International Journal of Hygiene and Environmental Health 223 (2020) 80–92

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Prenatal exposure to perfluoroalkyl substances and associations with symptoms of attention-deficit/hyperactivity disorder and cognitive functions in preschool children

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ARTICLE INFO

Keywords:
Perfluoroalkyl substances (PFASs)
Attention-deficit/hyperactivity disorder (ADHD)
Cognitive functions
Prenatal
The Norwegian Mother
Father and Child Cohort Study (MoBa)

ABSTRACT

Background: Perfluoroalkyl substances (PFASs) are persistent organic pollutants that are suspected to be neurodevelopmental toxicants, but epidemiological evidence on neurodevelopmental effects of PFAS exposure is inconsistent. We investigated the associations between prenatal exposure to PFASs and symptoms of attention-deficit/hyperactivity disorder (ADHD) and cognitive functioning (language skills, estimated IQ and working memory) in preschool children, as well as effect modification by child sex.

Material and methods: This study included 944 mother-child pairs enrolled in a longitudinal prospective study of ADHD symptoms (the ADHD Study), with participants recruited from The Norwegian Mother, Father and Child Cohort Study (MoBa). Boys and girls aged three and a half years, participated in extensive clinical assessments using well-validated tools; The Preschool Age Psychiatric Assessment interview, Child Development Inventory and Stanford-Binet (5th revision). Prenatal levels of 19 PFASs were measured in maternal blood at week 17 of gestation. Multivariable adjusted regression models were used to examine exposure-outcome associations with two principal components extracted from the seven detected PFASs. Based on these results, we performed regression analyses of individual PFASs categorized into quintiles.

Results: PFAS component 1 was mainly explained by perfluoroheptane sulfonate (PFHpS), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS) and perfluorooctanoic acid (PFOA). PFAS component 2 was mainly explained by perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA) and perfluorononanoic acid (PFNA). Regression models showed a negative association between PFAS component 1 and nonverbal working memory [β = -0.08 (CI: -0.12, -0.03)] and a positive association between PFAS component 2 and verbal working memory [β = 0.07 (CI: 0.01, 0.12)]. There were no associations with ADHD symptoms, language skills or IQ. For verbal working memory and PFAS component 2, we found evidence for effect modification by child sex, with associations only for boys. The results of quintile models with individual PFASs, showed the same pattern for working memory as the results in the component regression analyses. There were negative associations between nonverbal working memory and quintiles of PFOA, PFNA, PFHxS, PFHpS and PFOS and positive associations between verbal working memory and quintiles of PFOA, PFNA, PFDA and PFUnDA, with significant relationships mainly in the highest concentration groups.

Conclusions: Based on our results, we did not find consistent evidence to conclude that prenatal exposure to PFASs are associated with ADHD symptoms or cognitive dysfunctions in preschool children aged three and a half years, which is in line with the majority of studies in this area. Our results showed some associations between PFASs and working memory, particularly negative relationships with nonverbal working memory, but also

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https://doi.org/10.1016/j.ijheh.2019.10.003
Received 21 June 2019; Received in revised form 4 October 2019; Accepted 7 October 2019

positive relationships with verbal working memory. The relationships were weak, as well as both positive and negative, which suggest no clear association – and need for replication.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, affecting approximately 5% of children worldwide (Polanczyk et al., 2007). ADHD is characterized by inattention, impulsivity and hyperactivity (American Psychiatric Association, 2013). Symptoms of ADHD are often present in the preschool years (Skogan et al., 2014), which is also an important period for the development of cognitive functions and language (Garon et al., 2008; Rice et al., 2008). Childhood ADHD is 2–9 times more prevalent in boys, but there are smaller sex differences in population-based samples compared with clinical samples (Nussbaum, 2012; Polanczyk et al., 2007). The reasons for sex differences are not known, but it has been hypothesized that a higher degree of externalizing behavior problems among boys with ADHD compared to girls may result in a sex-based referral bias (Biederman, 2005; Martin et al., 2018; Nussbaum, 2012). The underlying causes of ADHD are most likely interplays between genetic and non-genetic factors (Faraone et al., 2005; Thapar et al., 2013). While the role of heritability in the etiology of ADHD is well documented (Chang et al., 2013; Faraone et al., 2005), knowledge about how environmental factors may affect the development of ADHD is still scarce (Thapar et al., 2013). Exposure to environmental toxicants during pregnancy has gained increased interest as a risk factor for neurodevelopmental disorders (Grandjean and Landrigan, 2014). During pregnancy, toxicants can be transferred from mother to fetus via the placenta (Grandjean and Landrigan, 2014; Gützkow et al., 2012; Kato et al., 2014). The fetus has an undeveloped blood-brain barrier and limited ability to eliminate toxicants (Grandjean and Landrigan, 2014) therefore, exposure to toxicants *in utero* may disrupt normal brain development and hence be a potential risk factor for impaired cognitive functions and neurodevelopmental disorders such as ADHD or related symptoms (Grandjean and Landrigan, 2006, 2014; Kajta and Wójtowicz, 2013).

Compared to other environmental toxicants, poly- and perfluoroalkyl substances (PFASs) are among those with highest levels in human blood, including pregnant women (Haug et al., 2018; Mariussen, 2012). PFAS is a large group of synthetic compounds developed for use in a multitude of different products (e.g. firefighting foam, textiles, cooking pans, and food packaging) because of its water, oil and dirt repelling properties (Buck et al., 2011; Kissa, 2001). Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are the two most prevalent and extensively studied PFASs. Due to phase-out by major producers as well as international legislation and reduced use, levels of some PFASs have declined in the environment during the last 10–15 years (EFSA CONTAM Panel, 2018; Mariussen, 2012). However, several PFASs are highly persistent in the environment and in humans, and PFOS and PFOA have estimated biological half-lives of around two to five years in the human body (EFSA CONTAM Panel, 2018; Lau et al., 2007). Furthermore, new types of PFASs with longer half-lives have replaced PFOS and PFOA (Sunderland et al., 2019; Wang et al., 2017). Bound to protein-rich tissues, many of the PFASs will accumulate in animals and magnify up the food chain (Conder et al., 2008; Houde et al., 2006). In Norway, the major sources of exposure to these substances are food, especially seafood (Haug et al., 2010). Experimental rodent studies suggest that PFASs may be developmental neurotoxicants (Grandjean and Landrigan, 2014; Johansson et al., 2009; Mariussen, 2012; Viberg et al., 2013). Importantly, PFASs have endocrine-disruptive abilities and can affect the maternal and fetal thyroid hormone systems, which are essential for a normal development of the fetal nervous system and brain (De Cock et al., 2012; Mariussen, 2012; Tran and Miyake, 2017). Experimental animal studies have suggested that there are sex differences regarding the elimination of PFASs and that it is possibly linked to prenatal gonadal hormone levels (Lau et al., 2007). In addition, studies suggest interaction between PFAS exposure and sex hormone homeostasis (Kjeldsen and Bonefeld-Jørgensen, 2013; Mariussen, 2012).

