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Prenatal exposure to per- and polyfluoroalkyl substances and cognitive development in infancy and toddlerhood

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Author's contributions

JO and HS conceived the study and IH oversaw its coordination. JO conducted data analyses and drafted the initial manuscript. HS, RS and IH helped oversee the study. AC quantified PFAS in maternal serum samples. DT advised on data analysis, interpretation, and reporting. DR oversaw cognitive assessment of children. All authors read and approved the final manuscript.

Jiwon Oh: Conceptualization, Formal analysis, Visualization, Writing- Original Draft

Rebecca Schmidt: Methodology, Project administration, Writing- Reviewing and Editing

Daniel Tancredi: Methodology, Writing- Reviewing and Editing

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Dorcas Loa: Methodology, Writing- Reviewing and Editing

Irva Hertz-Picciotto: Methodology, Writing- Reviewing and Editing, Funding acquisition

Hyeong-Moo Shin: Conceptualization, Methodology, Writing- Reviewing and Editing, Supervision, Funding acquisition, Project administration

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

Ethics approval and consent to participate

The MARBLES study protocol and this study were approved by the institutional review boards for the State of California, the University of California-Davis (UC-Davis), and the University of Texas-Arlington (UT-Arlington). Participants provided written informed consent before collection of any data. The analysis of coded specimens at the Centers for Disease Control and Prevention (CDC) laboratory was determined by CDC not to constitute engagement in human subject research.

Consent for publication

Not applicable.

Availability of data and material

Portions of the datasets generated and analyzed during this study are publicly available in the National Institute of Mental Health (NIMH) Data Archive. The entire non-identifiable dataset is available from the authors upon reasonable request and with permission from the IRBs at UT-Arlington and UC-Davis.

Competing interests

RJ has received lodging for the Baby Siblings Research Consortium Meeting; travel and lodging for invited talks at the University of Sherbrooke, Sherbrooke, Québec, Canada; the University of California, Santa Cruz, California (Lodging); Epigenomics 2016, Puerto Rico (Lodging); Neurotoxicity Society & International Neurotoxicology Association, Florianópolis, Brazil; RISE 2017 Second International Meeting on Environmental Health in Strasbourg, France. RJ also received Autism Speaks grant funding to develop an online autism environmental questionnaire. Other authors declare they have no actual or potential competing financial interests.

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Abstract

Background/Objective: Per- and polyfluoroalkyl substances (PFAS) have neurobehavioral toxicity in experimental studies. Evidence on associations between prenatal PFAS exposure and child's cognitive development is inconsistent partly due to differences in assessment time points and tools. We examined associations of prenatal maternal PFAS serum concentrations with child's cognitive development assessed at multiple time points in infancy and toddlerhood.

Methods: We included 140 mother-child pairs from MARBLES (**M**arkers of **A**utism **R**isk in **B**abies – **L**earning **E**arly **S**igns), a longitudinal cohort of children with a first degree relative who was diagnosed with autism spectrum disorder followed from birth. Study children's cognitive development was assessed at 6, 12, 24, and 36 months of age using the Mullen Scales of Early Learning (MSEL) which provides an overall Early Learning Composite (normative mean of 100 and SD of 15) and four subscales (i.e., fine motor, visual reception, receptive language, and expressive language abilities; normative mean of 50 and SD of 10). Nine PFAS were quantified in maternal serum collected during pregnancy. We examined associations of log 2-transformed prenatal maternal serum PFAS concentrations with the MSEL Composite and each of the subscale scores at each time point as well as longitudinal changes in the scores over the four time points. We also classified trajectories into low- and high-score groups and fit Poisson regression models to estimate associations expressed as relative risks (RR).

Results: Among six PFAS detected in more than 60% of the samples, prenatal maternal serum perfluorooctanoate (PFOA) was inversely associated with child's Composite score at 24 months ($\beta = -5.22$, 95% CI: −8.27, −2.17) and 36 months of age ($\beta = -5.18$, 95% CI: −9.46, −0.91), while other five PFAS were not strongly associated with Composite score at any time points. When assessing longitudinal changes in the scores over the four time points, PFOA was associated with trajectories having a negative slope for Composite scores and all four subscales. When examining trajectories of the scores between low- and high-score groups, PFOA was associated with having lower and/or decreasing Composite scores (RR = 1.49, 95% CI: 1.09, 2.03).

Conclusions: Prenatal PFOA appears to adversely affect child's cognitive development in toddlerhood in this study population. Because a large fraction of MARBLES children is at risk for atypical development, population-based studies are needed to confirm our findings.

1. BACKGROUND

Per- and polyfluoroalkyl substances (PFAS) are a group of synthetic fluorine-containing compounds that have been widely used in consumer and industrial applications, including non-stick cookware, food packaging materials, and stain- and water-repellent fabrics (ATSDR 2018). The widespread applications of PFAS in consumer products resulted in ubiquitous detection of several PFAS in serum of the general U.S. population (CDC 2019; Kato et al. 2011a; Olsen et al. 2017). PFAS have also been detected in blood of pregnant women as well as in amniotic fluid, umbilical cord blood, and breast milk (Bjerregaard-Olesen et al. 2016; Inoue et al. 2004; Kato et al. 2014; Kim et al. 2011; Liu et al. 2011; Long et al. 2019; Monroy et al. 2008; Tsai et al. 2018; von Ehrenstein et al. 2009). In addition, concentrations of commonly-detected PFAS, including perfluorooctane sulfonate (PFOS)

and perfluorooctanoate (PFOA), in prenatal maternal blood are moderately to highly correlated with corresponding measurements in amniotic fluid and cord blood (Beesoon et al. 2011; Gützkow et al. 2012; Stein et al. 2012), supporting the transfer of PFAS across the placenta.

Prenatal exposure to PFAS is of concern for young child's cognitive development because PFAS have shown neurobehavioral toxicity in prenatally-exposed offspring of laboratory animals (Mariussen 2012). In mice, gestational exposure to PFOS resulted in delayed neuromotor maturation (Fuentes et al. 2007) and decreased locomotion (Onishchenko et al. 2011). Among mice prenatally exposed to PFOA, males showed more active exploratory behaviors, while females displayed decreased activity (Onishchenko et al. 2011). In rats, gestational exposure to PFOS increased motor activity and reduced habituation in male offspring on postnatal day (PND) 17 but not on PND 13, 21, and 61 (Butenhoff et al. 2009), suggesting that PFOS may have neurobehavioral effects at a certain life stage of offspring. Collectively, these findings highlight the relevance of examining the potential effect of prenatal maternal exposure to PFAS on child's cognitive development.

