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

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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

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None.

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.

Keywords

Prenatal; Childhood; Perfluoroalkyl substances (PFASs); Reading skills

1. Introduction

Perfluoroalkyl substances (PFASs) are a group of chemicals and widely used in textile coatings (Fromme et al. 2009; Gremmel et al. 2016; Heydebreck 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 (Johansson et al. 2009). 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. 2011) 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: $^{13}\text{C}_2$ -PFOA, $^{13}\text{C}_4$ -PFOS, $^{18}\text{O}_2$ -PFHxS, $^{13}\text{C}_5$ -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 scores indicating better reading skills.

2.4 Statistical analysis

These PFASs (PFOA, PFOS, PFHxS, PFNA) were detected in >90 % of prenatal and childhood serum samples. Prenatal or childhood serum PFASs concentrations <LOD were replaced with the LOD divided by the square root of 2 (Hornung and Reed 1990). The PFASs concentrations were not normally distributed and were natural-log (Ln) transformed (due to a lower range of concentrations) as similarly done in other studies (Apelberg et al. 2007; Chen et al. 2013; Stein et al. 2014). We used “prenatal PFAS”, “3-year PFAS”, and “8-year PFAS” to describe prenatal serum LnPFAS, children’s serum LnPFAS at ages 3 and 8 years, respectively. Pearson correlation was analyzed among different PFASs (PFOA, PFOS, PFHxS, PFNA) and at different times (prenatal, 3-year, and 8-year). The approximate linearity between serum PFASs concentrations and reading scores was confirmed using the generalized additive models of spline regression. Then we used general linear regression to examine the associations of serum PFAS concentrations with children’s reading scores, and used the multiple informant models with a non-standard version of generalized estimating equations (GEE) (Sanchez et al. 2011) to examine potential critical windows of susceptibility of serum PFASs concentrations on children’s reading skills. The associations between quartiles of PFASs and WRAT-4 Reading Composite were assessed for linear trend using the median value in each quartile as a continuous variable in the regression models (Greenland 1995).

The covariates included in final regression models were based on the prior knowledge, and their significant associations with both exposure (PFAS concentration) and outcome (reading score) ($p < 0.05$) by use of analysis of variance (ANOVA) or t-test for continuous variables or chi-square test for categorical variables, and then the change-of-estimate method (add or remove one covariate at a time and watch if change is >10% in regression coefficient of the exposure). Final models included the following 8 covariates: maternal race, age, education, parity, household-income, breastfeeding duration (weeks), maternal smoking (serum cotinine concentration, ng/mL), maternal IQ (assessed by Wechsler Abbreviated Scale of Intelligence, continuous) (Wechsler 1999), and the Home Observation for Measurement of the Environment (HOME) score measured at the 1-year home visit to describe the quality of the care-giving environment (Caldwell and Bradley 1984). We additionally estimated the regression coefficients of PFASs with adjustment for additional potential covariates including marital status, depression assessed by Beck Depression Inventory II at enrollment (Beck et al. 1996), fish consumption during pregnancy (total times of fish-containing meals from the baseline visit to childbirth, continuous), and child sex in separate models to determine whether regression estimates and interpretation changed.

We performed the spline regression in R 3.2 (R Developmental Team) mgcv package, and conducted statistical analyses for all available subjects and a subset of subjects having reading skills assessed at both 5 and 8 years of age using SAS 9.4 (SAS Institute Inc., NC, USA). Statistical significance was set at a two-sided p value of 0.05. We provided regression coefficients (β) and 95% confidential intervals (95% CIs) for the associations examined.

3. Results

This analysis was based on 167 mother-child pairs who had serum samples available for measuring PFAS concentrations at 16 ± 3 weeks of gestation, at ages 3 and 8 years in children, and had children's reading scores measured at ages 5 or 8 years. We found no significant difference in prenatal serum PFAS concentrations and demographic characteristics between the 167 subjects included in this analysis and those not included (data not shown).

