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Authors

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Oken, Emily

Rifas-Shiman, Sheryl

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Prenatal and childhood exposure to per- and polyfluoroalkyl substances (PFAS) and child executive function and behavioral problems

Maria H. Harris[a,*], **Emily Oken**[b,c], **Sheryl L. Rifas-Shiman**[b], **Antonia M. Calafat**[d], **David C. Bellinger**[e], **Thomas F. Webster**[f], **Roberta F. White**[f], **Sharon K. Sagiv**[a,g]

[a]Center for Environmental Research and Children's Health, University of California, Berkeley School of Public Health, Berkeley, CA, USA

[b]Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

[c]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[d]Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA, USA

[e]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA

[f]Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA

[g]Division of Epidemiology, University of California, Berkeley School of Public Health, Berkeley, CA, USA

Abstract

Early life exposure to per- and polyfluoroalkyl substances (PFAS) may adversely impact neurodevelopment, but epidemiological findings are inconsistent. In the Project Viva pre-birth cohort, we examined associations of prenatal and childhood PFAS plasma concentrations with parent and teacher assessments of children's behavior problems [Strengths and Difficulties

[*]Corresponding author. Center for Environmental Research and Children's Health, University of California, Berkeley School of Public Health, 1995 University Ave., Suite 265, Berkeley, CA, 94720, USA. mariaharris@berkeley.edu (M.H. Harris).

Credit author statement

Maria H. Harris: Methodology, Software, Formal analysis, Data curation, Writing – original draft, Visualization. Emily Oken: Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition. Sheryl L. Rifas-Shiman: Validation, Resources, Data curation, Writing – review & editing. Antonia M. Calafat: Methodology, Resources, Writing – review & editing. David C. Bellinger: Methodology, Resources, Writing – review & editing. Thomas F. Webster: Conceptualization, Methodology, Writing – review & editing. Roberta F. White: Conceptualization, Methodology, Writing – review & editing. Sharon K. Sagiv: Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

Dr. Harris is currently employed as an Environmental Epidemiologist for Environmental Defense Fund. The authors declare that they have no other known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111621.

Questionnaire (SDQ)] and executive function abilities [Behavior Rating Inventory of Executive Function (BRIEF)] at age 6–10 years (sample sizes 485–933). PFAS concentrations in pregnant Project Viva mothers (in 1999–2002) and children at ages 6–10 (in 2007–10) were similar to concentrations at similar time points in women and children in the nationally representative U.S. National Health and Nutrition Examination Survey. We observed no consistent associations of prenatal PFAS concentrations with behavior or executive function. Childhood concentrations of perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), perfluorononanoate (PFNA) and perfluorodecanoate (PFDA) were associated with higher parent-rated SDQ Total Difficulties scores (mean = 6.7, standard deviation (SD) = 4.9), suggesting greater behavioral problems (top (Q4) versus bottom (Q1) quartile PFOA: 1.5, 95% confidence interval (CI): 0.3, 2.7; PFOS: 1.4, 95% CI: 0.3, 2.5; PFHxS: 1.2, 95% CI: 0.1, 2.3; PFNA: 1.2, 95% CI: 0.1, 2.2; PFDA: 1.1, 95% CI: 0.0, 1.1); teacher-rated SDQ scores did not show associations. Higher childhood PFOS was associated with higher (indicating more problems) parent-rated BRIEF General Executive Composite (GEC) scores (standardized to mean = 50, SD = 10) (Q4 vs. Q1: 2.4, 95% CI: 0.2, 4.6), while teacher BRIEF GEC scores indicated more problems among children with higher PFHxS (Q4 vs. Q1: 3.5, 95% CI: −0.8, 6.3). There were no consistent patterns of sexual dimorphism in associations. In a cohort of U.S. children, we observed cross-sectional associations of childhood PFAS concentrations with greater behavioral and executive function problems, but no consistent associations with prenatal PFAS.

Keywords

Neurodevelopment; Behavior; Executive function; Per- and polyfluoroalkyl substances; PFAS; Persistent organic pollutants

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are common synthetic chemicals used in products including fabric and carpet treatments, food packaging, cookware, fire retardant foams, and lubricants (Lau et al., 2007; Mariussen, 2012). Due to the strength of their carbon-fluorine bonds, PFAS tend to persist in the environment and have been detected broadly in human biomonitoring studies (Lau et al., 2007; Mariussen, 2012), including among children and pregnant women (CDC, 2021; Fromme et al., 2010; Kato et al., 2014). PFAS are known to cross the placenta, and PFAS concentrations in pregnant women's peripheral blood have been shown to correlate strongly with cord blood PFAS concentrations (Fromme et al., 2010; Kato et al., 2014; Kim et al., 2011).

Toxicological and epidemiological studies have suggested that early life exposure to PFAS may disrupt neurodevelopment, with potential adverse impacts to many aspects of behavior and executive function (Liew et al., 2018; Mariussen, 2012). Prior research has reported cross-sectional associations of childhood PFAS exposure with behavior and executive function problems (Gump et al., 2011; Hoffman et al., 2010; Vuong et al., 2018), and selected studies also suggest impacts of prenatal exposure on behavior (Ghassabian et al., 2018; Høyer et al., 2015), though findings have been inconsistent (Liew et al., 2018; Rappazzo et al., 2017). Only a few prior studies have examined repeated prenatal and

childhood longitudinal measures of PFAS exposure in relation to childhood behavior and executive function. In a Faroe Islands cohort (n = 539), behavioral difficulties in 7 year old children were associated with PFAS concentrations at age 5, but not with prenatal concentrations (Oulhote et al., 2016). In a Cincinnati, Ohio cohort, prenatal (n = 256) and age 8 (n = 208) concentrations of certain PFAS were associated with executive function problems at age 8, but PFAS concentrations at age 3 were not (Vuong et al. 2016, 2018).

In a prospective pre-birth cohort of U.S. children, we examined associations of plasma PFAS concentrations measured prenatally (in mothers during pregnancy) and in mid-childhood (in children aged 6–10 years) with mid-childhood behavior problems and executive function abilities as assessed by teachers and parents. We hypothesized that prenatal and childhood PFAS exposure would be associated with greater behavioral and executive function problems, and aimed to evaluate whether certain periods of neurodevelopment may be particularly vulnerable to potential adverse impacts of PFAS.

