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Prenatal and childhood phthalate exposure and attention deficit hyperactivity disorder traits in child temperament: A 12-year follow-up birth cohort study

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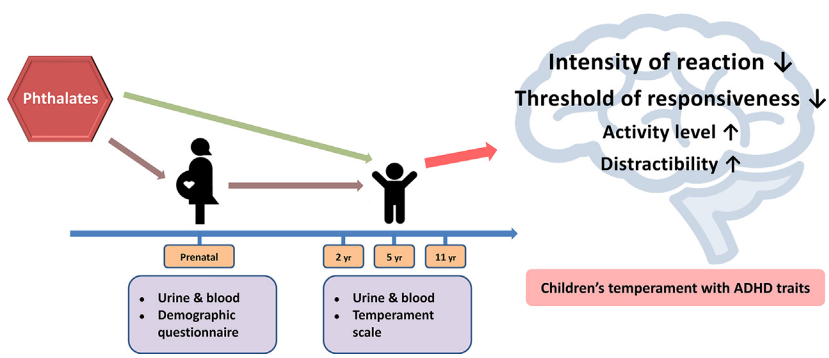
HIGHLIGHTS

- Phthalate metabolite concentrations are high in the 2- and 5-year-old children.
- Postnatal high exposure to PAEs is related to ADHD symptoms in children.
- Prenatal PAEs exposure associates with different aspects of temperament scores.

GRAPHICAL ABSTRACT



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ABSTRACT

Temperamental tendencies may form the basis of personality development, and specific personality constellations are associated with increased incidences of behavioural problems. Phthalic acid ester (PAE) has been associated with symptoms of attention deficit hyperactivity disorder (ADHD) in cross-sectional studies. We hypothesised that early-life exposure to PAE affects the temperaments of children, particularly ADHD traits. In this study, we analysed the temperament evaluations completed at least once by maternal–infant pairs ($n = 208$) when the child was aged 2, 5, and/or 11 years between 2000 and 2012.

Abbreviations: ADHD, attention deficit hyperactivity disorder; BBzP, butyl benzyl phthalate; BSQ-C, Behavior Style Questionnaire–Chinese version; CTTS, Chinese Toddler Temperament Scale; DBP, di-butyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEP, diethyl phthalate; DMP, dimethyl phthalate; EDCs, endocrine-disrupting chemicals; HOME, Home Observation for Measurement of the Environment; LOD, limit of detection; MBP, mono-butyl phthalate; MBzP, mono-benzyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate; MMP, mono-methyl phthalate; OR, odds ratio; PAE, phthalic acid ester; PVC, polyvinyl chloride; ΣMEHP, combined MEHP, MEHHP, and MEOHP concentrations.

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We measured seven PAE metabolites in the urine of the mothers during pregnancy and their children using liquid chromatography-electrospray ionisation-tandem mass spectrometry. These metabolites included mono-methyl phthalate, mono-ethyl phthalate, mono-butyl phthalate (MBP), mono-benzyl phthalate (MBzP), and three metabolites of di (2-ethylhexyl) phthalate. The phthalate metabolite levels in pregnant women were significantly associated with a decreased threshold of responsiveness (coefficients from −0.21 to −0.46) and increased distractibility (coefficients from 0.23 to 0.46) in pre-school children. After adjustment for maternal exposure, the phthalate metabolite concentrations of the children exhibited significantly increased odds ratios (ORs) with respect to the ADHD symptom traits. Specifically, mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), the sum of the DEHP metabolites, and MBzP yielded ORs and 95% confidence intervals of 2.98 (1.05–8.48), 3.28 (1.15–9.35), and 9.12 (1.07–78.06), respectively, for every $\log_{10}$ creatinine unit (g/g creatinine) increase. Thus, early-life phthalate exposure was found to be associated with the behavioural characteristics of children, particularly temperamental traits associated with ADHD.

1. Introduction

Phthalic esters, also known as phthalates, are endocrine-disrupting chemicals (EDCs) widely used as plasticisers in polyvinyl chloride (PVC), solvents in adhesives, and in various consumer products. The most commonly used phthalate is di(2-ethylhexyl) phthalate (DEHP), which is a component of many daily consumer products, including food containers, building materials, and toys (Dobrzynska, 2016). Urinary levels of butyl benzyl phthalate (BBzP) metabolites during infancy are associated with the use of PVC flooring in bedrooms (Carlstedt et al., 2013). Additionally, personal care products are likely predominant sources of diethyl phthalate (DEP) and di-butyl phthalate (DBP) and possible sources of dimethyl phthalate (DMP) (Koniecki et al., 2011).

Temperament is an aspect of the personality and behavioural style of an individual that is often regarded as innate rather than learned (Chess and Thomas, 1987). Genetic, biological (e.g., size with respect to gestational age), and environmental (e.g., parenting style, nutrition, and illness) factors contribute to temperamental variability (Lengua and Wachs, 2012; Muhtadie et al., 2013; Ponsonby et al., 2016; Saudino, 2005). Preliminary evidence has indicated that childhood temperament may be associated with various internalising and externalising disorders as well as cognitive outcomes (Frick, 2004; Zhou et al., 2008). The temperament of a child may be an early marker of later mental health problems and worthy of further investigation, particularly regarding the influences of environmental factors (Laceulle et al., 2014). In our previous study, maternal urinary mono-butyl phthalate (MBP) and the concentrations of two DEHP metabolites (i.e., mono-(2-ethylhexyl) phthalate [MEHP] and mono-2-ethyl-5-oxohexyl phthalate [MEOHP]) were positively associated with external behavioural problems at 8 years of age (Lien et al., 2015). However, the association between prenatal phthalate exposure and postnatal temperament is yet to be investigated.

Studies examining the associations between phthalates and temperament traits are scarce. Kim et al. (2009) and Won et al. (2016) found that 6–11-year-old children who had higher levels of DEHP and DBP in their urine exhibited symptoms of attention deficit hyperactivity disorder (ADHD). A recent case-control study also showed that maternal urinary concentrations of DEHP were monotonically associated with increased risk of ADHD (Engel et al., 2018). Philippat et al. (2015) found that higher indoor dust concentrations of DEP and DBP were associated with greater hyperactivity impulsivity and inattention in autism spectrum disorder or developmental delay in boys. Two cross-sectional studies suggested that urinary MBzP concentration in girls were significantly associated with emotional symptoms and that high molecular weight phthalates were marginally associated with increased odds of the co-occurrence of attention deficit disorder (ADD) and learning disabilities in children (Arbuckle et al., 2016; Chopra et al., 2014). Singer et al. have observed the association between prenatal phthalate exposures and child temperament at 12 and 24 months (Singer et al., 2017). However, very few long-term follow-up studies assess the associations between prenatal phthalate exposure and temperament traits in school-aged children.