3.1 Participant characteristics

Prenatal median serum concentrations of PFASs were 5.4 ng/mL (PFOA), 13.0 ng/mL (PFOS), 1.5 ng/mL (PFHxS), and 0.9 ng/mL (PFNA) in HOME Study participants (Table 1), and the comparisons with National Health And Nutrition Examination Survey (NHANES) are shown in Figure 1. Prenatal serum PFASs concentrations were correlated with those in 3-year serum ($r: 0.21-0.48, p<0.01$) and 8-year serum in children ($r: 0.15-0.65, p<0.05$). Pearson correlation coefficients among the 4 PFASs compounds were 0.08–0.63 in prenatal serum ($p<0.01$), 0.28–0.68 in 3-year children serum ($p<0.01$), and 0.22–0.39 in 8-year children serum ($p<0.05$) (Supplement material, Table S1).

The majority of women in the HOME Study were 25–34 years of age at delivery (63%), with college education or above (77%), non-Hispanic White (63%), multiparous (55%), married or living with a partner (79%), had middle or high level of household income ($> \$40,000/y$, 77%). Most of them did not smoke tobacco (90%), did not drink alcohol (56%), but ate fish-containing food (84%) during pregnancy, and breastfed their babies after delivery (84%) (Table 2). The median breastfeeding duration is 23 weeks. Prenatal serum PFOA concentration was significantly increased in women who were non-Hispanic White ($p=0.005$), nulliparous ($p<0.001$), or had middle or high household income ($> \$40,000/y$) ($p=0.045$). Prenatal serum PFOA concentrations did not differ by maternal age, education, marital status, smoking, fish-consumption during pregnancy, and child sex. Moreover, the breastfed children had significant higher serum PFOA concentrations at ages 3 years ($p<0.0001$) and 8 years ($p=0.039$) as compared to the non-breastfed children. Prenatal serum, 3-year, and 8-year PFASs concentrations were comparable between boys and girls (data not shown).

Children's average reading subset scores at ages 5 and 8 years ranged from 104 to 119 (Table 3). Reading scores at age 5 and 8 years showed normal distributions and were highly correlated with each other ($r=0.61$ between Basic Reading and Reading composite, $p<0.0001$) (Supplement material, Table S2). Children had higher reading composite scores at age 8 years if their mothers were >25 years old at enrollment ($p<0.0001$), above college education level ($p<0.0001$), non-Hispanic White ($p<0.0001$), nulliparous at enrollment ($p=0.074$), married or living with partners ($p=0.0004$), had middle or higher level of household income ($> \$40,000/y$) ($p<0.0001$), and when the child was reared in a higher quality care-giving environments (HOME inventory score ≥ 40) ($p<0.0001$) (Table 1). Considering the very different sample sizes of secondhand tobacco exposure (ETS, $n=12$) and active smokers ($n=4$) among the total participants ($n=167$), we combined ETS and active smokers into one subgroup, and found a significant decrease in reading composite score at

age 8 years as compared to the non-smokers ($p=0.001$). Reading composite score was significantly higher in the breastfed children than the non-breastfed children in this study ($p=0.036$). In addition, reading composite score at age 8 years did not significantly differ by maternal alcohol-drinking, fish-consumption during pregnancy, depression, and child sex.

3.2 Serum PFASs concentrations and children reading scores

Serum PFOA and PFOS concentrations were positively related to children's reading scores at age 5 and 8 years in the Spline regression models (Supplement material, Figure S1). In trend test, Passage Comprehension score ($p=0.071$) at age 5 years showed an increasing trend with 3-year serum PFOA concentration, and Reading Composite score ($p=0.079$) and Word Reading score ($p=0.081$) at age 8 years showed increasing trends with prenatal serum PFOS concentration. In unadjusted general linear regression, prenatal, 3-year, and 8-year PFOA, PFOS, and PFNA were positively associated with higher reading scores at ages 5 and/or 8 years (Supplement material, Table S3). No association was found between PFHxS and reading scores ($p>0.05$).

