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The association between prenatal exposure to perfluoroalkyl substances and childhood neurodevelopment☆

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ABSTRACT

Perfluoroalkyl substances (PFAS) were among various persistent organic pollutants suspected to have been released during the collapse of the World Trade Center (WTC) on 9/11. Evidence on the association between prenatal PFAS exposure and child neurodevelopment is limited and inconsistent. This study evaluated the association between prenatal PFAS exposure and child cognitive outcomes measured at 5 different time points in a population prenatally exposed to the WTC disaster. The study population included 302 pregnant women in the Columbia University WTC birth cohort enrolled between December 13, 2001 and June 26, 2002 at three hospitals located near the WTC site: Beth Israel, St. Vincent's, and New York University Downtown. We evaluated the association between prenatal exposure to four PFAS (perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA)) and child neurodevelopment measured using the Bayley Scales of Infant Development (BSID-II) at approximately 1, 2 and 3 years of age and using The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at approximately 4 and 6 years of age. Geometric mean (range) concentrations of PFAS were 6.03 (1.05, 33.7), 2.31 (0.18, 8.14), 0.43 (<LOQ, 10.3) and 0.67 (<LOQ, 15.8) ng/mL for PFOS, PFOA, PFNA and PFHxS, respectively. Several PFAS were associated with increases in cognitive outcomes in females and overall (males and females combined). Child sex modified the association between PFOS and the mental development index measured using BSID-II, with the observed relationship being positive for females and negative for males. Through principal component analyses, we observed a negative relationship between PFNA and the psychomotor development index measured using BSID-II and the verbal IQ measured using WPPSI. Our results suggest a sex- and compound-specific relationship between prenatal PFAS exposures and childhood neurodevelopment.

1. Introduction

Perfluoralkyl substances (PFAS) are a class of synthetic chemicals that have been used in commercial and industrial products, including fire-fighting foam, carpets, food packaging, clothing and non-stick cookware, since the 1940s (US Environmental Protection Agency, 2017a). Recently, the main PFAS manufacturers in the US have mostly phased out production of the two most widespread PFAS, perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA); however, their long half-lives, global dispersion, and resistance to degradation suggest that

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exposure to these compounds will remain a public health concern for some time (US Environmental Protection Agency, 2017a). Indeed, despite reductions in levels of exposure, national estimates for PFOS and PFOA indicate that they remain at levels that have been associated with adverse health effects in humans (US Environmental Protection Agency, 2016a, US Environmental Protection Agency, 2016b, US Environmental Protection Agency, 2016c). Further, other PFAS, including replacement PFAS, may actually be increasing: levels of perfluorononanoic acid (PFNA) in women of child-bearing age increased between 1999-2000 and 2007–2008, before decreasing back to earlier levels in 2013–2014 (US Environmental Protection Agency, 2017a). Exposure in humans occurs through ingestion of contaminated food and water, inhalation/ingestion of dust and fumes from PFAS-containing products in homes and offices, and occupational exposure in workplaces that produce or use PFAS (Trudel et al., 2008; Fraser et al., 2012). PFAS have been shown to cross the placental barrier resulting in *in utero* fetal exposure, and in turn, have been associated with reductions in fetal growth in both humans and animals (Olsen et al., 2009; Bach et al., 2015; Lau et al., 2006).

Development during the prenatal period is particularly vulnerable to neurotoxic exposures because of the rapid and fundamental developmental processes that occur during this time. Some (Fuentes et al., 2007; Johansson et al., 2009; Johansson et al., 2008; Onishchenko et al., 2011; Butenhoff et al., 2009), but not all (Lau et al., 2003), experimental studies suggest prenatal PFAS exposure may have neurodevelopmental effects. Alterations in offspring behavior and motor function (Johansson et al., 2008; Onishchenko et al., 2011), as well as in levels of proteins required for normal brain development (Johansson et al., 2009), have been observed in mice exposed prenatally to PFOS and PFOA. Several mechanisms have been proposed to explain the neurotoxic effect of PFAS including modifications in the expression of calcium-related signaling molecules in the hippocampus (Johansson et al., 2009; Liu et al., 2010), changes to the functioning of the cholinergic system (Lau et al., 2003), and interference with thyroid hormone homeostasis (Ballesteros et al., 2017; Mariussen, 2012).

Evaluation of the relationship of prenatal PFAS exposure and cognitive outcomes in humans is understudied and findings have been inconsistent. Of the five studies that have looked at PFAS and measures of IQ specifically, two studies, conducted in Japan (Goudarzi et al., 2016) and Taiwan (Wang et al., 2015), found significant inverse associations. However, studies conducted in the US (Stein et al., 2013; Vuong et al., 2019) and Denmark (Liew et al., 2018) found evidence of a positive association between PFAS and IQ. Studies that have looked at prenatal PFAS exposure and other childhood cognitive outcomes have also reported inconsistent findings. A study conducted among British girls found both positive and negative associations between PFNA, PFOA, PFOS and early communication development, and only positive associations for perfluorohexanesulfonic acid (PFHxS) with early communication development outcomes at 15 and 28 months (Jeddy et al., 2017). A study conducted in the Danish Birth Cohort found positive and negative associations between PFOS and developmental milestones measured at 6 and 18 months, respectively, but null associations for PFOA (Fei et al., 2008). A US-based study found associations between higher PFOA, PFOS and PFNA and better reading skills at 5 and 8 years (Zhang et al., 2018). Finally, another US-based study found positive associations between PFNA, PFHxS and PFOS and visual memory, but negative associations for PFOA and PFHxS with visual motor abilities (Harris et al., 2018). Several studies have also reported sex-specific associations between PFAS and neurodevelopment in humans (Goudarzi et al., 2016; Vuong et al., 2019; Liew et al., 2018) and animals (Fuentes et al., 2007; Onishchenko et al., 2011).

In this study, we attempt to better understand the inconsistent associations that have been observed between prenatal PFAS exposure and neurodevelopment through the evaluation of four PFAS (PFOS, PFOA, PFHxS, PFNA) in a population of pregnant mothers that delivered in New York City hospitals and whose children had childhood cognitive outcomes assessed from age 1 through 6 years.

2. Methods

2.1. Study population

We included mother-child dyads from a Columbia University birth cohort originally selected to evaluate the effects of exposure to the World Trade Center (WTC) disaster on September 11, 2001 (9/11) on pregnancy outcomes and child development in women who were pregnant at that time. Detailed methods have been described previously (Lederman et al., 2004). Briefly, 329 women with singleton pregnancies were enrolled between December 13, 2001 and June 26, 2002 at one of three hospitals located near the WTC site: Beth Israel, St. Vincent's, and New York University Downtown. Eligibility requirements included: maternal age between 18 and 39 years, had not smoked during pregnancy (<1 cigarette/day at any time), self-report of no diabetes, hypertension, HIV infection or AIDS, and no use of illegal drugs in the last year. Participants provided at least one blood sample (maternal blood at the time of delivery and/or cord blood), access to their medical record and to their newborn's medical record, and completion of a 30- to 45-min interview after delivery. PFAS was measured in either cord or maternal blood, and participants missing both PFAS measurements (n = 27) were excluded from this analysis, resulting in a sample size of 302. Participants missing maternal IQ (n = 104), maternal race (n = 19), pre-pregnancy BMI (n = 4), parity (n = 1), maternal demoralization (n = 4) were excluded from complete case sensitivity analyses. Participants were further excluded from age-specific analyses if they were missing cognitive measures at these time points, resulting in the following sample sizes for complete case sensitivity analyses: 1 year (n = 156), 2 years (n = 157), 3 years (n = 127), 4 years (n = 124) and 6 years (n = 110) (Fig. 1).

