.54)	1.08 (0.67, 1.75)	1.07 (0.63, 1.81)
Atypicality	1.18 (0.89, 1.57)	1.01 (0.73, 1.40)	0.94 (0.67, 1.33)	0.97 (0.70, 1.36)	1.12 (0.83, 1.52)	0.99 (0.71, 1.37)
Withdrawal	0.95 (0.67, 1.35)	0.89 (0.59, 1.34)	0.92 (0.61, 1.38)	0.98 (0.65, 1.48)	1.67** (1.13, 2.45)	1.30 (0.87, 1.94)
Attention Problems	1.06 (0.76, 1.50)	1.22 (0.82, 1.80)	1.27 (0.85, 1.89)	1.06 (0.71, 1.57)	1.18 (0.82, 1.70)	1.27 (0.86, 1.87)
CBCL						
Externalizing Problems	1.05 (0.72, 1.51)	1.15 (0.76, 1.75)	1.04 (0.68, 1.60)	1.09 (0.72, 1.67)	1.80*** (1.19, 2.72)	1.34 (0.88, 2.04)
Internalizing Problems	1.17 (0.82, 1.67)	0.97 (0.64, 1.46)	1.10 (0.72, 1.67)	0.97 (0.64, 1.47)	1.08 (0.74, 1.58)	0.96 (0.63, 1.44)
Total Problems	1.07 (0.73, 1.56)	1.01 (0.65, 1.56)	1.11 (0.72, 1.73)	1.15 (0.74, 1.79)	1.26 (0.84, 1.90)	1.10 (0.71, 1.70)
ADH Problems	0.85 (0.19, 3.73)	0.90 (0.17, 4.70)	0.87 (0.15, 4.85)	0.41 (0.06, 2.93)	1.71 (0.35, 8.35)	0.91 (0.17, 4.74)
Aggressive Behaviour	1.23 (0.64, 2.37)	1.44 (0.70, 2.94)	1.24 (0.59, 2.62)	1.47 (0.70, 3.10)	2.05 (0.97, 4.31)	1.88 (0.91, 3.90)
Anxious/Depressed	3.28** (1.09, 9.88)	2.31 (0.90, 5.95)	2.38 (0.91, 6.27)	3.21** (1.11, 9.25)	2.31 (0.90, 5.96)	3.00** (1.09, 8.24)
Anxiety Problems	1.08 (0.63, 1.84)	0.99 (0.54, 1.82)	1.32 (0.71, 2.43)	1.08 (0.59, 2.00)	1.31 (0.74, 2.32)	1.07 (0.59, 1.95)
Affective Problems	1.05 (0.71, 1.56)	1.06 (0.68, 1.68)	0.95 (0.59, 1.51)	1.28 (0.81, 2.03)	1.02 (0.67, 1.56)	1.13 (0.72, 1.79)
Somatic Complaints	0.93 (0.58, 1.49)	0.81 (0.46, 1.40)	0.93 (0.53, 1.62)	0.85 (0.49, 1.47)	1.09 (0.65, 1.81)	0.85 (0.49, 1.47)
PD Problems	1.30 (0.82, 2.06)	1.18 (0.71, 1.96)	1.26 (0.74, 2.14)	1.12 (0.67, 1.87)	1.44 (0.88, 2.38)	1.19 (0.71, 1.99)
Withdrawn	1.50 (0.80, 2.82)	1.07 (0.54, 2.10)	1.53 (0.75, 3.09)	1.13 (0.57, 2.21)	1.35 (0.70, 2.58)	1.07 (0.55, 2.11)
Attention Problems	1.24 (0.74, 2.07)	1.42 (0.80, 2.52)	1.44 (0.80, 2.58)	1.26 (0.70, 2.27)	1.00 (0.58, 1.74)	1.48 (0.84, 2.63)

All models are adjusted for urinary creatinine, family income, child sex, and Full-Scale Intelligence Quotient (FSIQ).

[a] µg/L.

[b] µmol/L.

[*] Raw *p*-value < 0.05.

[**] $q < 0.10$.

[***] $q < 0.05$.

Table 3

Adjusted ORs for BASC-2 and CBCL scores in the borderline or clinical range for each 1-unit increase in unadjusted prenatal phthalate concentration quartiles for low molecular weight phthalates (i.e., MBP, MiBP, MEP, MMP, ΣLMWP).