Results from epidemiologic studies investigating prenatal exposure to PFASs and neurodevelopment, such as ADHD diagnosis/symptoms and cognitive functions, are inconsistent (Liew et al., 2018a; Rappazzo et al., 2017). Most studies on ADHD or related symptoms report no associations (Fei and Olsen, 2011; Lien et al., 2016; Liew et al., 2015; Ode et al., 2014; Oulhote et al., 2016; Quaak et al., 2016; Stein et al., 2013; Strøm et al., 2014; Vuong et al., 2018). Two studies report positive associations between prenatal PFAS exposure and hyperactivity symptoms (Høyer et al., 2015, 2018). Research on prenatal exposure to PFASs and offspring cognitive functions report weak or lack of associations, or report conflicting evidence (Chen et al., 2013; Harris et al., 2018; Jeddy et al., 2017; Liew et al., 2018b; Stein et al., 2013; Vuong et al., 2019; Zhang et al., 2018). However, one study did report negative associations between higher PFAS levels and lower IQ in the child at ages five and eight (Wang et al., 2015). In addition, another study reported associations between higher prenatal PFOS levels and increased impairments in metacognition (Vuong et al., 2016). Taken together, there is considerable uncertainty about the effect of PFASs as far as these types of neurodevelopmental outcomes are concerned. Among the studies, there is a large variety of different instruments and methods and several of them have small sample sizes. Furthermore, no previous studies have investigated prenatal PFAS exposure in relation to ADHD symptoms using neuropsychological assessments of three-year-old children.

The present study's overall aim is to investigate the associations between prenatal exposure to PFASs and ADHD symptoms, language skills, estimated IQ and working memory in preschool children, as well as to investigate effect modification by child sex of these associations.

2. Methods

2.1. Study design and participants

2.1.1. The Norwegian Mother, Father and Child Cohort Study

The Norwegian Mother, Father and Child Cohort Study (MoBa) is an ongoing prospective population-based cohort study conducted by the Norwegian Institute of Public Health (Magnus et al., 2016). The cohort now includes over 114,000 children, 95,000 mothers, and 75,000 fathers. Participants (41% participation rate) were recruited from all over Norway from 1999 to 2008. Pregnant women were invited to participate when scheduling their first free ultrasound scanning around the 17th week of pregnancy. Blood samples were collected from both parents in pregnancy and from the mother and child at birth (Magnus et al., 2016).

2.1.2. The ADHD study

The current paper is based on the ADHD Study, a sub-study of children with high levels of ADHD symptoms. The children were identified through the MoBa questionnaire that mothers completed when the child was three years of age (Overgaard et al., 2018). This questionnaire included 11 items about ADHD, of which six items were from the Child Behavior Checklist/1.5–5 (Achenbach and Rescorla, 2010) and five items from the DSM-IV-TR criteria for ADHD (American Psychiatric Association, 2000). Children with scores ≥ 90th percentile

on these 11 items (n = 2798) were invited to participate in a clinical assessment, along with randomly selected children from the MoBa cohort (n = 654). Among those eligible for the present sub-study, 149 children with high scores on autistic symptoms were sampled to another MoBa sub-study of autism (Fig. 1). In total, about 35% agreed to participate in the present sub-study. From 2007 to 2011, 1195 children (mean age: 3.5 years, age range: 3.1–3.8 years) took part in a one-day clinical assessment including a neuropsychological assessment with the child and a diagnostic interview with one of the parents, usually the mother. Details about the screening criteria are described elsewhere (Overgaard et al., 2018). In the overall sample, the proportions of girls and boys who met symptom criteria for ADHD diagnosis according to the parent interview were about 17% and 20%, respectively (Overgaard et al., 2018, 2019).

When excluding non-singleton pregnancies, withdrawals from the study, and those without available blood samples, the total number of mother-child pairs was 944 in the present study (Fig. 1). None of the children participating in this study had been or was medicated for ADHD at the time of assessment. We used version 9 of the MoBa quality-assured data files. MoBa is regulated under the Health Registry Act. Participation in MoBa is based on written informed consent from the parents. The ADHD Study has approval from the Regional Committee for Health Research Ethics for Southeast Norway. Participation in the clinical assessments of the ADHD Study required an additional written informed consent. This study was approved by The Regional Committee for Medical Research Ethics (ref. nu. 2012/985–1).

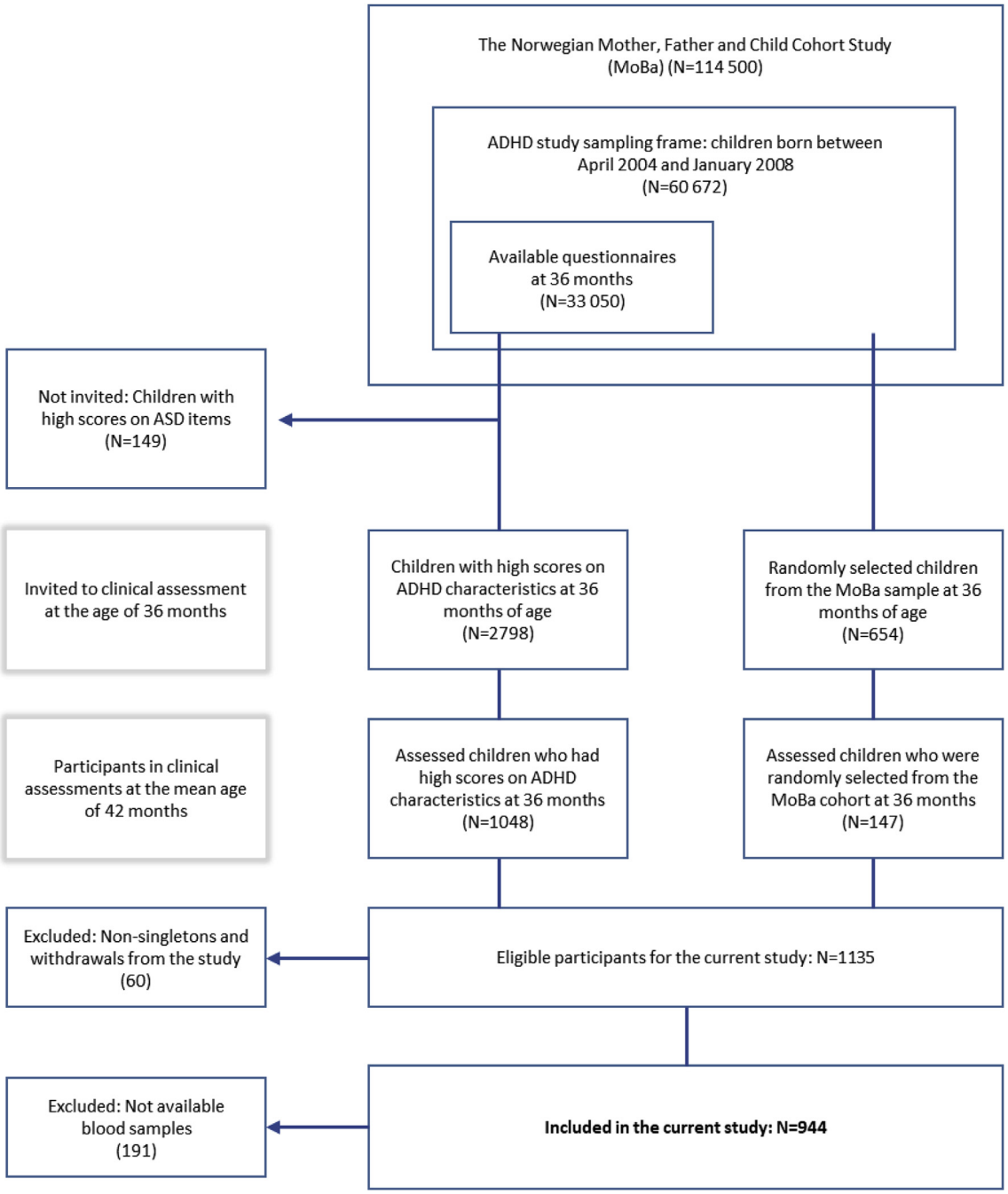


Fig. 1. Recruitment of participants and inclusion in the current study in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort Study (MoBa), 2004–2008. Abbreviations: Attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), The Norwegian Mother, Father and Child Cohort Study (MoBa).

