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Prenatal and childhood exposure to poly- and perfluoroalkyl substances (PFAS) and cognitive development in children at age 8 years

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Abstract

Background: Toxicological studies indicate that poly- and perfluoroalkyl substances (PFAS) may be neurotoxic, but human studies have yet to provide compelling evidence for PFAS' impact on cognitive abilities.

Objective: To test whether prenatal and childhood PFAS are associated with cognitive abilities at 8 years and whether sex modifies these associations.

Methods: We included 221 mother-child pairs from the Health Outcomes and Measures of the Environment (HOME) Study, a birth cohort in Cincinnati, OH (USA). We quantified PFAS in maternal serum at 16±3 weeks gestation and in child serum at 3 and 8 years. We used the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) at age 8 years, assessing Full Scale IQ (FSIQ), verbal comprehension, perceptual reasoning, working memory, and processing speed. We

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used multiple informant models to estimate covariate-adjusted differences in WISC-IV scores by repeated ln-transformed PFAS.

Results: Prenatal and childhood perfluorooctane sulfonate (PFOS) and perfluorohexane sulfonate (PFHxS) were not associated with WISC-IV measures. We observed an increase of 4.1-points (95% CI 0.3, 8.0) and 5.7-points (95% CI 1.2, 10.2) in working memory with 1-ln unit increase in prenatal perfluorooctanoate (PFOA) and perfluorononanoate (PFNA), respectively. In addition, PFNA at 3 years was associated with better FSIQ and perceptual reasoning. Child sex modified the relationship between prenatal PFOA and FSIQ; the association was positive in females only. Sex also modified the association between concurrent PFOS and FSIQ, with males having higher scores.

Conclusion: We did not observe adverse associations between prenatal and childhood PFAS and cognitive function at age 8 years.

Keywords

Poly – and perfluoroalkyl substances (PFAS); neurodevelopment; cognitive development; IQ; prenatal; childhood

1. Introduction

Poly- and perfluoroalkyl substances (PFAS) are anthropogenic chemicals that are widely used as processing aids in fluoropolymer manufacturing due to their stability and amphipathic properties. They are highly persistent and pervasive in the environment because the strong C-F bond makes them resistant to degradation (Lindstrom et al. 2011). As such, several PFAS have been detected in a wide range of environmental media worldwide, including water, soil, sediment, wildlife, and humans (Lau et al. 2007). Human exposure to PFAS occurs primarily via oral ingestion of contaminated food, water, and dust (Fromme et al. 2009), with half-lives ranging from 2-9 years in humans (Li et al. 2018; Olsen et al. 2007).

PFAS may impact child neurodevelopment. Toxicological studies have shown that PFAS exposure during development impacts cognition and behavior in mice (Fuentes et al. 2007; Johansson et al. 2008; Johansson et al. 2009). A number of mechanisms have been proposed to explain how PFAS may negatively affect brain development, including affecting synaptogenesis and synaptic plasticity by altering neuroprotein and neurotransmitter levels, disrupting neural cell differentiation, increasing neuronal cell apoptosis and oxidative stress, and thyroid hormone disruption (Berntsen et al. 2017; Eggers Pedersen et al. 2015; Johansson et al. 2009; Lee and Viberg 2013; Lee et al. 2013; Lee et al. 2016; Liu et al. 2013; Liu et al. 2015; Long et al. 2013; Reistad et al. 2013; Slotkin et al. 2008; Yu et al. 2016). Despite the observed biological mechanisms for PFAS neurotoxicity, epidemiological studies have been inconclusive about PFAS' potential to affect cognitive development. Cohort studies from Denmark, Great Britain, Japan, Taiwan, and the United States that examined the relationship between prenatal and childhood PFAS and cognition have reported discordant findings, with associations that were adverse (Chen et al. 2013; Wang et al. 2015), protective (Stein et al. 2013), null (Strom et al. 2014), and mixed (Fei et al. 2008;

Goudarzi et al. 2016; Harris et al. 2018; Jeddy et al. 2017; Liew et al. 2018). Only two studies have investigated associations between PFAS concentrations during childhood and cognitive development (Harris et al. 2018; Stein et al. 2013). In addition, only one study examined whether there was sexual dimorphism present between these associations and reported inconsistent patterns (Harris et al. 2018).

We utilized the Health Outcomes and Measures of the Environment (HOME) Study to examine the hypothesis that prenatal and childhood PFAS were associated with poorer cognitive development in children at age 8 years. We further considered whether any associations were modified by child sex.