2. Materials and methods

2.1. Study population

Study participants were members of Project Viva, a pre-birth cohort of mother-child pairs enrolled in 1999–2002 at eight Eastern Massachusetts locations of Atrius Harvard Vanguard Medical Associates, a multispecialty group practice (Oken et al., 2015). Mothers were enrolled at their first prenatal visits (at median 9.9 weeks of gestation) with the following inclusion criteria: singleton pregnancy; gestational age <22 weeks; ability to answer questions in English; and intention to remain in the study area through delivery. Of 2128 enrolled mothers with live births, a subset (n = 1668; 78%) contributed blood samples during pregnancy (median 9.7 weeks gestation, range 4.8–21.4). Project Viva conducted in-person visits during pregnancy and childhood to assess maternal and child health and development, including a visit in mid-childhood (6.6–10.9 years) attended by 1116 children (52%) in 2007–2010 at which a subset of children (n = 702; 63% of those attending visit, 34% of those enrolled at birth) contributed blood samples. Mothers also completed annual questionnaires reporting additional health and developmental information. Further information on Project Viva protocols and participant flow is available in a previously published cohort profile (Oken et al., 2015).

Project Viva study forms are available at https://www.hms.harvard.edu/viva/. All study protocols were approved by the Institutional Review Boards of participating institutions. Mothers provided written informed consent at all study visits; children also provided verbal assent at the mid-childhood visit. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects research.

2.2. Behavioral assessments

In connection with the mid-childhood visit (at age 6.6–10.9 years), parents and teachers assessed children's executive function and behavior using two validated instruments: the Behavior Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ). The BRIEF is validated for use in 5–18 year old children and

includes 86 items assessing aspects of observed executive function, including working memory, impulse inhibition, emotional control, planning/organization, and flexibility in problem solving (Gioia et al., 2002). Trained Project Viva staff used published guidelines and reference data to calculate standardized scores for two BRIEF indices ((Metacognition (MI) and Behavioral Regulation (BRI)) and a Global Executive Composite (GEC) score combining MI and BRI; for each, standardized mean = 50 and standard deviation (SD) = 10, with higher scores indicating greater executive function problems (Gioia et al., 2000). The SDQ is a 25-item behavioral screening questionnaire validated for use among children aged 4–16 and used frequently in clinical and research settings (Goodman, 1997; Vostanis, 2006) that correlates well with the Child Behavior Checklist (Goodman and Scott, 1999; Stone et al., 2010). Project Viva staff scored SDQ questionnaires based on published guidelines, yielding sub-scores for behaviors in five categories (emotional problems, peer problems, hyperactivity, conduct problems, and prosocial), subscales for internalizing (emotional problems + peer problems) and externalizing (hyperactivity + conduct problems) behaviors, and a measure of total behavioral difficulties (hyperactivity + conduct problems + emotional problems + peer problems); possible total difficulties scores are 0–40, with higher scores indicating greater behavioral difficulties (Goodman et al., 2010; Goodman, 1997).

2.3. PFAS concentrations

The Division of Laboratory Sciences at CDC measured PFAS concentrations in two sets of Project Viva samples: maternal plasma from pregnancy (n = 1645 with sufficient volume for PFAS quantification, 99% of 1668 originally collected) and child plasma samples from mid-childhood (n = 653, 93% of 702 originally collected). Following collection, plasma samples were stored in liquid nitrogen freezers in PFAS-free cryovials. In 2014 (for maternal samples) and 2015 (for child samples), plasma samples were thawed, aliquoted, and shipped to CDC for PFAS analysis. Analytical methods for the maternal samples were the same as those used to quantify PFAS in the 2011–2012 National Health and Nutrition Examination Survey (NHANES) cycle, and have been described previously (CDC, 2013a). Analytical methods for the child samples were those used for the 2013–2014 NHANES cycle (CDC, 2013b). Briefly, the laboratory used on-line solid-phase extraction coupled with isotope dilution high-performance liquid chromatography-tandem mass spectrometry to quantify concentrations of eight PFAS: perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), perfluorononanoate (PFNA), 2-(N-ethyl-perfluorooctane sulfonamido) acetate (EtFOSAA; also known as Et-PFOSA-AcOH), 2-(N-methyl-perfluorooctane sulfonamido) acetate (MeFOSAA; also known as Me-PFOSA-AcOH), perfluorodecanoate (PFDA; also known as PFDeA), and perfluorooctane sulfonamide (FOSA; also known as PFOSA). PFOA and PFOS concentrations represented total PFOA and PFOS (sum of linear and branched isomers). The laboratory ensured accuracy and reliability by analyzing low and high-concentration quality control materials, analytical standards, and reagent and serum blanks along with the study samples (Kato et al., 2011a). The limit of detection (LOD) was 0.2 ng/mL for prenatal PFOS measures and 0.1 ng/mL for all other PFAS measures; we replaced values below LOD with LOD/√2 (Hornung and Reed, 1990).

2.4. Covariates

We obtained information from Project Viva questionnaires and interview responses on potential covariates including breastfeeding duration, race/ethnicity, parental education, household income, and maternal parity, body mass index and smoking status. Project Viva staff evaluated maternal IQ at the time of the mid-childhood visit using the Kaufman Brief Intelligence Test Second Edition (KBIT-2) (Kaufman and Kaufman, 2004). Parents also completed the Home Observation for Measurement of the Environment - Short Form (HOME-SF) questionnaire, which evaluates the degree of cognitive stimulation and emotional support in a child's home (Frankenburg and Coons, 1986). As a proxy measure for pregnancy-related plasma volume expansion (Savitz, 2014), we used the Cockcroft-Gault equation to estimate maternal glomerular filtration rate (eGFR) based on plasma creatinine concentrations from prenatal maternal blood samples (Morken et al., 2014).

Breastfeeding is both a potential PFAS exposure route for infants and a PFAS excretion mechanism for mothers, and prior breastfeeding has been shown to impact maternal PFAS concentrations (Mogensen et al., 2015; Mondal et al., 2014). Though records on breastfeeding of prior children were not available in Project Viva, Sagiv and colleagues reported that a proxy indicator of prior breastfeeding based on report of breastfeeding of the Project Viva child among parous mothers was associated with maternal PFAS concentrations; in multivariable models also including maternal parity, the prior breastfeeding indicator and parity appeared independently associated with maternal PFAS (Sagiv et al., 2015). For this study, we generated a categorical indicator variable combining parity and the proxy for prior breastfeeding (nulliparous, parous with no breastfeeding, parous with breastfeeding) using maternal parity (0, ≥1) and report of breastfeeding of the Project Viva child (for at least one month).

2.5. Statistical analyses

We assessed associations of each mid-childhood behavioral assessment score with each measure of maternal plasma PFAS (from pregnancy) and child plasma PFAS (from mid-childhood) using multivariable linear regression models. Although behavioral assessment scores were not normally distributed, model residuals were approximately normal. We conducted sensitivity analyses using standard errors robust to violations of normality and homoscedasticity assumptions; these results were similar to those of linear models, so we employed linear models in our primary analyses.