	MBP[a] OR (95% CI)	**MiBP[a] OR (95% CI)**	**MEP[a] OR (95% CI)**	**MMP[a] OR (95% CI)**	**ΣLMWP[b] OR (95% CI)**
BASC-2					
Externalizing Problems	1.33 (0.82, 2.15)	1.39 (0.83, 2.32)	1.34 (0.89, 2.02)	1.09 (0.71, 1.68)	1.36 (0.89, 2.08)
Internalizing Problems	1.46 (0.99, 2.14)	1.93*** (1.25, 3.00)	1.13 (0.81, 1.57)	1.12 (0.80, 1.57)	1.32 (0.92, 1.87)
BSI	1.45 (0.94, 2.24)	1.59 (0.99, 2.55)	1.09 (0.76, 1.58)	1.23 (0.83, 1.83)	1.14 (0.78, 1.67)
Hyperactivity	1.33 (0.89, 1.98)	1.18 (0.77, 1.82)	1.13 (0.81, 1.58)	0.99 (0.69, 1.42)	1.16 (0.82, 1.65)
Aggression	1.21 (0.77, 1.90)	1.78** (1.10, 2.88)	1.02 (0.71, 1.47)	1.16 (0.78, 1.72)	1.12 (0.76, 1.65)
Anxiety	1.37* (1.00, 1.88)	1.47* (1.03, 2.11)	0.96 (0.73, 1.26)	1.17 (0.88, 1.56)	1.10 (0.82, 1.46)
Depression	1.04 (0.70, 1.56)	1.78** (1.14, 2.79)	1.11 (0.79, 1.56)	0.96 (0.68, 1.36)	1.31 (0.91, 1.88)
Somatization	1.43 (0.85, 2.41)	1.73 (0.95, 3.14)	1.04 (0.67, 1.64)	0.95 (0.60, 1.50)	1.09 (0.67, 1.78)
Atypicality	1.11 (0.80, 1.54)	1.25 (0.87, 1.80)	0.98 (0.75, 1.30)	1.09 (0.82, 1.46)	0.94 (0.70, 1.27)
Withdrawal	1.14 (0.76, 1.71)	1.28 (0.82, 2.00)	1.19 (0.85, 1.68)	1.03 (0.73, 1.47)	1.09 (0.76, 1.58)
Attention Problems	1.30 (0.88, 1.93)	1.27 (0.83, 1.94)	1.10 (0.79, 1.53)	0.97 (0.68, 1.37)	1.12 (0.79, 1.58)
CBCL					
Externalizing Problems	1.45 (0.95, 2.21)	1.47 (0.93, 2.32)	1.33 (0.93, 1.91)	1.18 (0.81, 1.72)	1.34 (0.92, 1.95)
Internalizing Problems	1.49 (0.99, 2.25)	1.12 (0.71, 1.75)	1.03 (0.73, 1.45)	1.09 (0.76, 1.56)	1.02 (0.71, 1.48)
Total Problems	1.25 (0.80, 1.93)	1.30 (0.80, 2.11)	1.02 (0.71, 1.48)	1.29 (0.87, 1.91)	0.99 (0.67, 1.47)
ADH Problems	1.78 (0.36, 8.78)	0.91 (0.15, 5.66)	0.55 (0.11, 2.67)	0.98 (0.21, 4.56)	0.46 (0.08, 2.74)
Aggressive Behaviour	1.12 (0.53, 2.39)	1.84 (0.83, 4.07)	1.45 (0.77, 2.73)	1.31 (0.66, 2.63)	1.41 (0.75, 2.68)
Anxious/Depressed	1.55 (0.64, 3.78)	1.64 (0.63, 4.27)	2.56* (1.00, 6.57)	1.14 (0.50, 2.59)	2.48 (0.97, 6.34)
Anxiety Problems	1.42 (0.78, 2.57)	1.06 (0.55, 2.05)	1.61 (0.94, 2.74)	1.19 (0.69, 2.08)	1.59 (0.93, 2.72)
Affective Problems	1.05 (0.66, 1.66)	1.08 (0.65, 1.81)	0.91 (0.61, 1.34)	1.18 (0.79, 1.78)	0.92 (0.60, 1.40)
Somatic Complaints	1.11 (0.64, 1.93)	0.73 (0.39, 1.34)	1.19 (0.75, 1.88)	1.02 (0.64, 1.63)	1.08 (0.66, 1.77)
PD Problems	1.32 (0.79, 2.24)	1.24 (0.71, 2.16)	1.53 (0.97, 2.40)	1.14 (0.72, 1.81)	1.46 (0.92, 2.32)
Withdrawn	1.17 (0.59, 2.34)	1.08 (0.52, 2.25)	1.25 (0.70, 2.24)	1.34 (0.71, 2.52)	1.05 (0.58, 1.93)
Attention Problems	1.58 (0.90, 2.79)	1.71 (0.89, 3.27)	1.57 (0.94, 2.62)	0.85 (0.50, 1.47)	1.46 (0.87, 2.47)