2.2. Sociodemographic and risk factor variables

The postpartum interview was administered at the hospital, post-delivery and prior to discharge, in the woman's preferred or native language (English, Spanish, or Chinese). Information on maternal education, date of birth, race, parity, material hardship during pregnancy, marital status and family smoking exposure was collected through a structured questionnaire during the interview. Two study-specific variables relating to exposure to the 9/11 WTC event were also drawn from the structured questionnaire; these variables were trimester on 9/11 and residential and occupational (if applicable) distance to the 9/11 site. Gestational age on 9/11 was used to determine trimester on that day. Mothers were classified as being in their first trimester on 9/11 if their child had a gestational age of ≤91 days on 9/11, and in their second or third trimester if their child had a gestational age >91 days. Eighteen participants were not pregnant yet on 9/11 but were still included in the study in the first trimester group, because exposures to the disaster persisted for months following the initial collapse. Distance to the 9/11 site was categorized into two groups: those who either lived or worked within 2 miles of the 9/11 site versus those who did not, using geocoded residential and work addresses (for the 4 weeks starting on and following 9/11). Maternal pre-pregnancy BMI was calculated using weight in kilograms divided by height in meters squared, both abstracted from the participants' medical chart. In

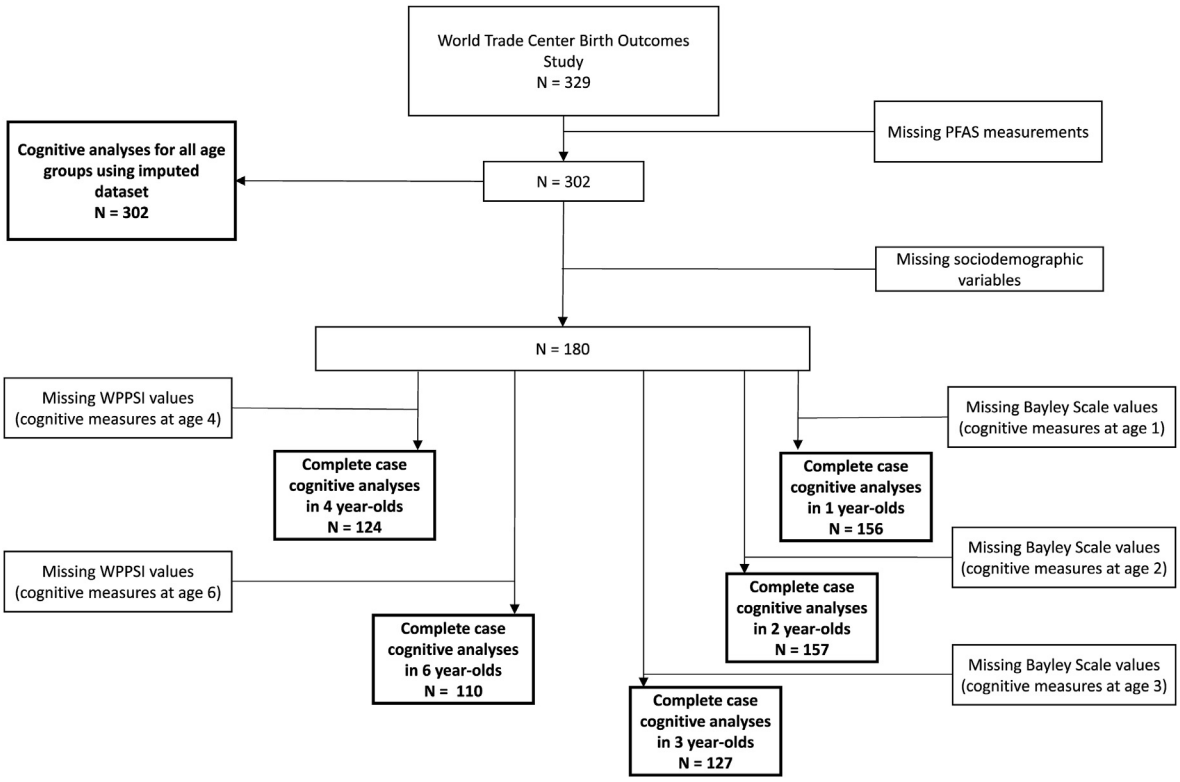

Fig. 1. Study Flow Diagram. Abbreviations: Perfluoralkyl substances (PFAS); Wechsler Preschool and Primary Scale of Intelligence (WPPSI).

the case of missing height (n = 41) or weight (n = 52) from the medical record, self-reported information on these variables from the hospital interview was used. Among participants with both self-reported and medical record weight and height, correlations were very high (r = 0.99 and r = 0.91, respectively). Child sex and date of birth were abstracted from the child's medical record. Gestational age in days was also abstracted from the medical record (if missing (n = 15), date of last menstrual period from the interview minus the child's date of birth was used). Maternal age at delivery was determined by subtracting the child's date of birth from the mother's date of birth. Maternal demoralization was measured during the post-partum interview using the Psychiatric Epidemiology Research Instrument Demoralization scale (PERI-D), which provides a measure of nonspecific psychological distress, with demonstrated reliability across different ethnic groups (Vernon and Roberts, 1981; Dohrenwend et al., 1980; Dohrenwend et al., 1981). Maternal intelligence was evaluated during the first study visit, which took place at approximately 12 months post-partum, using the Test of Non-Verbal Intelligence, Second Edition (TONI-2), a validated instrument for measuring general cognitive ability, considered to be free of cultural bias (Brown et al., 1997). Institutional Review Board approval was obtained before enrollment began and all women gave written informed consent before delivery.

2.3. Child cognitive outcomes

Child neurodevelopment was measured using the Bayley Scales of Infant Development (BSID-II) at approximately 1, 2 and 3 years of age. The BSID-II is a tool to evaluate neurodevelopment in infants and toddlers aged 1–42 months through two indices, the Mental Development Index (MDI), which measures memory, problem solving, sensory perception, hand–eye coordination, imitation and early language, and the Psychomotor Development Index (PDI), which measures fine and gross motor development (Bayley, 1993). The assessment provides a developmental quotient (raw score/chronological age), generating continuous MDI and PDI scores, which are normed and have a mean of 100 and a standard deviation of 15, with higher scores indicating better development. The BSID-II has demonstrated reliability and validity (Bayley, 1993). Child neurodevelopment at 4 and 6 years of age was measured using The Wechsler Preschool and Primary Scale of Intelligence (WPPSI). WPPSI-R, the first revision to the scale and the version used in this study, is a standardized assessment designed to measure the cognitive development of children ages 3 years–7 years and 3 months (Wechsler, 1989). The scale is composed of 12 core subtests which are used to develop three main index scores: verbal, performance and full scale IQ. Not all children were available for all developmental assessments, resulting in different numbers of children tested at each age. Assessments were conducted in the first language of the child (English or Chinese) by trained research technicians. In some cases, when the primary language of the child was not English or Chinese (e.g., Yiddish), we relied on maternal translation. The majority of follow-up assessments were conducted at the Columbia Center for Children's Environmental Health, however a small number of assessments were conducted in the child's home if the parents were unable or unwilling to travel to the Center.

2.4. PFAS collection and measurements

Blood samples from the umbilical cord were collected at the time of delivery; maternal samples were typically collected on the day after delivery. On average, 30.7 mL blood was collected from the umbilical cord, and 30–35 mL blood was collected from the mothers. Blood samples were transported to Columbia University

laboratory facilities in Northern Manhattan and processed within hours of collection. The buffy coat, packed red blood cells and plasma were separated and stored at −70 °C.