2.2. Exposures

The present study used maternal plasma samples from week 17 of gestation to measure PFAS levels. Details about the sampling procedure and handling and storage in the MoBa biobank is described elsewhere (Paltiel et al., 2014). Nineteen PFASs were determined in maternal plasma (Table S1), using liquid chromatography-triple quadruple mass spectrometry (LC-MS/MS) as described previously (Haug et al., 2009). This method has been thoroughly validated and used for determination of more than 5000 serum/plasma samples so far, including approximately 2000 samples from MoBa (Singer et al., 2018). Only PFASs with levels above limit of quantification (LOQ) in > 80% of the plasma samples were included in the present study; PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS) and PFOS. Internal quality control samples and procedure blanks were analyzed along with each batch of samples to ensure high quality of the determinations throughout the project. The samples were also randomized to batch.

2.3. Outcomes

2.3.1. ADHD symptoms

Diagnostic assessments of the children were based on the Preschool Age Psychiatric Assessment (PAPA) interviews with their parents (Egger and Angold, 2004). The ADHD classification/diagnosis defined by PAPA is not equivalent to clinical ADHD diagnoses that would require a broader assessment, including multiple sources of information and informants. In the ADHD Study, only symptoms lasting ≥3 months were counted as present. Psychologists, psychiatrists, or trained graduate psychology students conducted the interviews. When graduate students conducted the interviews, they were under supervision by a child psychologist or a psychiatrist. As an inter-rater reliability check, a separate rater who was blind to the parent and teacher screen ratings, rescored audiotapes of 79 randomly selected assessment interviews. The average intra-class correlations (ICCs) were 0.97 for hyperactivity and impulsivity (HI) symptoms, 0.99 for inattention (IA) symptoms, and 0.98 for the total number of ADHD symptoms. In the present study, ADHD symptom sum scores were based on symptoms of inattention, hyperactivity, and impulsivity from the PAPA interview. Higher scores indicated more ADHD symptoms and higher severity.

2.3.2. Expressive language skills

Experienced clinicians with specialization in pediatric neuropsychological assessments conducted the tests of cognitive abilities of the children, including language skills, estimated IQ, and working memory. Expressive language skills were measured with Child Development Inventory (CDI). The CDI is a questionnaire for assessment of children from 15 months to six years of age, where teachers and parents fill in the questionnaires (Ireton and Glascoe, 1995). The questionnaire is consistent with results from psychometric tests of children and has good sensitivity and specificity (> 80%) of identifying delayed development in children (Doig et al., 1999). In the CDI, delayed language is defined as at least 1.25 standard deviations below the mean (Rohrer-Baumgartner et al., 2016). In the present study, we used the language subscale that was filled in by the preschool teacher. The subscale contains 50 items that assess primarily expressive communication, from simple gestures to complex language expressions. We used the daycare teacher report instead of parental report, as preschool teachers generally are assumed to have a good reference base for the evaluations (Rohrer-Baumgartner et al., 2016). A higher score indicated better language skills.

2.3.3. Estimated IQ (verbal and nonverbal)

Intelligence quotient (IQ) refers to performance on standardized tests measuring intellectual abilities (Rohrer-Baumgartner et al., 2014). Two subtests from Stanford Binet Intelligence scales (5th edition), were used to assess estimated IQ. This test battery has good psychometric properties and is standardized for ages two to 85 (Roid, 2003). In the present study, an estimated verbal IQ score was based on the "Vocabulary Task" where the child is requested to point at different body parts or name objects (toys) and explain the meaning of selected words. An estimated nonverbal IQ score was based on the "Object Matrices Task", that entails tasks such as detection of shapes that are alike and to fill in a missing shape on the basis of abstract reasoning. The verbal task is a measure of knowledge and the nonverbal task is a measure of fluid reasoning, which together is a good estimate of global ability (Roid, 2003). Both of these subtests have high loadings on the hierarchical g factor in cognitive ability batteries (Roid, 2003). The stop rule of discontinuing the test after four consecutive null scores was applied in all tests from this battery. A higher score indicated higher estimated IQ.

2.3.4. Working memory (verbal and nonverbal)

Working memory consists of a multicomponent cognitive system that allows for the rehearsal, storage and manipulation of information for a few seconds, and is a vital part of higher-order cognitive processes (Baddeley, 2012). Stanford Binet Intelligence scales (5th edition) was utilized to measure verbal and nonverbal working memory. Verbal working memory was assessed with the subtask "Memory for Sentences", where the child is asked to repeat sentences that increases gradually in length. Nonverbal working memory was measured with two subtasks; "Block Span" and "Delayed Response". In the Block Span test, the child is asked to tap blocks in the same order as the administrator. In the Delayed Response task, a small toy is placed under one of three cups when the child is watching; he or she is then asked to indicate where the toy is hidden after a short delay (Roid, 2003). A higher score indicated better working memory function.

2.4. Covariates

We obtained information on potential confounding variables from the Medical Birth Registry of Norway (MBRN) and MoBa questionnaires that were completed during pregnancy and up to child's age three years, as well as from questionnaires administered at three and a half years of age in the ADHD Study. Potential confounders were selected *a priori* based on existing literature and were guided by directed acyclic graphs (DAGs). Potential confounders included maternal age, maternal education, maternal fish intake, parity, maternal ADHD symptoms, child sex, premature birth, birth weight, maternal BMI, maternal smoking, maternal alcohol consumption, maternal anxiety/depression and maternal iodine intake. We did not include breastfeeding/breastfeeding duration because it temporally follows exposure, and therefore cannot confound prenatal PFAS concentrations. Based on the DAGs (Fig. S1 and Fig. S2), a minimal adjustment set (the minimal selection of variables to be adjusted for in order to avoid a biased result) was suggested to include maternal age, maternal education, maternal fish intake and parity using dagitty.net to estimate the total effect (Textor et al., 2011). We also included child sex in our final models as a confounder and effect measure modifier, because of the strong association between sex and the outcomes in question, and because effects of PFAS may be sexually dimorphic (Kjeldsen and Bonefeld-Jørgensen, 2013; Mariussen, 2012). When investigating ADHD symptoms and language skills as outcomes, the child's age at testing (in months) was also included as confounders, estimated IQ and working memory scores were already age-standardized. Maternal ADHD symptoms measured by the Adult ADHD Self-Report Scale (ASRS screener) (Kessler et al., 2007), was also included as a covariate in analyses of child ADHD symptoms as outcome.

2.5. Statistical analysis

Among the seven PFASs included in our study, four of them had

missing values due to levels below the LOQ. In addition, some of the covariates had missing values. To replace missing data, we ran multiple imputation by chained equations. In our analyses, we generated 50 datasets with the exposure and outcome variables, covariates and auxiliary variables (Rubin, 1976; Sterne et al., 2009) using the mi ice command in Stata (Royston, 2008). We used the method for interval-censored data and specified upper and lower limit for imputed results for PFASs as limit of detection (LOD) and zero, respectively (Royston, 2008). In the imputation model, we included the following (% missing): PFOA (0), PFNA (0.1), PFDA (17.5), PFUnDA (13.1), PFHxS (0), PFHpS (10.6), PFOS (0), child birth year (0), maternal age (0), maternal ADHD symptoms (1.0), maternal education (2.1), parity (0) maternal fish intake (1.6), child age at testing (0.5), child sex (0), maternal folate supplement (0), and the outcome variables. Some subjects were not included in the analyses due to missing values in an outcome variable (% missing): ADHD symptoms (0.1), estimated nonverbal IQ (1.0), estimated verbal IQ (0.8), nonverbal working memory (1.1), verbal working memory (18.6), and language (4.8). The pooling procedure used in the present article was mi estimate (Stata Press, 2017).