In the present study, we examined the relationships between prenatal and postnatal phthalate exposure and ADHD temperament traits in a 12-year multiple follow-up study of a Taiwanese birth cohort for the first time. In addition, we assessed the interactions between both prenatal and postnatal exposure and temperament. We hypothesised that increased phthalate exposure in pregnant women and their children could be associated with maladaptive temperamental outcomes.

2. Methods

2.1. Subjects

This investigation was part of an on-going study of a birth cohort in central Taiwan that serves as a pilot for the larger-scale Taiwan Maternal and Infant Cohort Study. We recruited pregnant women between December 1, 2000 and November 30, 2001 to investigate prenatal and postnatal exposure to multiple environmental chemicals and related health outcomes in children (Fig. 1) (Wang et al., 2005). The pregnant women ($n = 610$) had no clinical complications (e.g., eclampsia or preeclampsia), were aged between 25 and 34 years, and delivered their babies in a medical centre. Among them, 430 completed a demographic questionnaire and follow-up visits with their children at the ages of 2, 5, and 11 years in 2003, 2006, and 2012, respectively. Urinary samples for phthalate analysis were collected from 391 pregnant women in their third trimester.

We performed detailed temperament evaluations of the children at 2, 5, and 11 years of age. At each follow-up visit, the primary caretakers completed a questionnaire, and a urine sample was obtained from the child. Fig. 1 depicts how the final sample was derived. A total of 391 mother-child pairs completed the maternal exposure evaluation and measurements of child temperament and potential confounders at least once during the three follow-up visits; some pairs provided data at multiple observation points. Informed and written consent was obtained from all participants after the study procedures were explained and before the commencement of the study.

2.2. Analysis of phthalate metabolites

Seven phthalate mono-ester metabolites, namely, MEHP, mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), MEOHP, mono-benzyl phthalate (MBzP), MBP, mono-ethyl phthalate, and

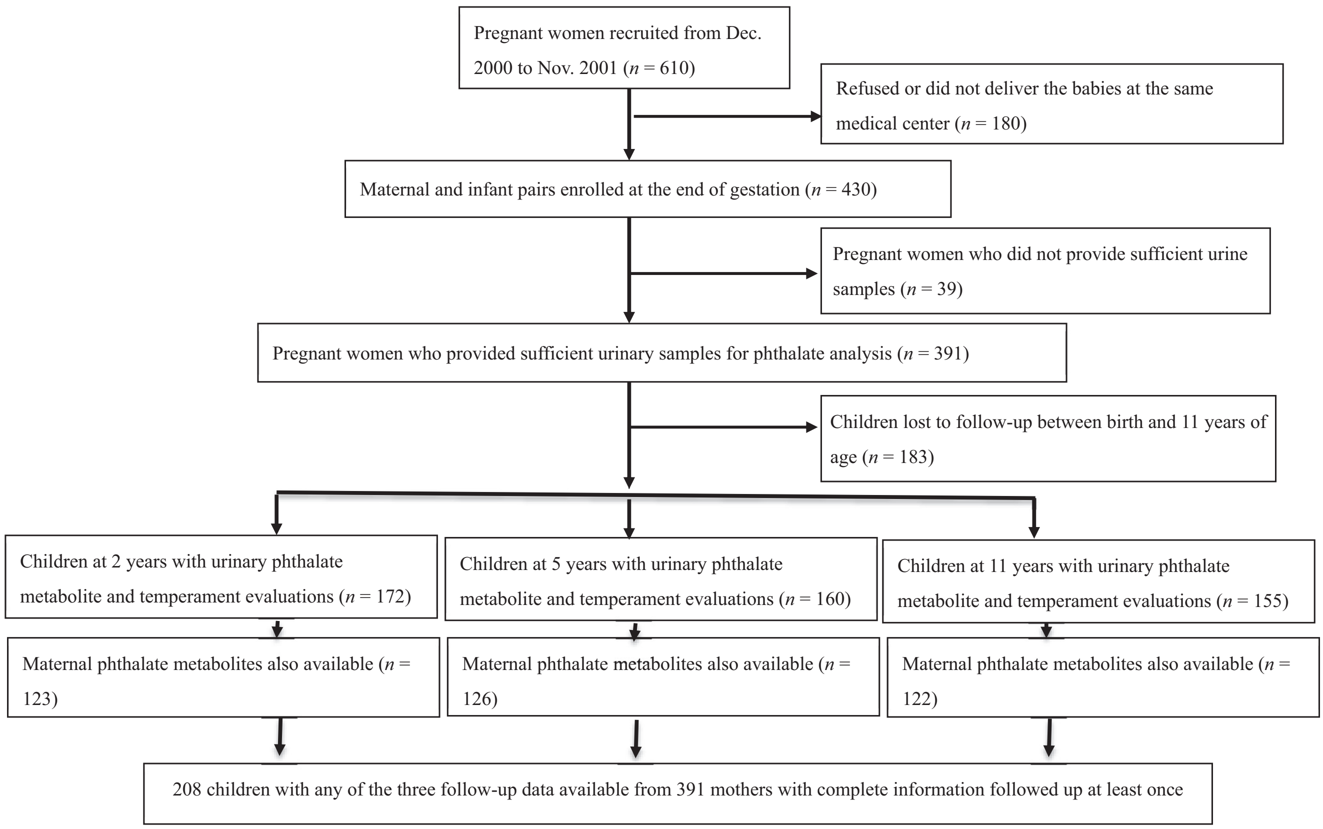

Fig. 1. Diagram of the follow-up study population from pregnancy to a child age of 11 years in central Taiwan.

mono-methyl phthalate (MMP), representing exposure to five commonly used phthalates (i.e., DEHP, BBzP, DBP, DEP, and DMP), were measured in the urine samples from both the mothers and children. The details of the analysis and quality control (QC) procedures for the samples collected from pregnant women can be found in our previous report (L.C. Lin et al., 2011; Huang et al., 2016). After a urine sample (100 μL) was thawed and sonicated for 10–15 min, it was loaded into a glass vial (2 mL). Briefly, the 100 μL urine sample was mixed with ammonium acetate (20 μL; 1 M, pH 6.5), β-glucuronidase enzyme (10 μL), and a mixture of isotopic ($^{13}C_4$) phthalate metabolite standards (100 μL). We incubated the urine sample mixtures at 37 °C for 1.5 h to ensure deconjugation and performed quantitative liquid chromatography-electrospray ionisation-tandem mass spectrometry to measure the urinary phthalate metabolites. Each batch of samples analysed included one blank, one repeat, and one QC sample. The concentration of the blank sample was required to be less than twice the detection limit of this method. The QC sample was spiked in each pooled urine sample with a mixture of phthalate metabolite standards (20–50 ng/mL). The percent difference between the repeat sample and recovered QC sample was required to be within ±30%. The detection limits of the metabolites were 0.7, 0.2, 0.2, 1, 2.5, 2.5, and 5 ng/mL for MEHP, MEHHP, MEOHP, MBzP, MBP, MEP, and MMP, respectively. Using the spectrophotometric method, we measured the urinary creatinine levels at Kaohsiung Medical University Chung-Ho Memorial Hospital. Finally, we performed creatinine adjustment to examine the associations between the urinary phthalate metabolite concentrations and temperament scores.

