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Bisphenol A exposure and behavioral problems among inner city children at 7–9 years of age

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ABSTRACT

Background: Bisphenol A (BPA) is a ubiquitous endocrine disrupting compound. Several experimental and epidemiological studies suggest that gestational BPA exposure can lead to neurodevelopmental and behavioral problems in early-life, but results have been inconsistent. We previously reported that prenatal BPA exposure may affect child behavior and differently among boys and girls at ages 3–5 years.
Objectives: We investigated the association of prenatal and early childhood BPA exposure with behavioral outcomes in 7–9 year old minority children and hypothesized that we would observe the same sex-specific pattern observed at earlier ages.
Methods: African-American and Dominican women enrolled in an inner-city prospective cohort study and their children were followed from mother's pregnancy through children's age 7–9 years. Women during the third trimester of pregnancy and children at ages 3 and 5 years provided spot urine samples. BPA exposure was categorized by tertiles of BPA urinary concentrations. The Child Behavioral Checklist (CBCL) was administered at ages 7 and 9 to assess multiple child behavior domains. Associations between behavior and prenatal (maternal) BPA concentrations and behavior and postnatal (child) BPA concentration were assessed via Poisson regression in models stratified by sex. These models accounted for potential confounders including prenatal or postnatal urinary BPA concentrations, child age at CBCL assessment, ethnicity, gestational age, maternal intelligence, maternal education and demoralization, quality of child's home environment, prenatal environmental tobacco smoke exposure, and prenatal mono-n-butyl phthalate concentration.
Results: The direction of the associations differed between boys and girls. Among boys ($n=115$), high prenatal BPA concentration (upper tertile vs. lower two tertiles) was associated with increased internalizing ($\beta=0.41$, $p<0.0001$) and externalizing composite scores ($\beta=0.40$, $p<0.0001$) and with their corresponding individual syndrome scales. There was a general decrease in scores among girls that was significant for the internalizing composite score ($\beta=-0.17$, $p=0.04$) ($n=135$). After accounting for possible selection bias, the results remained consistent for boys. Conversely, high postnatal BPA concentration was associated with increased behaviors on both the internalizing composite ($\beta=0.30$, $p=0.0002$) and externalizing composite scores ($\beta=0.33$, $p<0.0001$) and individual subscores in girls but fewer symptoms in boys. These results remained significant in girls after accounting for selection bias.
Conclusion: These results suggest BPA exposure may affect childhood behavioral outcomes in a sex-specific manner and differently depending on timing of exposure.

1. Introduction

Mental and behavioral disorders in children are a major and growing public health concern because of their increasing prevalence, early onset, and impact on the child, family, and

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community (Perou et al., 2013). On average, 17 percent of young people experience an emotional, mental, or behavioral disorder (Merikangas et al., 2010). Attention-deficit/ hyperactivity disorder (ADHD) is the most common mental disorder in children followed by behavior/conduct problems, anxiety and depression (Perou et al., 2013). These disorders affect children's ability to learn and their future well-being. In the United States the annual cost of mental and behavioral disorders in persons ≤ 24 years of age is $247 billion or $2380 per person (Eisenberg and Neighbors, 2007; Perou et al., 2013). Multiple social and environmental factors are known to play a role in the etiology of these disorders (Canfield et al., 2003; Grandjean et al., 1997; Perera et al., 2013).

Bisphenol A (BPA) is a ubiquitous endocrine disrupting chemical that has been associated, in both animals and humans, with a wide range of health effects, including behavioral problems in children (Braun et al., 2011b; Braun et al., 2009; Harley et al., 2013; Perera et al., 2012). BPA is commonly used to manufacture polymers found in food and drink containers, certain dental sealants (Maserejian et al., 2012), recycling thermal paper (Vandenberg et al., 2007), medical devices and receipts (Biedermann et al., 2010; Geens et al., 2011). According to a national survey, 93 percent of those sampled had detectable levels of BPA in their urine; and higher BPA urinary concentrations were seen among women and low-income individuals (Calafat et al., 2008; Nelson et al., 2012).

