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Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children

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A B S T R A C T

Introduction: Early life exposure to bisphenol A (BPA), an endocrine disrupting chemical used in some food and beverage containers, receipts, and dental sealants, has been associated with anxiety and hyperactivity in animal studies. A few human studies also show prenatal and childhood BPA exposure to be associated with behavior problems in children.

Methods: We measured BPA in urine from mothers during pregnancy and children at 5 years of age ($N=292$). Child behavior was assessed by mother and teacher report at age 7 years and direct assessment at age 9 years.

Results: Prenatal urinary BPA concentrations were associated with increased internalizing problems in boys, including anxiety and depression, at age 7. No associations were seen with prenatal BPA concentrations and behaviors in girls. Childhood urinary BPA concentrations were associated with increased externalizing behaviors, including conduct problems, in girls at age 7 and increased internalizing behaviors and inattention and hyperactivity behaviors in boys and girls at age 7.

Conclusions: This study adds to the existing literature showing associations of early life BPA exposure with behavior problems, including anxiety, depression, and hyperactivity in children. Additional information about timing of exposure and sex differences in effect is still needed.

1. Introduction

Bisphenol A (BPA) is an endocrine-disrupting compound used in the manufacture of polycarbonate plastics and epoxy resins and as an additive in thermal paper. Humans are exposed to BPA via plastic food and beverage containers, canned food, medical devices, dental sealants, and receipts (Biedermann et al., 2010; Geens et al., 2011). Exposure to BPA is nearly ubiquitous, with 95% of Americans participating in the National Health and Nutrition Examination Survey (NHANES) having detectable levels of BPA in their urine (Calafat et al., 2008).

In animal studies, gestational exposure to BPA has been associated with alterations in brain morphology, function, and behavior (Wolstenholme et al., 2011). In rats and mice, perinatal BPA exposure has been shown to feminize sexually dimorphic regions of the hypothalamus in males (Patisaul et al., 2006; Rubin et al., 2006) and masculinize these regions in females (Patisaul et al., 2007). Studies have also found loss of sex differences in rodent behavior (Cox et al., 2010; Nakagami et al., 2009; Rubin et al., 2006), including rearing, exploration, and mother–infant interactions. Several studies have found gestational BPA exposure in rodents to be associated with increased anxiety (Cox et al., 2010; Patisaul and Bateman, 2008; Ryan and Vandenbergh, 2006; Tian et al., 2010; Xu et al., 2011; Yu et al., 2011) and hyperactivity (Ishido et al., 2004, 2007; Masuo et al., 2004; Xu et al., 2007), although there is less consistency about whether these effects are present in males, females, or both.

Several human studies have investigated the role of prenatal BPA exposure on behavior in children (Braun et al., 2011, 2009; Miodovnik et al., 2011; Perera et al., 2012; Yolton et al., 2011). In a sociodemographically diverse population, Braun et al. found that maternal urinary BPA concentrations during pregnancy were associated with increased behavior problems in girls, but not boys, according to maternal report on the Behavioral Assessment Scale for Children (BASC-2) (Braun et al., 2011, 2009). Specifically, higher prenatal urinary BPA concentrations were associated with more externalizing problem behaviors in girls at age 2 years (Braun et al., 2009) and increased report of hyperactivity, anxiety, and

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depression behaviors in girls at age 3 (Braun et al., 2011). In contrast, in a low-income African-American population, Perera et al. found that maternal urinary BPA concentrations during pregnancy were associated with fewer behavior problems (anxious/depressed, aggressive behavior) in girls but increased aggressive behavior and emotional reactivity in boys between 3 and 5 years of age, according to maternal report on the Child Behavior Check List (CBCL) (Perera et al., 2012). Miodovnik et al. found suggestive, but non-significant associations of prenatal BPA concentrations with social responsiveness, or autistic spectrum-type behaviors, in another cohort of predominantly minority women (Miodovnik et al., 2011).

Two of the above-mentioned studies also examined post-natal BPA exposure (Braun et al., 2011; Perera et al., 2012), but found no association of children's urinary BPA concentrations between age 1 and 4 years with later behavior. However, in a randomized trial of dental restorations, children with higher cumulative exposure to BPA, categorized as surface-years of exposure to BPA-containing dental composites between 6 and 10 years of age, reported more anxiety, depression, maladjustment, and emotional symptoms on the self-reported BASC between age 11 and 16 years compared to children randomized to receive amalgam or non-BPA dental restorations (Maserejian et al., 2012). This study found no differences by sex.

The present study examined the association of BPA concentrations in maternal urine during pregnancy and in children's urine at age 5 years with mother- and teacher-reported behavior problems at age 7 and interviewer-administered tests of attention and hyperactivity at age 9. Based on previous animal and human literature, behaviors of particular interest were anxiety, depression, aggression, and hyperactivity.

2. Materials and methods

2.1. Study population

Data were collected from mothers and children participating in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal birth cohort study examining the role of environmental exposures on the health of pregnant women and their children. In 1999–2000, we enrolled 601 pregnant women living in the Salinas Valley, an agricultural region of California. Eligible women were less than 20 weeks gestation, were at least 18 years of age, qualified for low-income health insurance (MediCal), spoke English or Spanish, and were receiving prenatal care at one of 6 participating clinics serving the region's low-income, farmworker population. A total of 527 women were followed through the birth of a singleton, live born infant, and behavioral data at ages 7 and 9 years are available for 349 and 309 of these children, respectively. We excluded 3 children diagnosed with developmental disabilities (Down syndrome, autism, hydrocephaly), 1 deaf child, and 53 children missing BPA measures (7 were missing prenatal and 46 were missing early childhood urinary BPA concentrations). The final sample was 292 children with both prenatal and childhood BPA concentrations and behavior data at 7 and/or 9 years of age. All study activities were approved by the Committees for the Protection of Human Subjects at U.C. Berkeley and the Centers for Disease Control and Prevention (CDC).

