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Associations of phthalates exposure with attention deficits hyperactivity disorder: A case-control study among Chinese children☆

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Researches on associations between phthalates exposure and child attention deficit hyperactivity disorder (ADHD) are inconsistent. This study aimed to evaluate the associations of urinary phthalates with ADHD, co-occurring oppositional defiant disorder (ODD), related symptoms and behavior problems among Chinese children. We enrolled 225 ADHD cases and 225 healthy controls aged 6–13 years old in Liuzhou, China. Each child provided repeated urine samples at 4 visits. Eight phthalate metabolites were measured by high-performance liquid chromatography and tandem mass spectrometry. Child ADHD symptoms and related behaviors were assessed using Swanson, Nolan, and Pelham Version IV scale and child behavior checklist. Higher urinary concentrations of mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl)-hexyl phthalate (MEHP) were dose-dependently associated with ADHD [odds ratios (ORs) ranged from 2.35 to 3.04 for the highest vs. the lowest tertile] and co-occurring ODD (ORs ranged from 3.27 to 4.44 for the highest vs. the lowest tertile) in the multivariable logistic regression models (all p for trend ≤ 0.01), which were consistent with positive trends of increased scores of inattention domain, hyperactive domain and ODD symptoms (all p for trend ≤ 0.01). Besides, the monomethyl phthalate (MMP) concentration was associated with higher scores of inattention domain and ODD symptoms (both $p < 0.05$). Additionally, the MEHHP, MEOHP and MEHP concentrations were related to child attention problems, aggressive behaviors and externalizing behaviors (all $p < 0.05$). We also observed positive associations of the MEHP concentration with depressed behaviors and internalizing behaviors (all $p < 0.05$). Our results indicate that child exposure to phthalates may contribute to ADHD, ODD and externalizing and internalizing behavior problems.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common childhood-onset neurodevelopmental disorders, mainly characterized by developmentally inappropriate inattention, motor hyperactivity and impulsivity, and it shows high comorbidity with oppositional defiant disorder (ODD) (American Psychiatric Association, 2000; Jensen and Steinhausen, 2015;

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Thapar and Cooper, 2015). With a nearly 30% increase in prevalence throughout the past decade (Akinbami et al., 2011), child ADHD has raised a health concern. The estimated prevalence of child ADHD is 5%–7% in China (Tong et al., 2013), similar to 5%–10% worldwide (Polanczyk et al., 2007). Children with ADHD cannot be cured, and they are more likely to have difficulties in social communication, academic performance, adaptability and health related quality of life (Barkley, 2002; Cuffe et al., 2015; Klassen et al., 2004). Although the causes and pathogenesis of ADHD remain unclear, both genetic and environmental factors have been verified to participate the etiology of ADHD (Aguiar et al., 2010; Christakis, 2016; Thapar and Cooper, 2015). Previous studies have shown that some environmental disruptors are related to ADHD (Eubig et al., 2010; Hoffman et al., 2010; Verner et al., 2015; Wang et al., 2008), including phthalates (Kim et al., 2009).

Phthalates, one of the major environmental disruptors, is a group of high-production-volume chemicals commonly used to induce the flexibility of polymeric materials (Wormuth et al., 2006). Children expose to phthalates ubiquitously though a wide variety of consumer products, such as personal care products, plastic toys, polyvinyl decoration and food containers. Once absorbed, phthalates are rapidly metabolized into monoesters or hydrophilic oxidative metabolites before being excreted in urine (Heudorf et al., 2007). Phthalate metabolites have been detected among children worldwide (Boas et al., 2010; Lee et al., 2014), including in China (Wang et al., 2015a; Zhang et al., 2015). Moreover, several studies have proven that children excrete higher phthalate metabolite concentrations than adults (Hartmann et al., 2015; Koch et al., 2003a, 2003b).

Emerging evidence indicate some phthalates may have adverse impacts on nervous system (Holahan and Smith, 2015; Miodovnik et al., 2014; Smith et al., 2011). Animal studies have documented exposure to di-2-ethylhexyl phthalate (DEHP) or dibutyl phthalate (DBP) inhibit cell proliferation, promote cell differentiation, and induce cell apoptosis in neurocytes (Chen et al., 2011; Li et al., 2013; Lin et al., 2011). Moreover, phthalates exposure in rodent studies are associated with motor hyperactivities behaviors, social investigation and sociability impairment, depression-like behavior and anxiety-like behavior (Ishido et al., 2004; Masuo et al., 2004a, 2004b; Zuo et al., 2014).