Twelve PFAS [PFOS, PFOA, PFHxS, PFNA, perfluorodecanesulfonic acid (PFDS), perfluorobutanesulfonic acid (PFBS), perfluorooctane sulfonamide (PFOSA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorodecanoic acid (PFDA), perfluoroundecanoic (PFUnDA) and perfluorododecanoate (PFDoDA)] were measured in maternal plasma (n = 48) and cord blood (n = 231) using a solid phase extraction procedure and high-performance liquid chromatograph interfaced with an electrospray tandem mass spectrometer, at the New York State Department of Health Wadsworth Center Laboratory, using methods similar to those used in prior studies (Kannan et al., 2004; Taniyasu et al., 2005). Internal standards for C-labeled PFAS were added into plasma samples prior to the addition of reagents for extraction (Sakr et al., 2007). Solvents and method blanks (blinded to the laboratory) were tested for the presence of the PFAS. Target chemicals were not found in procedural blanks at concentrations above the limits of quantification (LOQs). The LOQs of target chemicals ranged from 0.08 to 0.20 ng/mL. A standard reference material from the National Institute of Standards and Technology was analyzed with every batch of 50 samples, and recoveries of target chemicals were between 90% and 115% of the certified values. Recoveries of target chemicals passed through the entire analytical procedure ranged between 100% and 124%. Quantification was by isotope dilution and target chemicals were monitored by multiple reaction monitoring mode under negative ionization.

2.5. Statistical analyses

All statistical analyses were conducted in R software (version 3.5.1; R Project for Statistical Computing). A threshold of $P < 0.05$ was used to define associations as statistically significant. PFAS assessment was restricted to compounds detected in ≥50% of samples (PFOS, PFOA, PFNA, PFHxS and PFDS). To maximize sample size, we used both maternal plasma and cord blood concentrations in analyses. However, to account for differences in maternal versus cord blood samples, we used a prediction model developed using 78 paired cord blood and maternal plasma PFAS samples from the HOME study (Apelberg et al., 2007), a US-based cohort with comparable PFAS concentrations, to transform maternal PFAS concentrations to cord blood concentrations in participants with maternal measurements but no cord blood measurements in our study as previously described (Spratlen et al., 2019). We were unable to create prediction models from our own data because we did not have paired samples. Instead, participants had either a cord PFAS measurement or maternal PFAS measurement. Separate prediction models were run for PFOS, PFOA, PFNA and PFHxS. Prediction models were not available for PFDS; therefore, analyses focused on the previously listed four PFAS compounds and did not include PFDS. All analyses report concentrations and associations using both transformed maternal-to-cord concentrations and cord blood concentrations. PFOS, PFOA, PFNA and PFHxS were log-transformed to account for right-skewed distributions. Both PFOA and PFOS were detected in 100% of samples. Two samples (<1%) were below the LOQ (0.08 ng/ml) for PFHxS and 40 samples (13%) were below the LOQ (0.20 ng/ml) for PFNA. In accord with published practices, (Kataria et al., 2015) samples < LOQ were imputed as the LOQ divided by the square root of 2.

We used separate linear models to evaluate the association between log-transformed PFAS variables and cognitive outcomes measured at 1, 2 and 3 years of age through BSID-II (outcomes = MDI and PDI indices) and at 4 and 6 years of age through WPPSI (outcomes = Performance, Verbal and Full IQ scales). We also evaluated the combined effect of exposure to all four PFAS variables on cognitive outcomes through principal component analyses, a data reduction technique in which the linear relationships between observed correlated variables are captured into a smaller number of principal components, as has been done in previous PFAS epidemiologic studies (Hoffman et al., 2010). Each input variable, in this case the four PFAS variables, is given a "factor loading", reflecting the correlation of each PFAS with that component (Birgisdottir et al., 2013). We followed the Kaiser criterion (Kaiser, 1960) and included all principal factors with eigenvalues ≥1.0 (Kaiser, 1958). Main analyses were conducted using imputed data for missing variables and regressions were run with and without covariate adjustments. Adjustments for all models were selected *a priori* based on previous literature and included maternal age; material hardship during pregnancy (defined as having gone without either food, shelter, gas/electric, clothing, or medication/medical care because of financial constraint); pre-pregnancy BMI; maternal IQ; maternal race (Black, White, Asian, Native American/other); maternal education (<high school degree, high school degree, > high school degree); home smoking exposure (no reported family member smoking in household, any reported family member smoking in household); marital status (not married, married); parity (primiparous, multiparous); child's gestational age at birth; exact child age on test date; child's sex; trimester on 9/11 (first trimester, second/third trimester); maternal demoralization score; and child breastfeeding history (ever breastfed or never). To evaluate the potential for sex-specific associations, we included an interaction term between the child's sex and the PFAS variable and reported the *P*-value from a two-sided Wald *t*-test on the coefficient for the 2-way multiplicative term.

Due to substantial missing data for outcome variables (cognitive measures) and maternal intelligence, we imputed variables using multivariate imputation by chained equations (MICE). MICE is a highly flexible statistical imputation method that generates multiple predictions for missing values by creating multiple complete datasets based on the observed values for a given individual and its relationship with the observed values in the data for other participants. This method takes into account uncertainty in missing value imputation and therefore, yields accurate standard errors. Described in detail by Schafer and Graham (2002) (Schafer and Graham, 2002), MICE is now a common statistical method for dealing with missing data in both observational and clinical trials with demonstrated effectiveness in handling substantial missing data, including in outcome variables (Morisot et al., 2015; Hayati Rezvan et al., 2015; Moons et al., 2006). Proportions of variables with imputed values in our data ranged from 0% to 52.6% and included maternal race, maternal pre-pregnancy BMI, parity, breastfeeding status, maternal IQ, maternal demoralization and all cognitive outcome measures. Imputation methods included predictive mean modeling for continuous variables and logistic regression for binary variables. For our imputation model, as generally advised, we used all variables potentially predictive of the exposure (PFAS) − outcome (cognition) relationship, covariates or missingness (Collins et al., 2001). These variables included all model covariates (listed above), exposure and outcome variables, in addition to marital status and proximity to the 9/11 site, a variable relevant to this dataset specifically. Setting model iterations to 20 and imputations to 30 achieved healthy convergence of the imputation model, evaluated visually through trace and density plots. To visually display sex-specific trends, results from adjusted imputed PFOS models at all time-points, overall and by sex, were plotted (Fig. 2).

In sensitivity analyses, we ran regressions using only complete cases at each age (i.e., 1, 2, 3, 4 and 6 years).