2.2. Urinary BPA concentrations

Spot urine samples were collected in 1999–2000 from mothers at two time points during pregnancy (mean $\pm$ sd: 13.6 ± 4.8 and 26.4 ± 2.5 weeks gestation) and from children at 5 years of age (mean $\pm$ sd: 5.0 ± 0.2 years). Urine samples were collected in polypropylene urine cups, aliquotted into glass vials, and frozen at −80 °C. Samples were shipped to the CDC for analysis.

Total urinary BPA concentration (conjugated plus unconjugated) was measured using online solid phase extraction coupled to high performance liquid chromatography–isotope dilution tandem mass spectrometry (Ye et al., 2005). The limit of detection (LOD) was 0.4 μg/L. Concentrations below the LOD for which a signal was detected were reported as measured. Concentrations below the LOD with no signal detected were randomly imputed based on a log-normal probability distribution using maximum likelihood estimation (Lubin et al., 2004). Each batch of study samples also included analytical standards, reagent blanks, and matrix-based quality control (QC) materials at two concentrations (~10 μg/L and ~2.5 μg/L). The method accuracy, expressed as a spiked recovery percentage, ranged from 98 to 113% at four different spiking levels (Ye et al., 2005). The method precision, determined from the coefficients of variation of repeated measurements of the QC materials, was below 10%.

Specific gravity was measured with a refractometer (National Instrument Company Inc., Baltimore, MD) for the maternal urine samples, but was unavailable for the children's samples. Thus, maternal concentrations were normalized for urinary dilution using urine specific gravity (Mahalingaiah et al., 2008) and child BPA concentrations were normalized by dividing by urinary creatinine concentration.

For the prenatal samples, the two urinary measures were available for 221 women and were averaged to better approximate exposure over the course of pregnancy. In the 71 women for whom only one BPA measurement was available, the single measurement was used. For children, the single measure of urinary BPA concentration at 5 years of age was used.

2.3. Childhood behavior

Children's behavior was assessed by maternal and teacher report at age 7 and by direct assessment at age 9.

At 7 years of age, the Behavior Assessment System for Children 2 (BASC-2) (Reynolds and Kamphaus, 2004) and the Conners' ADHD/DSM-IV Scales (CADS) (Conners, 2001) were interviewer-administered to the mother (due to low literacy rates) and self-administered by the child's teacher. Both instruments have been validated in English and Spanish. The BASC-2 Parent Rating Scale asks how often the child exhibits certain behaviors in the home setting (160 questions) while the Teacher Rating Scale asks about similar behaviors at school (139 questions). Frequencies were summed into raw scores and compared to national norms to generate age-standardized *T*-scores for several clinical scales, with higher values indicating more frequent problem behaviors. Scales of interest from the BASC-2 were anxiety, depression, and somatization (which can be combined into the internalizing problems composite scale); aggression, conduct problems, and hyperactivity (combined into the externalizing problems composite scale); and attention problems. The CADS Parent and Teacher Forms assess attention and hyperactivity using 26 questions that correspond to the DSM-IV criteria for Attention-Deficit/Hyperactivity Disorder (ADHD). Answers were summed into raw scores and compared to national norms to generate *T*-scores standardized for age and sex for three DSM-IV-oriented scales (inattention, hyperactivity, and ADHD DSM-IV scales).

At 9 years of age, we also assessed ADHD directly using the Connors' Continuous Performance Test (CPT), a computerized test that assesses reaction time, accuracy, and impulse control by having the child press the space bar as quickly as possible when any letter except the letter X appears on the screen (Conners and Staff, 2001). This program yields age- and sex-standardized *T*-scores for errors of commission (i.e. failure to withhold the response for an X, suggesting lack of response inhibition), errors of omission (i.e. failure to respond to other letters, suggesting inattention), reaction time, reaction time variability, and response bias (β, a measure of response style with high scores indicating a more cautious style).

2.4. Covariates

Information about possible confounders was gathered through structured maternal interviews conducted in English or Spanish by trained interviewers. During pregnancy, we gathered information about maternal age, race/ethnicity, education level, marital status, country of birth, years of residence in the United States and health behaviors, including smoking during pregnancy. Maternal interviews when the children were 7 years old assessed factors that might impact child behavior or mothers' perception of child behavior, including number of siblings in the home, family income, maternal depression, and the level of stimulation in the home environment. Family income was compared to the federal poverty threshold for families of the same size to generate a variable for ≤poverty vs. > poverty. Maternal depression was assessed using the Center for Epidemiologic Studies-Depression (CES-D) scale (Radloff, 1977) and analyzed as depressed vs. not depressed (≥16 vs. < 16). The caregiving environment and level of stimulation was assessed using the Home Observation for Measurement of the Environment (HOME) Inventory (Caldwell and Bradley, 1984). HOME score, age and parity were included in multivariable models as continuous variables. All other covariates were categorized as shown in Table 1.

Because the study participants are from an agricultural region and because we have previously found prenatal exposure to organophosphate pesticides to be associated with attention problems in this cohort (Marks et al., 2010), we also controlled for maternal urinary concentrations of dialkyl phosphate (DAP) metabolites of organophosphate pesticides. DAP metabolites were measured in the same maternal urine samples as BPA using isotope dilutions gas chromatography-tandem mass spectrometry (Bradman et al., 2005) and were averaged to approximate exposure throughout pregnancy. Polybrominated diphenyl ether (PBDE) flame retardants are also an important exposure in this population that has been associated with neurobehavior (Eskenazi et al. 2013). However, because PBDEs