As a first step, we performed an exploratory principal component analysis (PCA) of log-transformed PFAS variables to investigate intercorrelation among the PFASs and to extract principal components. Oblimin rotation was chosen as this allows the components to be correlated, which can be the case when it comes to PFASs, independent of whether they are sulfonates or carboxylates. Delta was set at the default of zero. We performed multivariable analyses with negative binomial regression for ADHD symptoms and generalized linear regression analyses for language skills, nonverbal working memory, verbal working memory, estimated nonverbal IQ, and estimated verbal IQ with PFAS component scores as predictors, adjusting for the other component in the analyses. To optimize interpretation, the IQ and working memory scores were standardized into z-scores. For ADHD symptoms and language skills, sum scores were used. We also fitted models that included interaction terms of child sex and PFAS. In addition, we performed a sensitivity analysis in the models with PFASs as principal components, where we only included participants who were first-born. Based on significant findings from the component models, we further investigated the dose-response relationships between levels of individual PFASs categorized into quintiles and outcome variables in separate linear regression models, with the lowest quintile as the reference group. Investigation of dose-response relationships is important as this can give information on the function shape of PFAS-neurodevelopmental outcome relationships, which will not be interpretable by associations with component scores. We also performed a sensitivity analysis in the quintile models where fish intake was excluded as a covariate.

All regression models were expressed with regression coefficient (β) and accompanying 95% confidence intervals (CIs) or p-value (Wald's test, interaction term) with significance set at $p \leq 0.05$. The number of tests in this study was considerably reduced by using principal components as predictors in the regression models instead of single PFASs. Acknowledging that the number of tests performed is still fairly high ($n = 92$) and thus inflating the probability of type 1 error, we also evaluated the results with 99% CI and $p \leq 0.01$. This would correspond to Šidák correction to control for familywise error rate (false discoveries or type I errors) for $k = 92$ number of tests calculated by $100(1-\alpha)1/k$ % confidence intervals with $\alpha = 0.05$. Statistical analyses were performed in Stata version 15 (StataCorp, 2019).

3. Results

Characteristics of the study sample are displayed in Table 1. Mothers' mean age was 30.6 years. More than one third of the mothers had higher education (college or university) and almost all the mothers were married or cohabitating. The majority did not report smoking during pregnancy and most of them were primiparous. The sex distribution among the children was near equal with 51.4% boys. The sample characteristics by clinical symptoms are shown in the supplementary material (Table S2).

Table 2 shows the PFAS distribution of our sample including the mean, median and interquartile range of maternal PFAS concentrations during pregnancy. Three of the PFASs (PFOA, PFHxS and PFOS) were above LOQ in all measurements. These three also had the highest concentrations. The correlations among the PFASs are displayed in Table 3. The PFASs could largely be explained by two principal components and this model was chosen because it effectively captured the main correlation structure among the PFASs. Component one accounted for 42% of the covariation in the PFAS data with high loadings of PFOA, PFHxS, PFHpS and PFOS (Table S3). Component two accounted for 34% of the covariation and had high loadings of PFNA, PFDA and PFUnDA (Table S3). The distribution of the outcomes in the present study is presented in Table 4 and inter-correlations between the outcome variables are presented in Table 5.

The imputed and adjusted results are presented in this article, while complete case analyses (Table S4 and Fig. S3) and crude results (Table S5 and Fig. S4) are presented in supplementary material. The regression models showed a negative association between PFAS component one (mainly explained by PFOA, PFHxS, PFHpS and PFOS) and nonverbal working memory [β = -0.08 (95% CI: -0.12, -0.03)] (Table 6). This association remained with 99% confidence intervals. Between PFAS

Table 1
Characteristics of study population in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort Study (MoBa), 2004–2008.

Characteristic	Mean ± SD or n (%)
Total N	944
Maternal age at delivery (years)	30.58 ± 4.24
Missing (*n*)	0
Child sex	
Boy	485 (51.38)
Girl	459 (48.62)
Missing (*n*)	0
Maternal education	
< College/university	219 (23.70)
College/university	705 (76.30)
Missing (*n*)	20
Maternal marital status	
Married/Cohabitant	915 (96.93)
Single/Other	29 (3.07)
Missing (*n*)	0
Parity	
0	603 (63.88)
1 or more	341 (36.12)
Missing (*n*)	0
Maternal ADHD score	2.35 ± 0.62
Missing (*n*)	9
Maternal fish intake (g/day)	26.62 ± 17.73
Missing (*n*)	15
Child year of birth	
2004	109 (11.54)
2005	239 (25.32)
2006	303 (32.10)
2007–2008	293 (31.04)
Missing (*n*)	0
Smoking during pregnancy	
No	846 (89.62)
Yes	98 (10.38)
Missing (*n*)	0
Folate supplement	
No	166
Yes*	778
Missing (*n*)	0

Abbreviations: Attention-deficit/hyperactivity disorder (ADHD), standard deviation (SD). Note: *Any folate supplements between 4 weeks before and 8 weeks after conception.

Table 2
PFAS distribution in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.

	N	% > LOQ	Mean	SD	Min	25%	50%	75%	Max
PFOA (ng/mL)	944	100%	2.61	1.18	0.33	1.77	2.50	3.21	9.81
PFNA (ng/mL)	943	99.89%	0.45	0.28	0.06	0.29	0.41	0.53	5.32
PFDA (ng/mL)	779	82.52%	0.19	0.14	0.05	0.10	0.15	0.23	1.77
PFUnDA (ng/mL)	820	86.86%	0.25	0.15	0.05	0.14	0.22	0.32	1.46
PFHxS (ng/mL)	944	100%	0.79	0.99	0.06	0.46	0.65	0.88	22.48
PFHpS (ng/mL)	844	89.41%	0.16	0.08	0.05	0.10	0.15	0.20	0.62
PFOS (ng/mL)	944	100%	12.32	5.38	2.38	8.77	11.51	14.84	42.23

Abbreviations: Perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorohexane sulfonate (PFHxS), perfluoroheptanesulfonic acid (PFHpS), perfluorooctane sulfonate (PFOS), limit of quantification (LOQ).

Table 3
Pearson correlations of PFASs in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.

	PFOA	PFNA	PFDA	PFUnDA	PFHxS	PFHpS	PFOS
PFOA	1.00						
PFNA	0.67	1.00					
PFDA	0.50	0.77	1.00				
PFUnDA	0.26	0.57	0.71	1.00			
PFHxS	0.51	0.42	0.31	0.30	1.00		
PFHpS	0.64	0.47	0.39	0.32	0.61	1.00	
PFOS	0.62	0.51	0.44	0.42	0.54	0.80	1.00

Note: Correlation color coding goes from strong (green) to medium (yellow) and weak (red).

Table 4
Outcome distribution in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.

	N	Mean	SD	Range
ADHD symptoms	943	5.54	6.10	0, 33
Language skills	899	49.31	7.02	15, 58
Nonverbal working memory	934	10.40	2.80	2, 17
Verbal working memory	768	7.60	1.91	5, 13
Nonverbal IQ	935	10.97	2.03	5, 18
Verbal IQ	936	9.72	2.11	2, 16

Note: Unscaled outcome variables. Abbreviation: Standard deviation (SD).

component two (mainly explained by PFNA, PFDA and PFUnDA) and verbal working memory there was a positive association [β = 0.07 (95% CI: 0.01, 0.12)] (Table 6). In the interaction models, we found effect modification by child sex (p = 0.01) for PFAS component two (PFNA, PFDA and PFUnDA) and verbal working memory. There was a stronger association in boys [β = 0.13 (95% CI: 0.06, 0.20)] compared to girls [β = 0.01 (95% CI: -0.06, 0.07)]. Among the girls, the confidence intervals contained the null (Table 6). The association for boys remained with 99% CI.

