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Prenatal and childhood perfluoroalkyl substances exposures and children's reading skills at ages 5 and 8 years

Hongmei Zhang[a], Kimberly Yolton[b], Glenys M. Webster[c], Xiaoyun Ye[d], Antonia M. Calafat[d], Kim N. Dietrich[e], Yingying Xu[b], Changchun Xie[e], Joseph M. Braun[f], Bruce P. Lanphear[c], Aimin Chen[e,*]

[a] Department of Environmental Health, School of Public Health, Shanxi Medical University, Taiyuan, Shanxi Province, China
[b] Division of General and Community Pediatrics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[c] BC Children's Hospital Research Institute, Simon Fraser University, Vancouver, British Columbia, Canada
[d] Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA, USA
[e] Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[f] Department of Epidemiology, Brown University School of Public Health, Providence, RI, USA

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ABSTRACT

Background: Exposure to perfluoroalkyl substances (PFASs) may impact children's neurodevelopment.
Objective: To examine the association of prenatal and early childhood serum PFAS concentrations with children's reading skills at ages 5 and 8 years.
Methods: We used data from 167 mother-child pairs recruited during pregnancy (2003–2006) in Cincinnati, OH, quantified prenatal serum PFAS concentrations at 16 ± 3 weeks of gestation and childhood sera at ages 3 and 8 years. We assessed children's reading skills using Woodcock-Johnson Tests of Achievement III at age 5 years and Wide Range Achievement Test-4 at age 8 years. We used general linear regression to quantify the covariate-adjusted associations between natural log-transformed PFAS concentrations and reading skills, and used multiple informant model to identify the potential windows of susceptibility.
Results: Median serum PFASs concentrations were PFOS > PFOA > PFHxS > PFNA in prenatal, 3-year, and 8-year children. The covariate-adjusted general linear regression identified positive associations between serum PFOA, PFOS and PFNA concentrations and children's reading scores at ages 5 and 8 years, but no association between any PFHxS concentration and reading skills. The multiple informant model showed: a) Prenatal PFOA was positively associated with higher children's scores in Reading Composite (β: 4.0, 95% CI: 0.6, 7.4 per a natural log unit increase in exposure) and Sentence Comprehension (β: 4.2, 95% CI: 0.5, 8.0) at age 8 years; b) 3-year PFOA was positively associated with higher children's scores in Brief Reading (β: 7.3, 95% CI: 0.9, 13.8), Letter Word Identification (β: 6.6, 95% CI: 1.1, 12.0), and Passage Comprehension (β: 5.9, 95% CI: 1.5, 10.2) at age 5 years; c) 8-year PFOA was positively associated with higher children's Word Reading scores (β: 5.8, 95% CI: 0.8, 10.7) at age 8 years. Prenatal PFOS and PFNA were positively associated with children's reading abilities at age 5 years, but not at age 8 years; 3-year PFOS and PFNA were positively associated with reading scores at age 5 years. But PFHxS concentrations, at any exposure windows, were not associated with reading skills.
Conclusion: Prenatal and childhood serum PFOA, PFOS and PFNA concentrations were positively associated with better children's reading skills at ages 5 and 8 years, but no association was found between serum PFHxS and reading skills.

Abbreviations: PFASs, perfluoroalkyl substances; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; IQ, Intelligence Quotient; HOME, Health Outcomes and Measures of the Environment; LOD, limits of detection; QCs, quality control materials; WJ-III, Woodcock-Johnson Tests of Achievement-III; WRAT-4, Wide Range Achievement Test 4; Ln, natural-log; NHANES, National Health And Nutrition Examination Survey

* Corresponding author at: Division of Epidemiology, Department of Environmental Health, University of Cincinnati College of Medicine, P.O. Box 670056, Cincinnati, OH 45267-0056, USA.
E-mail address: aimin.chen@uc.edu (A. Chen).

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1. Introduction

Perfluoroalkyl substances (PFASs) are a group of chemicals and widely used in textile coatings (Fromme et al., 2009; Gremmel et al., 2016), food contact materials (Trier et al., 2011), and consumer products (Kotthoff et al., 2015) due to their oil and water repellency. PFASs have been detected in household dust (Karaskova et al., 2016), contaminated food including milk, fish, dairy products, and drinking water (Eriksson et al., 2013; Fromme et al., 2009), and even in human fetal organs, placenta, and maternal plasma (Mamsen et al., 2017). The predominant exposure route is *via* contaminated diet for the general population (Mogensen et al., 2015; Papadopoulou et al., 2016). Transplacental and lactational exposure routes are common for the developing children (Apelberg et al., 2007; Mamsen et al., 2017; Mogensen et al., 2015; Papadopoulou et al., 2016).

Animal experiments indicated PFAS neurotoxic effects in rats and mice, as manifested by impaired cognitive function in mice following neonatal treatment with perfluorooctane sulfonate (PFOS) or perfluorohexane sulfonic acid (PFHxS) (Hallgren et al., 2015; Viberg et al., 2013), and in adult mice or developing rats following chronic PFOS treatment (Long et al., 2013; Wang et al., 2015a), and altered synaptic plasticity in rats with prenatally PFOS treatment (Wang et al., 2015a; Zeng et al., 2011). Human epidemiological studies are sparse, and more focused on the associations of PFASs with behavior development in children. For example, inverse associations of PFAS concentrations with behavior development were reported in Dutch 18-month boys (prenatal PFOA concentration and behavior) (Quaak et al., 2016), in Asian 2-year children (cord blood PFOS concentration and gross-motor development) (Chen et al., 2013), and in Asian 7-year children (cord blood PFNA concentration and behavior) (Lien et al., 2016). No associations were reported between prenatal PFOA and PFOS concentrations and behavior or motor coordination in Danish 7-year children (Fei and Olsen, 2011). Childhood higher serum perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) concentrations at ages 5 and 7 years were associated with more behavioral problems in Faroese 7-year children (Hoyer et al., 2015). However, few study reported on the association of PFAS concentration with cognitive development in children. A protective association was suggested between prenatal PFOA concentration and Full Scale Intelligence Quotient (IQ) in 6–12 years old children in the C8 Health Project (Stein et al., 2013). The inconsistent associations between behavior and cognition indicate the need to investigate the associations between PFAS concentration and specific aspect of neurodevelopment in children.