2.3. Analysis of blood lead levels

Venous blood was collected from the children at 2, 5, and 11 years of age using plastic and lead-free containers. The blood samples were analysed for whole blood lead levels at the Center of Toxic Substances and Drugs Residue Analysis, Kaohsiung Medical University Hospital. The analytic procedure for lead determination was published previously (Huang et al., 2012). The samples were analysed via Zeeman-effect graphite furnace atomic absorption spectrometry (Perkin-Elmer 5100 PC with AS 71 autosampler), with intralaboratory QCs.

2.4. Temperament assessment

The main caregivers of the children completed temperament questionnaires when the children were aged 2, 5, and 11 years and were asked to rate the behaviour of their children in the past month. The temperament questionnaire included nine temperament dimensions, namely, activity level, rhythmicity, withdrawal approach, adaptability, reaction intensity, mood quality, attention span/persistence, distractibility, and responsiveness threshold. The revised Chinese Toddler Temperament Scale (CTTS) was used in the present study to assess the temperament of the children at 2 years of age on a six-point Likert scale (ranging from never to always) for each item. This 97-item parent-report CTTS was developed to determine the temperamental characteristics of 1–3-year-old children (Tsou et al., 1987). The CTTS was standardised to 308 toddlers with acceptable internal consistency (Cronbach's α = 0.55–0.82) (Tsou et al., 1987). For the children at 5 years of age, we used the Behavior Style Questionnaire–Chinese version (BSQ-C) for temperament assessment (Chen, 1981). The main caregivers rated the children on each item using a scale from one (never) to seven (always). The BSQ-C coefficients of the 2-week test–retest reliability ranged from 0.38 to 0.73 (Chen, 1981). For the 11-year-old children, we used the Middle Childhood Temperament Questionnaire–Chinese version consisting of 99 items with a five-point rating scale for behavioural assessment. The internal consistency and retest reliability were satisfactory (Cronbach's $\alpha = 0.69–0.80$) (Wang, 2004).

2.5. Covariate measurements

Potential confounders were selected based on directed acyclic graphs (http://www.dagitty.net/). When a DAG contained all relevant variables, their causal relationships were determined using marginally significant results ($p < 0.10$) and evidence from the literature, e.g., for maternal depression, for which there was a borderline significant difference (t-test $p = 0.098$) between boys and girls in our own study. The variables selected for adjustment were the sex, intelligence, and blood lead concentration of the child, as well as parental education, parity, parenting style, gestational age, maternal depression, Apgar scores at 1 min, maternal cigarette smoking, and environmental tobacco smoke. The minimal adjustment set for the total effect of phthalates on temperament included sex, parity, and parenting style (Fig. S1).

We collected information on parental education and parity from the pregnant women using self-report questionnaires. The parenting style was determined using the Home Observation for Measurement of the Environment (HOME) inventory at the three time points (Caldwell and Bradley, 1984). We assessed the dimensions of emotional and verbal responsiveness of the primary caregivers, avoidance of restriction and punishment, and parental involvement with the child using the Infant/Toddler Home Observation for Measurement of the Environment inventory–Chinese Version for each child at 2 years of age. For the children between 5 and 11 years of age, we scored language stimulation, responsiveness, and modelling, as well as the acceptance dimension subscales in a binary manner (yes/no) using the Early Childhood HOME–Chinese Version and Early Adolescence HOME–Chinese Version, respectively.

2.6. Statistical analyses

The differences between the pregnant women lost to follow-up ($n = 183$) and those included in the analysis ($n = 208$) were estimated using independent t-tests for the continuous variables and chi-square tests for the categorical variables. When the phthalate metabolite levels were below the limit of detection (LOD), we employed the conventional approach by replacing the values with 50% of the LOD values. To analyse the phthalate metabolite concentrations, the measurements were log-transformed because their distributions were right-skewed. We assessed the relationships between the temperament scores and the prenatal and postnatal urinary phthalate metabolite concentrations using linear regression for the current investigation of the three follow-ups at 2, 5, and 11 years of age.

ADHD is strongly associated with the temperament dimensions of distractibility, activity level, and persistence (McIntosh and Cole-Love, 1996). Foley et al. (2008) also demonstrated that low thresholds of responsiveness as well as impulsivity are strongly associated with ADHD in children. Therefore, we divided the children into two groups: a higher ADHD symptom score group and a reference group. One model makes use of a classification where children in the ADHD group have ADHD temperament traits above the median cut-off for high activity level, distractibility, and low persistence scores, with no requirement for threshold of responsiveness, whereas in the second model also the latter needs to be above the median. The children who scored below the median cut-off in all four categories formed the reference group. The adjusted odds ratios (ORs) for ADHD symptoms were calculated using the logistic model adjusted for sex, parity, parenting style, and maternal concentrations of urinary phthalate metabolites.

Finally, to examine the effects of a combination of prenatal and postnatal phthalate exposure, we divided the metabolite levels into low (equal to or below the median) and high (above the median) exposure groups. We categorised the children into four groups according to the following combinations: (1) low prenatal–low postnatal; (2) high prenatal–low postnatal; (3) low prenatal–high postnatal; and (4) high prenatal–high postnatal levels. The p-values utilised to compare the low–low levels of both the prenatal and postnatal phthalates were calculated using logistic regression at three ages separately. We used SPSS 22.0 software (Chicago, IL, USA) for all statistical analyses.

3. Results

The demographic characteristics of the pregnant women and children we followed ($n = 208$), as well as those lost to follow-up

Table 1
Demographic information and urinary phthalate metabolite concentrations (μg/g creatinine) in pregnant women by follow-up status.