Epidemiological studies have examined associations of prenatal PFAS exposure with child's neurobehaviors at different assessment time points in infancy and toddlerhood (Chen et al. 2013; Donauer et al. 2015; Goudarzi et al. 2016; Spratlen et al. 2020). Birth cohort studies in the United States and Japan observed that prenatal serum PFOA was associated with hypotonic response in 5-week-old infants and lower mental developmental index among 6-month-old females, respectively (Donauer et al. 2015; Goudarzi et al. 2016). In the Taiwanese Birth Panel Study, PFOS in cord blood was inversely associated with whole-test developmental quotients among children at 2 years of age (Chen et al. 2013). A recent study in the United States reported that prenatal exposures to PFOA and perfluorohexane sulfonate (PFHxS) were positively associated with mental developmental index in children at 3 years of age, but not at 1 and 2 years (Spratlen et al. 2020). Except for Spratlen et al., children in the previous studies were assessed for neurodevelopment at one or two time points in infancy or toddlerhood (before or at 36 months of age). In addition, little is known about trajectories of child' neurodevelopment over time or longitudinal changes in associations between prenatal maternal PFAS exposure and child's neurodevelopment.

The present study aimed to investigate associations between prenatal maternal serum PFAS concentrations and child's cognitive development assessed at four time points in infancy and toddlerhood (i.e., 6, 12, 24, 36 months of age). We also examined longitudinal changes in child's cognitive developmental scores as well as trajectories of the developmental scores over the four time points in association with prenatal maternal serum PFAS concentrations.

2. METHODS

2.1. Study population

The present study included participants from MARBLES (***M***arkers of ***A***utism ***R***isk in ***B***abies – ***L***earning ***E***arly ***S***igns) (Hertz-Picciotto et al. 2018). Launched in 2006, the MARBLES study is an ongoing cohort that follows pregnant women who previously had a child diagnosed with autism spectrum disorder (ASD) and are thus at high risk (~28%) of having

a child with delays or deficits in areas of development or behavior (Ozonoff et al. 2014). Participants are mostly recruited from the lists of families receiving state-funded services for a child with ASD. MARBLES eligibility criteria at enrollment include: a) mother or father has a child or other first degree relative with ASD; b) mother is 18 years old or older; c) mother is pregnant; d) mother speaks, reads, and understands English; e) mother resides within 2.5 hours of the Davis/Sacramento region. Informed consent is obtained from participants before collecting any data, and the protocols were approved by the institutional review boards for the State of California and the University of California Davis (UC Davis). The analysis of coded samples at the Centers for Disease Control and Prevention (CDC) laboratory did not constitute engagement in human subjects research. Details of study design, study population, inclusion criteria, recruitment, and data collection are available elsewhere (Hertz-Picciotto et al. 2018).

Enrollment of MARBLES began in 2006; in 2009, MARBLES started collecting serum. Therefore, we firstly selected 218 mother-child pairs (MARBLES baseline population) (1) who provided prenatal blood samples with sufficient volume for PFAS quantification since 2009 and conceived their babies by 2014 and (2) whose child has ever been assessed for cognitive development at any time point. We further restricted our study population to 140 children who were repeatedly evaluated for cognitive development at all four time points, i.e., at 6, 12, 24, and 36 months of age (Figure S1).

2.2. Serum sample collection and PFAS quantification

Each mother included in the present study provided one to three blood samples during pregnancy. Of 140 mother-child pairs, 91 pairs provided one sample, 14 pairs two samples, and 35 pairs three samples. Thus, a total of 224 blood samples were used in this study. Whole blood was centrifuged, and separated serum was stored at −80 °C at the UC Davis.

At the CDC, we quantified PFAS in maternal serum using online solid-phase extraction coupled to reversed-phase high-performance liquid chromatography–isotope dilution tandem mass spectrometry. Analytical methods for PFAS quantification are described elsewhere (Kato et al. 2011b). To ensure reproducibility, quality control samples spiked at low and high concentrations of PFAS were included in each batch. To assess the reliability of the data, 25 blind duplicate samples were analyzed with the study samples. The median coefficient of variation for these duplicate pairs of samples ranged from 0 to 11%, depending on the analyte.

We quantified nine PFAS: PFOA, PFOS, PFHxS, perfluorononanoate (PFNA), perfluorodecanoate (PFDA), perfluoroundecanoate (PFUnDA), perfluorododecanoate (PFDoDA), 2-(N-methyl-perfluorooctane sulfonamido) acetate (MeFOSAA), and 2-(N-ethyl-perfluorooctane sulfonamido) acetate (EtFOSAA). The limit of detection (LOD) was 0.1 ng/mL for all PFAS. For concentrations below the LOD, we used instrument-observed values to reduce bias (Lubin et al. 2004; Richardson and Ciampi 2003).

2.3. Assessment of child cognitive development

Licensed clinical psychologists at the UC Davis Medical Investigations of Neurodevelopmental Disorders (MIND) Institute assessed all children included in this study

for cognitive development. MARBLES staff who were trained by senior clinicians assessed child's cognitive development during home visits at 6 and 12 months of age and during participants' visits to the UC Davis MIND Institute at 24 and 36 months of age, which were then reviewed by senior clinicians (Hertz-Picciotto et al. 2018). Cognitive development in infancy and toddlerhood was assessed using Mullen Scales of Early Learning (MSEL), a performance-based measure of cognitive functions or abilities designed to evaluate infants and young children up to 68 months of age (Burns et al. 2013; Mullen 1995). Child's cognitive functions are scored on four subscales: Fine Motor, Visual Reception, Receptive Language, and Expressive Language. Raw scores of the four subscales are converted to age-standardized T-scores with a mean of 50 and a standard deviation (SD) of 10. The T-scores of four subscales are combined to yield an Early Learning Composite (Composite), which is a standardized score of overall cognitive development with a mean of 100 and an SD of 15 (Swineford et al. 2015; Turner-Brown et al. 2013). A higher score on Composite and each subscale indicates better cognitive functions.

When children became approximately 36 months of age, they were classified into three diagnostic groups, including ASD, non-typical development (Non-TD), and typical development (TD), using an algorithmic method based on Autism Diagnostic Observation Schedule and MSEL scores. The algorithmic method is described elsewhere (Oh et al. 2021).

