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Prenatal polybrominated diphenyl ether and perfluoroalkyl substance exposures and executive function in school-age children ☆

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ABSTRACT

Executive function is a critical behavioral trait rarely studied in relation to potential neurotoxicants. Prenatal exposure to polybrominated diphenyl ethers (PBDEs) and perfluoroalkyl substances (PFASs) has been associated with adverse neurodevelopment, but there is limited research on executive function. Data from 256 mother–child pairs in the Health Outcomes and Measures of the Environment Study, a prospective birth cohort (2003–2006, Cincinnati, OH), was used to examine maternal serum PBDEs and PFASs and executive function in children ages 5 and 8 years. Maternal serum PBDEs and PFASs were measured at 16 ± 3 weeks gestation. Executive function was assessed with the parent-rated Behavior Rating Inventory of Executive Function (BRIEF), which yields composite measures: behavioral regulation index, metacognition index, and global executive composite. Higher BRIEF scores indicate executive function impairments. Linear mixed models and generalized estimating equations were used to estimate covariate-adjusted associations between PBDEs and PFASs and executive function. A 10-fold increase in BDE-153 was associated with poorer behavior regulation ($\beta = 3.23$, 95% CI 0.60, 5.86). Higher odds of having a score ≥ 60 in behavior regulation (OR = 3.92, 95% CI 1.76, 8.73) or global executive functioning (OR = 2.34, 95% CI 1.05, 5.23) was observed with increased BDE-153. Each ln-unit increase in perfluorooctane sulfonate (PFOS) was associated with poorer behavior regulation ($\beta = 3.14$, 95% CI 0.68, 5.61), metacognition ($\beta = 3.10$, 95% CI 0.62, 5.58), and global executive functioning ($\beta = 3.38$, 95% CI 0.86, 5.90). However, no association was observed between perfluorooctanoate (PFOA) and executive function. Prenatal exposures to BDE-153 and PFOS may be associated with executive function deficits in school-age children.

1. Introduction

Beginning in the 1970s, PBDEs were used as synthetic flame retardants in a number of consumer products, including polyurethane foams, electronics, and some textiles. Since then, PBDEs have been detected throughout the environment and in humans (Darnerud et al., 2001). Dietary intake and dust ingestion are the primary sources of human exposure. Animal models have demonstrated that PBDEs are endocrine disruptors and neurotoxicants (Costa and Giordano, 2007). Several epidemiologic studies have suggested neurotoxic effects of prenatal exposure to PBDEs. Increased attention deficit/hyperactivity disorder (ADHD) related behaviors and decrements in cognitive function have been reported among children with higher exposures to prenatal PBDEs

Abbreviations: ADHD, Attention deficit/hyperactivity disorder; BRIEF, Behavior Rating Inventory of Executive Function; CDC, Centers for Disease Control and Prevention; CI, Confidence interval; DNBC, Danish National Birth Cohort; FSIQ, Full Scale IQ; GM, Geometric mean; HOME, Health Outcomes and Measures of the Environment; LOD, Limit of detection; NHANES, National Health and Nutrition Examination Survey; OR, Odds ratio; PBDEs, Polybrominated diphenyl ethers; PCBs, Polychlorinated biphenyls; PFASs, Perfluoroalkyl substances; PFDeA, Perfluorodecanoate; PFHxS, Perfluorohexane sulfonate; PFNA, Perfluorononanoate; PFOA, Perfluorooctanoate; PFOS, Perfluorooctane sulfonate; PFUnDA, Perfluoroundecanoate; QC, Quality control; SD, Standard deviation; T_4, Thyroxine; T_3, Triiodothyronine

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(Chen et al., 2014; Eskenazi et al., 2013; Herbstman et al., 2010; Roze et al., 2009). However, null associations have been reported between prenatal and perinatal PBDEs and neurodevelopment in a birth cohort in Menorca, Spain (Gascon et al., 2011) and among mother–child pairs in Taiwan (Chao et al., 2011; Shy et al., 2011), although the reported concentrations of PBDEs in Europe and Taiwan were much lower than in the US.

PFASs are used as surfactants and surface treatments in fire-fighting foams, personal care products, cleaning products, upholstery, and non-stick cookware (Kissa, 2001). Prenatal exposure to PFASs reduces thyroid hormone concentrations in animal studies and may be neurotoxic (Johansson et al., 2008; Lau et al., 2003; Luebker et al., 2005). However, human studies have yielded inconsistent results with regard to neurodevelopment. No association was reported between prenatal perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and neurologic development in the Danish National Birth Cohort (DNBC) (Fei et al., 2008; Fei and Olsen, 2011) or between perinatal PFOS and PFOA exposure and neuropsychological development in the Norwegian Human Milk Study (HUMIS) (Forns et al., 2015). In contrast, increases in Full Scale IQ (FSIQ) and decreases in ADHD behaviors were reported with prenatal PFOA exposure (Stein et al., 2013). In addition, a recent study reported prenatal perfluoroundecanoate (PFUnDA) and perfluorononanoate (PFNA) were associated with decrements in FSIQ in children (Wang et al., 2015).