Limited human analyses have investigated relationships between phthalate metabolites with attention deficit disorder or ADHD symptoms among children (Chopra et al., 2014; Kim et al., 2009; Park et al., 2015; Verstraete et al., 2016; Won et al., 2016), but these findings are inconsistent. Besides, several studies have observed significant variations of phthalate metabolites in childhood urine (Teitelbaum et al., 2008; Watkins et al., 2014), indicating repeated measurements of phthalate metabolites should be necessary. Moreover, the comorbidity and concurrent behavior problems of ADHD have not been further studied, such as ODD and externalizing behaviors. In addition, the associations of other common phthalate metabolites with diagnosed ADHD remain unknown.

To fill the knowledge gap, we conducted this case-control study to evaluate the associations of phthalates exposure with diagnosed ADHD, co-occurring ODD, ADHD related symptoms and other child behavior problems (i.e., withdrawal behaviors, depressed behaviors, somatic complaints, aggressive behaviors and delinquent behaviors) among Chinese children.

2. Materials and methods

2.1. Study design and population

The present study included 225 ADHD cases and 225 healthy controls aged 6–13 years old. They were recruited via two primary schools and the outpatient department of psychological and behavioral development in women and children healthcare hospital of Liuzhou city between November 2015 and MAY 2016. ADHD children were initially diagnosed according to DSM-IV criteria, and then ascertained by a semi-structured interview and a psychological doctor in light of Mini International Neuropsychiatric Interview for children and adolescents. Controls were the local healthy children without ADHD, and matched age and sex with cases. Exclusion criteria of cases and controls included: 1) a history of mental retardation, autism spectrum disorders, bipolar disorder, language disorders or learning disabilities, pervasive developmental disorder; 2) a history of brain disease, seizure disorder, or other neurological disorder; 3) intelligence quotient (IQ) < 70; 4) a history of ADHD drug treatment; and 5) other serious illness. After informed consent of children and parents, they were invited to participate child behavior assessment, questionnaire survey, urine sample collection and follow-up. Children were invited to provide repeated urine samples at the first visiting day and at the follow-up day (after two weeks), respectively. The Institutional Review Board of the School of Public Health of Tongji Medical College of Huazhong University of Science and Technology approved the study.

2.2. Measure of children ADHD symptoms and behavior development

Children's parents were asked to complete the Chinese-version of Swanson, Nolan, and Pelham Version IV (SNAP-IV) scale to evaluate ADHD and ODD symptoms. SNAP-IV scale includes inattention domain, hyperactivity domain and ODD domain, using a 4-point rating scale ranging from 0 to 3 according to DSM-IV diagnostic criteria, and a score of 2 or 3 was coded as positive symptom. The Chinese-version SNAP-IV scale was reported to be well-validated and reliable for assessing ADHD and ODD (Gau et al., 2008, 2009). The score of each domain is computed by the sum of each symptom score/total score. There were two approaches to identify controls based on SNAP-IV. First, the cutoff score of each domain is no more than 1.0 for controls (Su, 2014). Second, if the number of positive symptom is less than 6 in each domain, children would be included in controls, according to the diagnostic criteria stated in the DSM-IV. All parents completed this scale.

These parents were also invited to fill in the Child Behavior Checklist (CBCL) scale to assess child potential behavior problems. CBCL is a reliable and commonly used scale, which provides an early indicator of child potential behavior problems (Achenbach, 1991). We used 113-item CBCL for 4–18 years of age to evaluate child withdrawal behaviors, somatic complaints, depressed behaviors, attention problems, aggressive behaviors and delinquent behaviors, externalizing behaviors (the sum of aggressive behaviors and delinquent behaviors) and internalizing behaviors (the sum of withdrawal, somatic complaints and depressed behaviors). The cutoff scores of above behavior problems are less than the borderline scores stated in Rating Scale Mental Health (Wang et al., 1999). Children with high scores were excluded in controls. Of all 450 children, 311 participants finished this scale with the completion rate of 69.11%.

The CBCL and SNAP-IV tests were taken on the same day from the day children first urine samples collected.

2.3. Questionnaire survey

A face-to-face questionnaire survey was administered by trained research staffs to collect demographic and environmental information from children's parents or carriers. This questionnaire contained birthday, sex, ethnic, birth site, residence, indirect