2.4. Statistical analysis

All statistical analyses were conducted using STATA/IC version 15.1 (StataCorp LLC, College Station, TX, USA). At each assessment time point, we compared mean MSEL Composite scores with respect to demographic characteristics using the Wilcoxon rank-sum test or the Kruskal-Wallis test. Separately for the MSEL Composite scores and each of the subscale T-scores, we tested for whether mean scores differed across the four time points by fitting a panel data regression model with fixed effects for child and timepoint (as a categorical variable) and then assessing the Wald test for the omnibus null hypothesis associated with timepoint, using robust sandwich variance estimators to account for heteroskedasticity and Bonferroni correction for multiple comparison (Bland and Altman 1995).

To investigate prenatal maternal serum PFAS concentrations in association with MSEL Composite scores and T-scores of each subscale at each assessment time point, we constructed multiple linear regression models and estimated regression coefficients (βs) and 95% confidence intervals (CIs). Six PFAS with detection frequency greater than 60% were individually included in the regression models: PFOA, PFOS, PFHxS, PFNA, PFDA, and PFUnDA. Three PFAS that were detected in less than 60% of the samples were excluded from the further analyses. For mothers who provided multiple blood samples during different trimesters, PFAS concentrations were averaged per participant. Because most PFAS concentrations showed right-skewed distributions, we used log 2-transformed PFAS concentrations to reduce the impact driven by outliers and centered each log 2-transformed PFAS concentration by subtracting its median value, to facilitate the interpretability of models with interactions terms. We selected *a priori* potential confounders using a directed

acyclic graph (Figure S2) (Hernán et al. 2004). We retained the covariates that were associated with MSEL Composite scores at least one time point ($p < 0.10$) in the regression models. Covariates adjusted in the final models included: child's sex (female, male), parity (≤ 1, > 1), maternal pre-pregnancy body mass index (BMI) (normal/underweight, overweight, obese), gestational diabetes (yes, no), maternal education (high school or some college credit, bachelor's degree, graduate or professional degree), and breastfeeding duration (< 12 months, ≥ 12 months). Because two mothers participated in the study with twins, we applied clustered sandwich variance estimators to the regression models to adjust for within-family correlations. We imputed missing covariates with chained equations by including all exposures, outcomes, and covariates (White et al. 2011).

To examine longitudinal changes in MSEL Composite scores and T-scores of four subscales over the four assessment time points within subjects in relation to prenatal maternal serum PFAS concentrations, we used population-averaged generalized estimating equations (GEE) models with a linear link and autoregressive correlation structure, adjusting for the same covariate set as before (Ballinger 2004; Liang and Zeger 1986). In these models, age at assessment (expressed in months) was centered at 24 and included in the model in two terms; one for a main effect and the other for an interaction term with the log 2-transformed and centered PFAS exposure, with the interaction term considered statistically significant when $p < 0.10$. The GEE models used in this study can handle not only correlated data within individuals but also incomplete outcome data (e.g., Composite and subscale scores) by using all available observations (Hubbard et al. 2010). Therefore, as a sensitivity analysis, we ran the GEE models using the MARBLES baseline population that additionally include 78 children with incomplete MSEL outcomes.

To examine the trajectories of MSEL Composite scores over the four assessment time points within groups with distinct trajectories of the outcome, we performed a group-based trajectory analysis by characterizing the patterns of repeated outcomes (Nagin 2005). Due to the small sample size, we limited the number of trajectory groups to two, which were characterized by difference in the child's Composite score patterns from 6 to 36 months of age, and determined the trajectory shape of each group based on the Bayesian information criterion (Raftery 1995). We then classified children with decreasing and/or lower scores into a low-score group and those with increasing and/or higher scores into a high-score group. To estimate relative risks (RRs) of the low-score group compared to the high-score group in association with prenatal maternal serum PFAS concentrations, we used Poisson regression models with robust error variance, adjusting for the same covariate set as before.

To examine the combined effect of PFAS on child's cognitive development, we carried out a principal component analysis (PCA), a "variable reduction" strategy that can mitigate multicollinearity issues (Kaiser 1958). PCA has been used to identify patterns of exposure from chemical mixtures, including PFAS, in association with child's neurodevelopment due to its versatility and ease of application (Hoffman et al. 2010; Skogheim et al. 2020; Spratlen et al. 2020; Stafoggia et al. 2017). From a PCA with varimax rotation using six PFAS, we selected the first and second principal components (PC-1 and PC-2), which each had eigenvalues greater than one. We included them in regression models as independent variables (Kaiser 1960).

Previous studies reported effect modification of associations between prenatal PFAS and cognitive development of infants or young children by child's sex (Goudarzi et al. 2016; Harris et al. 2018; Niu et al. 2019). Breastfeeding was reported to not only serve as an important PFAS exposure route for infants (Mogensen et al. 2015; Mondal et al. 2012) but also affect child's cognitive development in infancy (McCrory and Murray 2013; Morrow-Tlucak et al. 1988). Thus, for each of these candidate effect modifiers (i.e., child's sex (female, male) and breastfeeding duration (< 12 months, ≥ 12 months)), we performed effect modification analyses by refitting regression models that included interaction terms involving the candidate effect modifier with PFAS (and, for the longitudinal analyses, with the age of assessment terms, as well). PFDA and PFUnDA were excluded from effect modification analyses because more than half of the samples had concentrations equal to or less than the LOD and the concentration range was narrow. As our study population included children diagnosed with neurodevelopmental concerns (i.e., ASD and Non-TD), we performed sensitivity analyses by restricting the multiple linear regression and longitudinal GEE analyses to the TD children ($n = 93$). Except for interactions specified above in the GEE analyses, the level of statistical significance was set at p-value < 0.05 for the rest.

3. RESULTS

3.1. Participant characteristics and MSEL scores

Of the 140 mother-child pairs included in the current study, 59% of children were males and 91% were full-term birth children (Table 1). Approximately 20% of mothers were obese before pregnancy, 19% had gestational diabetes, and 54% were multiparous at study enrollment. The majority of mothers were non-Hispanic white (51%) and were high school graduate or had some college credit without a degree in higher education (45%). There was no difference in population characteristics between this study population ($n = 140$) and the MARBLES baseline population ($n = 218$) enrolled during the same study period (Table S1).

Mean MSEL Composite scores differed among several participant characteristics (Table 1). At 12 and 24 months of age, females had higher scores than males. At 12, 24, and 36 months of age, children whose mothers had a bachelor's or higher degree had higher scores than those whose mothers did not have at least a bachelor's degree. At 24 months of age, children born to mothers who were older than 35 years at delivery had higher scores than those born to mothers younger than 35 years. At 36 months of age, children of mothers who were nulliparous or primiparous had higher scores than those of multiparous mothers.

