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Association of Bisphenol A exposure and Attention-Deficit/Hyperactivity Disorder in a national sample of U.S. children

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ABSTRACT

Background: Bisphenol A (BPA) has been linked to changes in the dopamine system and development of an Attention-Deficit/Hyperactivity Disorder (ADHD) phenotype in animal models, with differing effects in males compared to females. We examined the association between urinary BPA concentrations and ADHD in a national sample of U.S. children, and whether this association differs by child sex.
Methods: We used data from the 2003–2004 National Health and Nutrition Examination Survey, a cross-sectional, nationally representative sample of the U.S. population. Participants were 8-15 years of age (N=460). Using a diagnostic interview to ascertain the presence of ADHD in the past year, multivariable logistic regression examined the link between concurrent urinary BPA concentrations and ADHD status.
Results: Of the 460 participants, 7.1% [95% CI: 4.4–11.3] met Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) criteria for ADHD. Children who had BPA concentrations at or above the median of the sample had higher prevalence of meeting criteria for ADHD (11.2% [95% CI: 6.8–17.8]) than those with BPA concentrations below the median (2.9% [95% CI: 1.1–7.2]). Higher urinary BPA concentrations were associated with ADHD (adjusted odds ratio [aOR]: 5.68 [95% CI: 1.6–19.8] for BPA concentrations above vs. below the median). In sex-stratified analyses, these associations were stronger in boys (aOR=10.9 [95% CI: 1.4–86.0]) than in girls (aOR=2.8 [95% CI: 0.4–21.3]), although the BPA by sex interaction term was not significant (p=0.25).
Conclusion: We found evidence that higher urinary BPA concentrations were associated with ADHD in U.S. children; these associations were stronger in boys than in girls. Considering the widespread use of BPA and growing literature on neurobehavioral effects of BPA in children, further study is warranted to determine if reducing exposure to BPA may represent an important avenue for ADHD prevention.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD), the most common neurobehavioral disorder in children, is characterized by difficulty sustaining attention, controlling impulsivity and modulating activity levels (Froehlich et al., 2007; Merikangas et al., 2010). Both familial and environmental factors have been implicated in the development of ADHD (Braun et al., 2006; Nigg, 2006). Concerns have been raised regarding the possible association between Bisphenol A (BPA) exposure and childhood neurobehavioral disorders (Center for the Evaluation of Risks to Human Reproduction, 2008), such as ADHD (Harley et al., 2013; Hong et al., 2013). BPA is an industrial chemical widely used to manufacture polycarbonate plastics and epoxy resins, and can be found in a broad range of products, including metal food can linings, reusable water bottles, dental sealants, sports safety equipment, thermal receipts, and adhesives (Vandenberg et al., 2007). The primary source of human exposure to BPA is the ingestion of food and drink containing BPA (Kang et al., 2006; Miyamoto and Kotake, 2006; Vandenberg et al., 2010; Vandenberg et al., 2007;

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; ACR, Adjusted Count Ratio; aOR, Adjusted Odds Ratio; BPA, Bisphenol A; CI, Confidence Interval; DAT, Dopamine Transporter; DMAP, 3-dimethyl alkylphosphate; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition; DISC, Diagnostic Interview Schedule for Children; LOD, Limit of Detection; NHANES, National Health and Nutrition Examination Survey; PIR, Income to Poverty line Ratio

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Wilson et al., 2007). BPA exposure is widespread in developed countries (Calafat et al., 2008; Vandenberg et al., 2010). For example, BPA was detected in the urine of 93% of the general U.S. population (Calafat et al., 2008).

Animal studies of BPA's neuroendocrine effects offer potential mechanisms supporting a linkage to ADHD. BPA has been implicated in modulating dopaminergic neurotransmission (Jones and Miller, 2008). Animal studies have shown that perinatal exposure to BPA causes accelerated turnover of dopamine (Honma et al., 2006), reduction in functional dopamine D3 receptors in the forebrain (Mizuo et al., 2004b), and abnormalities in dopamine transporter (DAT) gene expression in the neuronal membrane (Alyea and Watson, 2009; Ishido et al., 2007; Masuo et al., 2004). Given that imbalance in dopamine neurotransmission is believed to underlie the pathophysiology of ADHD (Levy, 1991; Levy and Swanson, 2001; Swanson et al., 2007), it is plausible that exposure to BPA may contribute to the development of an ADHD phenotype. Indeed, animal studies have shown that changes in the dopaminergic system with BPA exposure are associated with hyperactivity (Ishido et al., 2004, 2005b, 2007, 2011; Masuo et al., 2004).

