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Prenatal phthalate exposures and child temperament at 12 and 24 months

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ABSTRACT

Introduction: Gestational phthalate exposures have been adversely associated with attention, externalizing, and internalizing behaviors in childhood. Early childhood temperament may be a marker of later behavioral patterns. We therefore sought to determine whether gestational phthalate exposures were associated with infant and toddler temperament.
Methods: The Mount Sinai Children's Environmental Health Study is a prospective cohort study of children born between May 1998 and July 2001 in New York City (N = 404). Phthalate metabolites were measured in spot urine samples collected from pregnant women in their third trimester. Child temperament was assessed by parental report at 12-months using the Infant Behavior Questionnaire (IBQ) (N = 204) and at 24-months using the Toddler Behavior Assessment Questionnaire (TBAQ) (N = 279). We used multiple linear regression to evaluate associations between urinary phthalate metabolites and eleven temperament domains.
Results: Phthalate biomarker concentrations were weakly associated with lower gross motor activity levels as well as higher duration of orienting at the 12-month assessment. Mono(3-carboxypropyl) phthalate (MCPP), monobenzyl phthalate (MBzP) and the sum of metabolites of di(2-ethylhexyl) phthalate (∑DEHP) were associated with lower levels of smiling and laughing at 12 months. At 24-months, social fear and lower pleasure was linked to higher concentrations of MCPP and MBzP, and higher ∑DEHP was weakly associated with increased anger levels at 24-months.
Conclusions: Though we observed some weak associations between biomarkers of prenatal exposure to phthalates and temperament at 12- and 24-months, overall phthalates biomarkers were not strongly associated with alterations in temperament.

1. Introduction

Temperament has been conceptualized as enduring individual differences in behavioral propensities (Rothbart et al., 2000). Early childhood temperament patterns have been suggested to be potential precursors or modifiers of later psychopathology (reviewed in Nigg, 2006; De Pauw and Mervielde 2010), including Attention-Deficit/Hyperactivity Disorder (ADHD) (Nigg, 2006; Willoughby et al., 2016) and internalizing disorders (Nigg, 2006). While twin studies suggest moderate genetic heritability of temperament (20-60%) (Saudino, 2005), it is also suspected that environmental factors influence its development. For example, studies have found associations between certain dimensions of temperament and socioeconomic status (Jansen et al., 2009), prenatal drug use (Locke et al., 2016; Weiss et al., 2007; Richardson et al., 2008), prenatal binge drinking (Molteno et al., 2014; Alvik et al., 2011), maternal depression (Davis et al., 2007; Stroustrup et al., 2016; Sugawara et al., 1999; Melchior et al., 2012), and anxiety during pregnancy (Blair et al., 2011; Austin et al., 2005).

While much attention has been focused on the potential influence of prenatal toxicant exposure and child cognitive and behavioral development (Grandjean and Landrigan, 2014) comparatively little attention has been paid to the influence of early life toxicant exposures and the development of temperament. However, temperament may indeed mediate or modify the association between early life exposures, such as maternal stress (Zhu et al., 2014), prenatal depression (Stroustrup et al., 2016), and

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perhaps exposures to environmental toxicants, on later neurodevelopmental outcomes. For example, recently maternal lead exposure was found to increase risk for a difficult infant temperament (i.e. high activity, low approach, low adaptability, high intensity, negative mood, low persistence), and to enhance the already deleterious effect of maternal depression on infant temperament (Stroustrup et al., 2016). Consequently, temperament may be associated with later childhood behavioral development, and associations with toxicant exposures may highlight early developmental impacts on self-regulatory processes.

Phthalates are used as plasticizers in a variety of commercial products. Low molecular weight (LMW) phthalates (for example, diethyl phthalate (DEP)) are sometimes present in personal care products, such as perfume, shampoo, nail polish, and lotion (ATSDR, 1995, 2001). High molecular weight (HMW) phthalates (for example, di(2-ethylhexyl) phthalate (DEHP)) are typically used as polyvinyl chloride plasticizers in applications such as flooring, tubing, wall covering, and medical devices (ATSDR, 1997, 2002). People may be exposed to phthalates by dermal contact, ingestion of contaminated food products, and inhalation. Phthalates are quickly metabolized and excreted from the body in urine and feces. Despite rapid metabolism, studies suggest moderate stability in concentrations of some phthalate metabolites over time because of frequent, albeit episodic, exposure to some phthalate sources (e.g., cosmetics) (Adibi et al., 2008; Dewalque et al., 2015; Hauser et al., 2004; Teitelbaum et al., 2008).