After adjusting for the covariates in general linear models (Table 4), significant associations for PFOA remained between prenatal exposure and Passage Comprehension score at age 5 years, between 3-year exposure and Brief Reading, Letter Word Identification, Passage Comprehension scores at age 5 years, and between 8-year exposure and Word Reading score at age 8 years. For PFOS exposures, 3-year exposure was positively associated with Passage Comprehension score with marginal significance and 8-year exposure was significantly associated with Word Reading score. No associations were found between serum PFHxS concentrations and reading scores at age 5 or 8 years. Prenatal serum PFNA concentration was positively associated with Basic Reading, Brief Reading at age 5 years, as well as Reading Composite and Sentence comprehension scores at age 8 years.

3.3 Potential windows of susceptibility for PFASs in association with reading scores

In unadjusted multiple informant models, prenatal, 3-year, and 8-year serum PFASs concentrations was positively associated with higher reading scores at ages 5 and/or 8 years (Supplement material, Table S4). When adjusted for the covariates in the multiple informant models (Table 5), prenatal serum PFOA concentrations were positively associated with Reading Composite (β : 4.0, 95% CI: 0.6, 7.4) ($p=0.023$) and Sentence Comprehension (β : 4.2, 95% CI: 0.5, 8.0) ($p=0.028$) at age 8 years. The 3-year PFOA concentrations were positively associated with scores of Brief Reading, Letter Word Identification, and Passage Comprehension at age 5 years, but not at age 8 years. The 8-year serum PFOA concentrations were positively associated with Word Reading scores measured concurrently. Prenatal PFOS concentrations were associated with Word Attack score at age 5 years, Reading Composite (β : 3.6, 95% CI: 1.0, 6.2) ($p=0.007$), Word Reading (β : 3.4, 95% CI: 0.5, 6.2) ($p=0.020$), and Sentence Comprehension (β : 3.8, 95% CI: 1.0, 6.7) ($p=0.009$) at age 8 years. The 8-year PFOS concentrations were significantly associated with Word Reading score (β : 4.7, 95% CI: 1.1, 8.2) ($p=0.011$), and marginally associated with Reading Composite score (β : 3.3, 95% CI: -0.4, 7.0) ($p=0.080$) at age 8 years. Several reading scores at ages 5 and 8 years were higher in children with increased prenatal PFNA exposure. No

associations were found between serum PFHxS concentrations with reading score at age 5 or 8 years.

Additional adjustment for maternal marital status, depression, fish consumption, and child sex in general linear models or GEE models slightly attenuated the estimates, but did not change the associations (see Supplement Materials Table S5–6). The results also did not appreciably change when we examined the subset of children who had reading skills data at both 5 and 8 years of age (n=148).

4. Discussion

In the HOME Study, we examined the association of PFAS concentrations in prenatal serum at 16±3 weeks of gestation and in childhood sera at ages 3 and 8 years with children's reading abilities at two time points of ages 5 and 8 years, and identified the potential critical windows of susceptibility. Opposite to our hypothesis, both maternal and children's serum PFOA, PFOS and PFNA concentrations are positively associated with children's better reading skills at ages 5 and 8 years, while no associations were found for PFHxS exposures. The results and interpretation did not significantly change when we additionally adjusted for other potential covariates.

To our knowledge, few previous studies have examined the association of repeated measurements of prenatal and childhood serum PFAS concentrations and repeated measures of child's reading abilities. Only one prior study has examined associations between prenatal and childhood PFOA concentrations and children's reading skills. The U.S. C8 Health Project (2005–2006) recruited children in a Mid-Ohio Valley community highly exposed to PFOA through contaminated drinking water, reported a higher Full Scale IQ (β : 4.6, 95% CI: 0.7, 8.5) at age 6–12 years in children with the highest quartile of prenatal PFOA concentration (estimated), compared to those in the lowest quartile (Stein et al. 2013). The authors also examined the association of prenatal PFOA (estimated) or child PFOA concentration (measured 3–4 years before outcome measurement) with Reading Fluency (a composite of Word Attack and Decoding, using the Wechsler Individual Achievement Test-II), and Instruction Comprehension and Word Generation (using the NEPSY-II), and found that the modeled prenatal PFOA was not associated with reading skills (n=320). The median prenatal PFOA concentration in the C8 cohort (43.7 ng/mL) is 8-fold higher than those concentrations in the HOME Study (5.4 ng/mL), and 17-fold higher than those in U.S. pregnant women (2.6 ng/mL). Moreover, Stein et al. (2013) only considered PFOA, the average age of children was 5.7±1.8 years at serum PFOA measurement, and was 9.9±1.7 years (range 6–12) at neuropsychological assessment. In contrast, our study measured prenatal and childhood serum concentrations of 4 different PFASs at ages 3 and 8 years, and assessed children's reading skills twice at ages 5 and 8 years. In a Taiwan birth cohort study, prenatal PFNA concentration (median: 1.4 ng/mL) was inversely associated with children's Verbal IQ (β : -2.1, 95% CI: -3.9, -0.2) at age 8 years (n=120) (Wang et al. 2015b), however, Wang et al (2015) did not adjusted potential confounding factors, such as maternal age, smoking, parity, maternal IQ, and breastfeeding duration. The difference in reading skills findings between the HOME Study and the C8 cohort may be due to measurements of PFASs, exposure levels, reading skills assessments, or residual confounding.