All models are adjusted for urinary creatinine, family income, child sex, and Full-Scale Intelligence Quotient (FSIQ).

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[a] µg/L..

[b] µmol/L..

* Raw *p*-value < 0.05.

** $q < 0.10$.

*** $q < 0.05$.

Table 4

Standardized regression coefficients (95% CIs) for the associations between unadjusted prenatal phthalate concentration quartiles and BASC-2 scores in 3–4-year-old children.

Phthalate Metabolite	Sex	BASC-2: Externalizing Problems	p_{int}	BASC-2: Internalizing Problems	p_{int}	BASC-2: Behavioral Symptoms Index	p_{int}
MEHP[a]	Overall	0.01 (−0.11, 0.12)	0.12	−0.05 (−0.17, 0.07)	0.36	0.04 (−0.08, 0.15)	0.28
	Females	−0.08 (−0.24, 0.08)		−0.11 (−0.28, 0.07)		−0.02 (−0.19, 0.15)	
	Males	0.10 (−0.07, 0.27)		−0.01 (−0.18, 0.16)		0.09 (−0.07, 0.25)	
MEHHP[a]	Overall	−0.03 (−0.16, 0.11)	0.51	−0.01 (−0.15, 0.13)	0.46	0.02 (−0.12, 0.15)	0.33
	Females	−0.04 (−0.22, 0.14)		−0.06 (−0.26, 0.14)		−0.02 (−0.21, 0.17)	
	Males	−0.01 (−0.20, 0.19)		0.02 (−0.18, 0.22)		0.05 (−0.14, 0.24)	
MEOHP[a]	Overall	−0.04 (−0.17, 0.10)	0.76	0.00 (−0.14, 0.15)	0.28	0.00 (−0.14, 0.14)	0.40
	Females	−0.03 (−0.21, 0.15)		−0.08 (−0.28, 0.12)		−0.03 (−0.23, 0.16)	
	Males	−0.06 (−0.26, 0.14)		0.07 (−0.14, 0.27)		0.02 (−0.17, 0.22)	
MECPP[a]	Overall	−0.04 (−0.18, 0.09)	0.62	0.00 (−0.14, 0.14)	0.48	−0.02 (−0.16, 0.12)	0.42
	Females	−0.06 (−0.25, 0.13)		−0.06 (−0.27, 0.14)		−0.06 (−0.26, 0.14)	
	Males	−0.03 (−0.23, 0.16)		0.03 (−0.17, 0.23)		0.01 (−0.19, 0.20)	
MBzP[a]	Overall	0.16 ** (0.04, 0.28)	0.16	0.16 ** (0.04, 0.29)	0.28	0.18 *** (0.05, 0.30)	0.21
	Females	0.08 (−0.09, 0.25)		0.09 (−0.09, 0.28)		0.10 (−0.08, 0.28)	
	Males	0.26 *** (0.08, 0.44)		0.24 *** (0.06, 0.42)		0.26 *** (0.09, 0.43)	
ΣHMWP[b]	Overall	0.02 (−0.11, 0.15)	0.11	0.00 (−0.13, 0.14)	0.27	0.05 (−0.08, 0.19)	0.14
	Females	−0.09 (−0.28, 0.09)		−0.09 (−0.29, 0.11)		−0.05 (−0.23, 0.15)	
	Males	0.13 (−0.06, 0.32)		0.08 (−0.12, 0.27)		0.14 (−0.04, 0.33)	
MBP[a]	Overall	0.12 (−0.01, 0.25)	0.50	0.11 (−0.03, 0.25)	0.50	0.12 (−0.02, 0.25)	0.20
	Females	0.10 (−0.09, 0.29)		0.07 (−0.14, 0.27)		0.04 (−0.16, 0.24)	
	Males	0.13 (−0.06, 0.33)		0.15 (−0.05, 0.34)		0.19 ** (0.01, 0.37)	
MiBP[a]	Overall	0.16 * (0.01, 0.31)	0.95	0.20 * (0.05, 0.36)	0.72	0.21 *** (0.06, 0.36)	0.48
	Females	0.22 (−0.01, 0.45)		0.20 (−0.05, 0.44)		0.20 (−0.05, 0.44)	
	Males	0.12 (−0.09, 0.32)		0.21 ** (0.01, 0.41)		0.22 ** (0.03, 0.42)	