Experimental studies have reported associations between BPA exposure and sex-specific changes in brain structure, function and behavior, including loss of sexual dimorphism in animals (Cox et al., 2010; Kundakovic et al., 2013; Nakagami et al., 2009; Palanza et al., 2008; Patisaul et al., 2006; Patisaul et al., 2007; Rubin et al., 2006; Wolstenholme et al., 2011). There is evidence that these effects may be occurring via changes in gene expression and DNA methylation in estrogen signaling pathways and estrogen receptors in a sex-specific, dose-dependent manner (Kundakovic et al., 2013; Naciff et al., 2002; Vandenberg et al., 2009; Wetherill et al., 2007). Epidemiologic studies have reported sex-specific changes in child behavior with increased prenatal BPA exposure (Braun et al., 2011b; Braun et al., 2009; Harley et al., 2013; Perera et al., 2012). However, these associations and sex-specific relationships observed in epidemiological studies have not always been consistent. For example, in our previous analysis of behavioral symptoms on the Child Behavior Checklist (CBCL) at ages 3–5 years in our New York City (NYC) cohort, prenatal BPA urinary concentrations were associated with significant increases in emotional reactivity, and aggression and borderline significant increases in externalizing and internalizing symptoms in boys, and a decrease in anxiety/depression symptoms, aggressive behavior, and internalizing symptoms in girls (Perera et al., 2012). Harley et al. reported significant and positive associations between prenatal BPA urinary concentrations and aggression, anxiety, depression, somatization, and internalizing symptoms in boys, using the Behavioral Assessment Scale for Children (BASC-2). In girls, a decrease in many symptoms at age 7 years was observed, although none were significant (Harley et al., 2013). In contrast, Braun et al. reported that prenatal BPA urinary concentrations were linked to a decrease in hyperactivity in boys and increases in anxiety, depression, hyperactivity and externalizing symptoms in girls at ages 2–3 years using the BASC (Braun et al., 2011b, 2009). Results for childhood BPA exposure have also been mixed (Braun et al., 2011b; Braun et al., 2009; Harley et al., 2013; Perera et al., 2012). Further, Maserejian et al. were unable to attribute changes in child behavior specifically to the BPA in dental composites (Maserejian et al., 2012).

In the present study, we followed-up on our prior analyses (Perera et al., 2012) and examined the association between prenatal and early childhood BPA urinary concentrations on neurobehavioral symptoms in children at ages 7–9 years. We hypothesized that we would continue to observe the sex-specific relationships previously reported (Harley et al., 2013; Perera et al., 2012).

2. Methods

Sample selection. A complete description of the NYC cohort and study design appears elsewhere (Perera et al., 2003, 2006). Briefly, subjects included mothers and children participating in the Columbia Center for Children's Environmental Health (CCCEH) prospective cohort study. Between 1998 and 2006, 727 pregnant women residing in Washington Heights, Harlem and the South Bronx were recruited in prenatal clinics to participate in the study. To avoid potential confounding, only women ages 18–35 years, non-smokers, non-users of other tobacco products and/or illicit drugs, those generally in good health (free of known diabetes, hypertension and HIV) and those who initiated prenatal care by 20 weeks of pregnancy were included in the study. In-person postnatal questionnaires were given when the child was 6 months and annually thereafter with developmental questionnaires administered every 1–2 years. Informed consent was provided for children by the mothers until age 7 at which point the children gave assent to participate. The Institutional Review Boards of the Columbia University Medical Center and of the Centers for Disease Control and Prevention (CDC) approved this study. Collection of urine during pregnancy began in 1999 (Hoepner et al., 2013), the year after initial recruitment and data collection began. 370 mothers provided urine samples during pregnancy for measurement of BPA. 271 of their children were followed through ages 7–9 when CBCL data were obtained.

BPA measures. Spot urine samples were collected from the mother during the third trimester of pregnancy and from the children at ages 3 and 5 years. After collection, the samples were sent to the CCCEH laboratory, inventoried, stored at $-80\,^{\circ}C$ and subsequently shipped to the CDC for analysis. Total (free plus conjugated) urinary concentrations of BPA were measured using online solid-phase extraction coupled with high-performance liquid chromatography-isotope dilution-tandem mass spectrometry with peak focusing as described before (Ye et al., 2005) with appropriate quality control samples in each run. The limit of detection (LOD) was 0.4 μg/L. Concentrations below the LOD were given a value of LOD/2 for statistical analysis. Specific gravity (SG) measurements were obtained using a handheld refractometer (Urine-Specific-Gravity-Refractometer-PAL-10-S-P14643C0; TAGO USA, Inc., Bellevue, WA). To adjust for urinary dilution, we used the formula: $BPAc = BPA \times [(\text{mean SG} - 1)/(\text{individual SG} - 1)]$ where BPAc is the SG-corrected BPA concentration (μg/L), BPA is the measured BPA concentration (μg/L), SG is the specific gravity of the urine sample, and mean SG is the mean SG in the study population calculated separately for maternal, child age 3 and child age 5 samples (Hauser et al., 2004).

Behavioral outcomes. When children reached ages 7 and 9 years, research workers trained in neurodevelopmental testing oversaw the completion of the CBCL by the mothers, providing guidance as needed. The 113-item CBCL was available in both English and Spanish. The CBCL consists of eight syndrome scales (anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior and aggressive behavior) and two composite scales, internalizing problems (sum of scores on the anxious/depressed, withdrawn/depressed and somatic complaints scales) and externalizing problems (sum of scores on the rule-breaking behavior and aggressive behavior scales). The responses to each question are given a numeric value and summed to yield a raw score

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