When comparing the MSEL Composite scores and T-scores of four subscales across the four assessment time points, the mean scores of Composite and Visual Reception were lower at 24 months than other time points (Figure 1). At 12 months of age, the mean scores of Fine Motor and Receptive Language were higher and lower than other time points, respectively. The number of children whose Composite scores fell below 2 SD of the normative mean (i.e., Composite < 70, indicating low cognitive function) was 0 for 6 months, 2 for 12 months, 18 for 24 months, and 13 for 36 months.

3.2. Prenatal maternal serum PFAS concentrations

PFOA, PFOS, PFHxS, and PFNA were detected in more than 99% of the samples, while the detection frequency of PFDA, PFUnDA, PFDoDA, MeFOSAA, and EtFOSAA was 85%, 62%, 31%, 53%, and 4%, respectively (Table 2). PFOS had the highest median (2.8 ng/mL), followed by PFOA (0.9 ng/mL), PFNA (0.5 ng/mL), and PFHxS (0.4 ng/mL). The medians of PFDA, PFUnDA, and MeFOSAA were at the LOD of 0.1 ng/mL. Due to the narrow concentration ranges for PFDA and PFUnDA, the results for these two PFAS should be interpreted with caution.

As combinations of six PFAS, two PCs were identified (Table S2). The first principal component (PC-1) had moderate positive loadings mainly on PFOA, PFOS, PFHxS, and PFNA, explaining approximately 55% of the total variance (0.46 for PFOA, 0.50 for PFOS, 0.62 for PFHxS, 0.37 for PFNA, 0.07 for PFDA, and −0.12 for PFUnDA). The second principal component (PC-2) had positive loadings mainly on PFUnDA, PFDA, and PFNA as well as negative loadings on PFHxS, accounting for about 17% of the total variance (0.13 for PFOA, 0.07 for PFOS, −0.28 for PFHxS, 0.33 for PFNA, 0.55 for PFDA, and 0.70 for PFUnDA).

3.3. Associations between prenatal maternal PFAS exposure and child's cognitive development

Prenatal maternal serum PFOA was inversely associated with Composite scores at 24 months (β = −5.22, 95% CI: −8.27, −2.17) and 36 months of age (β = −5.18, 95% CI: −9.46, −0.91) (Figure 2). PFOA was also inversely associated with all four subscale scores at 24 and 36 months of age, except for Receptive Language at 36 months and Visual Reception at 24 months (see Table S3 for βs and 95% CIs). Receptive Language scores at 24 months were inversely associated with PFNA (β = −2.79, 95% CI: −5.38, −0.20) and PC-1 (β = −1.53, 95% CI: −3.04, −0.01). When assessing longitudinal changes in MSEL scores over the four assessment time points in GEE models, PFOA was inversely associated with scores on the Composite (β = −0.19, *p*-value for interaction = 0.01) and three subscales (β = −0.12 for Fine Motor, β = −0.14 for Visual Reception, β = −0.08 for Expressive Language; *p*-value for interaction < 0.06) (Table 3). When the GEE analyses were expanded to the MARBLES baseline population (Table S4) or when restricting timepoint-stratified multiple linear regression and longitudinal GEE analyses to the TD children (Figure S3 and Table S5, respectively), overall effect estimates slightly moved toward a positive direction, but the trends were similar.

When analyses were stratified by child's sex (Figure S4), at 12 months of age, higher PFHxS was associated with decreased Composite scores among females (β = −1.54, 95% CI: −3.29, 0.22), but with increased Composite scores among males (β = 3.48, 95% CI: 0.00, 6.96; *p*-value for interaction = 0.01). With respect to longitudinal changes in MSEL scores in GEE models, only among females, decreased Composite scores were associated with higher PFOA (β = −0.25, *p*-value for interaction = 0.02) over the four time points (Table S6). When analyses were stratified by breastfeeding duration, the associations of Composite scores with PFOA (*p*-value for interaction = 0.03), PFHxS (*p*-value for interaction = 0.09), and PFNA (*p*-value for interaction = 0.10) were modified at 12 months of age, showing inverse

associations among children who were breastfed < 12 months and positive associations among children who were breastfed ≥ 12 months (Figure S4).

3.4. Trajectories of child's cognitive developmental scores and their associations with prenatal maternal PFAS exposure

Two different groups were identified from the trajectory analysis. The low-score group (n = 40) showed lower and/or decreasing MSEL Composite scores over time, including 17 children with ASD, 10 Non-TD children, and 13 TD children (Figure 3). On the other hand, the high-score group (n = 100) showed higher and/or increasing scores over time, including 12 children with ASD, 8 Non-TD children, and 80 TD children. The trajectory of mean Composite scores for high-score group fell within 1 SD of the normative mean, while that for low-score group fell between 1 SD and 2 SD of the normative mean at 24 and 36 months of age. Compared to the high-score group, the low-score group included more males (73% versus 54%), more mothers who were younger than 35 years of age at delivery (65% versus 46%), less mothers with gestational diabetes (8% versus 24%), and more mothers who did not have at least a bachelor's degree (68% versus 36%) (Table S7). Having lower and/or decreasing Composite scores was associated with increasing prenatal maternal serum PFOA concentrations (RR = 1.49, 95% CI: 1.09, 2.03) (Table 4).

4. DISCUSSION

To better understand the potential effect of prenatal maternal exposure to PFAS on child's cognitive development, we used prenatal maternal serum PFAS concentrations and child's MSEL scores repeatedly evaluated at four time points (i.e., 6, 12, 24, 36 months of age) in the MARBLES cohort study and examined both cross-sectional associations at each time point and longitudinal associations over four assessment time points. To our knowledge, this is the first study that reported cross-sectional and longitudinal associations and showed the trajectories of child's cognitive development between low- and high-score groups. From cross-sectional associations at specific time points, PFOA was consistently associated with reduced scores on almost all subscales and the Composite at 24 and 36 months of age (Figure 2). From analyses of longitudinal changes over the four time points using GEE models, we observed prenatal PFOA to be associated with declining performance on the MSEL Composite and subscale scores (Table 3). When assessing trajectories of Composite scores from 6 to 36 months of age, PFOA was associated with having lower and/or decreasing Composite scores (Table 4). From effect modification analyses, we observed that the associations of PFOA, PFHxS, and PFNA with Composite scores were modified by breastfeeding duration at 12 months of age, in which higher exposures were associated with reduced scores among children who were breastfed < 12 months and with increased scores among children who were breastfed ≥ 12 months.