Phthalate Metabolite	Sex	BASC-2: Externalizing Problems	p_{int}	BASC-2: Internalizing Problems	p_{int}	BASC-2: Behavioral Symptoms Index	p_{int}
MEP[a]	Overall	0.05 (−0.06, 0.16)	0.46	0.02 (−0.09, 0.14)	0.28	0.04 (−0.07, 0.16)	0.35
	Females	0.01 (−0.16, 0.17)		−0.05 (−0.23, 0.12)		−0.01 (−0.18, 0.17)	
	Males	0.08 (−0.08, 0.23)		0.08 (−0.08, 0.24)		0.08 (−0.07, 0.23)	
MMP[a]	Overall	0.02 (−0.10, 0.14)	0.21	0.05 (−0.07, 0.17)	0.10	−0.06 (−0.18, 0.06)	0.16
	Females	−0.02 (−0.19, 0.14)		−0.04 (−0.22, 0.13)		−0.11 (−0.29, 0.06)	
	Males	0.11 (−0.06, 0.29)		0.17 (−0.01, 0.34)		0.04 (−0.13, 0.21)	
ΣLMWP[b]	Overall	0.09 (−0.03, 0.20)	0.36	0.11 (−0.01, 0.24)	0.29	0.11 (−0.02, 0.23)	0.17
	Females	0.03 (−0.15, 0.21)		0.04 (−0.16, 0.23)		0.01 (−0.18, 0.21)	
	Males	0.13 (−0.03, 0.29)		0.17 * (0.01, 0.33)		0.17 ** (0.02, 0.33)	

All models are adjusted for urinary creatinine, family income and Full-Scale Intelligence Quotient (FSIQ). Overall models are also adjusted for child sex.

[a] µg/L.

[b] µmol/L.

* Raw *p*-value < 0.05.

** *q* < 0.10.

*** *q* < 0.05.

Table 5

Standardized regression coefficients (95% CIs) for the associations between unadjusted prenatal phthalate concentration quartiles and CBCL scores in 3–4-year-old children.