We evaluated the shape of exposure-outcome relationships by fitting covariate-adjusted generalized additive models with PFAS concentrations modeled as continuous using cubic regression splines (three degrees of freedom). A number of the studied PFAS-behavioral assessment relationships appeared non-linear (based on visual inspection of the plotted splines), so we conducted primary analyses with PFAS concentrations treated as categorical (in quartiles). We defined quartiles for prenatal PFAS and childhood PFAS concentrations among all study participants with at least one behavioral assessment score (n = 950 for prenatal PFAS and n = 641 for childhood PFAS).

We adjusted all models for child sex and age at behavioral assessment, along with covariates identified as possible confounders using Directed Acyclic Graph theory (Figures S6 and S7) (Hernán et al., 2002; Textor et al., 2011). We adjusted all models for: year of blood collection (categorical), maternal race/ethnicity (Black, white, Hispanic, Asian, other), maternal age (<25, 25–34, ≥35 years), maternal and paternal education at enrollment (<college, college degree, graduate degree), maternal intelligence scores (KBIT-2) (continuous), annual household income at the mid-childhood visit (<$40 K, $40-≤70 K, $70-≤150 K, >$150 K) and HOME-SF score assessed at the mid-childhood visit (continuous). Annual income and HOME-SF score from mid-childhood were included in prenatal models as proxies for earlier socio-economic/behavioral factors that may have influenced maternal PFAS concentrations and could also influence child neurobehavioral development, therefore acting as confounders of associations of prenatal PFAS with mid-childhood behavior and executive function.

In addition to the core set of covariates listed above, in prenatal PFAS models, we also adjusted for gestational week of plasma collection (continuous), pre-pregnancy body mass index (continuous, in kg/m^2), maternal eGFR (continuous), maternal smoking status during pregnancy (smoker, former smoker, never smoker), and the proxy indicator of parity/prior breastfeeding (nulliparous, parous with no breastfeeding, parous with breastfeeding). In childhood PFAS models, we adjusted for the core set of covariates listed above, along with breastfeeding duration (in months) and maternal parity (0, 1, ≥2). We calculated variance inflation factors (VIF) to evaluate the degree of collinearity among included covariates for each model. VIFs indicated that collinearity between covariates did not have a substantial impact on the precision of effect estimates (all VIFs were <2).

Our analyses for each PFAS-behavioral assessment association included all participants with available data for the relevant PFAS measure and behavioral assessment score. We imputed missing covariates using a chained equation model (PROC MI in SAS) that included all PFAS measurements, behavioral assessment scores, and model covariates, along with additional variables potentially predictive of covariates or data missingness. Effect estimates based on multiply imputed variables are unbiased if all missingness is explained by variables included in the imputation model; this assumption is less restrictive than the assumptions required for unbiased effect estimates using complete case analyses (White et al., 2011). We generated 50 imputed data sets (White et al., 2011) and pooled beta estimates from imputed data sets using PROC MIANALYZE in SAS (according to Rubin's rules) (Rubin, 2004).

In secondary analyses (among participants with both prenatal and childhood PFAS measures, n = 511), we re-ran childhood PFAS models with additional adjustment for prenatal concentrations of the same PFAS (modeled continuously using cubic regression splines with 3 degrees of freedom) to evaluate potential confounding by prenatal PFAS exposure. We assessed potential effect measure modification by sex by comparing model fit with and without interaction terms for PFAS quartile × sex (using log-likelihood ratio tests); we also ran sex-stratified models.

We prepared data sets, completed multiple imputation, and generated some descriptive statistics in SAS Version 9.3 (SAS Institute Inc, Cary, NC); all other analyses were

conducted in R Version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Our conclusions about relationships between exposures and outcomes were based on observed patterns across results (including magnitude and precision of effect estimates).

3. Results

3.1. Participant characteristics and PFAS concentrations

Analyses included all children with at least one behavioral assessment completed in mid-childhood (parent or teacher-rated) and measured PFAS plasma concentrations (prenatal and/or mid-childhood). Sample sizes varied across analyses, ranging from 485 to 933 (23–43% of the 2128 children originally enrolled at birth), with 1080 children included in at least one analysis; characteristics of study participants are outlined in Table 1, with participant flow outlined in Figure S1. Proportions of covariate data that were imputed due to missingness ranged from 0 to 12% (Table S1). The majority of mothers in the study cohort had relatively high levels of education (67% with at least a college degree) and household income (72% greater than $70,000/year); 68% were white, 16% Black, 7% Hispanic, 5% Asian, and 5% other race/ethnicity.

Parent and teacher behavioral ratings were moderately correlated for the same assessments (Spearman r = 0.35 for the BRIEF GEC, 0.44 for the SDQ total difficulties score); BRIEF GEC and SDQ total difficulties scores for the same rater were more highly correlated (Spearman r = 0.78 for teachers, 0.69 for parents). Table 2 presents plasma concentrations of PFAS in prenatal and childhood samples. PFOS, PFOA, PFHxS, and PFNA were detected in >98% of prenatal and childhood samples. Due to low detection frequencies (>30% below detect), PFDA and FOSA were excluded from analyses of prenatal PFAS, and EtFOSAA, MeFOSAA, and FOSA were excluded from analyses of childhood PFAS. Correlations across different PFAS quantified at the same time point (prenatal or childhood) were moderate to high (Spearman r = 0.19–0.72 for prenatal, 0.14–0.78 for childhood) (Tables S2–S3). Prenatal versus childhood measures of the same PFAS had correlations ranging from 0.08 for PFNA to 0.41 for PFHxS (Table S4).

There were some differences between included participants and those excluded due to missing PFAS measures or behavioral assessments. For example, mother-child pairs excluded from analyses of childhood PFAS concentrations and parent-rated behavioral assessments were more likely to be white (68 vs. 62%) and less likely to be Black (15 vs. 21%), had somewhat higher maternal IQ (108.1 vs. 105.0 points), shorter duration of breastfeeding (5.4 vs. 6.3 months), and were less likely to have breastfed a previous child (29 vs. 42%) (Table S1). These excluded participants also had somewhat higher prenatal concentrations of PFOA (6.9 vs. 5.4 ng/mL) and PFOS (26.2 vs. 24.3 ng/mL), but behavioral assessment scores were similar between included and excluded groups (see Table S1).