Our finding should be interpreted in the context of mixed epidemiological literature on prenatal maternal exposure to PFAS and child's cognitive development before or at 3 years of age. For example, Fei et al. and Goudarzi et al. reported no convincing association of prenatal maternal PFOA or PFOS concentrations with mental or motor development of infants at 6 and 18 months of age in the Danish National Birth Cohort and a Japanese birth

cohort, respectively (Fei et al. 2008; Goudarzi et al. 2016). Chen et al. observed that higher PFOS concentrations in cord blood were adversely associated with the overall development, especially with gross-motor and fine-motor domains, among 2-year-old children in a Taiwanese population (Chen et al. 2013). In contrast, Spratlen et al. reported better mental development of children at 3 years of age, but not at 1 and 2 years, in association with prenatal exposure to PFOA and PFHxS (Spratlen et al. 2020). The previous studies used one to three assessment time points before or at 3 years of age, which were mostly similar to those of our studies, but they only examined cross-sectional associations. To assess the child's cognitive development, Fei et al. used mother's responses in questionnaires, mostly consisting of yes/no questions, while other studies, including the present study, used performance-based assessment tools, such as the Bayley Scales of Infant Development (Goudarzi et al. 2016; Spratlen et al. 2020) and Comprehensive Developmental Inventory for Infants and Toddlers (Chen et al. 2013). Thus, the differences in the assessment time points and tools across studies may affect the comparability of the results.

Beyond 3 years of age, a Norwegian cohort reported that the first principal component, mainly loaded with PFOA, PFOS, PFHxS, and perfluoroheptane sulfonate, was associated with decreased scores of nonverbal working memory among children at 3.5 years of age (Skogheim et al. 2020). The two principal components they selected showed very similar PFAS loading weights with our study (Table S2). A prospective cohort in Shanghai reported that prenatal plasma concentrations of PFNA and PFDA were associated with increased risk of developmental problems in personal-social skills among 4-year-old children (Niu et al. 2019). In contrast, in a U.S. birth cohort study, prenatal exposure to PFOA and MeFOSAA was associated with improved cognitive functions among 3- to 6-year-old children (Harris et al. 2018). As a child grows, we cannot exclude the possibility that increased interactions with siblings or other children in childcare settings contribute to changes in the child's cognitive development over time (Bontinck et al. 2018; Rutter 1985). Longer follow-up of the MARBLES cohort would allow us to evaluate delayed or persistent effects of prenatal PFAS exposures on child's cognitive development.

We observed sex-specific associations between prenatal exposure to certain PFAS and cognitive development: negative associations among females and positive associations among males for PFHxS at 12 months of age. Although the mechanisms underlying the sex-specific associations are unknown, PFAS exposure during gestation may alter fetal thyroid and sex hormone levels, which can adversely affect cognitive functions in later life, in sexually dimorphic manner (Collaer and Hines 1995; de Cock et al. 2014; Itoh et al. 2016; Nian et al. 2020; Yao et al. 2019). Furthermore, effect modification by child's sex for PFHxS may relate to the higher efficiency of placental transfer in females than in males. The mean ratios of cord serum to maternal serum among male ($n = 26$) and female ($n = 24$) infants were 0.71 and 1.15, respectively (Liu et al. 2011). Our findings are in line with the results from previous epidemiological studies investigating sex-specific associations between prenatal PFAS exposure and child's neurobehaviors. For example, Goudarzi et al. observed that prenatal PFOA was associated with decreased scores of the mental developmental index only among 6-month-old female infants (Goudarzi et al. 2016). Skogheim et al. reported that PFAS principal components were associated with decreased scores of verbal working memory and language skills among females than males at 3.5 years of age (Skogheim et al.

2020). Niu et al. reported that 4-year-old females had higher risk of having problems in developing personal-social skills in association with prenatal PFOA, PFOS, PFNA, PFDA, PFUnDA, and PFDoDA, compared to males at the same age (Niu et al. 2019).

Strengths of this study include adjustment for covariates prospectively collected during the study period and repeated child's cognitive developmental scores. The repeated measures in the same children over time allowed us to examine cross-sectional and longitudinal associations between prenatal maternal serum PFAS and child cognitive scores as well as trajectories of child's scores by low- and high-score groups. The MSEL used in this study is known to be a reliable and valid assessment tool for child's cognitive development and covers four subscales of child's cognitive function. However, limitations should be also noted. Approximately one-third of the children included in the current study were diagnosed with ASD or had other neurodevelopmental concerns, such as broader autism phenotype and attention-deficit/hyperactivity disorder, which can result in lower MSEL scores. Thus, our findings should be interpreted cautiously because their generalizability to the general population may be limited. Although we performed sensitivity analyses after restricting to those children who were typically developed at 36 months, it should be noted that this does not entirely address the issue of these children being at high risk for other neurodevelopmental outcomes that are usually diagnosed at a later age. Another limitation of this study is selection bias. Though the MARBLES study has a relatively high retention rate (84%) (Hertz-Picciotto et al., 2018), only 64% of our MARBLES baseline population completed all four MSEL tests from 6 to 36 months of age and were used in the analyses. Therefore, missing outcome measures of the rest of the children may have influenced our results. Child's postnatal environmental factors, such as breastfeeding duration, the intellectual home environment, and attendance at day-care centers, can influence cognitive development of infants and young children (National Institute of Child Health and Human Development Early Child Care Research Network 2000; McCrory and Murray 2013; Morrow-Tlucak et al. 1988; Yeates et al. 1983). We adjusted for breastfeeding duration as well as maternal education as a surrogate for the intellectual environment in the regression models and considered effect modification by breastfeeding duration, but we did not account for child's attendance at day-care centers nor did we have an assessment of the home environment during this time period. Because cognitive abilities are malleable in infancy and toddlerhood and child's postnatal environments can influence cognitive development, further studies should account for child's postnatal environmental factors. Longer follow-up into mid-childhood and beyond would also contribute to an understanding of the longer-term impacts of prenatal PFAS exposures.