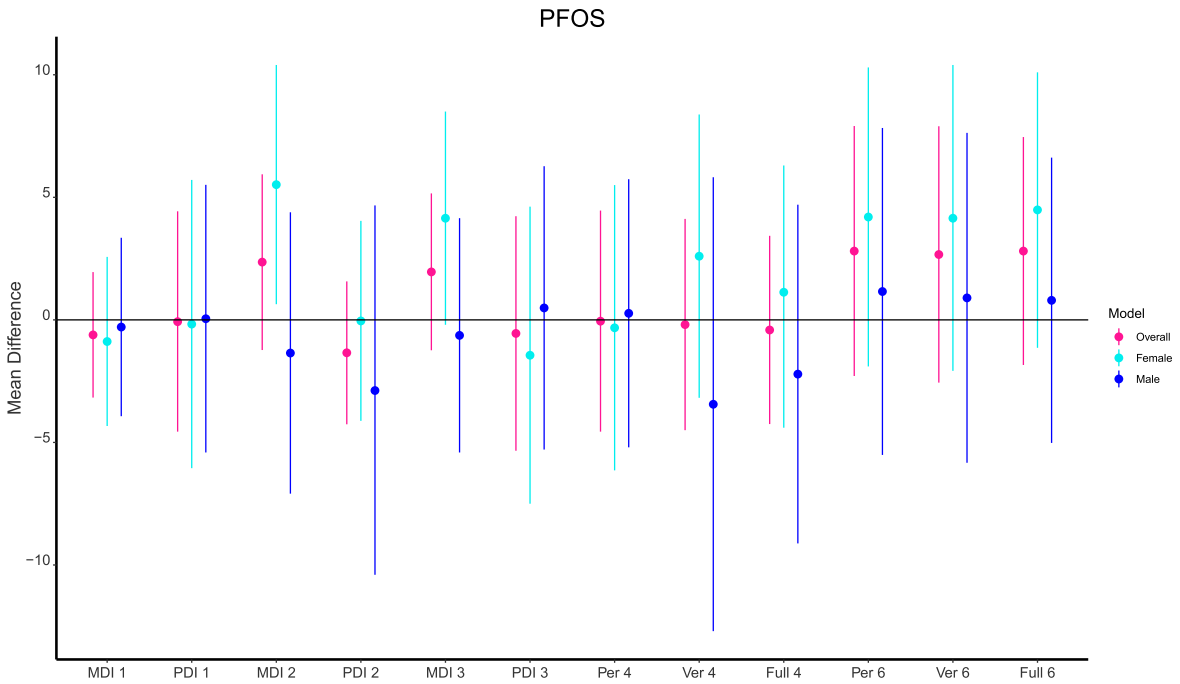

Fig. 2. Mean Difference (95% Confidence Interval) in Cognitive Outcomes per Log Unit Changes in Perfluorooctane Sulfonate (PFOS). MDI and PDI were measured using the Bayley Scales of Infant Development (BSID-II) when the child was approximately 1, 2 and 3 years of age. Per (Performance), Ver (Verbal) and Full scale IQ scores were measured using The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) when the child was approximately 4 and 6 years of age. WPPSI-R, is the first revision to the scale and the version used in this study. Models were adjusted for maternal age, material hardship, parity, pre-pregnancy BMI, maternal IQ, maternal race, maternal education, family smoking status, child age at testing, child's gestational age at birth, child sex and child breastfeeding history. The number following the outcome (MDI or PDI, etc.) is the age in years at testing. * indicates significance ($p < 0.05$) of an interaction by sex. Abbreviations: Mental development index (MDI); per (performance); perfluorooctane sulfonate (PFOS); psychomotor development index (PDI), ver (Verbal).

3. Results

3.1. Participant characteristics

Geometric mean (range) concentrations of PFAS variables (cord blood plus maternal-to-cord transformed) were 6.03 (1.05, 33.7) ng/ml for PFOS, 2.31 (0.18, 8.14) ng/ml for PFOA, 0.43 (<LOQ, 10.3) ng/ml for PFNA and 0.67 (<LOQ, 15.8) ng/ml for PFHxS (Table 1). Since there were no missing data for maternal age, child sex, trimester on 9/11, gestational age, material hardship during pregnancy, marital status, maternal education and family smoking status, none of these data were imputed (Table 2) . Median (interquartile range) maternal age was 30.6 (26.8, 34.5). Most women reported no family smoking (81.5%) and no material hardship during pregnancy (90.7%). The majority of women were married (79.8%) and pregnant less than 91 days (≤1st trimester) on 9/11 (69.5%). Half of the children born were female (49.7%) and among all children born, they had a median (IQR) gestational age of 280 (273, 280) days at birth. The majority of women had greater than a high school degree (65.2%), with 16.9% having a high school degree and 17.9% reporting less than a high school degree. Data on race, pre-pregnancy BMI, parity, maternal demoralization, breastfeeding status, maternal IQ and child cognitive outcomes were missing to varying degrees. The distributions of the variables with missing data did not differ substantially between participants with observed data and those with imputed data and are described in Table 2. Two distinct patterns of PFAS exposure were observed through principal component analyses. The first pattern, PFAS principal component (PC1), explained 57% of the variance and had high positive loadings for all four PFAS, reflecting higher overall PFAS exposure (Table 3). The second pattern, PFAS principal component (PC2), explained 25% of the variance and was dominated by positive loadings for PFNA, followed by negative loadings for PFOA and PFHxS.

3.2. Association between PFAS and cognitive outcomes at 1, 2 and 3 years

There were no significant associations or apparent trends between PFAS concentrations and MDI or PDI at 1 year of age in unadjusted (Table S3) or adjusted (Table 4) analyses. At 2 and 3 years of age, in general, increases in PFAS concentrations were associated with higher MDI scores, for the combined male and female data. In unadjusted analyses, these associations with MDI were significant for PFOA ($\beta = 4.74$, 95% CI: 0.88, 8.60) and PC1 ($\beta = 1.44$, 95% CI: 0.30, 2.58) at 3 years and for PFHxS at both 2 ($\beta = 4.29$, 95% CI: 1.27, 7.31) and 3 years ($\beta = 4.87$, 95% CI: 2.13, 7.61) (Table S3). In adjusted analyses, these findings were similar but slightly attenuated ($\beta = 3.93$, 95% CI: 0.08, 7.77 for PFOA; $\beta = 3.30$, 95% CI: 0.70, 5.90 for PFHxS; and $\beta = 1.23$, 95% CI: 0.13, 2.32 for PC1 at 3 years) and no longer significant for PFHxS at 2 years (Table 4). In unadjusted analyses, there were no interactions by sex at 1, 2 or 3 years. In adjusted analyses, at 2 years, there appeared to be a trend of stronger positive associations between PFAS and MDI for females compared to males. This sex-specific trend was significant only for PFOS (*P* interaction = 0.04) (Fig. 2). There were no significant associations between PFAS and PDI at 1 or 2 years. However, at 3 years, PC2 was associated with lower PDI scores in both unadjusted ($\beta = -2.28$, 95% CI: −4.53, −0.03) and adjusted models ($\beta = -3.51$, 95% CI: −6.01, −1.02). PC2 reflects higher PFNA and lower PFOA and PFHxS (Table 3); therefore, the associations between PC2 and PDI suggest a positive relationship for PFOA and PFHxS with PDI and a negative relationship for PFNA.

Findings from complete case sensitivity analyses were similar

Table 1
Geometric mean concentrations (ng/mL) and percent above detection of perfluoroalkyl substances (PFAS) in cord blood, maternal plasma, and cord + transformed cord blood.

PFAS	N	LOQ	% Above LOQ	Geometric Mean (Range)
PFOS				
Cord Blood	247	0.20	100%	6.27 (1.05, 33.7)
Maternal Plasma	55	0.20	100%	11.9 (2.90, 30.9)
Cord Blood + Transformed Cord Blood	302	0.20	100%	6.03 (1.05, 33.7)
PFOA				
Cord Blood	247	0.08	100%	2.37 (0.18, 8.14)
Maternal Plasma	55	0.08	100%	2.42 (0.88, 5.06)
Cord Blood + Transformed Cord Blood	302	0.08	100%	2.31 (0.18, 8.14)
PFNA				
Cord Blood	247	0.20	86%	0.45 (<LOQ, 10.3)
Maternal Plasma	55	0.20	96%	0.45 (<LOQ, 1.93)
Cord Blood + Transformed Cord Blood	302	0.20	88%	0.43 (<LOQ, 10.3)
PFHxS				
Cord Blooddu	247	0.08	99%	0.69 (<LOQ, 15.8)
Maternal Plasma	55	0.08	100%	0.94 (0.35, 3.20)
Cord Blood + Transformed Cord Blood	302	0.08	99%	0.67 (<LOQ, 15.8)
PFDS				
Cord Blood	247	0.08	97%	0.13 (<LOQ, 0.64)
Maternal Plasma	55	0.08	98%	0.16 (<LOQ, 0.82)
PFOSA				
Cord Blood	247	0.08	0%	<LOQ
Maternal Plasma	55	0.08	0%	<LOQ
PFBS				
Cord Blood	247	0.08	<1%	<LOQ (<LOQ, 0.28)
Maternal Plasma	55	0.08	0%	<LOQ
PFHxA				
Cord Blood	247	0.08	15%	<LOQ (<LOQ, 10.8)
Maternal Plasma	55	0.08	19%	<LOQ (<LOQ, 6.01)
PFHpA				
Cord Blood	247	0.08	36%	<LOQ (<LOQ, 0.59)
Maternal Plasma	55	0.08	23%	<LOQ (<LOQ, 0.23)
PFDA				
Cord Blood	247	0.08	45%	<LOQ (<LOQ, 1.69)
Maternal Plasma	55	0.08	75%	0.13 (<LOQ, 0.75)
PFUnDA				
Cord Blood	247	0.20	20%	<LOQ (<LOQ, 3.27)
Maternal Plasma	55	0.20	13%	<LOQ (<LOQ, 0.87)
PFDoDA				
Cord Blood	247	0.20	7%	<LOQ (<LOQ, 0.63)
Maternal Plasma	55	0.20	0%	<LOQ

Abbreviations: Limit of Quantification (LOQ); Interquartile Range (IQR); perfluorohexanesulfonic acid (PFHxS); perfluorononanoic acid (PFNA); perfluorooctane sulfonate (PFOS); perfluorooctanoic acid (PFOA).
Geometric mean is listed as <LOQ if >50% of observations are < LOQ.