PFAS components were not associated with ADHD symptoms, language skills or estimated IQ (Tables 7 and 8). For ADHD symptoms, language skills, estimated IQ and nonverbal working memory, we observed no effect modification and no difference in the associations of PFAS component one and two by child sex (Tables 6–8).

The results from the sensitivity analysis, where we restricted our sample to first-born children, were fairly similar to the main analyses (Table S6). However, the association between component two (PFNA, PFDA and PFUnDA) and verbal working memory did not remain in the restricted models (Table S6).

We investigated dose-response relationships of significant relationships identified in the PFAS component models, using individual PFASs categorized into quintiles. For PFOA, PFHpS and PFOS there appeared to be a monotonic dose-dependent decrease in nonverbal working memory, however, only the fifth (highest) quintiles were significant; PFOA [β = -0.38 (95% CI: -0.61, -0.15)], PFHpS [β = -0.37 (95% CI: -0.58, -0.15)] and PFOS [β = -0.26 (95% CI: -0.47, -0.05)] (Fig. 2). A somewhat similar dose-response trend was observed for PFNA. In addition, there were negative associations between nonverbal working memory and the fourth quintile of PFHxS and the third quintile of PFNA (Fig. 2). The associations between PFOA and PFHpS with nonverbal working memory were also significant at 99% CI.

Quintile regression models with verbal working memory as outcome variable showed positive associations for the fifth quintiles of PFNA [β = 0.34 (95% CI: 0.10, 0.57)], PFDA [β = 0.32 (95% CI: 0.09, 0.55] and PFUnDA [β = 0.29 (95% CI: 0.05, 0.52)] (Fig. 3). In addition, there was a positive association between the third quintile of PFOA and verbal working memory (Fig. 3). With 99% CI, the associations with PFNA and PFDA remained. Excluding fish intake as a covariate in the sensitivity analyses did not change the association between PFASs and nonverbal and verbal working memory (Fig. S5).

Table 5
Pearson correlations of outcome variables in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.

	ADHD symptoms	Language	Nonverbal IQ	Verbal IQ	Nonverbal WM	Verbal WM
ADHD symptoms	1.00					
Language	0.15	1.00				
Nonverbal IQ	-0.01	0.04	1.00			
Verbal IQ	0.09	0.23	0.10	1.00		
Nonverbal WM	0.15	0.12	0.02	0.22	1.00	
Verbal WM	0.06	0.16	0.02	0.26	0.13	1.00

Note: The variable ADHD symptoms is flipped. Correlation color coding goes from strong (green) to medium (yellow) and weak (red).

Table 6
Beta coefficients and 95% confidence intervals of adjusted regression models between PFAS components and working memory and interaction by child sex in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.

PFAS components	Nonverbal working memory (n = 934)			Verbal working memory (n = 768)		
	All	Interaction term p = 0.863		All	Interaction term p = 0.105	
		Boys	Girls		Boys	Girls
Component 1: PFOA, PFHxS, PFHpS, PFOS	−0.08 (−0.12, −0.03)*	−0.08 (−0.14, −0.02)	−0.07 (−0.14, −0.01)	−0.01 (−0.06, 0.04)	0.02 (−0.04, 0.09)	−0.04 (−0.11, 0.02)
		Interaction term p = 0.662			Interaction term p = 0.012*	
Component 2: PFNA, PFDA, PFUnDA	0.03 (−0.02, 0.08)	0.02 (−0.05, 0.09)	0.04 (−0.03, 0.10)	0.07 (0.01, 0.12)	0.13 (0.06, 0.20)*	0.01 (−0.06, 0.08)

Note: A separate linear regression model (with multiple imputation) was conducted for each outcome with additional interaction analyses. The following PFASs most heavily loaded on component 1: PFHpS, PFOS, PFHxS and PFOA. The following PFASs most heavily loaded on component 2: PFDA, PFNA and PFUnDA. The PFASs were log transformed before computing principal components. Each regression model was adjusted for maternal education, age, parity, fish intake and child sex. Interaction term was tested with Wald's test. *Indicates significant results with 99% CIs.

4. Discussion

4.1. Main findings of the study

In the present study, we investigated the influence of prenatal exposure to seven PFASs (measured in maternal plasma in week 17 of pregnancy) on ADHD symptoms and cognitive functions in preschool children. With a sample of 944 mother-child pairs, this is one of the largest studies examining these exposure and outcome associations. In addition, few other studies have conducted neuropsychological tests of young preschool children in this particular research context. We accounted for the joint action of inter-correlated PFASs by extracting two principal components explaining 76% of the covariation in the PFAS data. Then we used component scores for component one and two as predictors in multivariable regression models with neurodevelopmental outcome variables. The results showed a negative association between component one (mainly explained by PFOA, PFHxS, PFHpS and PFOS) and nonverbal working memory. In quintile regression models, the individual PFASs of component one indicated a monotonic-like decrease in nonverbal working memory with increasing PFAS concentrations. Between PFAS component two (mainly explained by PFNA, PFDA and PFUnDA) and verbal working memory, there was a positive association. Quintile regression models with individual PFASs and working memory indicated some linear dose-response, but the relationships were both positive and negative, which complicates interpretation of these findings. There were no associations between PFAS components and ADHD symptoms, language skills or estimated IQ. Except for the weak negative associations between PFASs in component one, we did not find consistent evidence to suggest that prenatal exposure to PFASs is associated with ADHD symptoms or cognitive dysfunctions among preschool children.

4.2. Verbal and nonverbal working memory

In our study, we found some weak associations between PFAS components and working memory. Quintile models with individual PFAS concentrations and working memory were largely in agreement with the factor models. This also indicated that the use of PCA to reduce number of exposure variables was reasonable in this research context. However, we found results that were both positive (verbal working memory) and negative (nonverbal working memory), meaning that no clear pattern emerged. We found negative associations between nonverbal working memory and component one (PFOA, PFHxS, PFHpS and PFOS), where higher PFAS levels were associated with decreasing scores of nonverbal working memory. In the quintile models, the respective PFASs, in addition to PFNA, showed a similar pattern. Furthermore, there were indications of negative monotonic dose-response relationships for several of the PFASs (PFOS, PFOA and PFHpS), although only the fifth quintiles were significant. The associations between PFASs and nonverbal working memory appear to be somewhat novel, as few studies have investigated these particular exposure-outcome associations. Still, our results are partly in line with a study from the USA that analyzed exposure to prenatal PFASs and cognitive functions in children at the ages of five and eight years (Vuong et al., 2016).

Table 7
Beta coefficients and 95% confidence intervals of adjusted regression models between PFAS components and ADHD symptoms and language skills and interaction by child sex in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.