3.2. PFAS and behavioral assessments

Associations of prenatal and childhood PFAS concentrations (in quartiles) with parent- and teacher-rated behavioral assessments in mid-childhood (age 6–10) are presented in Figs. 1–2 and Tables S5–S8. Secondary analyses evaluating associations of childhood PFAS

concentrations and behavioral assessments with additional adjustment for maternal plasma PFAS concentrations yielded similar results to primary models (data not shown). Figures S2 and S3 contrast adjusted model results with those of crude models adjusted only for year of blood collection.

3.2.1. Prenatal PFAS and SDQ scores—Parent-rated SDQ scores displayed no consistent patterns of association with prenatal PFAS concentrations. Third quartile MeFOSAA (but not second or fourth quartile) was associatedwith lower parent-rated SDQ total difficulties (−0.9, 95% CI: −1.8, 0.0) and internalizing scales (−0.6, 95% CI: −1.1, −0.1), indicating fewer behavioral problems (Fig. 1; Table S5). Conversely, teacher-rated SDQ total difficulty scores were higher (indicating greater behavioral problems) among children with higher prenatal PFOS concentrations (second quartile (Q2): 1.3, 95% CI: 0.1, 2.4; Q3: 1.2, 95% CI: 0.0, 2.4; Q4: 1.1, 95% CI: −0.2, 2.4), with elevated scores observed for both internalizing and externalizing SDQ subscales (Fig. 1; Table S6).

3.2.2. Prenatal PFAS and BRIEF scores—There were no consistent patterns of association of prenatal PFAS concentrations with parent-or teacher-rated BRIEF assessments (Fig. 1; Table S5). Third quartile versus first quartile prenatal PFHxS concentrations were associated with a somewhat higher teacher-rated BRIEF GEC (1.9 points, 95% CI: −0.1, 4.0) and metacognition index (2.6, 95% CI: 0.4, 4.7) scores (indicating greater executive function problems), but similar elevations were not observed for the top quartile of PFHxS. Second quartile EtFOSAA concentrations were associated with lower teacher-rated BRIEF GEC (−2.4, 95% CI: −4.5, −0.3), BRI (−1.9, 95% CI: −4.0, 0.1) and MI (−2.3, 95% CI: −4.4, −0.2) scores (indicating fewer problems), but no associations were observed for upper quartiles (Fig. 1; Table S6).

3.2.3. Mid-childhood PFAS and SDQ scores—Higher mid-childhood concentrations of PFOA, PFOS, PFHxS, PFNA and PFDA were associated with higher parent-rated SDQ total difficulties scores, indicating greater behavioral problems (top versus bottom quartile PFOA: 1.5, 95% CI: 0.3, 2.7; PFOS: 1.4, 95% CI: 0.3, 2.5; PFHxS: 1.2, 95% CI: 0.1, 2.3; PFNA: 1.2, 95% CI: 0.1, 2.2; PFDA: 1.1, 95% CI: 0.0, 1.1), with associations observed for both internalizing and externalizing SDQ subscales (Fig. 2; Table S7). Teacher-rated SDQ assessments generally did not display similar patterns of association, though the top quartile of childhood PFHxS was associated with higher teacher-rated SDQ externalizing scores (1.1, 95% CI: 0.0, 2.2) (Table S8), while some upper quartiles of childhood PFNA were associated with higher SDQ total difficulties scores (Q2 vs. Q1: 1.3, 95% CI: 0.0, 2.7) and externalizing scores (Q3 vs. Q1: 1.1, 95% CI: 0.0, 2.1) (Fig. 2; Table S8).

3.2.4. Mid-childhood PFAS and BRIEF scores—Top quartile versus first quartile childhood PFOS was associated with higher (indicating more problems) parent-rated BRIEF GEC (2.4, 95% CI: 0.2, 4.6), BRI (2.1, 95% CI: −0.2, 4.1), and MI (1.9, 95% CI: −0.2, 4.1) scores (Fig. 2; Table S7). In teacher-rated assessments, higher top quartile concentrations of PFHxS were associated with higher BRIEF GEC scores, with some suggestion of a dose-response with increasing PFHxS (Q2: 1.9, 95% CI: −0.6, 4.4; Q3: 2.0, 95% CI: −0.6, 4.7;

Q4: 3.5, 95% CI: −0.8, 6.3); associations were observed for both the behavioral regulation and metacognition indices (Fig. 2; Table S8).

3.3. Sex-stratified associations

We observed several instances of potential effect measure modification by sex, but no consistent patterns. Log-likelihood ratio tests indicated that models with PFAS × sex interaction terms were a better fit in models of prenatal PFHxS concentration and teacher-rated BRIEF and SDQ (p-value = 0.039 for BRIEF GEC, 0.004 for SDQ total difficulties), as well those for childhood PFOA and PFOS and teacher-rated BRIEF (p-value = 0.072 for PFOA and BRIEF GEC, 0.026 for PFOS and BRIEF GEC). In sex-stratified models, upper quartiles of prenatal PFHxS were associated with higher teacher-rated BRIEF GEC and SDQ total difficulties scores (indicating greater problems) among boys (Q3 vs. Q1 PFHxS and BRIEF: 3.1, 95% CI: 0.4, 5.8; Q4 vs. Q1 PFHxS and SDQ: 1.9, 95% CI: 0.1, 3.7), but not among girls (Figure S4). Sex-stratified models suggested that third vs. first quartile childhood PFOA concentrations were associated with higher teacher-rated BRIEF GEC scores among boys (3.5, 95% CI: 0.2, 6.8), with no associations observed among girls, while second vs. first quartile childhood PFOS concentrations were associated with lower teacher-rated BRIEF GEC scores (fewer problems) among girls (−5.2, 95% CI: −9.6, −0.9), with no associations observed among boys (Figure S5).

4. Discussion

In a prospective cohort of U.S. children, we did not observe consistent evidence of associations of prenatal PFAS exposure (measured in blood collected from mothers during pregnancy) with observer-assessed behavior and executive function problems among 6–10 year olds, though higher prenatal PFOS appeared associated with greater behavioral problems as assessed by teachers using the SDQ. In contrast, childhood PFAS concentrations were associated cross-sectionally with childhood assessments of behavior and executive function. Associations were most consistent for parent-rated measures of behavioral problems: parent-rated SDQ difficulties scores were higher (suggesting greater behavioral problems) among children with higher childhood plasma concentrations of PFOA, PFOS, PFHxS, PFNA and PFDA, with associations observed for both internalizing and the externalizing behaviors. Teacher-rated SDQ scores (total difficulties and externalizing subscale) were somewhat elevated among children with higher childhood PFHxS and PFNA, but not associated with other studied PFAS. We also observed associations of certain PFAS with parent- and teacher-rated assessments of executive function; higher childhood PFOS was associated with greater executive function problems as assessed by parents (including BRIEF Global Executive Composite, Behavioral Regulation Index and, Metacognition Index scores), while higher childhood PFHxS was associated with greater problems as assessed by teachers (also across GEC, BRI and MI scores). Although a few of the studied associations differed between boys and girls, patterns of effect measure modification by sex were not consistent.