(Table S1). Although associations between PFHxS and PC1 with MDI at 3 years were not significant as seen in adjusted imputed analyses, they were consistent in magnitude and direction. Further, the sex-specific trend of stronger positive associations between PFAS and MDI for females in adjusted imputed analyses was more apparent in complete case analyses. The significant interaction by sex for PFOS with MDI at 2 years was stronger (*P*-interaction <0.001) and also significant at 3 years (*P*-interaction = 0.03). In addition, there was a significant interaction by sex for PC1 and MDI at 2 years (*P*-interaction = 0.003).

3.3. Association between PFAS and cognitive outcomes at 4 and 6 years

In unadjusted models, similar to findings observed for MDI at 3 years, there were positive associations between PFOA and PFHxS and cognitive outcomes at 4 and 6 years. These associations were significant for verbal and full scale IQ at 4 years, and just verbal IQ at 6 years (Table S4). Results were similar but attenuated and no longer significant in adjusted models (Table 5). In unadjusted models, PC2 was associated with significantly lower verbal IQ scores at 4 ($\beta = -4.19$, 95% CI: −6.40, −1.98) and 6 ($\beta = -3.14$, 95% CI: −5.55, −0.73) years (Table S4). PC2 was also associated with lower full scale IQ scores ($\beta = -2.93$, 95% CI: −5.01, −0.85) at 4 years. In adjusted models, the association between PC2 and lower verbal IQ at 4 years was attenuated but remained significant ($\beta = -2.67$, 95% CI: −5.14, −0.20) (Table 5). This finding is consistent with the positive associations between PFOA and PFHxS with MDI at 3 years, as PC2 reflects higher PFNA but lower PFOA and PFHxS. In adjusted models, similar to findings for MDI at 2 and 3 years, there appeared to be a sex-specific trend between PFAS exposure and some cognitive outcomes (verbal and full scale IQ only) at 4 and 6 years, suggesting stronger positive associations for females compared to males (Table 5). For example, a log-unit increase in PFOA in adjusted models was associated with significantly higher verbal IQ scores among females ($\beta = 5.97$, 95% CI: 0.34, 11.6) but not males ($\beta = 1.92$, 95% CI: −4.76, 11.6) at 4 years. Further, although the interaction was not significant, at 4 years, PFOS was associated with 2.60 (95% CI: −3.18, 8.38) and 1.13 (95% CI: −4.04, 6.3) points higher verbal and full scale IQ scores, respectively, for females, but -3.44 (95% CI: −12.7, 5.82) and -2.21 (−9.12, 4.70) points lower verbal and full scale IQ scores, respectively, for males. This interaction by sex between PFAS and verbal and full scale IQ scores at 4 years reached significance in complete case analyses for PFOS (P-interaction = 0.02 for verbal IQ), PFOA (P-interaction = 0.04 for verbal and full scale IQ) and PC1 (P-interaction = 0.01 for verbal IQ and 0.04 for full scale IQ) (Table S2). The significant negative association between PC2 and verbal IQ at 4 years in adjusted imputed

Table 2
Participant characteristic distributions of observed and imputed data predicted through multiple imputation by chained Equations (MICE).

Variable	Number Missing (%)	Median (IQR) or %	
		Observed	Imputed
Total		302	
Maternal Age	0	30.6 (26.8, 34.5)	NA
Child Sex	0		
Female		49.7	NA
Male		50.3	NA
Trimester on 9/11	0		
≤1st Trimester		69.5	NA
2nd or 3rd Trimester		30.5	NA
Gestational Age at Birth (days)	0	280 (273, 280)	NA
Race[a]	19 (6.3)		
Black		16.6	17.1
White		43.5	43.6
Asian		36.0	34.5
Native American/Other		3.9	4.7
Pre-pregnancy BMI[a]	3 (1.0)	22.0 (20.2, 24.4)	22.0 (20.2, 24.4)
Parity[a]	1 (0.33)		
Primiparous		56.1	56.0
Multiparous		43.9	44.0
Material Hardship	0		
Yes		9.3	NA
No		90.7	NA
Maternal Demoralization[a]	4 (1.3)	0.70 (0.44, 1.11)	0.70 (0.44, 1.11)
Marital Status	0		
Married		79.8	NA
Not Married		20.2	NA
Education	0		
< High School Degree		17.9	NA
High School Degree		16.9	NA
> High School Degree		65.2	NA
Family Smoking Status	0		
No Family Smoking		81.5	NA
Any Family Smoking		18.5	NA
Breastfeeding History[a]	6 (2.0)		
Ever Breastfed		77.7	77.4
Never Breastfed		22.3	22.6
Maternal IQ [a]	104 (34.4)	94.0 (84.0, 106.5)	94.0 (83.0, 105.5)
Age at Test 1 (years)[a]	96 (31.8)	1.04 (1.01, 1.13)	1.04 (1.01, 1.13)
Age at Test 2 (years)[a]	99 (32.8)	2.01 (1.98, 2.07)	2.01 (1.98, 2.07)
Age at Test 3 (years)[a]	115 (38.1)	3.00 (2.96, 3.11)	3.01 (2.96, 3.13)
Age at Test 4 (years)[a]	145 (48.0)	4.05 (4.01, 4.11)	4.05 (4.01, 4.12)
Age at Test 6 (years)[a]	159 (52.6)	6.17 (6.10, 6.26)	6.17 (6.10, 6.26)
MDI Age 1[a]	119 (39.4)	95.0 (89.0, 102.0)	95.0 (89.0, 102.0)
PDI Age 1[a]	119 (39.4)	102.0 (90.0, 110.0)	101.0 (90.0, 110.0)
MDI Age 2[a]	119 (39.4)	96.0 (86.0,105.5)	96.0 (86.0, 105.0)
PDI Age 2[a]	121 (40.1)	96.0 (92.0, 106.0)	96.0 (90.0, 107.0)
MDI Age 3[a]	136 (45.0)	97.0 (87.3, 105.0)	95.0 (87.0, 104.0)
PDI Age 3[a]	141 (46.7)	97.0 (89.0, 108.0)	96.0 (88.0, 108.0)
Verbal Age 4[a]	145 (48.0)	94.0 (84.0, 103.0)	94.0 (84.0, 103.0)
Performance Age 4[a]	145 (48.0)	100.0 (89.0, 106.0)	98.0 (86.0, 106.0)
Full IQ Age 4[a]	145 (48.0)	95.0 (88.0, 103.0)	94.0 (88.0, 103.0)
Verbal Age 6[a]	159 (52.6)	99.0 (86.5, 109.0)	99.0 (87.0, 109.0)
Performance Age 6[a]	159 (52.6)	108.0 (97.0, 115.0)	108.0 (94.0, 116.0)
Full IQ Age 6[a]	159 (52.6)	103.0 (90.0, 113.0)	102.0 (90.0, 111.0)

Abbreviations: Body Mass Index (BMI); Gestational Age (GA); Interquartile Range (IQR); Mental Development Index (MDI); Psychomotor Development Index (PDI).
[a] Variable includes imputed values in analyses

Table 3
Principal components of perfluoroalkyl substances.