Variable	Pregnant women lost to follow-up ($n = 183$)	Pregnant women who were followed ($n = 208$)	p-Value[a]
Mean age (±SD) at delivery (years)	28.38 ± 4.45	29.09 ± 4.09	0.11
Age at delivery			0.66
≤34 years	166 (91.2)	187 (89.9)	
>34 years	16 (8.8)	21 (10.1)	
Maternal education			<0.001[**]
≤High school	20 (11.2)	5 (2.5)	
Junior college	81 (45.3)	74 (36.5)	
≥University	78 (43.5)	124 (61.0)	
Paternal education			0.05[*]
≤High school	21 (12.2)	13 (6.7)	
Junior college	70 (40.7)	67 (34.7)	
≥University	81 (47.1)	113 (58.5)	
Family income per year			0.23
≤$20,000	83 (46.9)	81 (39.3)	
$20,000–50,000	89 (50.3)	121 (58.7)	
>$50,000	5 (2.8)	4 (1.9)	
Smoking during pregnancy			0.10
Yes	5 (2.7)	1 (0.5)	
No	177 (97.3)	207 (99.5)	
Environ. tobacco smoke			0.61
Yes	106 (57.9)	114 (55.3)	
No	77 (42.1)	92 (44.7)	
Child parity (no.)			0.37
1	105 (57.4)	110 (52.9)	
≥2	78 (42.6)	98 (47.1)	
Child sex (% boys)	12 (41.4)	104 (50.0)	0.43
Parenting style score	–	17.80 ± 3.08	
MEHP[b]	18.22 (16.47–21.42)	19.20 (16.69–22.09)	0.72
MEHHP[b]	6.05 (5.96–7.86)	8.24 (6.39–10.62)	0.34
MEOHP[b]	9.41 (7.42–11.91)	12.41 (9.79–15.73)	0.27
MBzP[b]	18.04 (16.33–19.93)	17.09 (15.19–19.22)	0.84
MBP[b]	70.29 (60.55–78.56)	75.74 (65.96–86.97)	0.63
MEP[b]	64.21 (56.65–72.79)	63.58 (56.17–71.97)	0.96
MMP[b]	56.70 (49.81–64.53)	52.34 (44.82–61.13)	0.46
Maternal B-Pb (μg/dL)	2.40 (2.16–2.67)	2.24 (2.04–2.45)	0.14

[a] p-Values for difference between pregnant women with and without children followed using t-test for continuous variables and χ^2 test for categorical variables.
[b] Data presented as GM with 95% CI.
[**] $p < 0.001$.
[*] $p < 0.05$.

($n = 183$), are shown in Table 1. The parents whose children were successfully followed up had significantly higher education levels (p-value < 0.001); all other demographic characteristics and phthalate levels were similar between the participants and those lost to follow-up.

The urinary phthalate metabolite levels in the children at ages 2, 5, and 11 years are shown as creatinine-adjusted values (Table S1). Generally, the phthalate metabolite concentrations were found to be higher in the 2- and 5-year-old children than in the 11-year-old children. Meanwhile, the children aged 2 and 5 years appeared to have higher blood lead concentrations (geometric mean (GM) = 2.50 μg/dL and 2.63 μg/dL, respectively). The urinary metabolites MBP, MBzP, and MEOHP in the 2-year-old children in our study were higher than those in another birth cohort in northern Taiwan in 2013, after the 2011 Taiwan DEHP food contamination event (Hung and Wang, 2017). The original temperament scores in the children at ages 2, 5, and 11 years are shown in Table S2. Similar patterns are evident for both sexes.

Table 2 presents the associations between the maternal urinary phthalate metabolite concentrations and temperament scores of the 2-, 5-, and 11-year-old children for each of the three time points for both sexes combined. The results reveal significant neg-

Table 2
Regression coefficients (standard error (SE)) for temperament scores in relation to maternal urinary phthalate metabolite concentrations (μg/g creatinine).[a]