2. Materials and methods

2.1 Study participants

We analyzed data from the HOME Study, a prospective pregnancy and birth cohort study of environmental contaminants in the greater Cincinnati area (Ohio, USA). Details of the HOME Study have been published elsewhere (Braun et al. 2017). In brief, women were identified using medical scheduling systems of nine prenatal practices affiliated with three hospitals in the region. A total of 468 women in their second trimester of pregnancy (16 ± 3 weeks of gestation) were enrolled in the study from 2003-2006. Of these women, 66 dropped out before the delivery of the child, 9 delivered sets of twins, and 3 had stillbirths. Of the 390 women who delivered liveborn singleton infants, we used data from mother-child pairs with information on prenatal or childhood PFAS measurements as well as cognitive assessments at age 8 years, yielding an analytic sample of 221 (57%) participants. This study was approved by the institutional review board (IRB) at the Cincinnati Children's Hospital Medical Center (CCHMC); the Centers for Disease Control and Prevention (CDC) and collaborating institutions relied on CCHMC's IRB as the IRB of record.

2.2 Assessment of PFAS

We used on-line solid-phase extraction coupled to high-performance liquid chromatography-isotope dilution mass spectrometry to quantify: 1) perfluorooctanoate (PFOA); 2) perfluorooctane sulfonate (PFOS); 3) perfluorohexane sulfonate (PFHxS); and 4) perfluorononanoate (PFNA) (Kato et al. 2011). For gestational measurements of PFAS, we collected maternal blood samples at 16 ± 3 weeks of gestation ($n=180$), at 26 weeks of gestation ($n=19$), and within 24 hours of parturition ($n=48$). If more than one PFAS concentration was available ($n=40$), then an average of available PFAS measurements was used for prenatal PFAS concentrations. Prenatal measurements of PFAS were available for 207 mother-child dyads. PFAS concentrations during childhood were measured in sera collected at ages 3 ($n=143$) and 8 years ($n=192$). The limit of detection (LOD) for PFOS was 0.2 ng/mL and 0.1 ng/mL for all others. We replaced PFAS concentrations $< \text{LOD}$ with $\text{LOD}/2$ (Hornung and Reed 1990). Fewer than 1% of participants had prenatal PFOA, PFOS, PFHxS, and PFNA concentrations $< \text{LOD}$, and percent detection was 100% for these PFAS during childhood. PFAS concentrations were $\ln$ -transformed to reduce the influence of outliers. PFAS compounds were significantly correlated with each other in maternal serum ($r_p=0.44-0.70$, $p<0.0001$) and in child serum at age 3 years ($r_p=0.32-0.67$, $p<0.001$) and at 8

years ($r_p=0.15-0.68$, $p<0.05$) (Supplemental Table S1). We observed positive correlations between different measurement times, though the correlation coefficients decreased as the period of time between measurements increased. For instance, significant positive correlations were noted between prenatal PFOA and childhood concentrations, but the r_p between prenatal PFOA and 3 years was 0.36 compared to 0.31 between prenatal PFOA and 8 years. For PFHxS, prenatal concentrations were significantly correlated with concentrations at age 3 and 8 years, but with a lower correlation coefficient between prenatal PFHxS and 8 years ($r_p=0.27$) compared to concentrations at 3 years ($r_p=0.43$).

2.3 Cognitive assessment

We administered the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) to measure intelligence of children at age 8 years (Wechsler 2003). The WISC-IV provides a general measure of intellectual ability with Full Scale IQ (FSIQ), which consists of 10 core subtests. These subtests (listed with their respective composite) formed four indices: 1) verbal comprehension (similarities, comprehension, and information); 2) perceptual reasoning (block design, matrix reasoning, and picture completion); 3) working memory (digit span and letter-number sequencing); and 4) processing speed (coding and symbol search). All indices and FSIQ have a population mean of 100 ± 15 , with higher WISC-IV scores indicating better performance.

