Environmental Research 151 (2016) 195–202

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

# Bisphenol A exposure and symptoms of anxiety and depression among inner city children at 10–12 years of age

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ARTICLE INFO

*Article history:*
Received 24 February 2016
Received in revised form
28 June 2016
Accepted 19 July 2016

*Keywords:*
Prenatal
Bisphenol A
Child behavior
Sex-specific

ABSTRACT

*Background:* Experimental and epidemiological studies suggest that gestational exposure to Bisphenol A (BPA), an ubiquitous endocrine disrupting chemical, may lead to neurobehavioral problems in childhood; however, not all results have been consistent. We previously reported a positive association between prenatal BPA exposure and symptoms of anxiety/depression reported by the mother at child age 7–9 years in boys, but not girls.

*Objectives:* Here, in the same birth cohort, we investigated the association of prenatal BPA exposure with symptoms of depression and anxiety self-reported by the 10–12 year olds, hypothesizing that we would observe sex-specific differences in anxiety and depressive symptoms.

*Methods:* African-American and Dominican women living in Northern Manhattan and their children were followed from mother's pregnancy through children's age 10–12 years. BPA was quantified in maternal urine collected during the third trimester of pregnancy and in child urine collected at ages 3 and 5 years. Children were evaluated using the Revised Children's Manifest Anxiety Scale (RCMAS) and Children's Depression Rating Scale (CDRS). We compared the children in the highest tertile of BPA concentration to those in the lower two tertiles. Associations between behavior and prenatal (maternal) BPA concentration or postnatal (child) BPA concentration were assessed in regression models stratified by sex.

*Results:* Significant positive associations between prenatal BPA and symptoms of depression and anxiety were observed among boys. Postnatal BPA exposure was not significantly associated with outcomes. There was substantial co-occurrence of anxiety and depressive symptoms in this sample.

*Conclusion:* These results provide evidence that prenatal BPA exposure is associated with more symptoms of anxiety and depression in boys but not in girls at age 10–12 years.



## 1. Introduction

Becauseof their increasing prevalence, early onset, and impact on the child, family, and community, mental and behavioral disorders in children are a growing public health concern (Perou et al., 2013). An estimated 17% of US adolescents aged 13–18 experience an emotional, mental, or behavioral disorder, including anxiety and depression (Merikangas et al., 2010). These mental and behavioral disorders in persons $\leq$24 years of age impose an annual cost in the United States of $247 billion or $2,380 per person (Perou et al., 2013; Eisenberg and Neighbors, 2007). Their etiology is complex, including familial, genetic and environmental factors (Reinherz et al., 2000; Fendrich et al., 1990; López et al.,

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http://dx.doi.org/10.1016/j.envres.2016.07.028
0013-9351/

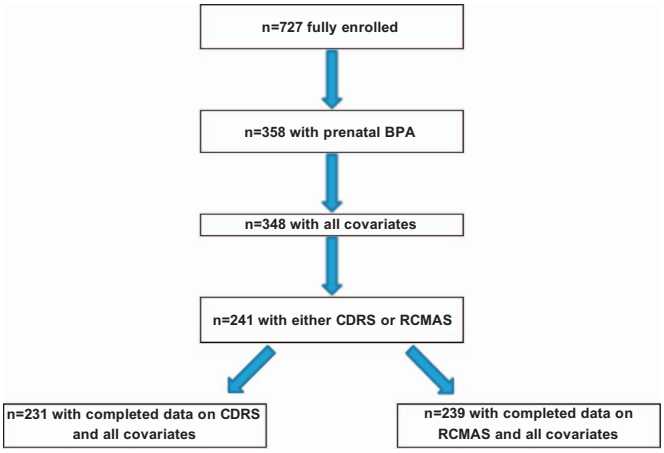


**Fig. 1.** Selection criteria for children included in the analysis.[1]

1999; Merikangas et al., 1999).

Bisphenol A (BPA) is a ubiquitous endocrine disrupting chemical commonly used to manufacture polymers found in food and drink containers, certain dental sealants (Maserejian et al., 2012), thermal receipt paper (Vandenberg et al., 2007), medical devices and sales receipts (Biedermann et al., 2010; Geens et al., 2011). According to a national survey, 93% of persons 6 years or older who were sampled had detectable levels of BPA in their urine; higher BPA urinary concentrations were seen among women and low-income individuals (Nelson et al., 2012; Calafat et al., 2008).