A growing literature suggests potential links between prenatal phthalate exposures and neurodevelopmental outcomes in children (Miodovnik et al., 2011; Factor-Litvak et al., 2014; Kim et al., 2011; Polanska et al., 2014; Whyatt et al., 2012; Engel et al., 2010; Kobrosly et al., 2014; Lien et al., 2015; Yolton et al., 2011; Swan et al., 2010), though not all studies report non-sex specific associations (Braun et al., 2014; Doherty et al., 2017; Gascon et al., 2015; Huang et al., 2015; Tellez-Rojo et al., 2013; Engel et al., 2009). A number of studies specifically reported associations between phthalate exposures and behavioral difficulties. For example, Kim et al. (2009) reported an association between metabolites of DEHP and parent-reported ADHD. Another study found associations between metabolites of LMW phthalates in maternal urine from pregnancy and aggression, conduct problems, attention difficulties, externalizing problems, and low adaptability on the Behavior Assessment System for Children- Parent Rating Scales (BASC) (Engel et al., 2010). This same study also reported links between increased prenatal LMW phthalate metabolites and lower emotional control and poorer executive function on the Behavior Rating Inventory of Executive Function (BRIEF) (Engel et al., 2010). Two studies also reported some associations between particular phthalates in prenatal urine samples and behavior problems in children as reported by mothers on the Child Behavior Checklist (CBCL) (Whyatt et al., 2012; Kobrosly et al., 2014). For example, Whyatt et al. (2012) described an association between monobutyl phthalate (MnBP; a metabolite of di-n-butyl phthalate [DnBP]) and monobenzyl phthalate (MzBP; a metabolite of butylbenzyl phthalate [BBzP]) and clinically withdrawn behaviors, and MBzP and clinically internalizing behaviors. Many of these studies also reported some differential associations between phthalates and behaviors in male compared to female children (Engel et al., 2010; Whyatt et al., 2012; Kobrosly et al., 2014).

Given the studies suggesting associations between phthalate exposures and childhood behavior and psychological literature implicating temperament patterns in development of psychopathology, we hypothesized that maternal prenatal concentrations of urinary phthalates biomarkers may also be associated with early childhood temperament. Thus, we sought to examine this hypothesis in a longitudinal study of child development with existing markers of prenatal phthalate exposure and multiple assessments of early childhood temperament. Since previous studies reported sex-phthalate interactions, we also assessed associations between phthalate and temperament among male and female children.

2. Material and methods

2.1. Study participants and data collection

The Mount Sinai Children's Environmental Health study is a prospective cohort study of primiparous women with singleton pregnancies. Pregnant women were enrolled during prenatal visits at Mount Sinai Diagnostic and Treatment Center or two private practice clinics. All children in the study were born between May 1998 and July 2001 at Mount Sinai Hospital.

A single urine sample was collected from women between weeks 25 and 40 of pregnancy. During the third trimester, the women were administered a questionnaire about sociodemographic characteristics, medical conditions and lifestyle. The quality of the home environment was assessed using the Home Observation for Measurement in the Environment (HOME) Inventory at 12 and 24 months of age (Caldwell and Bradley, 1984). Birth and delivery characteristics were collected from the medical record database at the Mount Sinai Department of Obstetrics, Gynecology and Reproductive Science. Institutional Review Boards at the Mount Sinai School of Medicine and the University of North Carolina at Chapel Hill approved the study. The analysis of blinded specimens at the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subjects research.

2.2. Phthalate metabolite measurements

Concentrations of ten phthalate metabolites in the maternal urine samples were quantified at the CDC according to methods described previously (Kato et al., 2005; Silva et al., 2008). For concentrations below the limit of detection (LOD), we imputed the value of the LOD divided by the square root of two.

For these analyses, we focused on five phthalate metabolites: monoisobutyl phthalate (MiBP, a metabolite of diisobutyl phthalate), MnBP, monoethyl phthalate (MEP, a metabolite of DEP), mono (3-carboxypropyl) phthalate (MCPP, a major di-n-octyl phthalate metabolite, a minor DnBP metabolite and a metabolite of several high molecular weight phthalates), and MBzP. We calculated the molar sum of four metabolites of DEHP: (mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethylhexyl) phthalate (MEHP)), and refer to this as $\sum$DEHP.

2.3. Temperament assessment

When the children were approximately 12-months old, mothers were asked to complete the Infant Behavior Questionnaire (IBQ) – 1978 version (Rothbart, 1981). This 91-item questionnaire contains Likert-type scales for which the parent is asked to indicate how often the infant engaged in certain behaviors in the past week. Item responses are averaged to create summary scores that represent six dimensions of toddler temperament: **activity** level (17 items) with higher scores indicating greater gross motor activity, **distress to limitations** (20 items) with higher scores revealing increased frustration in response to being prevented from completing certain actions, **distress and latency to sudden changes or novel** stimuli (16 items) with higher scores signifying greater distress, duration of **orienting** (11 items) with higher scores suggesting increased interaction and vocal communication