2.4 Statistical analyses

Assumption of linearity between ln-PFAS and WISC outcomes were assessed using augmented component-plus-residual plots and was satisfied. We used multiple informant models to estimate β s and 95% confidence intervals (CIs) for associations between concentrations of ln-transformed PFAS and WISC-IV measures of FSIQ, verbal comprehension, perceptual reasoning, working memory, and processing speed at age 8 years (Sanchez et al. 2011). As non-standardized versions of generalized estimating equations, multiple informant models allow for repeated PFAS measurements, providing us the ability to determine whether associations between PFAS and WISC-IV measures differ by the timing of PFAS measurement. We modeled each PFAS compound separately. Some interaction terms between PFAS and age at measurement had a $p<0.10$; therefore, age-at-exposure-measurement-specific β s are presented for each PFAS. Statistical significance of interaction terms was set at $p<0.10$ as $p<0.05$ is considered too stringent to examine interactions especially given our small sample size. Covariates included in the final models were based on a thorough literature review and bivariate analyses ($p<0.10$). Covariates were included in the final model if they were associated with all four of the WISC-IV measures. The following were considered as potential covariates, but did not meet our inclusion criteria for the final model: maternal parity and maternal employment. Covariates included in the final models were: maternal sociodemographics, behavioral factors, and biological measurements of environmental chemicals (as categorized in Table 1): age, race/ethnicity, marijuana use during pregnancy, depression during pregnancy (Beck et al. 1996), vitamin use during pregnancy, IQ (Wechsler 1999), marital status, and blood lead levels, serum sum of polychlorinated biphenyls (PCBs), and serum cotinine during pregnancy. We also included annual household income at enrollment (assessed via questionnaire), Home

Observation for Measurement of the Environment score at age 1 year, child sex, and whether the child was ever breastfed.

We included a 3-way interaction term between PFAS (continuous), child sex (categorical), and child age at PFAS measurement (categorical), as well as all possible 2-way interactions (PFAS×child sex, PFAS×child age, child age×child sex) in the models to determine whether effect measure modification by child sex was present. We considered modifications between PFAS and WISC-IV and child sex to be statistically significant if the 3-way interaction term was $p<0.10$. We determined whether a dose response relationship was present using the median value of each tertile as a continuous variable in multiple linear regression analyses between PFAS at either gestation, 3 years, or 8 years and WISC-IV outcomes at age 8 years, with $p<0.05$ considered statistically significant (Greenland 1995). We conducted several sensitivity analyses, including mutual adjustment of PFAS, adjustment for duration of breastfeeding (in months) and parity, and the removal of two outliers from the models. These two children had either relatively low concentrations of PFAS (close to LOD) or low FSIQ scores (~3 SDs lower than the population mean). We also performed a sensitivity analysis reexamining all models using only PFAS concentrations measured at 16 ± 3 weeks gestation as PFAS concentrations were lower when measured in maternal serum 24 hours after parturition compared to the early second trimester of pregnancy (Supplemental Table S2).

3. Results

3.1 Participant characteristics

The average age of HOME Study mothers was 29 years at time of delivery, with ~72% having completed some college or more, and 40% who self-identified as non-Hispanic black or other racial groups other than non-Hispanic white. PFOS and PFOA were the PFAS with the highest concentrations in maternal serum during pregnancy and in child serum (Supplemental Figure S1). Concentrations of PFAS decreased during childhood from age 3 to 8 years. In general, PFAS concentrations during gestation and at age 8 years were significantly higher among children who had mothers that were non-Hispanic white, had a higher household income, did not use marijuana, were minimally/mildly depressed, and had a HOME Score = 40 (Table 1). Children who were breastfed and had mothers who were older and were married or living with a partner had significantly higher concentrations of PFAS at age 8 years than other children. All these previously described demographic and behavioral characteristics were also associated with higher FSIQ in children at age 8 years.

3.2 PFAS and cognitive development

We did not observe adverse associations of prenatal or childhood PFAS with cognitive function as assessed by the WISC-IV at age 8 years (Table 2). However, we found some statistically significant positive associations of PFNA and PFOA with WISC-IV measures. For PFOA and PFNA, each ln-transformed increase in prenatal concentrations was associated with a 4.1-point (95% CI 0.3, 8.0) and 5.7-point (95% CI 1.2, 10.2) increase in working memory, respectively. In addition, a ln-increase in PFNA concentrations at age 3 years were associated with a 3.0-point (95% CI 0.5, 5.6) and 3.5-point (95% CI 0.1, 6.9) increase in FSIQ and perceptual reasoning, respectively. For PFOS and PFHxS, we did not

observe any statistically significant associations with cognitive development. There was one statistically significant linear trend across tertiles of PFAS compounds at various measurement timings (Supplemental Table S3), between prenatal PFOA and processing speed ($p_{\text{trend}}=0.039$). We observed an increase of 10.0-points (95% CI 4.1, 15.9) and 8.0-points (95% CI 2.1, 14.0) in processing speed scores of children who had prenatal PFOA concentrations between 4.0-6.3 ng/mL and 6.4 ng/mL, respectively, compared to children who had concentrations <3.9 ng/mL.