PFAS	Principal Component 1	Principal Component 2
Standard Deviation	1.51	1.01
Proportion of Variance	0.57	0.25
Weight for PFOS	0.59	0.27
Weight for PFOA	0.46	−0.48
Weight for PFNA	0.47	0.65
Weight for PFHxS	0.46	−0.53

Abbreviations: perfluorohexanesulfonic acid (PFHxS); perfluorononanoic acid (PFNA); perfluorooctane sulfonate (PFOS); perfluorooctanoic acid (PFOA).

analyses did not reach significance in complete case analyses but was similar in magnitude and direction.

4. Discussion

In this prospective birth cohort of 302 mother-child dyads recruited in New York City, we evaluated the association between prenatal PFAS exposure and cognitive outcomes in children at 1, 2, 3, 4 and 6 years. We found a trend of generally higher MDI scores at 2 and 3 years with higher PFAS exposure, reaching significance at 3 years for PFOA, PFHxS and for our summary measure of higher overall PFAS (PC1). We also found evidence of sex-specific relationships between PFAS and cognition, with results suggesting

Table 4
Mean Difference (95% Confidence Interval) in Cognitive Outcomes Assessed using Bayley Scales of Infant Development (BSID-II) per Log Unit Increase in Perfluoroalkyl Substances at 1, 2 and 3 Years (n = 302).

	Year 1		Year 2		Year 3	
	MDI	PDI	MDI	PDI	MDI	PDI
PFOS						
Overall	−0.61 (−3.17, 1.95)	−0.07 (−4.56, 4.43)	2.36 (−1.23, 5.94)	−1.34 (−4.26, 1.57)	1.96 (−1.24, 5.16)	−0.55 (−5.34, 4.23)
Female	−0.88 (−4.33, 2.57)	−0.17 (−6.05, 5.71)	5.52 (0.64, 10.4)	−0.04 (−4.12, 4.04)	4.15 (−0.2, 8.5)	−1.44 (−7.5, 4.62)
Male	−0.29 (−3.93, 3.35)	0.05 (−5.41, 5.51)	−1.35 (−7.09, 4.39)	−2.88 (−10.4, 4.67)	−0.63 (−5.41, 4.15)	0.49 (−5.29, 6.27)
P-Interaction	0.8	0.95	0.04	0.33	0.12	0.59
PFOA						
Overall	−1.10 (−3.83, 1.63)	−1.05 (−6.02, 3.92)	1.26 (−2.64, 5.16)	0.23 (−3.27, 3.74)	3.93 (0.08, 7.77)	2.35 (−2.84, 7.54)
Female	−1.34 (−5.12, 2.44)	−1.41 (−7.60, 4.78)	3.00 (−1.96, 7.96)	0.47 (−4.18, 5.12)	4.09 (−0.97, 9.15)	4.03 (−2.87, 10.9)
Male	−0.85 (−5.23, 3.53)	−0.67 (−7.12, 5.78)	−0.57 (−6.04, 4.90)	−0.02 (−4.79, 4.75)	3.76 (−4.94, 12.46)	0.58 (−5.78, 6.94)
P-Interaction	0.85	0.84	0.29	0.88	0.92	0.41
PFNA						
Overall	−0.14 (−2.30, 2.02)	−0.43 (−4.00, 3.14)	1.71 (−1.78, 5.20)	−1.62 (−4.18, 0.94)	2.05 (−0.80, 4.89)	−2.10 (−6.01, 1.81)
Female	−0.38 (−2.91, 2.15)	−0.14 (−4.28, 4.00)	2.15 (−2.01, 6.31)	−1.23 (−4.44, 1.98)	2.38 (−0.87, 5.63)	−2.77 (−7.32, 1.78)
Male	0.23 (−2.43, 2.89)	−0.89 (−5.85, 4.07)	1.02 (−3.4, 5.44)	−2.24 (−8.25, 3.77)	1.51 (−2.96, 5.98)	−1.04 (−6.19, 4.11)
P-Interaction	0.68	0.75	0.63	0.62	0.67	0.46
PFHxS						
Overall	0.20 (−2.06, 2.45)	0.23 (−3.26, 3.71)	1.71(-1.13, 4.54)	0.41 (−2.38, 3.21)	3.30 (0.70, 5.90)	2.620 (−1.270, 6.50)
Female	0.03 (−2.71, 2.77)	0.11 (−3.75, 3.97)	2.46 (−0.93, 5.85)	0.58 (−2.75, 3.91)	2.39 (−1, 5.78)	2.19 (−2.28, 6.66)
Male	0.45 (−2.69, 3.59)	0.38 (−4.94, 5.7)	0.62 (−3.82, 5.06)	0.17 (−3.92, 4.26)	4.62 (−5.08, 14.3)	3.23 (−5.13, 11.6)
P-Interaction	0.83	0.93	0.49	0.87	0.41	0.76
PC1						
Overall	−0.17 (−1.06, 0.71)	−0.12 (−1.70, 1.46)	0.80 (−0.49, 2.09)	−0.26 (−1.30, 0.77)	1.23 (0.13, 2.32)	0.255 (−1.49, 2.00)
Female	−0.29 (−1.47, 0.89)	−0.13 (−2.07, 1.81)	1.58 (−0.11, 3.27)	0.01 (−1.4, 1.42)	1.51 (0.04, 2.98)	0.09 (−2.07, 2.25)
Male	−0.03 (−1.35, 1.29)	−0.12 (−2.23, 1.99)	−0.13 (−1.98, 1.72)	−0.58 (−2.82, 1.66)	0.89 (−1.11, 2.89)	0.45 (−1.66, 2.56)
P-Interaction	0.74	1.00	0.12	0.55	0.56	0.77
PC2						
Overall	0.09 (−1.54, 1.72)	0.02 (−2.38, 2.42)	0.05 (−2.13, 2.23)	−1.48 (−3.77, 0.81)	−1.70 (−3.93, 0.54)	−3.51 (−6.01, −1.02)
Female	0.00 (−1.9, 1.9)	0.24 (−2.54, 3.02)	0.14 (−2.56, 2.84)	−1.22 (−3.89, 1.45)	−0.88 (−3.47, 1.71)	−4.17 (−7.27, −1.07)
Male	0.21 (−1.92, 2.34)	−0.28 (−3.79, 3.23)	−0.07 (−3.05, 2.91)	−1.85 (−7.01, 3.31)	−2.83 (−9.73, 4.07)	−2.61 (−9.3, 4.08)
P-Interaction	0.86	0.78	0.91	0.69	0.23	0.44

Models adjusted for maternal age, material hardship, parity, pre-pregnancy BMI, maternal IQ, maternal race, maternal education, family smoking status, child age at testing, child's gestational age at birth, maternal demoralization, trimester on 9/11, child's sex, and child's breastfeeding history.; Abbreviations: mental development index (MDI); perfluorohexanesulfonic acid (PFHxS); perfluorononanoic acid (PFNA); perfluorooctane sulfonate (PFOS); perfluorooctanoic acid (PFOA); principal component (PC); psychomotor development index (PDI).

that higher PFAS may be associated with higher scores for some measures of cognition among females but not males. We observed significantly higher cognitive scores with increases in PFOS at 2 years and with increases in PFOA at 4 years, for females but not males. An interaction by sex was significant between PFOS and MDI at 2 years. We also found some evidence of divergent associations across PFAS, such that there were significant associations between the second PFAS principal component and PDI at 3 years and verbal IQ at 4 years, reflecting a positive relationship for PFOA and PFHxS and an inverse relationship for PFNA.