Recently, animal experiments showed PFOA treatment did not cause cognitive deficit in adult rats (Kawabata et al. 2017), although the habituation defects and behavior problem were induced in adult mice following neonatal PFOA, PFOS or PFHxS administration (Johansson et al. 2008; Viberg et al. 2013). Similarly, despite the neurotoxic effect of PFASs was demonstrated by the reduced cell viability, and increased reactive stress and cell apoptosis *in vitro* (Lee et al. 2012; Mashayekhi et al. 2015; Reistad et al. 2013), PFASs were also identified some contradictory effects. Some essential proteins required for normal brain development (neuronal survival, growth, and synaptogenesis) including calcium/calmodulin-dependent protein kinase II (CaMKII), growth-associated protein-43 (GAP-43), synaptophysin, and tau were significantly increased in hippocampus or cerebral cortex in neonatal mice following an oral administration with PFOA, PFOS or PFHxS on postnatal day 10 (Johansson et al. 2009; Lee and Viberg 2013). PFOS promoted PC12 cells differentiating into the acetylcholine phenotype at the cost of the dopamine phenotype, while PFOA showed little or no effect on phenotypic specification (Slotkin et al. 2008). PFOA affected metabolism of amino acids, lipids, carbohydrates and energetics in brain of mice (Yu et al. 2016), increased concentrations of serotonin and dopamine, and decreased norepinephrine concentration at a PFOA concentration (mean: 29.3 µg/mL) in mice (Yu et al. 2016).

This study has several strengths and limitations. We repeatedly assessed children's reading abilities, an often-neglected area of child neurodevelopment in studies of environmental pollutants, highlighted the importance of understanding the potential impact of PFASs exposure during pregnancy and childhood on children's reading skills. We quantified serum PFAS concentrations at early pregnancy and developmental childhood at ages 3 and 8 years, successfully followed up into school age when reading assessments become more stable, and assessed children's reading abilities at two time points of ages 5 and 8 years. We adjusted for potential covariates including maternal race, IQ and breastfeeding duration, and quality of the home environment, assessed the potential window of susceptibility of PFAS concentrations on children's reading abilities using multiple informant models, taking into account the repeated exposure measures. With the inherent correlation between subscales and composite scores of reading skills, multiple informant models reduced the overall number of regression models. We observed a pattern of several positive associations that are likely not due to statistical chance findings.

Nevertheless, residual confounding cannot be ruled out in our study despite our efforts to adjust for a large set of covariates. Although we compared the characteristics between these participants in this analytic dataset and the excluded children and did not find differences, selection bias could not be entirely ruled out. The coexisting of higher socioeconomic status and higher PFAS exposure levels may have a role in the development of reading skills in the study children. As reading skills further improve over the elementary and junior high school period, our results cannot be directly extrapolated to later childhood and adolescence.