Some associations between the four PFAS and cognitive abilities were modified by child sex. Prenatal PFOA was significantly associated with higher FSIQ in females ($\beta=5.2$, 95% CI 1.0, 9.3), but not in males ($\beta=-0.7$, 95% CI -7.2, 5.8) ($p_{\text{PFOA} \times \text{child sex} \times \text{prenatal}}=0.047$) (Figure 1). Child sex additionally modified associations between PFOS at age 8 years and several WISC-IV measures $p_{\text{PFOS} \times \text{child sex} \times 8 \text{ years}} < 0.10$. Ln-increases in PFOS at age 8 years were associated with higher scores in males for FSIQ ($\beta=5.7$, 95% CI -0.3, 11.8), perceptual reasoning ($\beta=7.4$, 95% CI 0.4, 14.5), working memory ($\beta=6.7$, 95% CI 1.9, 11.4), and processing speed ($\beta=10.2$, 95% CI 3.5, 17.0), while null associations were noted among females. The estimated associations between PFNA and WISC-IV scores did not differ by child sex, and sex-specific associations for PFHxS were not statistically significant (Supplemental Table S4).

Results did not differ when we used PFAS concentrations measured at 16 ± 3 weeks gestation rather than average prenatal PFAS (Supplemental Table S5). Removing two participants resulted in few differences, and did not change overall conclusions (Supplemental Table S6). Specifically, the association between prenatal PFOA and working memory was no longer statistically significant ($\beta=2.7$, 95% CI -1.2, 6.5). However, PFNA concentrations prenatally and at 8 years were significantly associated with higher scores on processing speed and verbal comprehension, respectively. Since PFAS concentrations in maternal and child serum are significantly correlated with each other (Supplemental Table S1), we examined the relationship between PFAS and cognitive development with mutual adjustment for all PFAS compounds. Several previously significant positive associations were no longer present (Table 3). For instance, while we noted that a ln-increase in prenatal PFNA was associated with a 4.3-point (95% CI -0.3, 10.2) increase in working memory, the results were not statistically significant. The only notable associations were between PFNA at age 8 years and verbal comprehension ($\beta=4.3$, 95% CI 0.8, 7.9). Lastly, we performed two sensitivity analyses adjusting for breastfeeding duration in months and parity. Our overall conclusions did not differ for both sensitivity analyses, though we observed a few more statistically significant positive associations (Supplemental Table S7-8). For instance, a ln-unit increase in prenatal PFOA and PFNA was associated with higher scores in FSIQ ($\beta=4.4$ -points, 95% CI 0.6, 8.1 and $\beta=4.0$ -points, 95% CI 0.2, -7.7, respectively) after parity adjustment. With adjustment for duration of breastfeeding, we noted increases in scores for Verbal Comprehension $\beta=3.3$ -points, 95% CI 0.01, 6.6) and Processing Speed ($\beta=4.8$ -points, 95% CI 0.1, 9.6) with higher concurrent PFNA and PFOA at age 3 years, respectively.

4. Discussion

The findings in this study generally showed a null association between prenatal and childhood PFAS and cognitive development. We observed a few statistically significant associations with PFOA and PFNA but lack a clear understanding of the role PFAS play in cognitive development due to the inconsistency of the patterns of associations. For instance, one ln-unit increase in PFNA at age 3 years was associated with an increase of ~3 points in FSIQ and perceptual reasoning. However, no statistically significant associations were found with PFOS or PFHxS; nor were PFOA or PFNA positively associated with other WISC-IV measures. Thus, there is not enough strong evidence supporting that prenatal or childhood PFAS are associated with cognition at 8 years in the HOME Study.

Epidemiological studies examining PFAS and child cognition are inconclusive, with only two studies reporting clear adverse associations (Jeddy et al. 2017; Wang et al. 2015). However, most studies, like ours, have reported mixed conclusions, with the aggregate of the results suggesting null associations. In the Hokkaido Study, prenatal PFOA and PFOS were not associated with scores on the mental developmental index (MDI) assessed at 6 and 18 months. (Goudarzi et al. 2016). In addition, the Taiwan Birth Panel Study and the Danish Fetal Origins 1988 Cohort both reported null associations between prenatal PFAS and cognition at 2 years and among adolescents enrolled in 9th grade, respectively (Chen et al. 2013; Strom et al. 2014). In the Danish National Birth Cohort (DNBC), similar null associations were found between prenatal PFOA and PFOS and language development and cognition at 18 months as well as between prenatal PFAS and FSIQ and performance IQ at 5 years (Fei et al. 2008; Liew et al. 2018). However, prenatal PFNA was significantly associated with better verbal IQ at age 5 years (Liew et al. 2018). In addition to the positive associations observed in the DNBC (Liew et al. 2018), the C8 Health Project reported increased FSIQ and better math skills at ages 6-12 years with higher concentrations of prenatal PFOA (Stein et al. 2013). Previous results from the HOME Study have also indicated improvements in reading skills at ages 5 and 8 with both prenatal and childhood PFOA, PFOS, and PFNA (Zhang et al. 2018). And although Project Viva's (Boston, MA, USA) findings on prenatal and childhood (7.7 years) PFAS concentrations with verbal and non-verbal IQ scores at age 7.7 years were mixed, they did observe improved visual motor abilities and visual memory with prenatal PFAS (Harris et al. 2018).