5. CONCLUSIONS

In this prospective birth cohort study, prenatal maternal serum PFOA was associated with decreased scores of cognitive functions throughout infancy and toddlerhood among children who had an older sibling diagnosed with ASD. Further, we observed modified associations of PFOA, PFHxS, and PFNA with cognitive development at 12 months of age by breastfeeding duration. Because the current study included a large fraction of children with developmental delays or cognitive deficits, population-based studies are needed to confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

ASD	autism spectrum disorder
BMI	body mass index
Composite	Early Learning Composite
CDC	Centers for Disease Control and Prevention
CI	confidence interval
EtFOSAA	2-(N-ethyl-perfluorooctane sulfonamido) acetate
GEE	generalized estimating equations
LOD	limit of detection
MARBLES	Markers of Autism Risk in Babies – Learning Early Signs
MeFOSAA	2-(N-methyl-perfluorooctane sulfonamido) acetate
MIND	Medical Investigations of Neurodevelopmental Disorders
MSEL	Mullen Scales of Early Learning
Non-TD	non-typical development
PFAS	per- and polyfluoroalkyl substances
PFDA	perfluorodecanoate
PFDoDA	perfluorododecanoate
PFHxS	perfluorohexane sulfonate
PFNA	perfluorononanoate
PFOA	perfluorooctanoate
PFOS	perfluorooctane sulfonate

PFUnDA	perfluoroundecanoate
PND	postnatal day
RR	relative risk
SD	standard deviation
TD	typical development
UC Davis	University of California Davis

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- We investigated prenatal exposure to PFAS in association with cognitive development.
- Prenatal PFOA was inversely associated with MSEL scores at 24 and 36 months of age.
- Longitudinally, PFOA was inversely associated with MSEL scores from 6 to 36 months.
- In trajectory analysis, PFOA and PFNA were associated with risk of cognitive deficit.

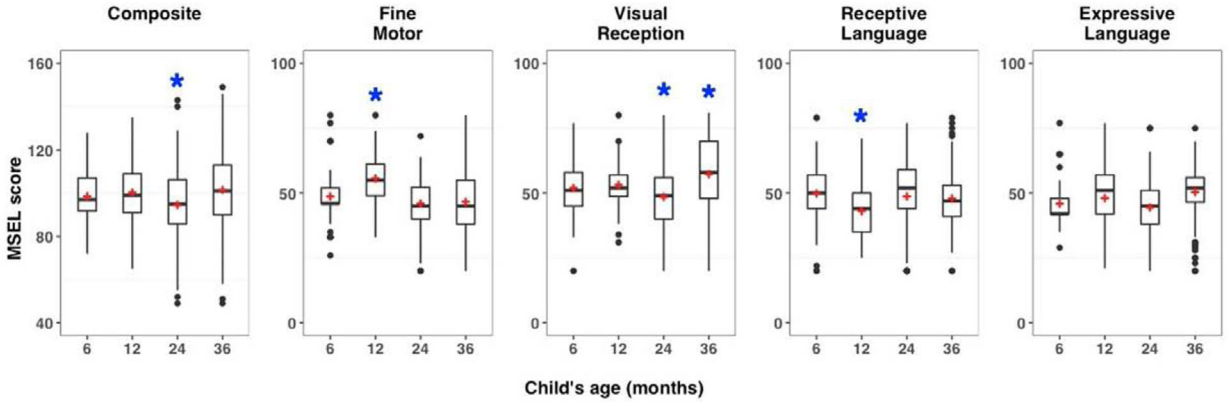

Figure 1.

Distributions of MSEL Composite scores and T-scores of four subscales at 6, 12, 24, and 36 months of age for 140 children included in the current study. Red crosses denote mean values at each time point. Blue asterisks denote differences in mean scores with other time points identified by the postestimation test with Bonferroni correction following the linear mixed model at the significance level of 0.05. Composite scores have a normative mean of 100 and an SD of 15 and T-scores of each subscale have a normative mean of 50 and an SD of 10.

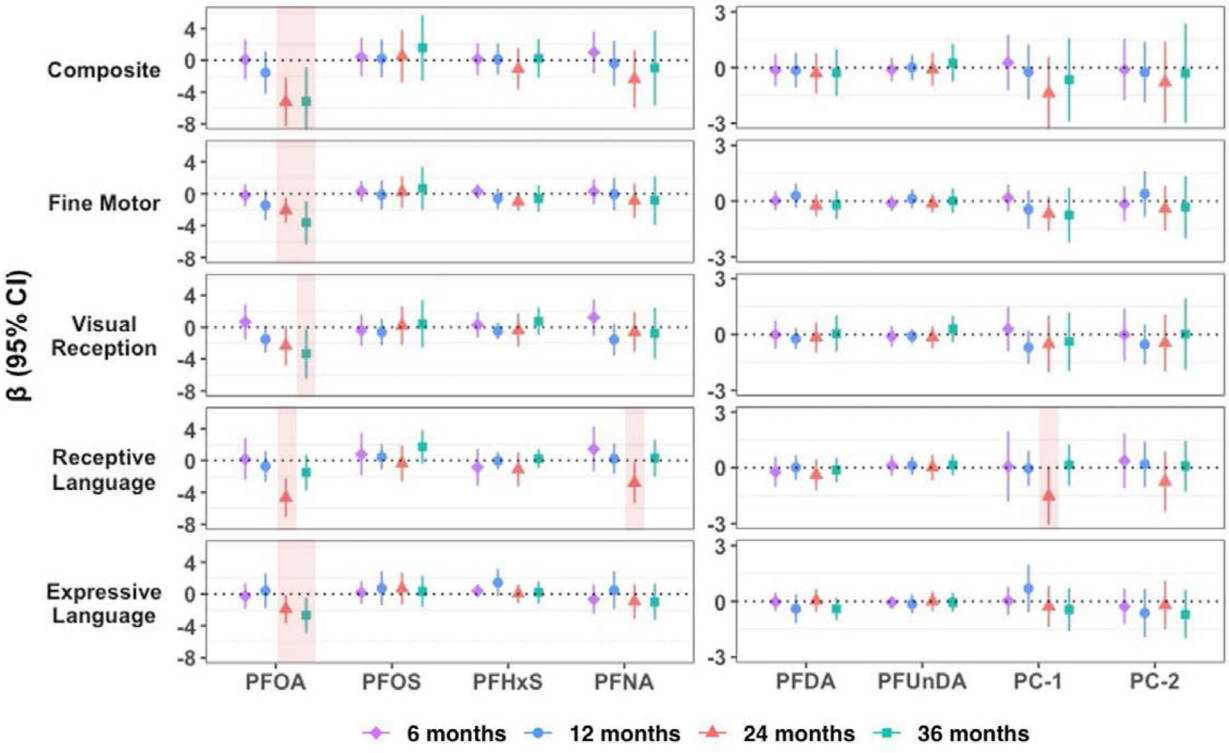

Figure 2.