PFAS are widespread and stable environmental toxicants, highly resistant to biotransformation and environmental degradation. Their ability to cross the placental barrier has led to increasing interest in understanding the effect of exposure to PFAS on the developing fetus. Epidemiologic studies evaluating the association between prenatal PFAS exposure and neurodevelopment have been limited and inconsistent. Two studies have reported significant inverse associations between prenatal PFAS and childhood cognitive outcomes. A study from Taiwan (Wang et al., 2015) found higher PFNA and PFUNDA to be associated with lower IQ at 5 and 8 years, and a study from Japan (Goudarzi et al., 2016) found higher PFOA to be associated with lower MDI in females at 6 months but not 18 months. In contrast, a recent study in the Danish Birth Cohort evaluated seven different PFAS and found an association between PFNA and higher verbal IQ among 5-year olds in the overall population and in females in sex-stratified analyses (Liew et al., 2018). Similarly, US-based studies have reported positive associations of prenatal PFOA (Stein et al., 2013; Vuong et al., 2019) and PFNA (Vuong et al., 2019) with cognitive outcomes, with evidence of sex-specific relationships for PFOA and PFOS. Another US-based study reported variable associations across PFAS compounds, cognitive measures and timing of cognitive assessments (early versus mid-childhood) (Harris et al., 2018). For example, for PFNA, there was a general trend of better cognition scores with increasing exposure; however, for PFOA, greater exposure was associated with higher design memory and composite scores, but lower verbal IQ and visual-motor scores. Studies evaluating PFAS with other measures of neurodevelopment (i.e., non-IQ measures) have also reported inconsistent findings. A study conducted among British girls found both positive and negative associations of PFOS, PFOA and PFNA with early communication development at 15 and 38 months, depending on the outcome measured and age of the mother, but only positive associations reported for PFHxS (Jeddy et al., 2017). In addition, a recent US study reported better reading skills at 5 and 8 years with higher prenatal exposure to PFOA, PFOS and PFNA (Zhang et al., 2018).

Our findings are reflective of the apparent complicated nature of the relationship between PFAS and neurodevelopment. The significant associations we observed between PFOA, PFHxS and PC1 (i.e., higher PFAS exposure overall) and better MDI scores at 3 years, are inconsistent with the results of studies from Taiwan and Japan, but consistent with the studies outlined above that have reported surprising protective associations between various PFAS and cognitive outcomes. The mechanism by which PFAS could exert neuroprotective effects is not clear, however, their activation of human peroxisome proliferator-activated receptor (PPAR) alpha and PPARγ in several experimental studies (Maloney and Waxman, 1999; Takacs and Abbott, 2007; Vanden Heuvel et al., 2006) has

Table 5
Mean Difference (95% Confidence Interval) in Cognitive Outcomes Assessed using The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) per Log Unit Increase in Perfluoroalkyl Substances at 4 and 6 Years (n = 302).

	Year 4			Year 6		
	Per	Ver	Full	Per	Ver	Full
PFOS						
Overall	−0.05 (−4.56, 4.46)	−0.19 (−4.5, 4.12)	−0.41 (−4.25, 3.43)	2.81 (−2.29, 7.91)	2.67 (−2.56, 7.9)	2.81 (−1.84, 7.46)
Female	−0.32 (−6.14, 5.5)	2.60 (−3.18, 8.38)	1.13 (−4.04, 6.30)	4.20 (−1.9, 10.3)	4.15 (−2.08, 10.38)	4.49 (−1.14, 10.1)
Male	0.27 (−5.20, 5.74)	−3.44 (−12.7, 5.82)	−2.21 (−9.12, 4.70)	1.16 (−5.51, 7.83)	0.90 (−5.83, 7.63)	0.80 (−5.02, 6.62)
P-Interaction	0.87	0.10	0.30	0.41	0.39	0.27
PFOA						
Overall	0.64 (−4.12, 5.4)	3.99 (−0.34, 8.32)	2.50 (−1.15, 6.15)	−1.37 (−6.25, 3.51)	3.02 (−2.49, 8.53)	0.87 (−3.89, 5.63)
Female	1.58 (−4.61, 7.77)	5.97 (0.34, 11.6)	4.17 (−0.87, 9.21)	−0.28 (−6.2, 5.64)	4.03 (−2.93, 10.99)	2.23 (−3.73, 8.19)
Male	−0.35 (−6.69, 5.99)	1.92 (−4.76, 8.60)	0.75 (−4.3, 5.8)	−2.50 (−11.3, 6.28)	1.95 (−5.49, 9.39)	−0.56 (−6.82, 5.7)
P-Interaction	0.64	0.29	0.33	0.59	0.61	0.45
PFNA						
Overall	−0.35 (−3.96, 3.26)	0.21 (−3.18, 3.6)	−0.23 (−3.37, 2.91)	1.42 (−2.32, 5.16)	1.53 (−2.55, 5.61)	1.55 (−2.12, 5.22)
Female	−0.61 (−4.84, 3.62)	0.95 (−3.11, 5.01)	0.1 (−3.62, 3.82)	1.82 (−2.47, 6.11)	1.83 (−2.72, 6.38)	1.98 (−2.21, 6.17)
Male	0.07 (−4.57, 4.71)	−0.99 (−5.92, 3.94)	−0.76 (−5.14, 3.62)	0.79 (−3.78, 5.36)	1.06 (−4.08, 6.2)	0.85 (−3.56, 5.26)
P-Interaction	0.79	0.43	0.70	0.66	0.75	0.61
PFHxS						
Overall	−2.45 (−5.9, 1)	2.35 (−0.98, 5.68)	0.04 (−2.78, 2.86)	−0.63 (−4.45, 3.19)	0.24 (−3.48, 3.96)	−0.34 (−3.71, 3.03)
Female	−2.61 (−6.75, 1.53)	2.90 (−1.24, 7.04)	0.35 (−3.20, 3.90)	0.27 (−3.9, 4.44)	0.88 (−3.49, 5.25)	0.57 (−3.13, 4.27)
Male	−2.24 (−9.44, 4.96)	1.56 (−3.90, 7.02)	−0.41 (−4.84, 4.02)	−1.92 (−8.97, 5.13)	−0.7 (−6.46, 5.06)	−1.64 (−8.07, 4.79)
P-Interaction	0.90	0.66	0.78	0.46	0.62	0.44
PC1						
Overall	−0.28 (−1.77, 1.21)	0.66 (−0.77, 2.09)	0.16 (−1.07, 1.39)	0.30 (−1.39, 1.99)	0.81 (−0.93, 2.55)	0.56 (−1.01, 2.13)
Female	−0.33 (−2.21, 1.55)	1.42 (−0.46, 3.30)	0.60 (−1.05, 2.25)	0.79 (−1.19, 2.77)	1.24 (−0.82, 3.30)	1.11 (−0.73, 2.95)
Male	−0.20 (−2.30, 1.90)	−0.24 (−2.31, 1.83)	−0.35 (−2.35, 1.65)	−0.28 (−2.72, 2.16)	0.29 (−1.94, 2.52)	−0.10 (−2.24, 2.04)
P-Interaction	0.91	0.17	0.37	0.39	0.46	0.29
PC2						
Overall	0.89 (−1.93, 3.71)	−2.67 (−5.14, −0.20)	−1.16 (−3.37, 1.05)	2.23 (−0.46, 4.92)	0.16 (−2.7, 3.02)	1.31 (−1.28, 3.9)
Female	0.60 (−2.83, 4.03)	−2.38 (−5.34, 0.58)	−1.15 (−3.91, 1.61)	2.10 (−1.04, 5.24)	0.19 (−3.14, 3.52)	1.24 (−1.8, 4.28)
Male	1.29 (−2.92, 5.50)	−3.09 (−10.7, 4.49)	−1.19 (−5.38, 3.00)	2.42 (−3.13, 7.97)	0.13 (−3.29, 3.55)	1.42 (−2.49, 5.33)
P-Interaction	0.76	0.72	0.98	0.87	0.98	0.92

Models adjusted for maternal age, material hardship, parity, pre-pregnancy BMI, maternal IQ, maternal race, maternal education, family smoking status, child's age at testing, child's gestational age at birth, maternal demoralization, trimester on 9/11, child's sex, and child's breastfeeding history.; Abbreviations: full IQ (Full); perfluorohexanesulfonic acid (PFHxS); perfluorononanoic acid (PFNA); perfluorooctane sulfonate (PFOS); perfluorooctanoic acid (PFOA); performance IQ (Per); principal component (PC); verbal IQ (Ver).

been identified as one potential pathway, since other PPARγ agonists have been shown to be neuroprotective (Power et al., 2013; Watson et al., 2005; Liu et al., 2015). Still, *in vivo* and *in vitro* models have also suggested PFAS have neurotoxic potential through effects on the cholinergic system (Johansson et al., 2008; Lau et al., 2003; Viberg et al., 2013), neuronal differentiation (Slotkin et al., 2008), protein levels necessary for proper brain development (Johansson et al., 2009; Liu et al., 2010) and thyroid homeostasis (Mariussen, 2012).