5. Conclusion

Prenatal serum PFOA, PFOS and PFNA concentrations were positively associated with reading abilities at ages 5 and 8 years, and children's 3-year serum PFOA and PFOS

concentrations were positively associated with reading abilities at age 5 years, but not at age 8 years. 8-year serum PFOA and PFOS concentrations in children were associated with increased Word Reading at age 8 years. Unlike the other PFASs, serum PFHxS concentrations were not associated with reading skills in our study. Despite the pattern of positive associations, the results should not be interpreted as a beneficial role of PFASs in child language development; at most, the interpretation is we did not observe an adverse impact in this study population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

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Highlights

- PFASs exposure may impact children's neurodevelopment.
- We investigated the association of prenatal and childhood serum PFASs concentrations with children's reading skills.
- Prenatal and childhood PFOA, PFOS and PFNA concentrations were positively associated with better children's reading ages 5 and 8 years.
- No associations were found between PFHxS concentration and reading skills in children.

Figure 1.

Medians of PFASs concentrations in prenatal serum, and in children's serum at ages 3 and 8 years.

^: Bars present the p75 percentile of PFASs concentrations in the HOME Study. We referenced prenatal median serum PFASs concentration (pregnant women or general women, NHANES, 2003–2004) or children's mean PFAS concentrations (NHANES, 2001–2002, pooled sera from 3–11 years of age children), the IQR or p25 and p75 percentiles was not provided in the publications (Kato et al. 2009; Woodruff et al. 2011). The Kato et al. reported the mean concentrations of the pooled samples in children, it is not the same median as we used in the HOME study.

Table 1

Serum PFASs concentrations during pregnancy and childhood at ages 3 and 8 years [median(p25, p75), n=167, ng/mL serum]

PFASs	prenatal	3-year	8-year
PFOA	5.4 (3.6, 7.3)	5.5 (3.9, 7.7)	2.4 (1.8, 3.2)
PFOS	13.0 (9.1, 17.8)	6.6 (4.6, 10.2)	3.6 (2.7, 4.9)
PFHxS	1.5 (0.9, 2.4)	1.9 (1.0, 3.3)	1.2 (0.9, 1.8)
PFNA	0.9 (0.7, 1.1)	1.2 (1.0, 1.8)	0.7 (0.5, 1.1)

Table 2

Participant's demographic characteristics [n (%)], prenatal serum PFOA concentrations [median (p25, p75)], and reading composite scores at age 8 years (mean $\pm$ SD)

Participant's characteristics	n (%)	prenatal PFOA concentration	Reading Composite score at age 8
Maternal age (yrs)	29.84 $\pm$ 5.59		
<25 yrs	37 (22.3)	5.8 (4.2, 7.4)	99.97 $\pm$ 17.13
25–34 yrs	104 (62.7)	5.1 (3.7, 7.2)	110.84 $\pm$ 15.03 [*]
35 yrs	25 (15.0)	5.6 (3.8, 9.1)	118.17 $\pm$ 13.41 [*]
Maternal education			
High school or less	38 (22.9)	4.9 (3.5, 7.2)	97.74 $\pm$ 16.54
Some college or 2 year degree	44 (26.5)	5.5 (3.7, 7.2)	105.26 $\pm$ 15.00 [*]
Bachelor's degree	56 (33.7)	5.6 (4.1, 8.9)	117.57 $\pm$ 13.00 [*]
Graduate or professional degree	28 (16.9)	6.2 (3.9, 8.3)	117.33 $\pm$ 11.01 [*]
Maternal race			
Non-Hispanic White	104 (62.65)	5.9 (4.0, 8.4)	115.00 $\pm$ 13.37
Non-Hispanic Black and Others	62 (37.35)	5.1 (3.6, 6.3) [*]	100.03 $\pm$ 16.77 [*]
Maternal parity			
Nulliparous	74 (44.6)	6.5 (5.1, 9.2)	112.84 $\pm$ 17.33
Parity=1	49 (29.5)	4.4 (3.5, 6.1)	106.75 $\pm$ 15.55 [#]
Parity>1	43 (25.9)	4.4 (3.3, 7.1)	106.19 $\pm$ 14.82 [#]
Marital status			
Married or living with partner	131 (78.9)	5.5 (3.7, 7.7)	112.03 $\pm$ 17.46
Not married, living alone	35 (21.1)	5.5 (4.2, 7.2)	100.61 $\pm$ 17.88 [*]
Household income			
<\$40,000/yr	38 (22.9)	4.5 (3.5, 6.1)	94.91 $\pm$ 16.02
40,000–79,999/yr	85 (51.2)	5.8 (4.4, 7.2) [*]	111.88 $\pm$ 13.59 [*]
\$80,000/yr	43 (25.9)	5.5 (3.6, 9.0) [*]	118.47 $\pm$ 12.22 [*]
Maternal Full Scale IQ	105.60 $\pm$ 15.80		
HOME inventory score at 1 year home visit	38.92 $\pm$ 5.56		
40	105 (65.2)	5.6 (3.9, 7.6)	115.21 $\pm$ 13.41
35–39	26 (16.2)	4.2 (2.5, 6.3)	106.21 $\pm$ 15.85 [*]
<35	30 (18.6)	4.9 (3.8, 7.3)	95.00 $\pm$ 15.66 [*]
Maternal smoking			
Non smoker (serum cotinine < 1 ng/ml)	151 (90.4)	5.8 (3.8, 7.9)	110.61 $\pm$ 15.56
Secondhand tobacco exposure (1 ng/ml serum cotinine < 10 ng/ml)	12 (7.2)	5.4 (3.9, 6.2)	90.90 $\pm$ 17.82 [*]
Active smoker (serum cotinine 10 ng/ml)	4 (2.4)	5.2 (3.6, 7.0)	116.33 $\pm$ 9.29
Maternal alcohol use			