Phthalate metabolite	Activity level	Rhythmicity	Withdrawal	Adaptability	Intensity of reaction	Positive mood	Persistence	Distractibility	Threshold of responsiveness
Children at 2 years (n = 123)									
MEHP	0.16 (0.11)	−0.05 (0.13)	0.25 (0.15)[#]	0.14 (0.12)	−0.25 (0.11)[*]	−0.13 (0.12)	0.17 (0.12)	0.26 (0.12)[*]	−0.20 (0.12)[#]
MEHHP	−0.02 (0.07)	0.004 (0.08)	0.20 (0.09)[*]	0.01 (0.08)	−0.05 (0.07)	0.09 (0.08)	0.01 (0.08)	−0.09 (0.08)	−0.61 (0.08)
MEOHP	0.05 (0.07)	−0.04 (0.08)	0.16 (0.09)[#]	0.04 (0.08)	−0.01 (0.07)	−0.03 (0.08)	0.06 (0.08)	−0.01 (0.08)	−0.14 (0.08)[#]
ΣMEHP	0.14 (0.13)	−0.14 (0.14)	0.32 (0.16)[#]	0.09 (0.13)	−0.21 (0.12)[#]	−0.06 (0.13)	0.16 (0.13)	0.23 (0.13)[#]	−0.29 (0.13)[*]
MBzP	−0.03 (0.14)	−0.19 (0.16)	0.13 (0.18)	0.05 (0.15)	−0.27 (0.13)[*]	−0.04 (0.14)	0.08 (0.15)	0.46 (0.14)[**]	−0.18 (0.15)
MBP	−0.03 (0.11)	−0.10 (0.12)	0.32 (0.14)[*]	−0.004 (0.12)	−0.15 (0.10)	−0.16 (0.11)	0.06 (0.12)	0.23 (0.12)[*]	−0.23 (0.11)[*]
MEP	−0.13 (0.13)	0.06 (0.14)	0.30 (0.16)[#]	0.05 (0.13)	−0.36 (0.11)[**]	−0.03 (0.13)	0.02 (0.13)	0.33 (0.13)[*]	−0.14 (0.13)
MMP	0.06 (0.10)	−0.08 (0.11)	0.18 (0.13)	−0.04 (0.11)	−0.17 (0.09)[#]	−0.02 (0.10)	0.001 (0.11)	0.28 (0.10)[**]	−0.12 (0.10)
Children at 5 years (n = 126)									
MEHP	−0.01 (0.16)	0.16 (0.16)	−0.15 (0.18)	−0.03 (0.15)	−0.04 (0.16)	−0.09 (0.12)	0.13 (0.11)	−0.05 (0.12)	−0.26 (0.14)[#]
MEHHP	0.01 (0.08)	0.005 (0.08)	−0.21 (0.09)[*]	0.07 (0.07)	−0.12 (0.08)	−0.04 (0.06)	−0.04 (0.05)	0.04 (0.06)	−0.07 (0.07)
MEOHP	−0.08 (0.09)	−0.09 (0.09)	−0.16 (0.10)[#]	0.11 (0.08)	−0.14 (0.09)	−0.07 (0.07)	−0.04 (0.06)	0.06 (0.07)	−0.21 (0.08)[**]
ΣMEHP	−0.06 (0.15)	−0.01 (0.15)	−0.24 (0.16)	0.05 (0.13)	−0.11 (0.14)	−0.12 (0.11)	0.06 (0.10)	−0.01 (0.11)	−0.30 (0.12)[*]
MBzP	0.12 (0.22)	0.08 (0.22)	−0.32 (0.24)	−0.24 (0.20)	0.10 (0.22)	−0.06 (0.16)	0.17 (0.14)	−0.23 (0.16)	−0.46 (0.18)[*]
MBP	−0.09 (0.16)	0.09 (0.16)	−0.21 (0.17)	0.04 (0.14)	−0.05 (0.15)	−0.12 (0.12)	0.01 (0.10)	0.001 (0.12)	−0.19 (0.14)
MEP	−0.12 (0.16)	0.35 (0.17)[*]	−0.07 (0.19)	−0.12 (0.15)	−0.18 (0.16)	−0.07 (0.12)	0.11 (0.11)	−0.06 (0.13)	0.15 (0.14)
MMP	0.07 (0.14)	−0.11 (0.14)	−0.12 (0.15)	−0.12 (0.13)	−0.35 (0.14)[*]	0.03 (0.11)	−0.02 (0.09)	0.11 (0.11)	−0.20 (0.12)
Children at 11 years (n = 122)									
MEHP	0.31 (0.16)[#]	0.04 (0.12)	0.14 (0.16)	−0.16 (0.10)	0.12 (0.15)	−0.20 (0.13)	0.08 (0.13)	0.01 (0.15)	0.15 (0.12)
MEHHP	0.02 (0.08)	0.06 (0.06)	0.01 (0.08)	−0.04 (0.05)	0.02 (0.07)	−0.02 (0.06)	0.07 (0.07)	0.03 (0.08)	0.02 (0.06)
MEOHP	−0.004 (0.09)	0.05 (0.07)	0.06 (0.09)	−0.06 (0.06)	−0.05 (0.09)	−0.02 (0.07)	0.08 (0.08)	0.02 (0.09)	0.03 (0.07)
ΣMEHP	0.16 (0.15)	0.06 (0.11)	0.06 (0.15)	−0.13 (0.09)	−0.01 (0.14)	−0.14 (0.11)	0.09 (0.12)	−0.04 (0.14)	0.14 (0.11)
MBzP	−0.01 (0.18)	0.08 (0.13)	0.39 (0.18)[*]	−0.04 (0.12)	0.01 (0.17)	−0.02 (0.14)	0.13 (0.15)	0.03 (0.17)	0.21 (0.14)
MBP	−0.01 (0.16)	−0.04 (0.12)	0.19 (0.16)	−0.04 (0.10)	−0.08 (0.15)	−0.27 (0.12)[*]	0.10 (0.13)	0.00 (0.15)	0.20 (0.12)[#]
MEP	−0.08 (0.18)	0.18 (0.13)	0.19 (0.17)	−0.03 (0.11)	−0.13 (0.16)	0.03 (0.14)	0.18 (0.14)	−0.04 (0.16)	0.16 (0.13)
MMP	−0.06 (0.14)	0.07 (0.10)	0.31 (0.13)[*]	0.02 (0.09)	−0.13 (0.13)	0.19 (0.11)[#]	0.21 (0.11)[#]	0.17 (0.13)	−0.09 (0.10)

ΣMEHP = MEHP + MEHHP + MEOHP.
[a] Adjusted for gender, parental education, parity, parenting style, and urinary phthalate metabolite concentrations of children at 2, 5, and 11 years. Regression coefficient: β for $\log_{10}$-unit increase in phthalate metabolites.
[#] $p < 0.10$.
[*] $p < 0.05$.
[**] $p < 0.01$.

ative associations between some of the maternal phthalate metabolite concentrations and the reaction intensities and responsiveness threshold scores of the 2- and 5-year-old, after adjusting for parity, parental education, parenting style, and the urinary phthalate metabolite concentrations of the children. Table S3 also reveals negative associations between some of the maternal phthalate metabolite concentrations and the reaction intensities, withdrawal and attention in the children, particularly the 2-year-old boys. Table 3 shows the associations between the phthalate metabolite levels of the children and their temperament scores according to the linear regression at three time points. After adjusting for the maternal phthalate metabolite concentrations, parity, and parenting style, we found a few associations between phthalate metabolite levels and some of the aspects of temperament.

The number of children classified as having "ADHD traits" at ages 2, 5, and 11 years was 22, 21, and 19 children, respectively (Fig. S2). The statistical models revealed that higher phthalate metabolite concentrations in children were associated with higher ORs with respect to symptoms associated with ADHD in child temperament at three different ages (Table 4). The ADHD symptoms in model 1 were defined as the activity level, distractibility, and low persistence scores of the children all being above the median scores of these three categories. In model 2, the criterion that the low threshold of responsiveness score must also be above the median was added. In children at 2 years of age, only MBzP exhibited increased ORs with respect to the ADHD symptom traits (ORs = 9.12; 95% CIs: 1.07–78.06 in model 1), after adjusting for parity, parenting style, and maternal urinary phthalate metabolite

Table 3
Regression coefficients (SE) of urinary phthalate metabolite concentrations of children with temperament score in 2-, 5-, and 11-year-old children obtained.[a]