PFAS components	ADHD symptoms (n = 943)			Language skills (n = 899)		
	All	Interaction term p = 0.212		All	Interaction term p = 0.078	
		Boys	Girls		Boys	Girls
Component 1: PFOA, PFHxS, PFHpS, PFOS	−0.01 (−0.07, 0.05)	−0.04 (−0.11, 0.03)	0.02 (−0.06, 0.09)	−0.09 (−0.42, 0.24)	0.12 (−0.29, 0.53)	−0.34 (−0.77, 0.09)
		Interaction term p = 0.526			Interaction term p = 0.024	
Component 2: PFNA, PFDA, PFUnDA	−0.00 (−0.06, 0.06)	−0.02 (−0.09, 0.06)	0.01 (−0.06, 0.09)	0.08 (−0.28, 0.43)	0.42 (−0.04, 0.89)	−0.24 (−0.69, 0.21)

Note: A separate regression model (with multiple imputation) was conducted for each outcome: negative binomial regression for ADHD symptoms and linear regression for language skills with additional interaction analyses. The following PFASs most heavily loaded on component 1: PFHpS, PFOS, PFHxS and PFOA. The following PFASs most heavily loaded on component 2: PFDA, PFNA and PFUnDA. The PFASs were log transformed before computing principal components. Each regression model was adjusted for maternal education, age, parity, fish intake, child sex and child age at testing. Child ADHD symptoms was adjusted for maternal ADHD symptoms. Interaction term was tested with Wald's test.

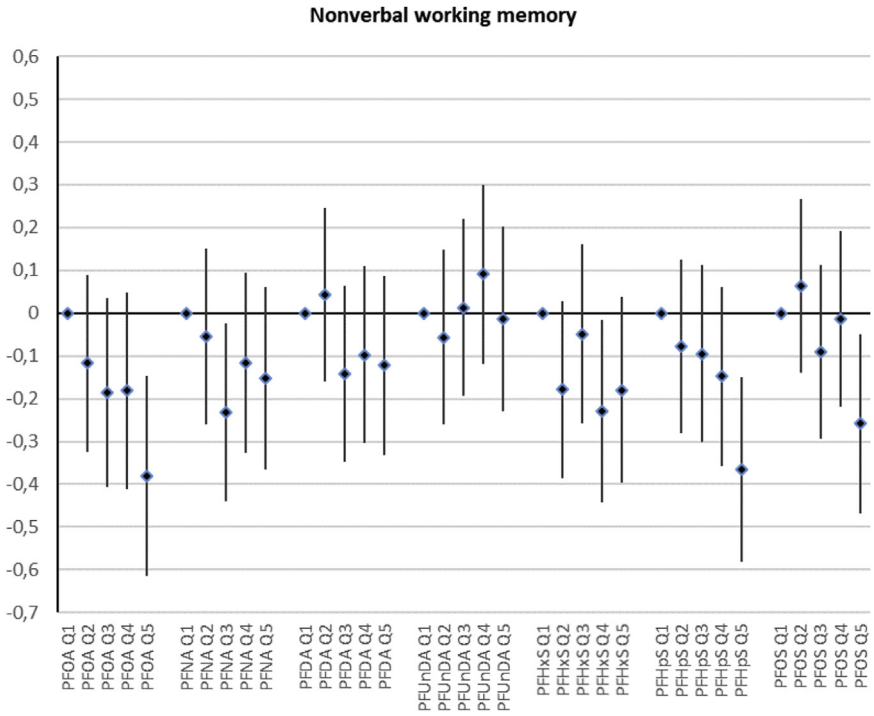
Table 8
Beta coefficients and 95% confidence intervals of adjusted regression models between PFAS components and estimated IQ and interaction by child sex in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.

PFAS components	Nonverbal IQ (n = 935)			Verbal IQ (n = 936)		
	All	Interaction term p = 0.876		All	Interaction term p = 0.701	
		Boys	Girls		Boys	Girls
Component 1: PFOA, PFHxS, PFHpS, PFOS	0.00 (−0.05, 0.05)	0.00 (−0.05, 0.06)	−0.00 (−0.06, 0.06)	−0.02 (−0.07, 0.03)	−0.01 (−0.07, 0.04)	−0.03 (−0.09, 0.03)
		Interaction term p = 0.658			Interaction term p = 0.619	
Component 2: PFNA, PFDA, PFUnDA	−0.04 (−0.09, 0.01)	−0.03 (−0.10, 0.03)	−0.05 (−0.12, 0.01)	0.03 (−0.02, 0.08)	0.04 (−0.02, 0.11)	0.02 (−0.04, 0.09)

Note: A separate linear regression model (with multiple imputation) was conducted for each outcome with additional interaction analyses. The following PFASs most heavily loaded on component 1: PFHpS, PFOS, PFHxS and PFOA. The following PFASs most heavily loaded on component 2: PFDA, PFNA and PFUnDA. The PFASs were log transformed before computing principal components. Each regression model was adjusted for maternal education, age, parity, fish intake and child sex. Interaction term was tested with Wald's test.

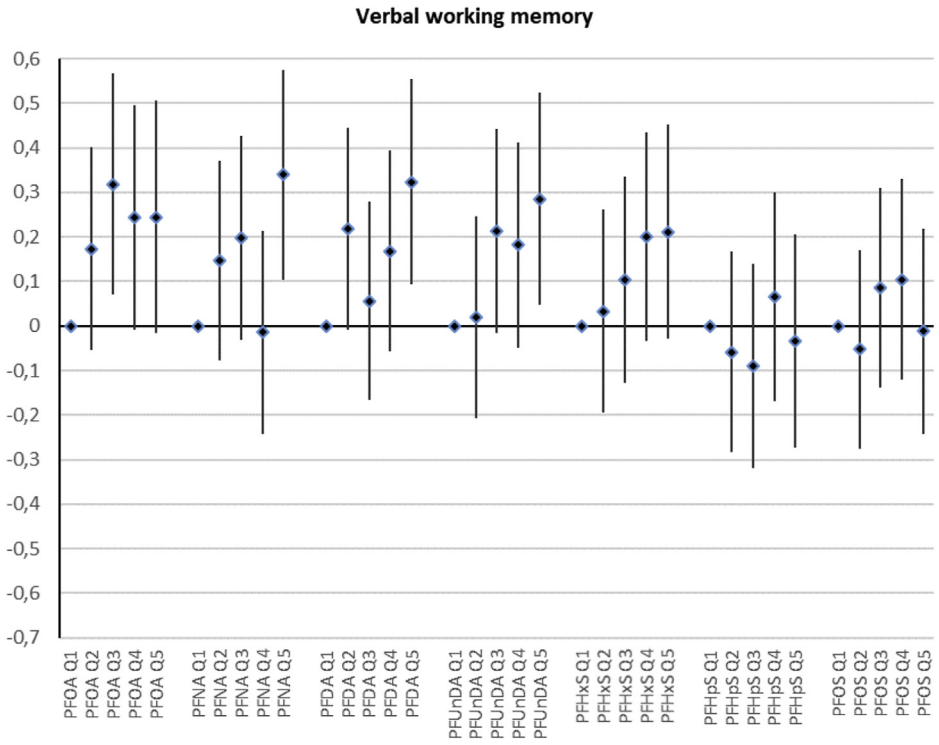
This study reported an association between increased levels of prenatal PFOS and impaired metacognition [β = 3.10 (95% CI: 0.62, 5.58)], which is dependent on multiple executive functions, such as working memory. However, there were no associations with the other investigated PFASs (PFOA, PFNA, PFHxS and PFDeA) and the sample size was quite small (n = 218) (Vuong et al., 2016).