Our study had some results that were suggestive of a possible improvement in FSIQ and perceptual reasoning with increased PFNA at age 3 years and better working memory scores with higher prenatal PFOA and PFNA. These associations are not uncommon between PFAS and cognitive outcomes in the epidemiological literature. While a number of mechanisms have been identified through which PFAS may adversely affect neurodevelopment, contradictory neuroprotective effects have also been recognized. Specifically, PFOA may be involved in reducing inflammation in the central nervous system, because of its role as a partial peroxisome proliferator-activated receptor-gamma agonist (Kapadia et al. 2008; Vanden Heuvel et al. 2006). Differences in chemical structure and activity between PFOA and PFNA compared to PFOS and PFHxS may have also contributed to our findings. Berntsen et al. (2017) reported that PFOA and PFNA have a more dispersed distribution

compared to the aggregate accumulation of PFOS and PFHxS. PFNA also accumulates more in human brain tissue compared to PFOS and PFOA (Eggers Pedersen et al. 2015).

Effect measure modification by child sex in our study revealed higher scores in FSIQ among females, but not in males, born to mothers with higher PFOA. However, the direction of associations was reversed between the sexes with concurrent PFOS and several WISC-IV measures, with improved scores found only in males. In contrast, Project Viva reported no consistent pattern of effect measure modification by child sex among associations of PFAS and measures of child cognition (Harris et al. 2018). Other studies examined sex-stratified associations and found either no differences (Strom et al. 2014), poorer MDI scores in females (Goudarzi et al. 2016), or better verbal IQ in females (Liew et al. 2018). Given that few studies have examined effect modification by sex and the inconsistent results, it is important that future studies with sufficient sample sizes investigate whether sex modifies these associations.

Several factors may contribute to inconsistent results of epidemiological studies examining this research question. In our study, we focused on intellectual ability as measured with WISC-IV's FSIQ and its four domains of verbal comprehension, perceptual reasoning, processing speed, and working memory. Only three previous studies used FSIQ as a measure of child cognition (Liew et al. 2018; Stein et al. 2013; Wang et al. 2015), whereas other studies relied on different cognitive assessments, including maternal self-reported questionnaires, scholastic achievement, the MacArthur Communicative Developmental Inventories (MCDI), and the Wide Range Achievement Test-4 (WRAT-4) (Fei et al. 2008; Jeddy et al. 2017; Strom et al. 2014; Zhang et al. 2018). Further, the age of cognitive assessment between studies ranged from infancy at 6 months to adolescence. Second, PFAS concentrations were measured at various times during childhood. While several PFAS have a relatively long half-life in humans, we generally noted declining concentrations as children reached age 8 years due to the phase out of PFOS in the USA in the early 2000s and subsequently PFOA. PFAS concentrations also varied greatly between study populations. For instance, the median serum PFOA concentration among children aged 2-8 years in the C8 Health Study was 35.1 ng/mL (interquartile range [IQR]: 15.8-94.1) (Stein et al. 2013), while the HOME Study children had a serum PFOA median of 5.4 ng/mL (IQR: 3.7-7.4) and 2.5 ng/mL (IQR: 1.7-3.2) at ages 3 and 8 years, respectively. Our childhood PFOA concentration at 8 years was slightly lower than Project Viva children at age 7.7 years (4.28 ng/mL; IQR: 3.15-5.49) (Harris et al. 2018). Further, samples from Project Viva were collected years before samples from the HOME Study. Third, model selection for statistical analyses and covariates included in regression models varied between studies. Residual confounding may have resulted. Cognitive abilities may be more influenced by socioeconomic status and other aspects related to the family and home environment that were unmeasured in our study than PFAS exposure itself.

The strengths of our study include a well-characterized cohort and availability of three PFAS measurements from gestation to age 8 years. We were able to include repeated PFAS measurements using multiple informant models to identify potential developmental windows with heightened susceptibility to the neurotoxic effects of PFAS. We were also able to account for a number of important maternal characteristics known to affect child cognition,

including IQ, depression, blood lead, cotinine, which represents tobacco exposure, and the home environment. However, the possibility of residual confounding from unmeasured maternal behaviors may still be present. Lastly, our study is relatively representative of the racially diverse population in the US, but it may not be reflective of the socioeconomic status of the general population.