Participant's characteristics	n (%)	prenatal PFOA concentration	Reading Composite score at age 8
Never drank alcohol	93 (56.0)	5.4 (3.7, 7.0)	107.43 ± 17.81
<1 drink/month	56 (33.7)	5.2 (3.8, 7.5)	112.23 ± 13.91
>1 drink/month or binge	17 (10.2)	7.7 (5.1, 10.3)	109.87 ± 15.50
Maternal fish-consumption during pregnancy			
Yes	142 (84.5)	5.5 (3.7, 7.6)	110.00 ± 16.44
No	26 (15.5)	5.5 (4.4, 6.5)	104.70 ± 15.66
Maternal depressive symptoms during pregnancy	10.02 ± 7.04		
Minimal or mild (19)	151 (91.5)	5.6 (3.9, 7.7)	109.50 ± 16.35
Moderate or severe (>19)	14 (8.5)	4.8 (3.3, 5.5)	109.80 ± 15.09
Breastfeeding			
Yes	140 (84.3)	5.9 (4.1, 8.1) ^a	110.60 ± 15.97
No	26 (15.7)	3.7 (3.2, 4.7) ^{a*}	103.00 ± 15.70 [*]
Child sex			
Male	74 (44.0)	5.1 (4.3, 9.8)	108.00 ± 16.27
Female	93 (56.0)	5.6 (3.6, 7.8)	110.30 ± 16.50

[^]: HOME, Home Observation for Measurement of the Environment; IQ, Intelligence Quotience.

^{*}: $p < 0.05$,

[#]: $p < 0.10$.

^a: 3-year serum PFOA concentration in children.

Table 3Children's reading scores at ages 5 and 8 years (mean $\pm$ SD)

Reading assessment	Score
WJ-III Score at age 5 (n=167)	
Basic Reading	110.05 $\pm$ 18.12
Brief Reading	104.42 $\pm$ 17.24
Letter Word	106.18 $\pm$ 15.99
Passage Comprehension	100.56 $\pm$ 11.31
Word Attack	119.83 $\pm$ 14.44
WRAT-4 Score at age 8 (n=158)	
Reading Composite	108.73 $\pm$ 16.41
Word Reading	108.50 $\pm$ 14.44
Sentence Comprehension	107.76 $\pm$ 19.25

[^]: WJ-III, Woodcock-Johnson Tests of Achievement-III; WRAT-4, Wide Range Achievement Test-4.