Our study showed positive associations between verbal working memory and PFAS component two (PFNA, PFDA and PFUnDA) and the respective, individual PFAS quintiles, in addition to PFOA. Nevertheless, positive associations between PFASs and cognitive functions, such as language, IQ and memory have also been reported in other studies (e.g. Jeddy et al., 2017; Liew et al., 2018b; Stein et al., 2013; Vuong et al., 2019). Like our results, a recent study, reported positive associations between working memory and increases in prenatal levels of PFOA and PFNA (Vuong et al., 2019). That study used Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and assessed children at the age of 8 years (Vuong et al., 2019). A cohort study from the USA, investigating prenatal PFAS exposure and cognitive functions, reported both better and worse cognitive performance associated with prenatal PFAS exposure in three- and seven-year-olds (Harris et al., 2018). A possible mechanism behind the positive associations could be a result of PFASs that activate peroxisome



Note: Each PFAS by nonverbal working memory was modelled using a separate linear regression (with multiple imputation). The beta coefficient and 95% confidence intervals for each PFAS quintile are represented on the vertical axis (the reference level is the first quintile). Each regression model was adjusted for maternal education, age, parity, fish intake and child sex. Higher working memory score indicates better working memory function. Significant with 99% CIs: fifth quintiles of PFOA and PFHpS.

Fig. 2. Beta coefficients and 95% confidence intervals for regression models predicting nonverbal working memory (n = 934) from quintile categories of each PFAS in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.



Note: Each PFAS by verbal working memory was modelled using a separate linear regression (with multiple imputation). The beta coefficient and 95% confidence intervals for each PFAS quintile are represented on the vertical axis (the reference level is the first quintile). Each regression model was adjusted for maternal education, age, parity, fish intake and child sex. Higher working memory score indicates better working memory function. Significant with 99% CIs: fifth quintiles of PFNA and PFDA.

Fig. 3. Beta coefficients and 95% confidence intervals for regression models predicting verbal working memory (n = 768) from quintile categories of each PFAS in a nested study of attention-deficit/hyperactivity disorder in The Norwegian Mother, Father and Child Cohort (MoBa), 2004–2008.

proliferator-activated receptors (PPARs) alpha and gamma, which have neuroprotective and central-nervous-system anti-inflammatory properties (Quaak et al., 2016; Stein et al., 2013). Research on working memory and prenatal PFAS exposure is scarce, and the results so far have been unclear and inconsistent. Our study showed some potential effects, especially for nonverbal working memory that needs to be replicated.

4.3. ADHD symptoms

In our study, we did not find any significant associations between PFAS exposure and ADHD symptoms, which is in line with other studies that have investigated ADHD symptoms as outcomes (Fei and Olsen, 2011; Quaak et al., 2016) as well as studies with ADHD diagnosis in children (Liew et al., 2015; Ode et al., 2014; Strøm et al., 2014). However, some studies have reported inverse relationships between prenatal PFAS exposure and ADHD symptoms or diagnosis (Lien et al., 2016; Liew et al., 2015; Stein et al., 2013; Vuong et al., 2018), although they concluded that there is a lack of evidence to support these associations. Contrary to our findings, birth cohort studies from Greenland, Ukraine and Poland found that increasing levels of PFOA in maternal blood during pregnancy was associated with increasing levels of hyperactivity in children between the ages of seven and nine [odds ratio = 3.1 (95% CI: 1.3, 7.2)] (Høyer et al., 2015). Furthermore, a recent study using data from these cohorts reported that increasing prenatal exposure to PFNA [odds ratio = 1.8 (95% CI: 1.0, 3.2) and PFDA [odds ratio = 1.7 (95% CI: 1.0, 3.1)] was associated with increasing hyperactivity symptoms in children between five and nine years in Greenland and Ukraine (Høyer et al., 2018). However, the authors did not rule out that it could be spurious findings (Høyer et al., 2018). Additionally, a cohort study from the Faroe Islands found significant positive associations between increasing levels of postnatal PFOA, PFNA, and PFDA and more hyperactivity/inattention problems among seven-year-olds, but not with prenatal PFAS exposure (Oulhote et al., 2016). Taken together, there remain uncertainties regarding the effect of prenatal PFAS exposure on ADHD symptoms and diagnosis, although most studies, like ours, have reported lack of associations.

4.4. Language skills

In accordance with our results, two other studies did not find associations between PFASs and language among two-year-olds and children between six and 12, respectively (Chen et al., 2013; Stein et al., 2013). Both of these studies had quite small sample sizes (n = 239 and n = 320 respectively). A larger study (n = 631 to 971), examining children at age three and seven and language comprehension, found only associations between one type of PFAS; 2-(N-methyl-perfluorooctane sulfonamido) acetate (MeFOSAA), but not the other seven PFASs (Harris et al., 2018). In that study, the second quartile of MeFOSAA was associated with higher receptive vocabulary scores (Harris et al., 2018). Other studies have reported positive relationships. A small study, examining prenatal PFAS exposure and reading ability among children at age five and eight, reported that increasing levels of PFOA, PFNA and PFOS were associated with improved reading skills at five years and at eight years of age (Zhang et al., 2018). Likewise, a study exploring early communication development among children at the ages of 15 and 38 months found both positive and negative associations between various prenatal PFASs and communication development among girls (Jeddy et al., 2017). The authors did point out that the results showed an inconsistent pattern of association across the

measured PFASs (Jeddy et al., 2017). Regarding language skills, there is limited knowledge about potential effects of prenatal PFAS exposure. In line with previous studies, we also report lacking associations.

4.5. Estimated verbal and nonverbal IQ

Our results showed no association between prenatal PFAS exposure and estimated IQ, neither verbal nor nonverbal. A large study (n = 1592) using data from the Danish National Birth Cohort found no associations between prenatal PFAS levels and IQ (full-scale, verbal and nonverbal) in their total sample, but some inconsistent associations in sex-stratified quartile analyses (Liew et al., 2018b). They concluded that overall, there was no evidence of an effect from prenatal PFAS on IQ in their study sample (Liew et al., 2018b). One study found associations between higher PFUnDA and lower nonverbal IQ at age five and higher PFNA levels with lower verbal IQ at age eight (Wang et al., 2015), however, the sample size was quite small (n = 120). In contrast, some studies have found positive associations between PFAS exposure and IQ measures (e.g. Harris et al., 2018; Stein et al., 2013; Vuong et al., 2019). A study that assessed children between six and 12 years of age reported that elevated PFOA levels was associated with improved full-scale IQ score (Stein et al., 2013). The study had a fairly small sample size (n = 320) and the authors concluded that the positive associations were imprecise and inconsistent (Stein et al., 2013). Likewise, a larger study (n = 631 to 971) found that higher prenatal levels of PFOS were associated with better nonverbal IQ among seven-year-olds (Harris et al., 2018). Furthermore, a recent study found associations between increases in child PFNA concentrations and full scale IQ and perceptual reasoning (Vuong et al., 2019). Altogether, our study and the varied results from relatively few studies indicate no association between prenatal PFAS exposure and child IQ.

4.6. Sex specific effects

Our results suggest effect modification by child sex, where the positive association between component two (PFNA, PFDA and PFUnDA) and verbal working memory were mainly driven by boys. Other studies that are comparable to our study have examined effect modification by child sex, although none of them utilized the same sub-task from Stanford Binet as herein. Most of them report no effect modification (Harris et al., 2018; Høyer et al., 2015, 2018; Liew et al., 2015; Stein et al., 2013; Strøm et al., 2014). Still, one study that examined ADHD symptoms and prenatal PFAS exposure found different results by child sex; some associations were stronger for boys and some were stronger for girls depending on the specific PFAS investigated (Lien et al., 2016). In addition, three studies examining different cognitive or behavioral measures in children in the same cohort, report effect modification by child sex in some of the associations between prenatal and postnatal PFAS exposure and these outcomes (Vuong et al., 2016, 2018, 2019). The mechanistic underpinnings of these observed sex differences is a relatively unexplored area. It could be linked to sex-specific differences in toxicokinetics of PFASs and that PFASs have the potential to disrupt sex hormone homeostasis (Kjeldsen and Bonefeld-Jørgensen, 2013; Mariussen, 2012). A later cognitive development among boys compared to girls could also contribute to the observed difference in boys and girls.