Inconsistencies across studies could be due to differences in study populations including ethnicity and exposure levels. For example, the populations in the studies from Japan (Goudarzi et al., 2016) and Taiwan (Wang et al., 2015) were Asian, whereas the populations in other studies were all (Liew et al., 2018; Jeddy et al., 2017), or predominately (Stein et al., 2013; Vuong et al., 2019), Caucasian. Further, the range of exposure for PFOS and PFOA across studies was substantial: the highest reported median PFOA concentration (Stein et al., 2013) was 36× the level of the lowest reported median (Goudarzi et al., 2016). In addition, associations between PFAS and cognitive outcomes varied in our study based on age and type of assessment used to measure cognition and likely contribute to differences observed in findings across studies. Inconsistent findings may also result from biological mechanisms that possibly vary by sex and PFAS compounds. For example, one indicated neurotoxic mechanism of PFAS in thyroid homeostasis is through competitive binding to the human thyroid hormone transport protein, transthyretin (TTR), and PFAS TTR binding potency has been shown to differ across PFAS compounds (Slotkin et al., 2008; Weiss et al., 2009). Our finding of a significant negative association between PC2 and PDI at 3 years and verbal scores at 4 years, suggesting a positive relationship with neurodevelopment for PFHxS and PFOA but negative for PFNA, adds evidence that neurotoxic mechanisms of action may differ across PFAS. Further, the sex-specific trends we observed of better cognitive outcomes with higher prenatal PFAS among females but not males suggest that PFAS neurotoxic mechanisms may also differ by sex. Our sex-specific findings are consistent with two recent studies that also found evidence of a positive relationship between PFAS and cognitive scores in females but not males. Still, these studies observed these trends for PFNA, (Liew et al., 2018) PFOA (Vuong et al., 2019) and PFHxS (Vuong et al., 2019), whereas our only significant interaction by sex was for PFOS. Sex-specific associations have also been observed between prenatal PFAS exposure and childhood behavioral outcomes in epidemiologic (Stein et al., 2013; Oulhote et al., 2016) and animal (Fuentes et al., 2007; Onishchenko et al., 2011) studies. Mechanistic evidence on the sex-specific associations between PFAS and cognitive outcomes is currently unexplored. However, DNA methylation may be one pathway: in a Faroese birth cohort, in males only, cord blood PFOS was associated with DNA methylation changes that were predicted to dysregulate genes involved in nervous system development (Leung et al., 2018). PFAS toxicokinetic differences between males and females may also play a role. Animal studies have consistently shown shorter PFAS half-lives and lower accumulation in tissues in females compared with males (Khazaee et al., 2019; Dzierlenga et al., 2019; Huang et al., 2019). Analysis of NHANES data revealing higher concentrations of all PFAS evaluated (PFOS, PFOA, PFNA and PFHxS) in males versus females, suggest these trends

may also be true in humans (Kato et al., 2011). Still these findings do not provide evidence for the positive association between PFAS and cognitive outcomes. As discussed earlier, the ability of PFAS to activate PPARγ has been identified as one pathway through which PFAS could exert neuroprotective effects. Clinical trials have reported sex-differences in the efficacy of PPARγ agonist treatments, possibly due to sex-specific expression of PPARγ, with greater effects (in response to diabetes) seen among females (ACTOS, 1999; AVANDIA, 2007). In theory, PPARγ therefore provides a potential mechanistic link between PFAS and positive cognitive outcomes in females, however, *in vivo* research on the mediating role of PPARγ in the sex-specific relationship between PFAS and cognitive outcomes is needed to test this hypothesis.

This study population is unique in that participants were initially recruited to evaluate the effects of the 9/11 event on pregnancy outcomes and child development. The collapse of the WTC resulted in the generation of thousands of tons of toxic chemicals dispersed across the surrounding area, with fires that burned for three months following the disaster (Landrigan et al., 2004). PFAS were a likely component of the toxic plume caused by the WTC, given their use as surfactants and stain-resistant coatings on numerous products that may been involved in the WTC collapse and response (e.g., carpets, food packaging, textiles, leather and fire-fighting foam) (US Environmental Protection Agency, 2017a). Indeed, proximity to the 9/11 site has been reported previously to be associated with higher cord blood PFAS levels in this population (prenatally) (Spratlen et al., 2019) and other WTC-exposed groups (Trasande et al., 2017; Tao et al., 2008). However, the range of prenatal exposures in this population is similar to other US-based studies, (Apelberg et al., 2007; Kato et al., 2014) and findings should therefore be generalizable to other multi-ethnic US populations. Despite the strength of participants in this study being drawn from a well-designed, rich longitudinal cohort, with information on many important confounders, our study has limitations that should be considered when interpreting findings, notably, the small sample size and substantial loss to follow-up. Still, MICE is an established statistical imputation technique shown to provide unbiased estimates when missing data are missing at random, including dealing with missing outcome data due to loss to follow-up in longitudinal studies (Rawlings et al., 2017). Further, the validity of multiple imputation has been reported to have less to do with the fraction of data missing, and more on the appropriate inclusion of predictors of missingness (Madley-Dowd et al., 2019). In addition, due to the number of regressions run (multiple exposure variables, multiple outcome variables, and five different time points), we cannot exclude the possibility of spurious significant associations resulting from multiple comparisons.

5. Conclusions

Our findings suggest sex-specific associations between prenatal PFAS and childhood neurodevelopment, with certain positive associations seen among females but not males. Further, our principal component analysis provided evidence of divergent neurotoxic findings across PFAS compounds, with positive associations observed for PFOA and PFHxS, but negative associations observed for PFNA, using a psychomotor-based scale at 3 years and verbal scores at 4. Our results highlight the complex and inconsistent relationships between prenatal PFAS exposures and childhood neurodevelopment. Given the large amount of missing data, as well as the number of statistical tests, these findings should be interpreted with caution. However, they emphasize the need for both experimental studies, to better elucidate the biological mechanisms behind these relationships, and large-scale epidemiologic studies with high retention to reduce any effects of missing data. Further, additional research should be dedicated to evaluating possible sex-specific associations between PFAS and neurodevelopment.

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Disclosure statement

The authors have nothing to disclose.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Miranda J. Spratlen: Visualization, Formal analysis, Methodology, Writing - original draft. **Frederica P. Perera:** Writing - review & editing, Funding acquisition, Conceptualization, Resources. **Sally Ann Lederman:** Writing - review & editing, Funding acquisition, Conceptualization. **Virginia A. Rauh:** Writing - review & editing, Funding acquisition, Conceptualization. **Morgan Robinson:** Writing - review & editing, Resources, Investigation. **Kurunthachalam Kannan:** Writing - review & editing, Resources, Investigation. **Leonardo Trasande:** Funding acquisition, Conceptualization, Supervision. **Julie Herbstman:** Funding acquisition, Conceptualization, Supervision, Resources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2020.114444.

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