Our findings that prenatal PFAS concentrations were not consistently associated with childhood behavior problems while childhood PFAS showed more consistent associations

are broadly similar to the findings of one prior prospective cohort study. In a birth cohort of children from the Faroe Islands (n = 539), higher PFOA, PFNA, and PFDA quantified at age 5 were associated with greater total difficulties scores on the parent-rated SDQ when children were aged 7, while prenatal PFAS concentrations were not associated with SDQ scores. In the Faroe Islands study, PFAS measured at age 7 were not associated with SDQ scores in the full cohort, but investigators described possible sexually dimorphic associations, with higher PFOS, PFHxS and PFNA associated with greater behavioral problems in girls and fewer problems in boys (Oulhote et al., 2016). In another prospective cohort (n = 256, Cincinnati, OH), higher prenatal PFOS concentrations were associated with higher parent-rated BRIEF GEC scores (indicating more executive function problems) at age 8, but prenatal PFOA was not associated with BRIEF scores (Vuong et al., 2016). In that cohort, age 8 PFNA was associated with higher age 8 BRIEF GEC scores and age 8 PFOA was associated with greater odds of clinical impairment in metacognition, but age 8 PFOS and PFHxS were not associated, nor were PFAS measures at age 3 (Vuong et al., 2018).

Several other studies of prenatal PFAS and childhood behavior have reported null results: in Danish studies, prenatal PFAS were not associated with parent-rated SDQ scores at age 7 (n = 787) (Fei and Olsen, 2011) or children's diagnoses of ADHD (Liew et al., 2015 [220 cases/550 controls]; Strøm et al., 2014 [n = 876]), a Swedish case-control study (206 cases/206 controls) reported no associations of cord blood PFAS with ADHD diagnosis (Ode et al., 2014), and a prospective cohort from Norway (n = 944) reported no consistent associations of prenatal PFAS with ADHD symptoms at age 3.5 (Skogheim et al., 2020). Conversely, in an upstate New York birth cohort (n = 788), higher PFOS concentrations in newborn blood spots were associated with greater parent-rated SDQ total difficulties scores at age 7 (Ghassabian et al., 2018). In a pooled cohort from Greenland and Poland (n = 1106), prenatal PFOA and PFOS were not associated with higher total difficulties scores on the parent-rated SDQ at ages 5–9, but higher PFOA was associated with greater hyperactivity, and odds of hyperactivity were also suggestively elevated among children with higher PFOS (Høyer et al., 2015).

Associations of childhood PFAS concentrations with childhood behavior and executive function problems have been examined in several other prior studies. Prevalence of ADHD was associated with PFOS, PFOA and PFHxS concentrations among 12–15 year olds in NHANES cohorts (1999–2000 and 2003–4 cycles) (n = 571) (Hoffman et al., 2010) and childhood PFOS, PFNA, and PFHxS concentrations were associated with greater impulsivity among 9–11 year olds in Oswego County, NY (n = 83) (Gump et al., 2011). Among children from the C8 Health Project cohort exposed to groundwater contaminated by PFOA from an industrial facility near Parkersburg, West Virginia (n = 321), PFOA concentrations at ages 2–8 were not consistently associated with executive function and behavior problems assessed at ages 6–12 using and parent and teacher-rated instruments including the BRIEF, though investigators reported potential patterns of sexual dimorphism in associations (Stein et al., 2014). In children from the full C8 Health Project cohort (n = 10,546), there was no consistent association of reported ADHD diagnosis with PFOA, but suggestion of potential association with PFHxS (Stein and Savitz, 2011).

PFAS concentrations measured in Project Viva mothers during pregnancy and children at ages 6–10 (in 1999–2002 and 2007–10, respectively) were similar to those measured at similar time points in women and children in the nationally representative NHANES study (Harris et al., 2017; Sagiv et al., 2015). For example, geometric mean (GM) PFOA was 5.7 ng/mL in Project Viva mothers (Sagiv et al., 2015) and 4.8 ng/mL in NHANES women in 1999–2000 CDC, 2021, while GM PFOA was 4.2 ng/mL in Project Viva children (Harris et al., 2017) and 3.9 ng/L in NHANES adolescents in 2007–8 CDC, 2021. Concentrations of most of the studied PFAS declined in the U.S. population over the 1999–2016 period following the phase out of production of PFOS, PFOA and related chemicals (Buck et al., 2011; CDC, 2021; D'Eon and Mabury, 2011; Kato et al., 2011b); we observed similar declines in concentration across the years of blood sampling in Project Viva (Harris et al., 2017; Sagiv et al., 2015). To reduce potential confounding related to trends in PFAS concentrations over time, we adjusted our models for year of blood sampling.

As patterns of PFAS production and use have changed over time, and also vary geographically, some of the inconsistency in findings between our study and others may stem from differences in PFAS concentrations across study cohorts. In some cases, these differences are substantial, especially for studies that have examined populations impacted by industrial contamination; for example, the median child PFOA concentration in the C8 Health Project cohort was 35.1 ng/mL (interquartile range: 15.8–94.1 ng/mL) (Stein et al., 2014), versus 4.4 (3.1–6.1) ng/mL in Project Viva (Table 2). Differences in population demographics across study populations and analytical approaches may also contribute to the inconsistency in findings.

There are several hypothesized mechanisms through which early life exposure to PFAS may influence neurodevelopment. In *in vitro* models, PFAS appear to influence neuronal differentiation (Slotkin et al., 2008). PFAS can activate the peroxisome proliferator-activated receptor alpha, a nuclear receptor that influences cell growth and metabolism (Lau et al., 2007; Mariussen, 2012; Rosen et al., 2009). In toxicological studies, mice with neonatal exposure to PFOA, PFOS, and PFHxS displayed disrupted spontaneous behavior in adulthood and irregular nicotinic response (Johansson et al., 2008; Viberg et al., 2013), and displayed altered levels of neuroproteins important for brain development in the hippocampus and cerebral cortex (Johansson et al., 2009; Lee and Viberg, 2013).