The study also has several limitations. While there were no statistically significant differences between participants included in the study and those excluded due to missing information aside from marital status, maternal IQ, and blood lead levels (Supplemental Table S9), we cannot entirely rule out the possibility of selection bias. Further, residual confounding from unmeasured factors, such as paternal IQ, childhood educational factors (e.g., type of schooling, quality of schooling), and social environment outside of the home may have influenced our study findings and contributed to some of the positive associations. Third, we performed a large number of statistical tests and cannot eliminate the possibility of type 1 error, although the correlation of cognitive domains may reduce this concern. Fourth, correlations of PFAS concentrations range from moderate to high. Therefore, it is difficult to fully separate and isolate their associations with cognition from each other. Finally, we had low statistical power to examine whether effect modification by child sex was present. Therefore, results from sex-specific analyses should be interpreted in the context of a moderate sample size.

5. Conclusions

Our study is the first study to examine associations of both prenatal and repeated assessments of childhood PFAS exposure with intellectual ability in children. There was no consistent evidence supporting an adverse association between PFAS and child cognition in the HOME Study. While we found a few associations that would indicate an improvement in cognition with increased prenatal PFOA and PFNA, as well as with PFNA at age 3 years, the associations were not consistent enough to rule out potential chance findings or residual confounding. Further, most of the positive associations were no longer statistically significant after mutual adjustment of all PFAS compounds. Potential PFAS developmental neurotoxicity warrants further investigation given the discordant results from epidemiologic research and the recent discovery of widespread PFAS contamination in the USA drinking water supply. We recommend that future studies with large sample sizes examine both prenatal and postnatal exposures and assess sex as a potential effect measure modifier.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- PFOS and PFHxS were not associated with Full Scale IQ (FSIQ) at 8 years
- Prenatal PFOA and PFNA were positively associated with working memory at 8 years
- Child sex modified prenatal PFOA associations, with higher FSIQ scores in females
- We observed higher scores on several WISC scales in males, but not in females
- Findings do not support that PFAS are adversely associated with cognitive function

Figure 1.

Estimated mean difference and 95% CIs in WISC-IV outcomes at age 8 years by a ln-increase in serum PFOA and PFOS, HOME Study. Asterisks denote $P_{PFAS \times Child\ Sex \times Child\ Age} < 0.10$. Adjusted by maternal age, race/ethnicity, household income, maternal marijuana use, maternal blood lead, maternal serum PCBs and cotinine, maternal depression, vitamin use, maternal IQ, marital status, HOME Score, child sex, and whether the child was breastfed.

Table 1. Serum concentrations of PFAS (ng/mL) and FSIQ at 8 years by demographic characteristics, HOME Study.

	N (%)	Prenatal (GM)				8 years (GM)				Mean (SD)	
		PFOA	PFOS	PFHxS	PFNA	PFOA	PFOS	PFHxS	PFNA	FSIQ	FSIQ
Overall	221	5.2	12.4	1.4	0.9	2.4	3.9	1.4	0.8	102	(16)
Age, years											
<25	59 (26.8)	5.6	12.2	1.2	0.9	2.0*	3.3*	1.1*	0.6*	93	(16)*
25-34	130 (59.1)	4.9	12.2	1.4	0.9	2.5	4.0	1.5	0.8	103	(15)
35	31 (14.1)	6.0	13.9	1.5	1.0	3.0	4.8	1.3	0.8	111	(13)
Race/ethnicity											
Non-Hispanic White	132 (60.0)	5.7*	14.0*	1.7*	0.9	2.8*	4.5*	1.6*	0.8	108	(13)*
Non-Hispanic Black and Others	88 (40.0)	4.6	10.5	1.0	0.8	2.0	3.1	1.1	0.7	93	(15)
Household income											
<\$40,000	93 (42.3)	4.8*	10.9*	1.1*	0.8*	2.1*	3.6*	1.2	0.7	94	(15)*
\$40,000-\$79,999	71 (32.3)	5.3	12.1	1.5	0.9	2.5	3.8	1.4	0.8	104	(14)
\$80,000	56 (25.5)	6.1	16.2	1.8	1.0	3.0	4.6	1.6	0.9	112	(12)
Maternal marijuana use											
No	205 (93.2)	5.3	12.9*	1.4*	0.9*	2.5	4.0*	1.4	0.8	103	(15)*
Yes	15 (6.8)	4.2	7.2	0.7	0.6	2.0	3.0	1.1	0.8	90	(15)
Maternal depression											
Minimal or mild	199 (91.3)	5.5*	13.2*	1.4*	0.9	2.5*	4.0	1.4	0.8	103	(15)*
Moderate or severe	19 (8.7)	3.7	7.3	0.8	0.7	2.0	3.1	1.1	0.7	95	(15)
Maternal vitamin use											
Daily	172 (78.2)	5.3	13.1*	1.5*	0.9*	2.5	4.0	1.4	0.8	104	(15)*
<Daily	34 (15.5)	4.9	11.3	1.2	0.9	2.4	3.5	1.5	0.8	96	(13)
Never	14 (6.4)	5.1	8.3	0.7	0.6	2.2	3.5	0.9	0.8	89	(18)
Parity											
Nulliparous	100 (45.5)	6.6*	15.1*	1.8*	1.0*	2.6	4.0	1.4	0.8	103	(16)
Primiparous	66 (30.0)	4.2	11.2	1.1	0.8	2.4	3.8	1.4	0.8	101	(15)
Multiparous	54 (24.6)	4.6	10.0	1.1	0.8	2.3	3.9	1.3	0.7	100	(15)