Phthalate metabolite	Activity level	Rhythmicity	Withdrawal	Adaptability	Intensity of reaction	Positive mood	Persistence	Distractibility	Threshold of responsiveness
Children at 2 years (n = 123)									
MEHP	−0.03 (0.13)	−0.05 (0.14)	−0.09 (0.16)	0.24 (0.13)[#]	0.001 (0.12)	0.02 (0.13)	−0.06 (0.14)	0.06 (0.13)	−0.04 (0.13)
MEHHP	−0.01 (0.13)	−0.07 (0.15)	−0.22 (0.16)	0.04 (0.14)	0.02 (0.12)	0.05 (0.13)	−0.23 (0.14)[#]	0.10 (0.14)	0.07 (0.14)
MEOHP	0.01 (0.12)	−0.09 (0.14)	−0.13 (0.15)	0.03 (0.13)	0.10 (0.11)	−0.07 (0.12)	−0.16 (0.13)	−0.01 (0.13)	0.08 (0.13)
ΣMEHP	0.02 (0.14)	−0.05 (0.16)	−0.18 (0.18)	0.07 (0.15)	0.06 (0.13)	0.06 (0.14)	−0.25 (0.15)[#]	0.09 (0.15)	−0.08 (0.14)
MBzP	0.16 (0.10)[#]	−0.14 (0.11)	0.01 (0.12)	−0.04 (0.10)	−0.04 (0.09)	0.02 (0.10)	−0.15 (0.10)	−0.06 (0.10)	0.03 (0.10)
MBP	0.20 (0.14)	−0.07 (0.16)	−0.07 (0.17)	−0.02 (0.15)	−0.20 (0.13)	−0.12 (0.14)	−0.15 (0.15)	−0.03 (0.14)	0.04 (0.14)
MEP	−0.003 (0.10)	−0.30 (0.11)[**]	−0.16 (0.12)	−0.15 (0.10)	0.10 (0.09)	−0.07 (0.10)	−0.14 (0.10)	0.01 (0.10)	0.11 (0.10)
MMP	0.22 (0.12)[#]	−0.02 (0.13)	0.09 (0.15)	0.004 (0.13)	−0.12 (0.11)	0.02 (0.12)	0.003 (0.13)	0.10 (0.12)	0.04 (0.12)
Children at 5 years (n = 126)									
MEHP	0.12 (0.15)	0.15 (0.15)	−0.23 (0.16)	−0.03 (0.13)	−0.04 (0.15)	−0.20 (0.11)[#]	−0.001 (0.10)	0.01 (0.11)	−0.11 (0.13)
MEHHP	−0.05 (0.16)	−0.01 (0.16)	−0.24 (0.17)	0.09 (0.14)	0.002 (0.15)	−0.02 (0.12)	−0.01 (0.10)	0.10 (0.12)	−0.08 (0.14)
MEOHP	0.11 (0.18)	0.05 (0.18)	−0.21 (0.20)[*]	0.25 (0.16)	0.07 (0.18)	−0.03 (0.14)	−0.01 (0.12)	0.21 (0.14)	−0.09 (0.16)
ΣMEHP	0.01 (0.18)	0.07 (0.18)	−0.35 (0.20)[#]	0.15 (0.16)	−0.01 (0.18)	−0.02 (0.14)	−0.01 (0.12)	0.14 (0.14)	−0.11 (0.15)
MBzP	−0.07 (0.19)	0.13 (0.19)	−0.45 (0.21)[*]	0.20 (0.17)	−0.03 (0.19)	0.03 (0.14)	0.02 (0.12)	0.16 (0.14)	−0.21 (0.16)
MBP	−0.25 (0.17)	0.03 (0.17)	−0.14 (0.19)	0.08 (0.16)	−0.07 (0.17)	0.21 (0.13)[#]	−0.06 (0.11)	0.04 (0.13)	0.26 (0.15)
MEP	0.44 (0.14)[**]	−0.06 (0.15)	−0.20 (0.17)	0.24 (0.13)[#]	−0.26 (0.14)[#]	0.17 (0.11)	−0.04 (0.10)	0.16 (0.11)	0.13 (0.13)
MMP	−0.03 (0.14)	−0.04 (0.14)	−0.18 (0.16)	0.17 (0.13)	−0.14 (0.14)	0.17 (0.11)	−0.11 (0.09)	−0.03 (0.11)	−0.12 (0.12)
Children at 11 years (n = 122)									
MEHP	−0.07 (0.15)	−0.01 (0.11)	−0.11 (0.15)	0.11 (0.10)	−0.29 (0.14)[*]	0.02 (0.12)	0.17 (0.12)	0.18 (0.14)	−0.13 (0.11)
MEHHP	0.20 (0.24)	0.11 (0.17)	−0.01 (0.23)	0.24 (0.15)	−0.43 (0.22)[*]	0.26 (0.18)	0.05 (0.19)	0.25 (0.22)	−0.11 (0.18)
MEOHP	−0.14 (0.14)	0.15 (0.10)	0.13 (0.14)	0.19 (0.09)[*]	−0.10 (0.13)	0.11 (0.11)	0.00 (0.12)	0.10 (0.13)	−0.02 (0.11)
ΣMEHP	0.10 (0.24)	0.13 (0.17)	0.03 (0.23)	0.23 (0.15)	−0.41 (0.21)[#]	0.19 (0.18)	0.09 (0.19)	0.27 (0.22)	−0.11 (0.18)
MBzP	0.22 (0.13)[#]	−0.16 (0.09)[#]	0.10 (0.13)	−0.06 (0.08)	−0.12 (0.12)	−0.21 (0.10)[*]	−0.12 (0.11)	−0.11 (0.12)	0.01 (0.10)
MBP	−0.20 (0.24)	0.20 (0.18)	0.20 (0.24)	0.32 (0.15)[*]	−0.04 (0.22)	0.19 (0.19)	0.21 (0.19)	0.12 (0.22)	−0.15 (0.18)
MEP	0.05 (0.08)	−0.01 (0.06)	−0.02 (0.08)	0.09 (0.05)[#]	0.01 (0.07)	0.03 (0.06)	−0.01 (0.06)	0.04 (0.07)	−0.03 (0.06)
MMP	0.18 (0.11)[#]	0.03 (0.08)	0.13 (0.11)	0.03 (0.07)	−0.10 (0.10)	−0.01 (0.09)	0.01 (0.09)	−0.09 (0.10)	0.13 (0.08)

[a] Adjusted for gener, parity, parenting style, and maternal urinary phthalate metabolite concentrations. *n*: number of observations. ΣMEHP = MEHP + MEHHP + MEOHP.
[#] $p < 0.10$.
[*] $p < 0.05$.
[**] $p < 0.001$.