Adjusted mean differences (β) in MSEL Composite scores and T-scores of subscales of children at 6, 12, 24, and 36 months of age in association with a unit increase in log 2-transformed prenatal maternal serum concentrations of six PFAS and two PCs. Models were adjusted for child's sex, parity, maternal pre-pregnancy BMI, gestational diabetes, maternal education, and breastfeeding duration. Red shaded areas represent associations with a *p*-value < 0.05.

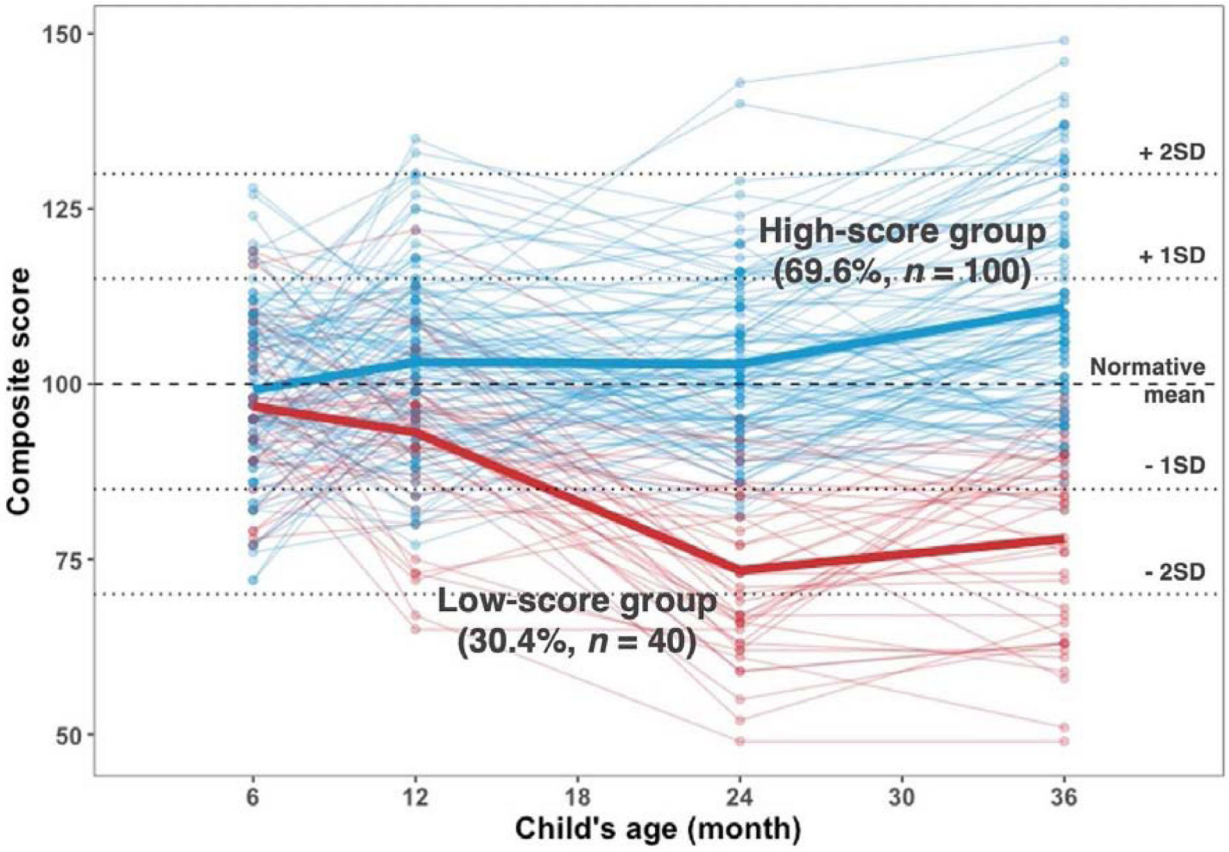

Figure 3.

Trajectories of child's Composite scores from 6 to 36 months of age for low- and high-score groups. Solid lines represent trajectories of group mean, and fine lines and dots represent trajectories of individuals.

Table 1.

MSEL Composite scores at 6, 12, 24, and 36 months by participant characteristics for children administered to the MSEL at all four time points.

Characteristic[a]	All (n = 140)		MSEL Composite							
			6 months		12 months		24 months		36 months	
	n	%	Mean (SD)	*p*[b]	Mean (SD)	*p*[b]	Mean (SD)	*p*[b]	Mean (SD)	*p*[b]
Child sex										
Female	57	41	99 (12)	0.99	104 (11)	0.01	99 (17)	0.05	105 (19)	0.12
Male	83	59	98 (12)		98 (15)		92 (18)		99 (22)	
Child's birth year										
2009–2010	46	33	96 (11)	0.15	97 (16)	0.22	94 (18)	0.39	102 (23)	0.77
2011–2013	50	36	101 (12)		101 (12)		92 (18)		99 (21)	
2014–2015	44	31	99 (11)		102 (13)		98 (17)		104 (19)	
Gestational age at delivery										
≤ 37 weeks	12	9	98 (15)	0.66	100 (18)	0.69	92 (16)	0.58	96 (20)	0.17
> 37 weeks	128	91	99 (12)		100 (13)		95 (18)		102 (21)	
Maternal age at delivery										
< 35 years	72	51	98 (12)	0.31	99 (14)	0.20	92 (19)	0.05	99 (21)	0.12
≥ 35 years	68	49	99 (12)		102 (13)		97 (17)		104 (21)	
Parity										
≤ 1	61	44	99 (12)	0.88	101 (16)	0.87	98 (17)	0.14	106 (19)	0.03
>1	76	54	98 (12)		100 (12)		92 (18)		98 (21)	
Maternal pre-pregnancy BMI										
Normal/underweight	71	51	98 (11)	0.84	101 (14)	0.33	98 (17)	0.04	103 (20)	0.52
Overweight	41	29	100 (11)		98 (15)		90 (20)		99 (24)	
Obese	28	20	98 (14)		102 (12)		92 (15)		102 (19)	
Gestational diabetes										
Yes	27	19	95 (11)	0.08	99 (14)	0.22	100 (14)	0.16	108 (16)	0.04
No	113	81	99 (12)		101 (14)		93 (19)		100 (22)	
Maternal race/ethnicity										
Non-Hispanic white	71	51	99 (12)	0.80	101 (14)	0.27	95 (16)	0.98	102 (20)	0.83
Hispanic	33	24	98 (10)		101 (13)		93 (20)		99 (22)	
Other[c]	36	26	98 (13)		98 (12)		94 (19)		103 (22)	
Maternal education										
Less than college degree	63	45	99 (12)	0.60	97 (12)	0.05	88 (19)	0.01	96 (21)	0.01
Bachelor's degree	46	33	100 (12)		105 (14)		100 (15)		106 (21)	
Graduate or professional degree	31	22	97 (11)		99 (14)		99 (17)		106 (19)	
Homeownership										
Yes	83	59	99 (12)	0.62	101 (13)	0.21	96 (15)	0.17	102 (20)	0.56
No	54	39	98 (12)		98 (14)		92 (21)		101 (23)	
Breastfeeding duration										