Reading skills are distinct functions in human species, which require a variety of cognitive processes including memory, concentration, visual perception, and discrimination. During the reading process, cortical neural networks are stimulated among reading-related brain regions (Aboitiz and Garcia, 1997; Friederici, 2011; Schoffelen et al., 2017). For example, reading development can reflect the connectivity of posterior middle temporal gyrus and inferior parietal lobule inside brain in children (Jefferies, 2013; Lee et al., 2016). The purpose of this study was to test the hypothesis that PFAS concentrations in maternal and children's sera are adversely associated with the development of children's reading skills.

2. Methods

2.1. Study subjects

We recruited 468 pregnant women between March 2003 and February 2006 in the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort, that is described in detail elsewhere (Braun et al., 2017). Eligible women were 16 ± 3 weeks' gestation, living in Cincinnati, OH, over 18 years old, did not take medicine for seizures or thyroid disorders during pregnancy, and did not have diabetes, hypertension or Human Immunodeficiency Virus infection. All participants provided written informed consent for themselves and their offspring. The HOME Study was approved by the Institutional Review Boards at the Cincinnati Children's Hospital Medical Center (CCHMC) and the Centers for Disease Control and Prevention (CDC). Three hundred and eighty-nine women delivered live singletons and continued to participate in the study. We excluded women and children with missing serum PFAS measures (n = 64), infants with congenital malformations or genetic abnormalities (n = 2), and children lost to follow-up and those who did not complete a reading assessment at ages 5 and 8 years (n = 156). The final 167 mother-child pairs were included in the current analysis.

2.2. Prenatal and childhood serum PFAS measurement

We obtained maternal blood samples at 16 ± 3 weeks of gestation at the time of recruitment, and obtained child blood samples at 3 and 8 years of age, separated the sera and stored them at −80 °C. The serum samples were shipped to the CDC for testing of environmental contaminants. Prenatal and childhood sera PFOA, PFOS, PFHxS and PFNA were quantified at the CDC's Persistent Organic Pollutants Biomonitoring Laboratory at the National Center for Environmental Health (NCEH), using online solid phase extraction coupled to liquid chromatography/isotope dilution tandem mass spectrometry (Kato et al., 2009) on a Symbiosis on-line SPE system (Spark Holland, Plainsboro, NJ) coupled with an API 4000 mass spectrometer (Applied Biosystems, Foster City, CA). Isotope-labeled internal standards for quantification included: $^{13}C_2$-PFOA, $^{13}C_4$-PFOS, $^{18}O_2$-PFHxS, $^{13}C_5$-PFNA. Calibration standards were spiked into calf serum to account for potential matrix effects (Kato et al., 2014). The limits of detection (LODs) were 0.1 ng/mL (PFOA, PFHxS, and PFNA), 0.082 ng/mL (prenatal PFNA), and 0.2 ng/mL (PFOS), respectively. To ensure the accuracy and reliability of the measuring data, each analytic batch of samples included reagent blanks, quality control materials (QCs) at low-concentration and high-concentration of PFASs, prepared from a calf serum pool. The variation coefficients of repeated measurements of the QCs were ~6% for prenatal samples within a period of almost ~1 year (Kato et al., 2011), and were ~8–11% for postnatal samples within a period of ~16 months (Calafat and Pirkle, 2013).

2.3. Reading ability assessments

Children's reading skills at age 5 years were assessed using the Woodcock-Johnson Tests of Achievement-III (WJ-III) (Woodcock et al., 2001). It yields the three subscales: Letter-Word Identification (identifying letters and reading individual words), Word Attack (ability to apply phonic and structural analysis when reading unfamiliar words), and Passage Comprehension (matching a symbol with an object's picture, pointing to the picture represented by a phrase, and identifying a missing key word within a passage based on contextual cues). Combining the WJ-III subscales generates two composite measures: Basic Reading (Letter-Word Identification + Word Attack) and Brief Reading (Letter-Word Identification + Passage Comprehension).

At age 8 years, we assessed children's basic academic reading skills using the Wide Range Achievement Test 4 (WRAT-4) (Wilkinson and Robertson, 2006), which was the most often used reading test in neuropsychology (Stevens and Price, 1999). Reading Composite combines scores from the two subscales: Word Reading (letter and word decoding) and Sentence Comprehension (ability to gain meaning from words and to comprehend ideas and information in sentences).

Trained and certified staff performed all reading assessments under supervision from a developmental psychologist (K.Y.). We converted the WJ-III or WRAT-4 raw scores to age-corrected norms according to manual instructions (Wilkinson and Robertson, 2006; Woodcock et al., 2001). The staff has no knowledge of serum PFASs concentrations before assessments. Age-standardized WJ-III or WRAT-4 scores had a population mean of 100 and a standard deviation of 15, with higher