Phthalate Metabolite	Sex	CBCL: Externalizing Problems	p_{int}	CBCL: Internalizing Problems	p_{int}	CBCL: Total Problems	p_{int}
MEHP[a]	Overall	−0.04 (−0.16, 0.08)	0.23	0.02 (−0.10, 0.14)	0.15	0.01 (−0.11, 0.13)	0.21
	Females	−0.13 (−0.29, 0.04)		−0.08 (−0.25, 0.09)		−0.09 (−0.26, 0.08)	
	Males	0.03 (−0.15, 0.20)		0.10 (−0.07, 0.27)		0.09 (−0.08, 0.25)	
MEHPP[a]	Overall	0.00 (−0.14, 0.14)	0.51	−0.01 (0.14, 0.13)	0.08	−0.01 (−0.14, 0.13)	0.33
	Females	−0.03 (−0.22, 0.15)		−0.13 (−0.32, 0.06)		−0.10 (−0.29, 0.10)	
	Males	0.03 (−0.17, 0.23)		0.11 (−0.09, 0.30)		0.07 (−0.12, 0.26)	
MEOHP[a]	Overall	−0.02 (−0.16, 0.12)	0.48	0.03 (−0.12, 0.17)	0.12	0.00 (−0.14, 0.14)	0.45
	Females	−0.07 (−0.26, 0.12)		−0.09 (−0.29, 0.10)		−0.08 (−0.27, 0.12)	
	Males	0.01 (−0.20, 0.22)		0.12 (−0.08, 0.33)		0.05 (−0.14, 0.25)	
MECPP[a]	Overall	−0.03 (−0.16, 0.11)	0.59	−0.02 (−0.16, 0.12)	0.21	−0.01 (−0.15, 0.13)	0.59
	Females	−0.06 (−0.26, 0.14)		−0.12 (−0.32, 0.08)		−0.08 (−0.28, 0.12)	
	Males	0.00 (−0.20, 0.20)		0.06 (−0.14, 0.26)		0.03 (−0.16, 0.22)	
MBzP[a]	Overall	0.10 (−0.03, 0.22)	0.25	0.07 (−0.06, 0.20)	0.71	0.08 (−0.05, 0.20)	0.41
	Females	0.01 (−0.16, 0.19)		0.05 (−0.13, 0.22)		−0.01 (−0.19, 0.17)	
	Males	0.19* (0.01, 0.37)		0.10 (−0.08, 0.29)		0.16 (−0.01, 0.34)	
ΣHMWP[b]	Overall	0.04 (−0.09, 0.18)	0.14	0.02 (−0.12, 0.15)	0.16	0.02 (−0.11, 0.16)	0.21
	Females	−0.08 (−0.27, 0.11)		−0.10 (−0.30, 0.10)		−0.12 (−0.31, 0.08)	
	Males	0.16 (−0.03, 0.36)		0.11 (−0.08, 0.31)		0.13 (−0.05, 0.32)	
MBP[a]	Overall	0.01 (−0.13, 0.14)	0.60	0.08 (−0.06, 0.22)	0.85	0.03 (−0.11, 0.16)	0.96
	Females	−0.02 (−0.22, 0.18)		0.09 (−0.11, 0.29)		0.02 (−0.18, 0.22)	
	Males	0.03 (−0.17, 0.22)		0.07 (−0.12, 0.27)		0.03 (−0.16, 0.21)	
MiBP[a]	Overall	0.04 (−0.12, 0.19)	0.63	0.09 (−0.07, 0.24)	0.26	0.04 (−0.11, 0.19)	0.94
	Females	−0.01 (−0.25, 0.23)		−0.04 (−0.28, 0.21)		−0.01 (−0.25, 0.24)	
	Males	0.07 (−0.14, 0.28)		0.16 (−0.05, 0.36)		0.05 (−0.15, 0.25)	

Phthalate Metabolite	Sex	CBCL: Externalizing Problems	p_{int}	CBCL: Internalizing Problems	p_{int}	CBCL: Total Problems	p_{int}
MEP[a]	Overall	0.09 (−0.03, 0.20)	0.64	0.05 (−0.06, 0.17)	0.64	0.09 (−0.02, 0.20)	0.98
	Females	0.07 (−0.10, 0.23)		0.04 (−0.14, 0.21)		0.09 (−0.08, 0.27)	
	Males	0.10 (−0.06, 0.26)		0.07 (−0.09, 0.22)		0.09 (−0.06, 0.24)	
MMP[a]	Overall	−0.05 (−0.17, 0.07)	0.06	−0.05 (−0.17, 0.07)	0.06	−0.05 (−0.17, 0.07)	0.03*
	Females	−0.16 (−0.32, 0.01)		−0.15 (−0.32, 0.02)		−0.19* (−0.36, −0.02)	
	Males	0.09 (−0.09, 0.26)		0.10 (−0.08, 0.27)		0.13 (−0.04, 0.30)	
ΣLMWP[b]	Overall	0.12 (−0.01, 0.24)	0.34	0.08 (−0.05, 0.20)	0.27	0.11 (−0.01, 0.23)	0.47
	Females	0.05 (−0.13, 0.24)		0.00 (−0.19, 0.20)		0.05 (−0.15, 0.24)	
	Males	0.16* (0.01, 0.32)		0.14 (−0.02, 0.30)		0.16* (0.01, 0.31)	

All models are adjusted for urinary creatinine, family income and Full-Scale Intelligence Quotient (FSIQ). Overall models are also adjusted for child sex.

* Raw *p*-value < 0.05.

** $q < 0.10$.

*** $q < 0.05$.

[a] µg/L.

[b] µmol/L.

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