	N (%)	Prenatal (GM)				8 years (GM)				Mean (SD)	
		PFOA	PFOS	PFHxS	PFNA	PFOA	PFOS	PFHxS	PFNA	FSIQ	
Marital status											
Married or living with partner	161 (73.2)	5.2	12.7	1.5*	0.9	2.6*	4.2*	1.5*	0.8	106 (14)*	
Not married or living alone	59 (26.8)	5.4	11.8	1.1	0.8	2.0	3.2	1.1	0.7	91 (15)	
HOME Score											
40	126 (61.8)	5.5	13.7*	1.6*	0.9*	2.8*	4.3*	1.6*	0.8*	108 (13)*	
35-39	42 (20.6)	5.3	12.0	1.3	0.9	1.9	3.3	1.2	0.6	96 (16)	
<35	36 (17.7)	4.8	10.3	1.0	0.7	2.2	3.6	1.1	0.8	91 (15)	
Ever breastfed current child											
No	47 (21.5)	5.7	12.5	1.2	0.9	2.0*	3.3*	1.1	0.7	95 (16)*	
Yes	172 (78.5)	5.2	12.5	1.4	0.9	2.6	4.0	1.4	0.8	104 (15)	
Child Sex											
Male	100 (45.3)	4.9	11.8	1.3	0.9	2.3	3.8	1.3	0.7	101 (15)	
Female	121 (54.8)	5.5	12.9	1.4	0.9	2.5	4.0	1.4	0.8	102 (16)	

Abbreviations: FSIQ, full scale IQ; GM, geometric mean; SD, standard deviation.

* $p < 0.05$

Table 2.

Associations between ln-transformed serum PFAS concentrations (ng/mL) and WISC-IV outcomes at age 8 years^a

	FSIQ	Verbal Comprehension	Perceptual Reasoning	Working Memory	Processing Speed
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
lnPFOA					
Prenatal	3.3 (−0.4, 6.9)	2.3 (−1.1, 5.6)	0.7 (−3.2, 4.6)	4.1 (0.3, 8.0)	3.3 (−0.8, 7.5)
3 years	2.4 (−1.5, 6.4)	1.0 (−2.9, 4.8)	1.2 (−3.0, 5.4)	2.9 (−1.0, 6.7)	1.7 (−2.6, 6.0)
8 years	2.3 (−3.3, 7.9)	−1.8 (−6.9, 3.2)	2.3 (−3.7, 8.2)	4.3 (−0.7, 9.3)	2.8 (−3.0, 8.5)
lnPFOS					
Prenatal	2.2 (−0.9, 5.2)	1.4 (−1.7, 4.5)	1.4 (−1.8, 4.7)	2.6 (−0.8, 5.9)	1.3 (−2.0, 4.7)
3 years	0.8 (−2.4, 4.0)	0.1 (−3.3, 3.5)	1.0 (−2.6, 4.5)	−0.1 (−3.4, 3.2)	1.6 (−1.9, 5.1)
8 years	1.6 (−2.7, 5.8)	−1.7 (−5.2, 1.8)	2.8 (−2.1, 7.7)	2.9 (−0.8, 6.5)	3.7 (−1.2, 8.5)
lnPFHxS					
Prenatal	0.5 (−1.8, 2.9)	0.5 (−1.9, 2.8)	0.8 (−1.7, 3.3)	1.1 (−1.8, 4.0)	−0.6 (−3.3, 2.2)
3 years	−0.4 (−2.5, 1.6)	−1.0 (−3.0, 1.0)	−0.6 (−2.9, 1.6)	0.5 (−1.8, 2.7)	−0.2 (−3.0, 2.6)
8 years	0.1 (−2.5, 2.7)	−2.0 (−4.4, 0.4)	0.5 (−2.4, 3.4)	1.5 (−1.3, 4.3)	1.7 (−1.1, 4.5)
lnPFNA					
Prenatal	3.5 (−0.4, 7.4)	2.0 (−2.0, 6.0)	0.6 (−3.5, 4.7)	5.7 (1.2, 10.2)	4.1 (−0.7, 8.9)
3 years	3.0 (0.5, 5.6)	1.8 (−0.8, 4.5)	3.5 (0.1, 6.9)	1.2 (−1.6, 3.9)	1.4 (−3.4, 6.3)
8 years	2.5 (−0.8, 5.9)	3.3 (−0.1, 6.6)	2.5 (−1.0, 6.1)	2.5 (−1.1, 6.0)	−0.6 (−4.4, 3.2)