Table 4
ORs (95% CIs) for temperament of children with ADHD traits compared to children without ADHD traits for increase in creatinine-corrected urinary phthalate metabolite concentrations of children obtained using logistic regression.[a]

Model/metabolite	Model 1[b]	Model 2[c]
Children at 2 years	(n = 123, ADHD n = 22)	(n = 123, ADHD n = 15)
MEHP	3.73 (0.73, 19.13)	1.76 (0.59, 5.28)
MEHHP	1.08 (0.26, 4.38)	1.26 (0.42, 3.72)
MEOHP	1.16 (0.29, 4.66)	1.70 (0.57, 5.09)
ΣMEHP	1.15 (0.29, 4.65)	1.29 (0.44, 3.81)
MBzP	9.12 (1.07, 78.06)*	2.38 (0.75, 7.56)
MBP	0.85 (0.21, 3.40)	1.43 (0.48, 4.19)
MEP	1.10 (0.27, 4.48)	0.70 (0.23, 2.08)
MMP	1.57 (0.38, 6.41)	2.08 (0.68, 6.37)
Children at 5 years	(n = 126, ADHD n = 21)	(n = 126, ADHD n = 14)
MEHP	0.96 (0.20, 4.70)	0.71 (0.09, 5.37)
MEHHP	2.24 (0.40, 12.55)	2.61 (0.26, 26.62)
MEOHP	2.79 (0.50, 15.62)	3.21 (0.32, 32.74)
ΣMEHP	2.24 (0.40, 12.56)	2.61 (0.26, 26.62)
MBzP	2.16 (0.44, 10.62)	1.52 (0.20, 11.58)
MBP	0.54 (0.11, 2.64)	0.76 (0.10, 5.76)
MEP	0.90 (0.18, 4.41)	3.96 (0.39, 40.38)
MMP	1.49 (0.30, 7.28)	3.44 (0.34, 35.09)
Children at 11 years	(n = 122, ADHD n = 19)	(n = 122, ADHD n = 13)
MEHP	1.92 (0.71, 5.19)	1.57 (0.45, 5.47)
MEHHP	2.98 (1.05, 8.48)*	2.20 (0..61, 7.98)
MEOHP	1.79 (0.66, 4.84)	1.47 (0.42, 5.11)
ΣMEHP	3.28 (1.15, 9.35)*	2.38 (0.66, 8.61)
MBzP	1.51 (0.55, 4.16)	1.52 (0.14, 5.93)
MBP	0.38 (0.13, 1.09)	0.77 (0.22, 2.69)
MEP	1.72 (0.63, 4.75)	2.65 (0.67, 10.57)
MMP	0.47 (0.17, 1.30)	0.31 (0.08, 1.22)

The logistic regression models estimate ORs comparing exposure among those classified as exhibiting ADHD symptom dimensions to the others. ΣMEHP = MEHP + MEHHP + MEOHP.

[a] Adjusted for sex, parity, parenting style, and maternal urinary phthalate metabolite concentrations.

[b] Definition of ADHD symptom dimensions: child activity level, distractibility, and low persistence scores are all above the median.

[c] Definition of ADHD symptom dimensions: child activity levels, distractibility, low persistence, and low threshold of responsiveness scores are all above the median.

* $p < 0.05$.

concentrations in the two models. In children at 11 years of age, MEHHP (ORs = 2.98; 95% CIs: 1.05–8.48) and ΣMEHP (ORs = 3.28; 95% CIs: 1.15–9.35) exhibited increased ORs with respect to the ADHD symptom traits in model 1. Other urinary phthalate metabolites were observed to be positively associated with ADHD traits, but the association was not statistically significant. In model 2, similar results were observed but revealed no statistical significance. Fig. 2 shows that there may be an interactive effect of temperament from prenatal and postnatal (at 2, 5 and 11 years of age) phthalate exposure to ΣMEHP (ΣMEHP = MEHP + MEHHP + MEOHP) and MBzP. However, possibly to due to the limited sample size and statistical power, there were no significant interactive effects of pre-and postnatal phthalate exposure on the threshold of responsiveness at the three time points.

4. Discussion

To our knowledge, this is the first study to assess the effects of both prenatal and postnatal phthalate exposure on the risk of ADHD behaviours using temperament dimensions in children, even after adjusting for other environmental disruptors. Maternal phthalate metabolite levels were generally positively associated with withdrawal, low intensity of reaction, distractibility, and a low threshold of responsiveness in children at 2 years of age, while some phthalate mono-esters showed similar but non-significant tendencies at three time points. Difficult temperament, such as high activity level, irregular biological rhythm, low persistence, and low threshold of responsiveness, has been shown to predict the predisposition of a child to ADHD behaviours (Armstrong, 1999; Bates, 1980; Guerin et al., 1997). In our study, the urine BBzP metabolite concentrations of the children were associated with higher ORs with respect to the ADHD temperament dimensions compared with children at 2 years who had scores below the medians of the ADHD temperament dimensions. Our study also provides evidence of significant associations between ∑MEHP metabolite and MBzP exposure and ADHD behaviours in both sexes combined. Our results suggest that early-life phthalate exposure may affect the behavioural development of children. These results are consistent with those of previous studies of children in which the risk of ADHD symptoms was significantly associated with urinary DEHP, DBP, and/or BBzP metabolite concentrations in both sexes (Arbuckle et al., 2016; Chopra et al., 2014; Kim et al., 2009). A recent study by Kim et al. (2018) revealed that MEP is mainly associated with behavioural problems in girls. Additionally, Kobrosly et al. (2014) found that higher prenatal urine concentrations of MBzP were associated with higher scores for oppositional/defiant problems and conduct problems in boys, while Arbuckle et al. (2016) found that urinary MBzP was associated with emotional symptoms in girls but not boys.

In the current study, the maternal phthalate metabolite levels were associated with reaction intensity and low threshold of responsiveness, particularly in the preschool-aged. However, the associations were lesser in the 11-year-old children than in the 2- and 5-year-old children. In addition, the MBzP concentrations of the children were positively associated with high activity levels, withdrawal, and a low threshold of responsiveness in the 2- and 11-years-old children after adjusting for the maternal phthalate metabolite concentrations. However, high withdrawal in children suggests that the first response of a child to a new stimulus is withdrawal, which may cause learning disabilities and be associated with internalising disorders (Dougherty et al., 2011; Eisenberg et al., 2000).

We found the urine BBzP metabolite concentrations at 2 years of age were associated with the ADHD temperament dimensions, and DEHP exposure were significantly associated with ADHD behaviours in children aged 11 years old. More research is needed to confirm the adverse effects of phthalates on temperament and to clarify the mechanisms that produce differential effects between the sexes. There is limited knowledge of the mechanism through which phthalate exposure in early life adversely affects temperament development. A recent study showed that MBzP was associated with higher odds of The Strengths and Difficulties Questionnaire (SDQ) emotional symptoms in girls (Arbuckle et al., 2016). DEHP and its metabolites may impair foetal brain development through peroxisome proliferator-activated receptor gamma, which suppresses neuronal cell proliferation and differentiation, leading to apoptosis (Chen et al., 2011; C.H. Lin et al., 2011). In addition, the dopamine D4 receptor gene (DRD4), one of the candidate genes of ADHD, appears to play multiple roles in temperament behaviours (Schmidt et al., 2009; Wang et al., 2016). Park et al. reported that DRD4 moderated the relationship between phthalate metabolite levels and neuropsychological performance in a case-controlled study (Park et al., 2014). Further research is needed to investigate the relationship between gene–environment interactions and temperament in children.