Table 4

Adjusted β coefficients (95% CIs) in the general linear models of child's reading scores with serum PFASs concentrations

Serum PFAS concentrations	WJ-III Score at age 5 years				WRAT-4 Score at age 8 years			
	Basic Reading	Brief Reading	Letter Word Identification	Passage Comprehension	Word Attack	Reading Composite	Word Reading	Sentence Comprehension
Prenatal PFOA	0.7 (-4.9, 6.2)	3.7 (-1.8, 9.3)	2.0 (-3.1, 7.1)	3.8 (0.1, 7.7)*	0.5 (-5.1, 6.1)	3.5 (-1.1, 8.2)	2.3 (-2.1, 6.7)	3.7 (-1.6, 9.0)
3-year PFOA	6.4 (-1.6, 14.1)	10.4 (2.8, 18.1)*	9.2 (2.1, 16.3)*	8.5 (3.3, 13.7)*	4.9 (-2.0, 11.8)	2.8 (-3.1, 8.8)	1.0 (-4.7, 6.7)	3.1 (-4.1, 10.1)
8-year PFOA	--	--	--	--	--	2.6 (-3.1, 8.2)	6.1 (0.9, 11.3)*	-0.1 (-6.6, 6.4)
Prenatal PFOS	3.2 (-2.0, 8.3)	2.9 (-2.2, 8.1)	2.0 (-2.7, 6.8)	1.7 (-1.9, 5.3)	4.1 (-1.2, 9.5)	3.1 (-1.3, 7.5)	3.1 (-1.0, 7.3)	3.2 (-1.8, 8.2)
3-year PFOS	1.1 (-4.8, 7.0)	3.2 (-2.6, 9.1)	2.1 (-3.4, 7.5)	3.5 (-0.5, 7.6)#	2.8 (-2.8, 8.4)	1.6 (-3.1, 6.4)	-0.3 (-4.8, 4.3)	2.5 (-3.1, 8.1)
8-year PFOS	--	--	--	--	--	2.6 (-1.7, 6.9)	4.4 (0.3, 8.4)*	1.6 (-3.3, 6.5)
Prenatal PFHxS	-0.1 (-3.9, 3.8)	0.1 (-3.8, 3.9)	0.4 (-3.8, 3.9)	-0.4 (-3.1, 2.3)	0 (-3.7, 3.7)	1.4 (-2.0, 4.7)	0.5 (-2.7, 3.7)	1.8 (-2.0, 5.6)
3-year PFHxS	-1.2 (-4.8, 2.4)	-0.6 (-4.2, 3.0)	0 (-3.3, 3.3)	0.1 (-2.4, 2.5)	0.2 (-3.4, 3.8)	0 (-2.8, 2.8)	-0.7 (-2.8, 2.8)	1.1 (-2.3, 4.4)
8-year PFHxS	--	--	--	--	--	0.8 (-2.32, 3.8)	0.8 (-2.1, 3.8)	1.1 (-2.4, 4.6)
Prenatal PFNA	5.9 (-0.9, 12.7)#	6.6 (-0.2, 13.5)#	4.3 (-2.0, 10.5)	3.8 (-1.0, 8.6)	5.3 (-1.4, 12.0)	5.7 (0, 11.3)*	3.6 (-1.7, 8.9)	5.6 (-0.9, 12.1)#
3-year PFNA	2.5 (-2.4, 7.3)	2.7 (-2.2, 7.5)	2.5 (-2.0, 7.0)	2.2 (-1.2, 5.5)	5.9 (1.0, 10.8)*	0.3 (-3.6, 4.1)-0.1	0.6 (-3.1, 4.2) 1.5	-0.6 (-5.2, 3.9)
8-year PFNA	--	--	--	--	--	-0.1 (-3.6, 3.5)	1.5 (-1.8, 4.9)	-0.6 (-4.6, 3.4)

^ : Adjusted for maternal age, race, education, household-income, parity, smoking (serum cotinine concentration, ng/mL), maternal IQ, breastfeeding duration (weeks), and HOME score.

* : $p < 0.05$,# : $p < 0.10$.