Although the relation between prenatal PBDEs and PFASs and several components of neurodevelopment have been explored, there is limited research on their relation with executive function in children. Executive function encompasses higher order neurocognitive processes, including cognitive flexibility, goal planning, and information processing. Deficits in executive functioning can hinder an individual's ability to formulate goals, effectively perform, and focus. Identifying and providing intervention to children with executive function deficits at an early age is imperative as individuals who have undergone substantial cognitive loss can still be independent and functional if executive function is intact (Lezak et al., 2004). Environmental chemical exposure may disrupt normal neurodevelopment, particularly during brain development when rapid structural and functional changes occur (Viberg et al., 2003). Previous studies have reported poorer executive function among children exposed to maternal tobacco smoking during pregnancy and lead exposure during childhood (Canfield et al., 2004; Piper and Corbett, 2012; Roy et al., 2009).

Only one study has examined prenatal PBDEs and its relation with executive function. Sagiv et al. (2015) recently reported poorer executive function in children aged 9 and 12 years with measured concentrations of prenatal ∑PBDEs (BDE-47, -99, -100, and -153). While there are no studies on prenatal PFASs and executive function, Stein et al. (2014) examined childhood PFOA concentrations at 2–8 years of age and executive function at 6–12 years. Compared to the lowest quartile of PFOA concentrations, boys in the highest quartile had better executive functioning, while girls had poorer executive functioning based on mother reports. Given that PBDEs and PFASs are environmentally persistent and PBDEs are an order of magnitude higher in the US compared with Europe or Asia, their potential neurotoxicity could imply considerable impact on children's neurodevelopment at the population level. In this study, we examined the relation between prenatal exposure to PBDEs or PFASs and executive function in children at ages 5 and 8 years.

2. Materials and methods

2.1. Study participants and design

Our sample consisted of participants enrolled between March 2003 and February 2006 in the Health Outcomes and Measures of the Environment (HOME) Study, an ongoing prospective birth cohort in the Greater Cincinnati area (Ohio, USA). To be enrolled in the study, women had to meet the following eligibility criteria: (1) ≥ 18 years of age; (2) 16 ± 3 weeks of gestation; (3) residing in a home built prior to 1978 (a criterion relating to a goal of the larger HOME Study examining lead exposures); (4) intending to continue prenatal care and deliver at any of the collaborating obstetric practices and hospitals; (5) HIV negative; and (6) not receiving seizure, thyroid, or chemotherapy/radiation medications. Of the 468 enrolled women, 65 dropped out prior to delivery, 3 delivered stillborn infants, and 10 delivered twins. From the 390 women who remained to deliver live singleton infants, we restricted our study to 256 mother–child pairs who had concentrations of PBDEs ($n=246$) or PFASs ($n=242$) measured at enrollment and at least one executive function assessment at age 5 ($n=201$) or 8 years ($n=222$). The study protocol was approved by the Institutional Review Boards at the Cincinnati Children's Hospital Medical Center and the Centers for Disease Control and Prevention (CDC).

2.2. Prenatal PBDE measurements

Maternal serum samples were collected at 16 ± 3 weeks of gestation and stored at -80 °C until analysis. Two grams of serum were used for measurements of PBDEs, with samples assigned to 24 sample batches (Jones et al., 2012; Sjodin et al., 2004). Every batch included three quality control and three method blank samples comprised of bovine serum (Gibco Inc., Grand Island, NY) diluted 1:40 with water, to reduce any target analytes in the blank serum to a level less than one order of magnitude lower than the limit of detection (LOD). No PBDEs were detected in the bovine serum prior to dilution. Measurements of PBDEs (BDE-17, -28, -47, -66, -85, -99, -100, -153, -154, and -183) were made using gas chromatography/isotope dilution-high resolution mass spectrometry using DFS instruments (ThermoFisher, Bremen, Germany) (Sjodin et al., 2004). Analytical data were corrected by subtracting the median blank value. The LODs were determined as the higher of 3 times the standard deviation (SD) of the method blanks analyzed or as instrumental LOD defined as the injected amount known to produce a signal/noise ratio >10. The LODs were 0.2–2.0 ng/g lipid (BDE-17, -28, -66, -85, -100, -153, -154, and -183), 0.3–8.2 ng/g lipid (BDE-47), and 0.2–5.7 ng/g lipid (BDE-99). We analyzed data of congeners with detection frequencies $>80\%$ (BDEs 28, 47, 99, 100, and 153) and total PBDEs (∑PBDEs), sum of BDE-28, -47, -99, -100, and -153, resulting in a total of 246 samples of PBDEs. Total serum lipids were determined based on measurements of triglycerides and total cholesterol using standard enzymatic methods (Phillips et al., 1989). Concentrations of PBDEs were expressed on a serum lipid basis (ng/g lipid).

2.3. Prenatal PFAS measurements

Maternal serum samples collected at 16 ± 3 weeks of gestation were also used to measure PFASs with additional subjects collected at 26 weeks of gestation (21 of 242 participants) and within 24 hours of parturition (56 of 242 participants). PFOA, PFOS, perfluorohexane sulfonate (PFHxS), PFNA, and perfluorodecanoate (PFDeA) were quantified using on-line solid-phase extraction coupled to high-performance liquid chromatography-tandem