Characteristic[a]	All (n = 140)		MSEL Composite							
			6 months		12 months		24 months		36 months	
	n	%	Mean (SD)	*p*[b]	Mean (SD)	*p*[b]	Mean (SD)	*p*[b]	Mean (SD)	*p*[b]
< 12 months	77	55	98 (11)	0.59	102 (13)	0.05	95 (18)	0.94	103 (22)	0.23
≥ 12 months	57	41	100 (12)		98 (14)		93 (18)		99 (20)	

[a] Missing information (*n*): parity (3), homeownership (3), breastfeeding duration (6).

[b] P-value from the Wilcoxon rank-sum test or the Kruskal-Wallis test.

[c] Includes Black (3%), Asian (20%), and others (3%).

Table 2.

Distribution of nine PFAS concentrations (ng/mL) in 224 maternal serum samples collected from 140 mother-child pairs.

PFAS[a]	% detect	Geometric Mean (ng/mL)	Percentiles (ng/mL)				
			5th	25th	50th	75th	95th
PFOA	100.0	0.88	0.30	0.60	0.90	1.25	2.20
PFOS	100.0	2.82	1.00	1.90	2.80	4.10	7.00
PFHxS	99.6	0.45	0.10	0.30	0.40	0.70	1.60
PFNA	100.0	0.48	0.20	0.30	0.50	0.70	1.10
PFDA	84.8	0.16	<LOD	0.10	0.10	0.20	0.40
PFUnDA	61.6	0.14	<LOD	<LOD	0.10	0.10	0.30
PFDoDA	31.3	0.11	<LOD	<LOD	<LOD	0.10	0.10
MeFOSAA	53.1	0.19	<LOD	<LOD	0.10	0.20	0.80
EtFOSAA	3.6	0.10	<LOD	<LOD	<LOD	<LOD	<LOD

[a]Limit of detection for all nine PFAS was 0.1 ng/mL.

Table 3.

Longitudinal changes (β) in MSEL Composite scores and T-scores of subscales of children over the four assessment time points in association with a unit increase in log 2-transformed prenatal maternal serum concentrations of six PFAS and two PCs in generalized estimating equations.

MSEL	PFOA β (95% CI)[a]	PFOS β (95% CI)[a]	PFHxS β (95% CI)[a]	PFNA β (95% CI)[a]
Composite	−0.19 (−0.33, −0.04)[#]	0.02 (−0.12, 0.17)	−0.02 (−0.11, 0.07)	−0.09 (−0.27, 0.08)
Fine Motor	−0.12 (−0.20, −0.03)[#]	0.00 (−0.09, 0.09)	−0.04 (−0.09, 0.02)	−0.06 (−0.17, 0.05)
Visual Reception	−0.14 (−0.26, −0.03)[#]	0.00 (−0.11, 0.12)	−0.01 (−0.07, 0.06)	−0.08 (−0.21, 0.05)
Receptive Language	−0.07 (−0.16, 0.02)	0.03 (−0.06, 0.11)	0.01 (−0.06, 0.09)	−0.05 (−0.15, 0.05)
Expressive Language	−0.08 (−0.16, 0.00)[#]	0.02 (−0.06, 0.09)	−0.01 (−0.06, 0.04)	−0.03 (−0.12, 0.06)
MSEL	**PFDA β (95% CI)[a]**	**PFUnDA β (95% CI)[a]**	**PC-1 β (95% CI)[a]**	**PC-2 β (95% CI)[a]**
Composite	−0.01 (−0.06, 0.04)	0.01 (−0.03, 0.05)	−0.04 (−0.13, 0.04)	−0.02 (−0.12, 0.09)
Fine Motor	−0.01 (−0.04, 0.01)	0.00 (−0.02, 0.02)	−0.04 (−0.08, 0.01)	−0.02 (−0.08, 0.04)
Visual Reception	0.00 (−0.04, 0.04)	0.01 (−0.02, 0.04)	−0.04 (−0.10, 0.03)	0.00 (−0.08, 0.07)
Receptive Language	0.00 (−0.03, 0.03)	0.00 (−0.02, 0.02)	−0.01 (−0.07, 0.05)	−0.01 (−0.07, 0.05)
Expressive Language	−0.01 (−0.04, 0.01)	0.00 (−0.02, 0.02)	−0.02 (−0.06, 0.02)	−0.01 (−0.07, 0.04)

[a]Models were adjusted for child's sex, parity, maternal pre-pregnancy BMI, gestational diabetes, maternal education, and breastfeeding duration. Regression coefficients (β) were derived from interaction terms between continuous age in months (centered at 24) and continuous log 2-transformed PFAS concentrations, after including the two main effects and their interaction term in the GEE model.

[#]*p*-value for interaction between age at assessment and PFAS concentrations < 0.10

Table 4.

Adjusted relative risk (RR) and 95% confidence interval (CI) for the low-score group versus the high-score group in association with prenatal maternal serum concentrations of six PFAS and two principle components (PCs)

Log 2-transformed PFAS or two primary principal components	Low-score group vs. high-score group RR[a] (95% CI)
PFOA	1.49 (1.09, 2.03) *
PFOS	0.92 (0.70, 1.21)
PFHxS	1.10 (0.90, 1.35)
PFNA	1.19 (0.83, 1.72)
PFDA	1.02 (0.91, 1.15)
PFUnDA	0.95 (0.89, 1.02)
PC-1	1.12 (0.94, 1.33)
PC-2	0.97 (0.79, 1.20)

[a]Models were adjusted for child's sex, parity, maternal pre-pregnancy BMI, gestational diabetes, maternal education, and breastfeeding duration.

*p-value <0.05