Experimental studies in laboratory animals have reported associations between BPA exposure and sex-specific changes in brain structure, function, alterations in DNA methylation of the genome, and behavioral problems (including anxiety-like behavior, inhibition of spatial skills, problems in spatial learning, and aggressiveness) (Wolstenholme et al., 2011; Patisaul et al., 2006; Rubin et al., 2006; Patisaul et al., 2007; Cox et al., 2010; Nakagami et al., 2009; Palanza et al., 2008; Kundakovic et al., 2013; Peluso et al., 2014). In mice, prenatal BPA induced lasting changes in DNA methylation in the transcriptionally relevant region of the gene encoding BDNF (brain derived neurotrophic factor), which plays an important role in fetal brain development; these changes were consistent with BDNF changes in the cord blood of children exposed to BPA in utero (Kundakovic et al., 2015). Similarly, the various adverse effects observed in these studies may be occurring in a sex-specific, dose-dependent manner via changes in DNA methylation and gene expression in estrogen signaling pathways and estrogen receptors (Kundakovic et al., 2013; Naciff et al., 2002; Vandenberg et al., 2009; Wetherill et al., 2007).

Epidemiologic studies have reported sex-specific differences in child behavior associated with increased prenatal BPA/maternal urinary concentrations (Perera et al., 2012; Harley et al., 2013; Braun et al., 2011a, 2009; Evans et al., 2014; Roen et al., 2015). However, the associations and sex-specific relationships observed in epidemiological studies have not always been consistent (Perera et al., 2012; Harley et al., 2013; Braun et al., 2011a, 2009) (see details in Section 4).

Using assessment instruments with reporting by the child, rather than by the parent, to elicit information on symptoms of anxiety and depression, we hypothesized that we would continue to observe sex-specific associations between prenatal BPA urinary concentrations and symptoms of both anxiety and depression at 10–12 years of age. Further, we hypothesized that we would observe extensive comorbidity of anxiety and depression in this inner city cohort, as has been reported in many other studies (Cummings et al., 2014).

## 2. Methods

### 2.1. Sample selection

A complete description of the NYC cohort and study design appears elsewhere (Perera et al., 2003, 2006). Briefly, participants 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. 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 after which age the children gave their assent to participate. The Institutional Review Boards of the Columbia University Medical Center and the Centers for Disease Control and Prevention (CDC) approved this study.

### 2.2. Chemical measures

Collection of spot urine samples during the third trimester of pregnancy began in 1999 (Hoepner et al., 2013), the year after initial recruitment and data collection began. 348 mothers provided urine samples during pregnancy for measurement of BPA and mono-n-butyl phthalate (MnBP), as a major phthalate metabolite. Not all participants had BPA measures because of limitations in amount of urine available and limited funding for these analyses. A subset of the 348 children was followed through ages 10–12, when data from the Revised Children's Manifest Anxiety Scale (RCMAS) and Children's Depression Rating Scale-Revised (CDRS) were obtained on 239 and 231 children, respectively (Fig. 1). Urine samples were collected at ages 3 and/or 5 years during the same visit when questionnaires were administered. 218 of the 241 children included in this analysis had data on postnatal BPA concentrations: age 5 urinary BPA measures were used for 181 children and age 3 year measures were used for 37 children who were missing the 5 year sample.

After collection, the samples were sent to the CCCEH laboratory, inventoried, stored at −80 °C, and subsequently shipped to the CDC for analysis. Total (free plus conjugated) urinary concentrations of BPA and MnBP were measured separately using online solid-phase extraction coupled with high-performance liquid chromatography–isotope dilution–tandem mass spectrometry as described previously (Ye et al., 2005; Kato et al., 2005), with appropriate quality control samples in each run. The limits of detection (LOD) were 0.4 μg/L (BPA) and 0.4–1.1 μg/L (MnBP). Concentrations below the LOD were given a value of LOD/2 for statistical analysis. To adjust for urinary dilution, BPA and phthalate metabolite values were adjusted for specific gravity (SG) obtained using a handheld refractometer (Urine-Specific-Gravity-Refractometer-PAL-10-S-P14643C0; TAGO USA, Inc., Bellevue, WA). We used the formula: Chemicalc = BPA or MnBP × [(mean SG − 1)/(individual SG − 1)] where Chemicalc is the SG-corrected chemical concentration (μg/L), BPA or MnBP is the measured chemical 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

[1] Due to limitations in available maternal urine and limited funding for analysis of BPA concentrations, BPA data were available only for a subset of participants enrolled in the parent study.