NeuroToxicology 62 (2017) 192–199

Contents lists available at ScienceDirect

NeuroToxicology

Full Length Article

Prenatal environmental chemical exposures and longitudinal patterns of child neurobehavior

Joseph M. Braun[a,*], Kimberly Yolton[b], Shaina L Stacy[a], Bahar Erar[c], George D. Papandonatos[c], David C. Bellinger[d], Bruce P. Lanphear[e], Aimin Chen[f]

[a] Department of Epidemiology, Brown University, Providence, RI, United States
[b] Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States
[c] Department of Biostatistics, Brown University, Providence, RI, United States
[d] Departments of Environmental Health, Harvard TH Chan School of Public Health, Boston, MA, United States
[e] Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada
[f] Department of Environmental Health, University of Cincinnati, Cincinnati, OH, United States

ARTICLE INFO

Article history:
Received 7 April 2017
Received in revised form 21 June 2017
Accepted 17 July 2017
Available online 20 July 2017

Keywords:
Children
Bisphenol A
Epidemiology
Halogenated flame retardants
Prenatal
Neurodevelopment

ABSTRACT

Background: Prenatal chemical exposures may adversely affect neurodevelopment, but few studies have examined the persistence of these associations. We examined whether associations between prenatal bisphenol A (BPA) or polybrominated diphenyl ether (PBDE) exposures persist or resolve as children age.
Methods: We followed 346 mother-child pairs (enrolled 2003–2006) from Cincinnati, OH from pregnancy until children were 8 years old. We measured BPA in urine collected at 16 and 26 weeks gestation and PBDE-47 in serum collected at 16 weeks gestation. We administered repeated measures of children's behavior, mental/psychomotor development, and IQ from ages 1–8 years. We determined if associations of BPA or PBDE-47 with child neurobehavior persisted or resolved as children aged using linear mixed models and estimated neurobehavioral measure reproducibility using intraclass correlation coefficients (ICCs).
Results: Higher BPA in girls and higher PBDE-47 in both boys and girls were associated with more externalizing behaviors; these associations persisted from ages 2–8 years (exposure × age interaction p-values ≥ 0.36). Higher PBDE-47 concentrations were associated with decreases in MDI from ages 1–3 years (PBDE–47 x age interaction p-value = 0.03) and persistently lower IQ at ages 5 and 8 years (PBDE–47 × age interaction p-value = 0.56). Mental/psychomotor abilities had fair reproducibility from ages 1–3 years (ICCs ~ 0.4), cognitive abilities from ages 5 to 8 years had excellent reproducibility (ICCs = 0.7-0.8), and parent-reported behaviors from ages 2–8 years had poor to good reproducibility (ICCs = 0.38–0.59).
Conclusions: Prenatal BPA and PBDE-47 concentrations were persistently associated with more externalizing behaviors. PBDE-47 concentrations were inversely associated with cognitive abilities that strengthened over time.

1. Introduction

The developing brain is exquisitely sensitive to environmental inputs, and there are many neurotoxicant exposures that increase the risk of neurobehavioral disorders (Rice and Barone, 2000; Grandjean and Landrigan, 2014). However, studies of potential neurotoxicants have generally not considered whether these exposures influence the trajectory of children's behavior and cognition (Bellinger et al., 2016). Two potential neurotoxicants of interest are bisphenol A (BPA) and polybrominated diphenyl ethers (PBDEs); exposure to both is ubiquitous among pregnant women in the United States and associated with decrements in cognitive abilities and behavior problems among children in prior cohort studies (Chen et al., 2014; Braun et al., 2011a; Cowell et al., 2015; Eskenazi et al., 2013; Herbstman and Mall, 2014; Sagiv et al., 2015; Vuong et al., 2016; Woodruff et al., 2011).

Determining if the effects of neurotoxicant exposures change over time requires studies with repeated neurobehavioral assessments. Since some epidemiological studies only assess neurobehavior once, it is not possible to determine if the effect of these exposures persists, strengthens, or resolves as children age. Identifying persistent effects is important as toxicant-induced deficits early in life may be a prelude to more severe impairments

* Corresponding author at: Brown University, Box G-S121(2), Providence, RI, 02912, United States.
E-mail address: joseph_braun_1@brown.edu (J.M. Braun).

http://dx.doi.org/10.1016/j.neuro.2017.07.027
0161-813X/

later in life, as is the case with lead (Wright et al., 2008). Alternatively, neurotoxicant-associated deficits that manifest in infancy or early childhood may not persist if the plasticity of the developing brain allows for recovery from early life insults. In addition, neurobehavioral trajectories of typically developing children have not been well described, yet understanding variations and progression in development could help define what level of deviation is within normal limits. While some studies have explored this, they are limited by a focus on specific domains (e.g., IQ), use of outdated versions of instruments, or short follow-up intervals (Iverson, 2012; Moffitt et al., 1993; Watkins and Smith, 2013; Verhulst and van der Ende, 1992; Verhulst and Van der Ende, 1995).

To address these gaps, we used a prospective birth cohort study of 346 mother-child dyads with repeated measures of child behaviors, mental and psychomotor development, and cognition to determine if previously observed associations of prenatal BPA and PBDE exposure with child behavior and IQ in this cohort were associated with trajectories of neurobehavior between ages 1 and 8 years. We also characterized the variability and patterns of these neurobehavioral measures over the first 8 years of life.