One strength of our study was repeated quantification of PFAS at multiple time points, which allowed for evaluation of the relative influence of prenatal versus childhood PFAS concentrations on behavior and executive function in childhood. Prior research in Project Viva reported that maternal plasma PFAS concentrations were associated with mid-childhood PFOA, PFOS, PFHxS and MeFOSAA concentrations (Harris et al., 2017), so we evaluated potential confounding by prenatal PFAS exposure of cross-sectional associations of mid-childhood PFAS concentrations with behavioral and executive function assessments. The effect estimates we observed for associations of childhood PFAS concentrations with greater behavior and executive function problems did not change appreciably following adjustment for prenatal plasma PFAS concentrations, suggesting that the observed associations with childhood PFAS concentrations were not explained by gestational PFAS exposure.

The differences in associations we observed for childhood versus prenatal PFAS concentrations in our study may relate to the timing of sensitive windows of development for brain regions involved in regulating behavior and executive function. For example, the prefrontal cortex, a region important for inhibitory control and executive function, undergoes critical growth and development throughout childhood (Casey et al., 2000; Tsujimoto, 2008). It should be noted, however, that the cross-sectional associations we observed with mid-childhood PFAS concentrations could also result from reverse causation if the behavioral problems assessed influenced childhood PFAS concentrations, for example, by affecting dietary patterns. Mid-childhood PFAS concentrations in Project Viva were higher among children with an early childhood (median age 3.3 years) dietary pattern characterized by higher intake of packaged foods and fish, although dietary intake of these foods in mid-childhood was not associated with PFAS concentrations (Seshasayee et al., 2021). Childhood diet could also potentially be a cause of residual confounding if dietary patterns associated with higher PFAS independently influenced neurodevelopment. Additional longitudinal studies examining behavior and executive function in relation to PFAS exposure and diet at multiple time points could help further elucidate these potentially complex relationships.

Our study examined multiple measures of behavior and executive function, assessed by both parents and teachers. As has been observed in other populations and normative samples (Gioia et al., 2002; Mares et al., 2007; Stone et al., 2010), correlations between parent and teacher ratings in our study were only moderate. The associations we observed were not consistent across parent and teacher assessments; in particular, we observed consistent associations of childhood PFAS with parent-rated, but not teacher-rated SDQ scores. As parents and teachers observe children in different settings, it may be that certain behaviors are more apparent in a home rather than school context. It is also possible, however, that the associations we observed with parent ratings could be impacted by confounding due to factors related to both childhood PFAS concentrations and parental characteristics that influenced the evaluations. In an attempt to address this type of possible confounding, we adjusted our models for a number of parental characteristics, including maternal and paternal education level, household income, maternal age, parity, IQ, and race/ethnicity, but there is still a possibility of residual confounding due to these or other factors.

Several other limitations should be considered in the interpreting our study results. While we examined multiple PFAS, moderate to high correlations among the measured PFAS limited our ability to fully distinguish the impacts of individual PFAS. Our analyses included only participants with available PFAS concentrations and behavioral assessments (23–43% of the full Project Viva cohort, depending on analysis), and there were some differences in the characteristics of included and excluded participants. Notably, however, behavioral assessment scores were very similar between included and excluded groups. That fact, coupled with statistical adjustments in our models for covariates observed to predict drop-out, should have minimized selection bias from differential loss to follow-up, but some bias is still possible.

5. Conclusions

In a birth cohort of U.S. children with PFAS concentrations similar to those of the U.S. general population, prenatal PFAS concentrations were not consistently associated with childhood assessments of behavior and executive function, but we observed cross-sectional associations of childhood PFAS with greater behavioral and executive function problems at ages 6–10. Specifically, PFOA, PFOS, PFHxS, PFNA and PFDA were each associated with more behavioral problems as evaluated by parents using the SDQ, with teacher-rated SDQ scores also suggestively elevated (indicating greater problems) in children with higher PFHxS and PFNA concentrations. Childhood PFOS was associated with greater executive function problems as assessed by parents using the BRIEF, while higher childhood PFHxS was associated with greater teacher-rated executive function problems. We did not observe consistent patterns of sexual dimorphism in associations. Our findings add to a mixed literature on the associations of prenatal and childhood PFAS concentrations with behavioral and executive function problems, and point to the need for further research into potential neurodevelopmental impacts of PFAS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ADHD	attention deficit hyperactivity disorder
BRI	BRIEF Behavioral Regulation Index (BRI)
BRIEF	Behavior Rating Inventory of Executive Function
CDC	Centers for Disease Control and Prevention
EtFOSAA	2-(N-ethyl-perfluorooctane sulfonamido) acetate
FOSA	perfluorooctane sulfonamide
GEC	BRIEF Global Executive Composite (GEC)
GM	geometric mean

HOME-SF	Home Observation for Measurement of the Environment - Short Form
IQ	intelligence quotient
KBIT-2	Kaufman Brief Intelligence Test
LOD	limit of detection
MeFOSAA	2-(N-methyl-perfluorooctane sulfonamido) acetate
MI	BRIEF Metacognition Index (MI)
NHANES	National Health and Nutrition Examination Survey
PFAS	per- and polyfluoroalkyl substance
PFDA	perfluorodecanoate
PFHxS	perfluorohexane sulfonate
PFNA	perfluorononanoate
PFOA	perfluorooctanoate
PFOS	perfluorooctane sulfonate
SD	standard deviation
SDQ	Strengths and Difficulties Questionnaire
VIF	variance inflation factor