Table 5

Adjusted β coefficients (95% CIs) in the multiple informant models of child's reading scores with serum PFASs concentrations

Serum PFAS concentrations	WJ-III Score at age 5 years				WRAT-4 Score at age 8 years			
	Basic Reading	Brief Reading	Letter Word Identification	Passage Comprehension	Word Attack	Reading Composite	Word Reading	Sentence Comprehension
Prenatal PFOA	1.1 (-3.9, 6.2)	3.8 (-1.8, 9.3)	2.3 (-2.5, 7.0)	3.6 (-0.2, 7.4) [#]	0.6 (-4.1, 5.2)	4.0 (0.6, 7.4) [*]	2.7 (-0.5, 5.8)	4.2 (0.5, 8.0) [*]
3-year PFOA	4.3 (-1.3, 9.9)	7.3 (0.9, 13.8) [*]	6.6 (1.1, 12.0) [*]	5.9 (1.5, 10.2) [*]	3.1 (-1.5, 7.8)	2.4 (-1.6, 6.5)	2.0 (-1.6, 5.6)	2.3 (-2.6, 7.2)
8-year PFOA	--	--	--	--	--	3.2 (-1.9, 8.3)	5.8 (0.8, 10.7) [*]	0.8 (-5.5, 7.1)
Prenatal PFOS	3.2 (-0.9, 7.3)	2.9 (-1.4, 7.2)	2.2 (-1.5, 5.9)	1.6 (-1.4, 4.6)	4.2 (-0.1, 8.4) [#]	3.6 (1.0, 6.2) [*]	3.4 (0.5, 6.2) [*]	3.8 (1.0, 6.7) [*]
3-year PFOS	1.1 (-3.3, 5.5)	3.0 (-1.8, 7.8)	2.1 (-2.0, 6.2)	3.0 (-0.1, 6.1) [#]	2.0 (-1.5, 5.4)	1.9 (-1.1, 4.9)	0.9 (-1.7, 3.5)	2.4 (-1.1, 6.0)
8-year PFOS	--	--	--	--	--	3.3 (-0.4, 7.0) [#]	4.7 (1.1, 8.2) [*]	2.3 (-2.2, 6.8)
Prenatal PFHxS	-0.2 (-3.1, 2.6)	0 (-2.9, 2.9)	0.4 (-2.2, 3.0)	-0.3 (-2.5, 1.8)	0.1 (-2.8, 3.0)	1.8 (-0.6, 4.1)	0.7 (-1.4, 2.9)	2.3 (-0.3, 4.9)
3-year PFHxS	-1.1 (-4.2, 2.0)	-0.4 (-3.4, 2.6)	0.2 (-2.8, 3.2)	0.2 (-1.8, 2.1)	0 (-2.9, 2.9)	0.3 (-1.7, 2.2)	-0.2 (-1.9, 1.5)	1.2 (-1.2, 3.6)
8-year PFHxS	--	--	--	--	--	0.8 (-1.5, 3.2)	0.8 (-1.7, 3.3)	1.1 (-1.7, 3.9)
Prenatal PFNA	5.6 (0.7, 10.5) [*]	5.9 (1.2, 10.7) [*]	3.9 (-0.8, 8.7)	3.2 (-0.3, 6.7) [#]	4.7 (0.1, 9.5) [*]	5.5 (2.1, 9.0) [*]	3.4 (0.1, 6.7) [*]	5.6 (1.6, 9.6) [*]
3-year PFNA	2.0 (-2.2, 6.1)	2.1 (-1.9, 6.4)	2.2 (-1.4, 5.8)	1.7 (-1.2, 4.7)	4.7 (0.2, 9.3) [*]	0.2 (-2.1, 2.5)	0.7 (-1.5, 2.9)	-0.5 (-3.6, 2.5)
8-year PFNA	--	--	--	--	--	0.3 (-3.6, 4.2)	1.8 (-1.5, 5.0)	-0.3 (-5.0, 4.4)

[^] : Adjusted for maternal age, race, education, household-income, parity, smoking (serum cotinine concentration, ng/mL), maternal IQ, breastfeeding duration (weeks), and HOME score.^{*} : $p < 0.05$,[#] : $p < 0.10$.