2. Methods

2.1. Study participants

The Health Outcomes and Measures of the Environment (HOME) Study is a prospective pregnancy and birth cohort that has followed mothers and their children in the greater Cincinnati, OH metropolitan area from the 2nd trimester of pregnancy (March 2003-January 2006) until their singleton children were on average age 8.1 (range: 7.5-10) years (March 2012-July 2014) (Braun et al., 2016; Stacy et al., 2016). We designed the study to assess the relationship between low-level environmental chemical exposures and child neurobehavior. Inclusion criteria for pregnant women at enrollment included: 1) 16 ± 3 weeks gestation, 2) $\geq$18 years old, 3) living in a home built before 1978, 4) no history of HIV infection, and 5) not taking medications for seizure or thyroid disorders. We enrolled women living in homes built before 1978 in order to study the neurotoxic effects of early life lead exposure, as these homes would be more likely to have lead hazards. All women provided informed consent for themselves and their children. The institutional review boards of Cincinnati Children's Hospital Medical Center, the cooperating delivery hospitals, and the Centers for Disease Control and Prevention (CDC) approved this study.

2.2. Prenatal BPA and PBDE exposure assessment

We assessed prenatal BPA exposure by measuring total (free + conjugated) BPA concentrations in urine samples collected in polypropylene specimen cups at 16 and 26 weeks gestation using previously described analytic chemistry methods (Ye et al., 2008). To account for urine dilution, we measured urinary creatinine concentrations using a kinetic assay and creatinine-standardized BPA concentrations (BPA in ng/mL divided by creatinine in mg/dL) (Larsen, 1972). If a woman had two urine samples (~95% of women), we averaged $\log_{10}$-transformed creatinine-standardized urinary BPA concentrations; otherwise, we used the available $\log_{10}$-transformed creatinine-standardized concentration. We assessed PBDE exposure by measuring concentrations of PBDE-47, the most abundant PBDE congener in our participants, in serum collected from women at 16 weeks gestation using previously described analytic chemistry methods (Jones et al., 2010). To account for inter-individual differences in blood lipid concentrations we measured serum triglycerides and total cholesterol concentrations using an enzymatic assay (Phillips et al., 1989); PBDE-47 concentrations were lipid-standardized (PBDE-47 in pg/mL divided by mg/dL of lipids) and $\log_{10}$-transformed for analyses.

Urine and serum samples were collected following the recommended best practices for collecting and processing biospecimens that are to be used for environmental chemical exposure assessment (Calafat, 2016). Both urine and serum samples were refrigerated after collection, stored at or below -20°C within 24 h of collection, and shipped to the CDC laboratories on dry ice where they were analyzed using previously described methods that included quality control samples and reagent blanks (Ye et al., 2008; Jones et al., 2010). The limit of detection (LOD) for the BPA assay was 0.4 ng/ml, while the LOD for the PBDE-47 assay was defined as the highest of the lowest point on the calibration curve (0.5 pg/μL) or three times the standard deviation of the method blank concentrations. Concentrations $<$LOD were assigned a value of LOD/$\sqrt{2}$ (Hornung and Reed, 1990). The coefficients of variation for quality control samples were $<$10%.

2.3. Infant and child neurobehavioral battery

We repeatedly assessed children's behaviors, mental and psychomotor development, and cognitive abilities from ages 1 to 8 years (Supplemental Table 1). We administered valid and reliable neurobehavioral instruments that have been used extensively in epidemiological studies and for which measured domains of these instruments have been associated with several early life neurotoxicant exposures (see Supplemental Methods for description of testing procedures) (Dietrich et al., 2005). For the purpose of this analysis, we focused on neurobehavioral domains previously associated with prenatal exposure to BPA or PBDEs in this cohort; these included behavior measured with the Behavioral Assessment System for Children-2 (BASC-2), mental and psychomotor development measured with the Bayley Scales of Infant Development-II (BSID-II), and child cognitive abilities measured with two age-specific Wechsler instruments (Wechsler Preschool and Primary Scales of Intelligence-III [WPPSI-III] and the Wechsler Intelligence Scale for Children-IV [WISC-IV]).

We evaluated children's behavior using the preschool and child versions of the BASC-2 at ages 2, 3, 4, 5, and 8 years. The BASC-2 is a valid and reliable parent-reported assessment of a child's adaptive and problem behaviors in community and home settings (Reynolds and Kamphaus, 2002). We examined three of the BASC-2 composite scales: Externalizing Problems, which reflects disruptive behavior problems; Internalizing Problems, such as depression and anxiety; and the Behavioral Symptoms Index, a measure of a child's overall level of problem behaviors. We also examined eight clinical subscales (in secondary analysis of reproducibility described below): hyperactivity, aggression, anxiety, depression, somatization, atypicality, withdrawal, and attention.

Higher scores on the BASC-2 indicate worse behaviors, and values $\geq$60 (i.e., $\geq$1 standard deviation above the mean) are used to identify children with "at-risk" scores. At-risk scores are indicative of behaviors significant enough to warrant treatment, further evaluation, and assignment of a possible clinical diagnosis (Reynolds and Kamphaus, 2002). Few children had clinically significant scores ($\geq$70) on the BASC-2, so we did not evaluate this as an outcome.

We assessed children's mental and psychomotor development using the BSID-II at ages 1, 2, and 3 years (Bayley, 1993). The BSID-II produces two scaled scores, the mental development index (MDI) and the psychomotor development index (PDI). The MDI assesses cognitive and language abilities, while the PDI assesses gross and fine motor skills. We administered the WPPSI-III and the WISC-IV at ages 5 and 8 years, respectively, to evaluate children's overall cognitive ability (Full-Scale IQ [FSIQ]), perceptual reasoning and organization skills (Performance IQ [PIQ]), and verbal abilities (Verbal IQ [VIQ]) (Wechsler, 2002, 2003).