There is a growing body of literature examining the impact of BPA exposure on neurodevelopmental outcomes in children (Braun et al., 2009, 2011; Casas et al., 2015; Evans et al., 2014; Findlay and Kohen, 2015; Harley et al., 2013; Hong et al., 2013; Miodovnik et al., 2011; Perera et al., 2012; Roen et al., 2015; Yolton et al., 2011). For example, prenatal exposure to BPA has been associated with externalizing behaviors in early childhood (Braun et al., 2009, 2011; Casas et al., 2015; Perera et al., 2012). However, there have been few published studies examining the association between childhood BPA exposure and meeting diagnostic criteria for ADHD (Harley et al., 2013). Of note, the majority of prior studies of childhood BPA exposure and neurobehavior have been conducted in regional cohorts and have focused on children younger than 8 years of age (Braun et al., 2009, 2011; Casas et al., 2015; Harley et al., 2013; Maserejian et al., 2012; Perera et al., 2012), whereas ADHD and its impairments are often not fully manifest until children enter school. The findings of these prior studies have been mixed, with some reporting an association between childhood exposure to BPA and hyperactivity and inattention (Casas et al., 2015; Findlay and Kohen, 2015; Harley et al., 2013; Hong et al., 2013) while others did not (Braun et al., 2011; Maserejian et al., 2012; Perera et al., 2012).

Due to BPA's endocrine disrupting properties and agonist effects on estrogen receptors, concerns have been raised regarding possible sex specific effects on neurobehavior (Adriani et al., 2003; Gioiosa et al., 2007; Patisaul and Polston, 2008; Tando et al., 2007). *Postnatal exposure* to BPA has been associated with hyperactivity in male rats in animal studies (Ishido et al., 2007; Nojima et al., 2013), but there is a paucity of data regarding effects in female animals. Most animal models used only males to study BPA effects on these outcomes (Ishido et al., 2004, 2005a, 2007; Masuo et al., 2004; Mizuo et al., 2004a; Zhou et al., 2011). In addition, findings regarding possible sex-specific effects of BPA on human neurodevelopment, specifically ADHD-related behaviors, have been mixed. Prenatal BPA exposure was associated with increased hyperactivity and inattention symptoms in preschool boys (Casas et al., 2015), but these associations did not persist at later ages. A study by Hong et al. showed childhood BPA exposure was associated with increased externalizing problems and aggressive behaviors in boys but not in girls (Hong et al., 2013), while Harley et al. (2013) reported an association between childhood BPA exposure and increased inattention and hyperactivity in children of both sexes at seven years of age. Two additional studies found that childhood BPA exposure was associated with hyperactivity and externalizing behaviors in girls but not boys (Findlay and Kohen, 2015; Roen et al., 2015). Given these mixed findings, the purpose of our study was to determine the association between childhood BPA exposure and ADHD in a national sample of U.S. children aged 8–15 years old, and whether sex modifies this association.

2. Materials and methods

2.1. Study participants

This study was reviewed by the Institutional Review Board (IRB) of Cincinnati Children's Hospital Medical Center and was determined to be exempt from regulatory criteria for research involving human subjects (Study # 2011–1686) due to its use of de-identified data. Our study sample was derived from the 2003–2004 dataset of the National Health and Nutrition Examination Survey (NHANES). NHANES is a stratified multistage probability sample of the civilian non-institutionalized population of the U.S. with an oversampling of certain minority populations (Centers for Disease Control and Prevention, 2014). Urine samples were analyzed for BPA in one third of the random subset of participants in the NHANES 2003–2004. Among children 8–15 years old who participated in the NHANES 2003–2004 cycle (N = 1,771), data for both urinary BPA and ADHD diagnostic interview was available for 460 participants (30% of total) for analyses. There were no significant differences observed between participants included versus excluded from the analyses with regards to demographic characteristics, ADHD status, and measured environmental exposures (See Table 1).

2.2. ADHD measurement

Our primary outcome was the presence of ADHD, defined as meeting DSM-IV criteria for ADHD using the National Institute of Mental Health Diagnostic Interview Schedule for Children–IV (DISC-IV), a structured diagnostic interview module. The DISC was administered to caregivers by a telephone interview within one to four weeks of urine collection. Caregivers were queried about the child's ADHD symptoms, age of onset, symptom pervasiveness and related impairments at both home and school during the past 12 months. The ADHD DISC-IV caregiver module has evidence of substantial validity (Shaffer et al., 2000), and reliability in both English (Shaffer et al., 2000), and Spanish versions (Bravo et al., 2001; Canino et al., 2004).

Given that more than half of the children diagnosed with ADHD earlier in life continue to experience ADHD symptoms despite no longer meeting the DSM criteria for ADHD later during adolescence (Biederman et al., 2000; Oord et al., 2012), we also examined the secondary outcomes of 1) having a caregiver report of a previous diagnosis of ADHD and, 2) having DSM-defined ADHD and/or caregiver report of ADHD. To determine whether children had a prior diagnosis of ADHD, caregivers were asked, “has a doctor or a health professional ever told you that (child's name) had attention deficit disorder?” (National Health and Nutrition Examination Survey, 2006).

2.3. Measurement of Bisphenol A

Our independent variable was childhood exposure to BPA. BPA concentrations were measured by a single, spot urine sample collected during the child's Mobile Examination Center visit. The total urine concentration of BPA was measured using online solid-phase extraction (SPE) coupled to high-performance liquid chromatography (HPLC)- isotope dilution tandem mass spectrometry (MS/MA) with peak focusing as described previously (Calafat et al., 2008; Ye et al., 2005). The limit of detection (LOD) was 0.36 μg/L; concentrations below the LOD were ascribed a value of LOD/$\sqrt{2}$