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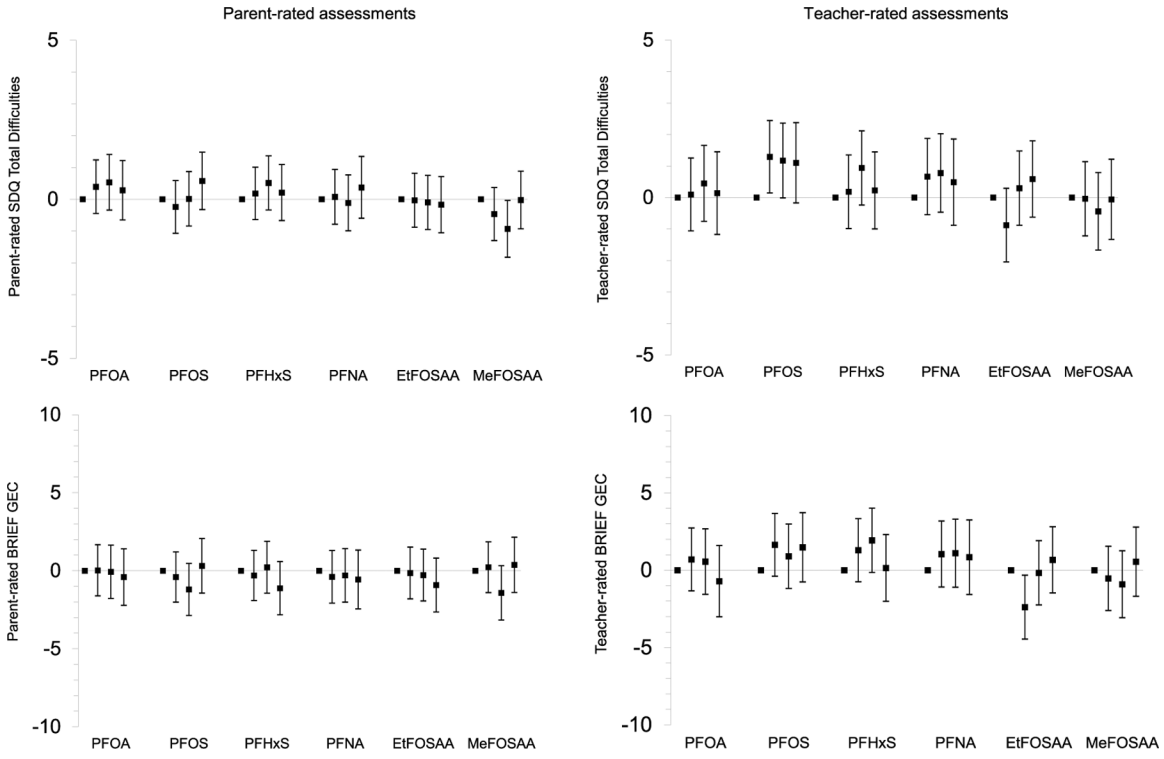

Fig. 1.

Mean differences (+95% confidence intervals) in mid-childhood (age 6–10) behavioral assessment scores associated with maternal pregnancy plasma PFAS concentrations in quartiles, adjusted for relevant covariates (n = 933 for parent-rated SDQ, 921 for parent-rated BRIEF, 713 for teacher-rated SDQ, 693 for teacher-rated BRIEF). All models adjusted for: year of pregnancy blood collection (1999, 2000, 2001, 2002), gestational age (in weeks) at time of pregnancy blood collection, estimated glomerular filtration rate (mL/min per 1.73 m^2) at blood draw (derived from plasma creatinine levels using Cockcroft-Gault equation), maternal race/ethnicity (Black, white, Hispanic, Asian or other), age (<25, 25–34, ≥35 years), education (<college degree, college degree, graduate degree), KBIT-2 score, pre-pregnancy body mass index (kg/m2), smoking status (never, former, smoked in pregnancy), paternal education (<college degree, college degree, graduate degree), annual household income in mid-childhood (<$40 K, $40–70 K, $70–150 K, ≥$150 K), HOME-SF score, child's sex and age (days) at mid-childhood behavioral assessment, and proxy indicator for maternal parity/prior breastfeeding (nulliparous, parous with no breastfeeding, parous with breastfeeding).

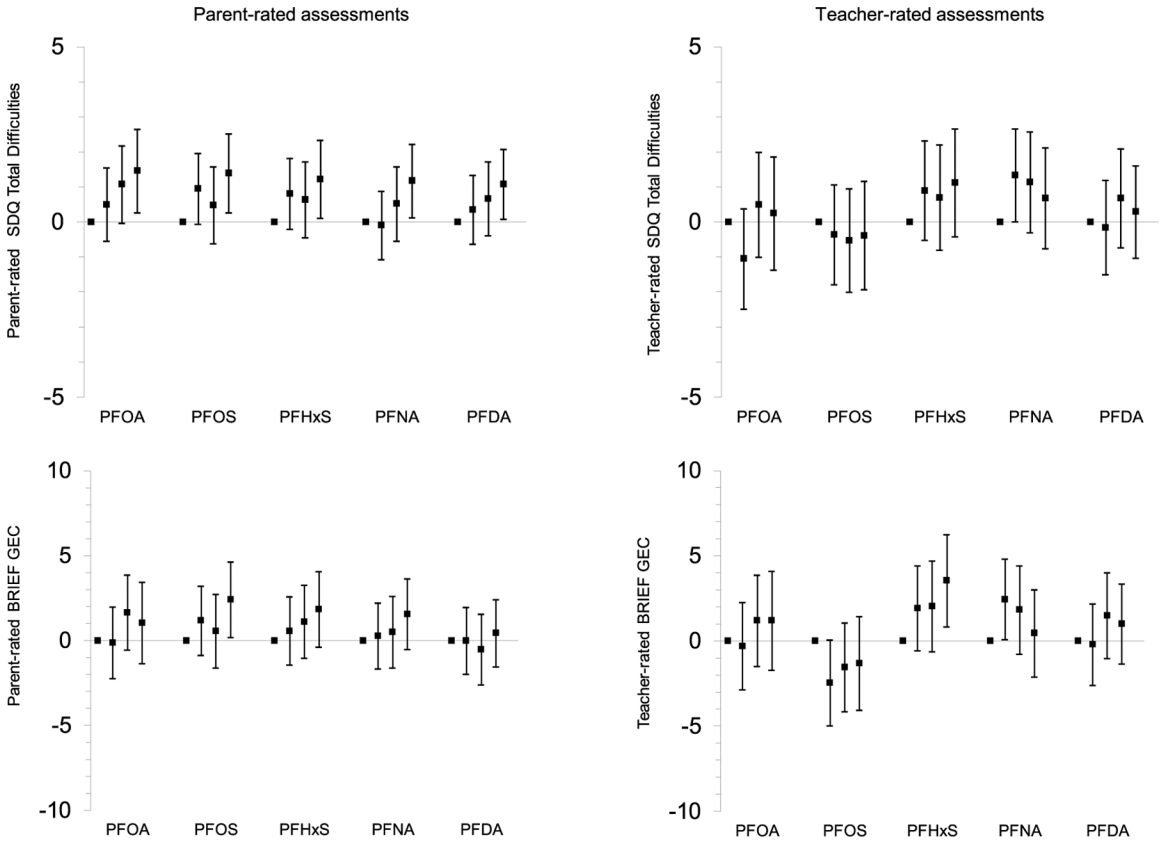

Fig. 2.