The primary strength of this study is the long-term follow-up that allowed us to relate prenatal and postnatal phthalate exposure to repeated measurements of temperament traits in pre-school- and school-aged children at three time points. Additionally, when we further adjusted for prenatal and postnatal exposure, the results showed similar tendencies and yielded similar conclusions regarding these associations (data not shown).

The limitations of our study include the fact that phthalate mono-esters have a short biologic half-life and that spot urine sam-

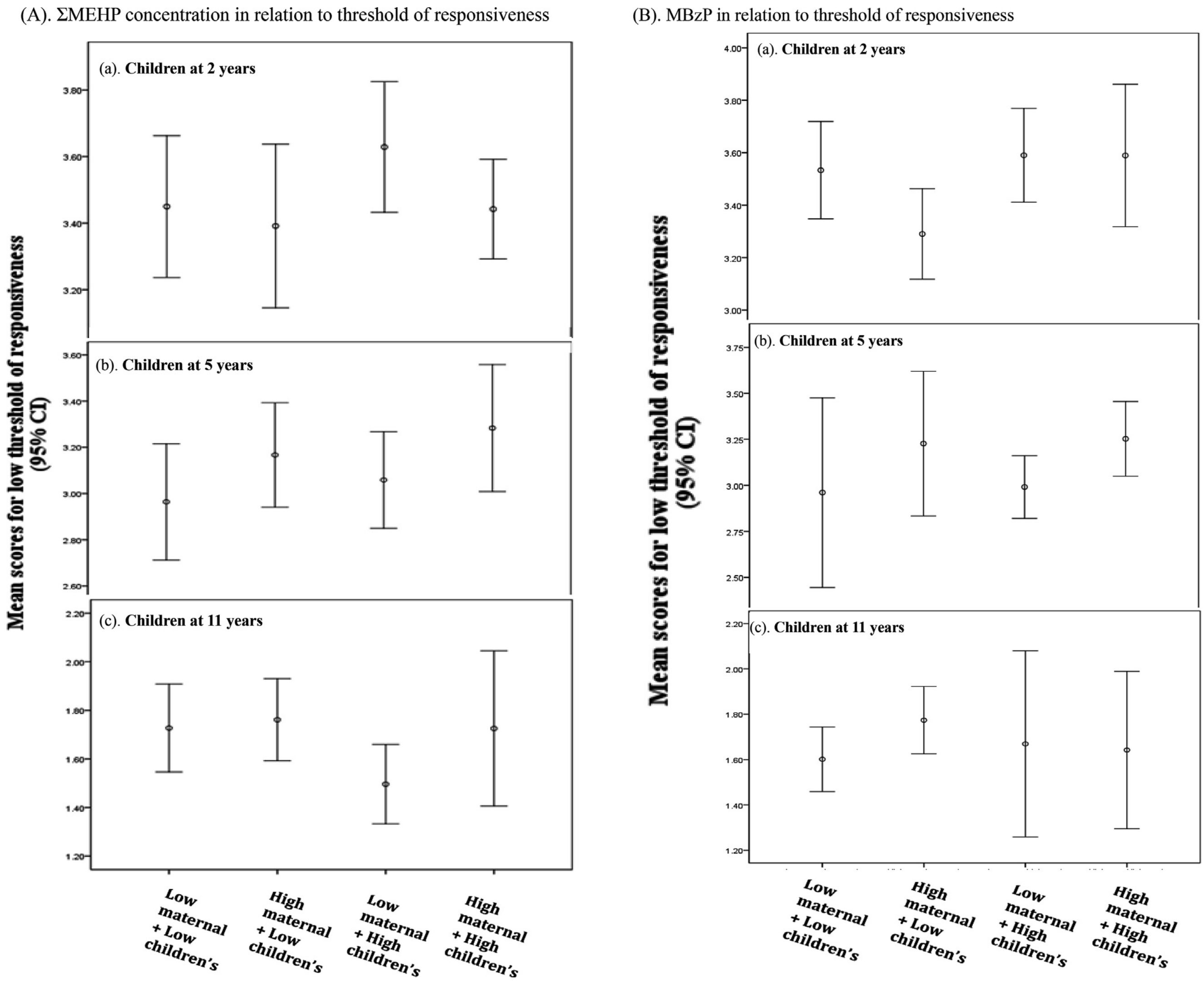

Fig. 2. Mean (95% CI) for the association between pre- and postnatal phthalate exposure and temperament scores.

ples in the third trimester may not reflect long-term exposure levels. The urinary metabolites MBP, MBzP, and MEOHP in the 2-year-old children in our study were higher than those in another birth cohort in northern Taiwan in 2013, after the 2011 Taiwan DEHP food contamination event (Hung and Wang, 2017). However, if the exposure patterns are unchanged in pregnant women, it can be assumed that a single urinary phthalate concentration reflects a typical measurement at any time during pregnancy. Additionally, on-going cell development processes, such as myelination and synaptogenesis, are particularly sensitive to thyroid hormone status during the latter half of pregnancy (Bernal, 2005). According to a previous study, it is necessary for the urinary concentrations of chemicals to be adjusted by all factors that affect urinary creatinine concentrations, i.e., age, gender, race/ethnicity, BMI, and impaired kidney function (Jain, 2016). The participants in our study had normal ranges of urinary creatinine concentrations, and the effects of phthalates and temperament were similar when unadjusted and creatinine-adjusted urinary concentrations were employed (data not shown). Finally, some variables known to affect temperament development in children were not included in the study, such as exposure to persistent organic pollutants and heavy metals and a history of psychiatric disorder in the parents. Kim et al. (2018) obtained evidence that prenatal exposure to PCBs and DEHP is associated with adverse neurodevelopmental performance among children aged 1–2 years. Given the impacts of these potential confounders on the development of child temperament, our findings should be interpreted cautiously.

5. Conclusions

Early-life phthalate exposure was found to be associated with the behavioural characteristics of children, particularly temperamental traits associated with ADHD. Prenatal exposure appeared to be more predictive of the threshold of responsiveness and withdrawal behaviours than postnatal exposure, regardless of whether we made adjustments for the exposure of the mothers. Further studies are needed to investigate the impacts of gene–environment interactions on the development of child temperament.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.134053.

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