^aAdjusted by maternal age, race/ethnicity, household income, maternal marijuana use, maternal blood lead, maternal serum PCBs and cotinine, maternal depression, vitamin use, maternal IQ, marital status, Home Observation for Measurement of the Environment Score, child sex, and whether the child was breastfed.

Table 3.

Associations for ln-transformed serum PFAS concentrations (ng/mL) with WISC-IV outcomes at age 8 years with mutual adjustment for all PFAS^a

	FSIQ	Verbal Comprehension	Perceptual Reasoning	Working Memory	Processing Speed
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
lnPFOA					
Prenatal	2.8 (−1.9, 7.4)	2.1 (−2.6, 6.8)	−0.4 (−5.4, 4.6)	3.1 (−1.8, 7.9)	3.9 (−1.3, 9.1)
3 years	1.9 (−2.9, 6.7)	1.0 (−3.8, 5.7)	−0.6 (−5.8, 4.7)	4.8 (−0.4, 10.0)	0.1 (−5.6, 5.9)
8 years	0.9 (−5.1, 6.8)	−2.6 (−9.1, 3.9)	−0.4 (−6.7, 5.9)	2.8 (−3.3, 9.0)	0.3 (−6.2, 6.8)
lnPFOS					
Prenatal	0.2 (−4.1, 4.4)	0.04 (−4.7, 4.7)	1.5 (−3.3, 6.3)	−1.2 (−6.1, 3.6)	−1.2 (−6.6, 4.3)
3 years	−0.1 (−5.4, 5.1)	0.7 (−5.1, 6.5)	1.5 (−4.0, 7.1)	−4.1 (−9.6, 1.4)	2.6 (−3.9, 9.0)
8 years	1.0 (−4.4, 6.4)	−0.4 (−5.8, 5.0)	3.2 (−3.0, 9.5)	0.4 (−5.1, 5.9)	4.0 (−3.2, 11.2)
lnPFHxS					
Prenatal	−0.8 (−3.7, 2.2)	−0.3 (−3.4, 2.7)	0.5 (−2.8, 3.8)	−0.3 (−3.6, 3.1)	−2.1 (−5.9, 1.6)
3 years	−0.9 (−4.0, 2.1)	−1.6 (−4.6, 1.4)	−1.4 (−4.5, 1.8)	1.2 (−1.8, 4.2)	−1.4 (−5.5, 2.6)
8 years	−0.8 (−3.9, 2.3)	−1.8 (−4.9, 1.3)	−1.0 (−4.3, 2.3)	0.5 (−2.9, 4.0)	0.2 (−3.5, 3.8)
lnPFNA					
Prenatal	2.1 (−2.6, 6.8)	0.8 (−4.4, 6.0)	−0.6 (−5.8, 4.7)	4.9 (−0.3, 10.2)	3.8 (−1.8, 9.4)
3 years	2.6 (−0.1, 5.2)	1.4 (−1.4, 4.2)	3.5 (−0.4, 7.4)	0.7 (−2.0, 3.4)	0.8 (−4.7, 6.2)
8 years	2.2 (−1.2, 5.6)	4.3 (0.8, 7.9)	2.0 (−1.5, 5.5)	1.6 (−2.1, 5.3)	−1.9 (−5.8, 2.1)

^aAdjusted by maternal age, race/ethnicity, household income, maternal marijuana use, maternal blood lead, maternal serum PCBs and cotinine, maternal depression, vitamin use, maternal IQ, marital status, Home Observation for Measurement of the Environment Score, child sex, whether the child was breastfed, and PFAS compounds.