Mean differences (+95% confidence intervals) in mid-childhood (age 6–10) behavioral assessment scores associated with mid-childhood plasma PFAS concentrations in quartiles, adjusted for relevant covariates (n = 628 for parent-rated SDQ, 622 for parent-rated BRIEF, 499 for teacher-rated SDQ, 485 for teacher-rated BRIEF). All models adjusted for: year of blood draw (2007, 2008, 2009, 2010), maternal race/ethnicity (Black, white, Hispanic, Asian or other), age (<25, 25–34, ≥35 years), education (<college degree, college degree, graduate degree), parity (0, 1, ≥2), KBIT-2 score, paternal education (<college degree, college degree, graduate degree), annual household income in mid-childhood (<$40 K, $40–70 K, $70–150 K, ≥$150 K), HOME-SF score, child's sex and age (days) at mid-childhood behavioral assessment, and breastfeeding duration (months up to 12).

Table 1

Characteristics of study participants (included in at least one analysis, n = 1080) after imputation of covariates.

Characteristic	N (%) or mean ± standard deviation
Parent-Rated Behavioral Assessments	
Strengths and Difficulties Questionnaire (SDQ) Total Difficulties score[a] (n = 1061)	6.7 ± 4.9
SDQ Internalizing Subscale[a]	2.7 ± 2.6
SDQ Externalizing Subscale[a]	4.0 ± 3.2
Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite (GEC) score[b] (n = 1048)	48.8 ± 9.1
BRIEF Behavior Regulation Index (BRI) score[b]	48.3 ± 8.9
BRIEF Metacognition Index (MI) score[b]	48.5 ± 8.7
Teacher-Rated Behavioral Assessments	
Strengths and Difficulties Questionnaire (SDQ) Total Difficulties score[a] (n = 811)	6.4 ± 5.8
SDQ Internalizing Subscale[a]	2.4 ± 2.7
SDQ Externalizing Subscale[a]	3.9 ± 4.1
Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite (GEC) score[b] (n = 790)	51.0 ± 10.5
BRIEF Behavior Regulation Index (BRI) score[b]	50.7 ± 10.1
BRIEF Metacognition Index (MI) score[b]	51.1 ± 10.7
Child characteristics	
Sex	
Female	525 (49)
Male	555 (51)
Duration of breastfeeding (months up to 12)	6.3 ± 4.7
Age at parent-rated behavioral assessments (years) (n = 1065)	7.9 ± 0.8
Age at teacher-rated behavioral assessments (years) (n = 812)	8.0 ± 0.8
Year of mid-childhood blood draw (n = 641)	
2007	68 (11)
2008	219 (34)
2009	207 (32)
2010	147 (23)
Maternal characteristics	
Year of enrollment	
1999	253 (23)
2000	396 (37)
2001	382 (35)
2002	49 (5)
Age at enrollment (years)	32.1 ± 5.4
Parity at enrollment	
Nulliparous	510 (47)
1	388 (36)

Characteristic	N (%) or mean ± standard deviation
≥2	182 (17)
Breastfed a prior child [c]	
Yes	455 (42)
No	625 (58)
Education (at enrollment)	
Less than college degree	350 (32)
College degree	380 (35)
Graduate degree	350 (32)
Race/ethnicity	
White	731 (68)
Black	171 (16)
Asian	51 (5)
Hispanic	77 (7)
Other	50 (5)
Smoking in pregnancy	
Smoked in pregnancy	111 (10)
Former smoker	210 (19)
Never smoker	759 (70)
Pre-pregnancy body mass index (kg/m^2)	24.8 ± 5.3
Gestational duration at time of pregnancy blood draw (weeks)	10.1 ± 2.5
Estimated glomerular filtration rate at time of pregnancy blood draw (mL/min per 1.73 m^2)	111.0 ± 55.3
IQ (KBIT-2 composite) at mid-childhood cognitive assessment	106.4 ± 15.7
Paternal characteristics	
Education (at enrollment)	
Less than college degree	393 (36)
College degree	374 (35)
Graduate degree	313 (29)
Household characteristics	
Household annual income at mid-childhood	
≤$40 K	138 (13)
>$40–≤$70 K	161 (15)
>$70–≤$150 K	487 (45)
>$150 K	294 (27)
HOME-SF score[d] at mid-childhood	18.3 ± 2.2

[a] Strengths and Difficulties Questionnaire (SDQ) Total Difficulties scores have possible values of 0–40, SDQ Internalizing and Externalizing subscales have possible values of 0–20; higher scores represent greater behavioral problems. SDQ Total Difficulties score combines Internalizing and Externalizing subscales.

[b] Behavior Rating Inventory of Executive Function (BRIEF) Index and Composite scores standardized to mean = 50, standard deviation = 10 with higher scores representing greater executive function problems. BRIEF Global Executive Composite score combines Metacognition Index and Behavior Regulation Index scores.

[c] Estimated using maternal parity and breastfeeding data for the Project Viva child.

[d]Home Observation for Measurement of the Environment (Short Form); scale: 0–22, with higher scores representing better support for cognitive development in home.

Table 2

Concentrations (in ng/mL) of per- and polyfluoroalkyl substances (PFAS) in maternal pregnancy plasma and child plasma (median age 7.7) for study participants (included in at least one analysis, n = 1080).

PFAS	% Detect	Median (25%–75%)	Minimum	Maximum
Prenatal concentrations (sampled 1999–2002, n = 950)				
PFOA	100	5.6 (3.9–7.7)	0.3	49.3
PFOS	99.8	24.7 (18.2–33.5)	<LOD[a]	168.0
PFHxS	99.2	2.3 (1.6–3.7)	<LOD	43.2
PFNA	98.8	0.6 (0.5–0.9)	<LOD	6.0
EtFOSAA	99.5	1.1 (0.7–1.8)	<LOD	33.6
MeFOSAA	100	1.9 (1.2–3.0)	0.1	29.7
PFDA	45.5	<LOD (<LOD −0.3)	<LOD	3.0
FOSA	10.5	All < LOD	<LOD	1.8
Childhood concentrations (sampled 2007–2010, n = 641)				
PFOA	99.5	4.4 (3.1–6.1)	<LOD	14.3
PFOS	99.5	6.2 (4.2–9.7)	<LOD	51.4
PFHxS	99.5	1.9 (1.2–3.4)	<LOD	56.8
PFNA	99.5	1.5 (1.1–2.3)	<LOD	25.7
EtFOSAA	5.2	All < LOD	<LOD	1.4
MeFOSAA	65.4	0.3 (<LOD–0.6)	<LOD	6.7
PFDA	88.5	0.3 (0.2–0.5)	<LOD	1.9
FOSA	0.8	All < LOD	<LOD	0.5

[a]Limit of detection (LOD) was 0.1 ng/mL except for prenatal PFOS concentrations (LOD = 0.2 ng/mL).