4.7. Dose-response relationships and potential mechanisms

Our findings are in accordance with previous epidemiologic literature showing lack of associations and some inconclusive effects between prenatal PFAS exposure and adverse neurodevelopment. Although the reported associations in our sample are weak and difficult to interpret as clinically meaningful, these associations could be stronger and clearer in other populations where PFAS exposure levels are higher and with larger variability in the outcomes. Reasons for these inconsistencies across studies could be difference in PFAS exposure levels and patterns as well as timing of PFAS measurements during pregnancy. They could also be due to differences in study design and methodology. Another possible reason for the few significant results could be that exposure concentrations are below levels or at the threshold of neurodevelopmental toxicity, as indicated by our findings mainly in the group of highest PFAS exposure compared to the lowest group in the quintile models. This could indicate a dose-response relationship and that our population is in the lower part of this curve, while the top 20% of those with the highest PFAS exposure *in utero* could be at risk of adverse outcomes. Indeed, for some of the associations between the PFASs and nonverbal working memory, there were indications of negative linear dose-response trends in the quintile models, with a monotonic decrease of nonverbal working memory scores as the PFASs increased. Compared with previous studies of prenatal exposure and neurodevelopmental outcomes in children (e.g. Harris et al., 2018; Høyer et al., 2015; Liew et al., 2018b; Oulhote et al., 2016), the concentration levels of PFASs are generally lower in the present study. However, results from a study comparing PFAS levels in several European cohort studies showed that the PFAS levels (PFOA, PFNA, PFUnDA, PFHxS and PFOS) in a sample of pregnant women from the Norwegian MoBa cohort are equal or higher compared to the other cohorts (Haug et al., 2018). The levels reported from the MoBa sample in that study (Haug et al., 2018) are similar to the levels in the present sample.

It appears that effects of PFASs on neurodevelopment found in experimental rodent studies are not easily replicated in human studies. Experimental animal studies have shown that PFASs may be developmentally neurotoxic and endocrine disruptive and that PFAS exposure during critical phases of gestation can affect brain development (Johansson et al., 2008, 2009; Lau et al., 2003; Long et al., 2019; Mariussen, 2012). Mechanistic studies indicate that exposure to PFASs may potentially affect important factors or regulators of brain development such as the thyroid hormone system, calcium homeostasis, protein kinase C, synaptic plasticity, and cellular differentiation (Liew et al., 2018a; Mariussen, 2012). Findings from animal studies show that PFAS exposure may be connected to memory, learning and neuro-motor development and the results indicate that the critical windows of exposure are during early brain development (Mariussen, 2012). However, the exposure levels in animal studies are often higher than in human populations and the contaminants have shorter half-lives in for example rodents compared to humans (Fei and Olsen, 2011; Mariussen, 2012). The higher doses that the animals are exposed to, can cause other detrimental effects like increased mortality and birth defects (Mariussen, 2012). The real-life exposure scenario for the human fetus consists of a range of highly inter-correlated PFASs and other toxicants that can interfere with brain development in combination (Mariussen, 2012; Quaak et al., 2016). Species-specific differences in sensitivity of the various stages of brain development and ability to eliminate compounds in relation to the exposure timing and level, may in part explain these inconsistent findings in experimental versus epidemiological studies. In addition, it could be that only noticeable effects from prenatal PFAS exposure appear when the child is older and their cognitive functions are more developed.

4.8. Study limitations and strengths

Limitations to our study include potential selection bias. The participant rate in the MoBa cohort was 41%, and it was 35% for the clinical assessments of the ADHD Study. The participants in MoBa and the sub studies are in general older, have higher educational level and a healthier lifestyle compared with the general population (Nilsen et al., 2009). This might have led to underrepresentation of children with a higher exposure to risk factors or less variability of the cognitive test scores. Furthermore, since most participants in the ADHD Study were recruited based on high scores on ADHD-related symptoms, it is a

selected group and our study sample thus has more symptoms than a general child population. Another limitation is that we could not account for variation in maternal glomerular filtration rate (GFR), which may be a source of residual bias in our study. GFR influences the urinary excretion of PFASs, which can lead to the appearance of higher PFAS levels among people with lower GFR (Verner et al., 2015). Low GFR during pregnancy has also been associated with lower birthweights (Gibson, 1973; Morken et al., 2014), and lower birthweights with subsequent ADHD symptoms (Lim et al., 2018; Momany et al., 2018). Thus, the potential exists for residual confounding by GFR, which should be addressed in future studies. In addition, interactions between the outcome measures could impact the results, as interactions between ADHD symptoms and estimated IQ with language skills have been reported in another study using data from the ADHD Study (Rohrer-Baumgartner et al., 2014). It should be noted that the estimated nonverbal IQ measure employed in the present study were not significantly related to any of the other included variables (in the expected direction) in the full ADHD Study sample (data not presented). We cannot rule out the possibility that a considerable amount of random error in this variable has cancelled out potential associations between estimated nonverbal IQ and exposure to PFASs. Furthermore, participants with delayed language development were sampled to other sub studies in MoBa, meaning that our language measure is not very discriminative. Hence, regardless of our null findings, this does not prevent detection of associations between PFASs and language related outcomes in other studies.

Our study also has several strengths. Particularly, the use of clinical tests performed by specialized clinicians is a major advantage. In addition, we had a large sample size of 944 mother-child pairs, as well as a nearly equal sex distribution, meaning that we were able to explore potential sex-specific effects, which are lacking in several studies. Further, we investigated PFAS levels as principal components, which allowed us to investigate possible joint influence of correlated PFASs mutually adjusted for the other component. PCA is also a way to reduce the number of tests. To our knowledge, investigating prenatal PFAS exposure and ADHD symptoms with neuropsychological tests among preschoolers has not been done before. We also had the benefit of a large number of relevant covariates collected prospectively during pregnancy, in order to account for residual confounding pathways. Although certain other covariates, such as breastfeeding duration, may influence postnatal exposure and/or neurodevelopmental outcomes through other pathways, since breastfeeding occurs temporally after prenatal exposure, it could not confound prenatal estimates. Other studies have been conducted in MoBa to assess the neurodevelopmental impact of postnatal PFAS exposure (Forns et al., 2015; Lenters et al., 2019), however these studies have not considered prenatal exposure.

5. Conclusion

Based on our results, we did not find consistent evidence to conclude that prenatal exposure to PFASs are associated with ADHD symptoms or cognitive dysfunctions in preschool children aged three and a half years, which is in line with the majority of studies in this area. Our results did however, show some weak negative associations between PFASs and nonverbal working memory, we also observed weak positive relationships with verbal working memory. As exposure to PFASs can be high among small children, more studies measuring both postnatal and prenatal exposure to PFASs with regard to neurodevelopment and cognitive functioning, including measures of working memory, should be performed in future studies. Further studies should also investigate combined effects of the exposed PFAS mixture as well as together with other environmental contaminants. Additionally, there is an imminent need for studies investigating underlying mechanisms linking PFAS exposure to the suspected adverse effects on human brain development.

Declaration of competing interest

None.

Acknowledgements

This research was funded by the Research Council of Norway (MILJØFORSK, project no. 267984/E50 “NeuroTox”), National Institutes of Health (NIH) R01ES021777, and National Institute of Environmental Health Sciences (NIEHS) P30 ES010126. The ADHD Study, from which the present data were drawn, was supported by funds and grants from the Norwegian Ministry of Health, the Norwegian Health Directorate, the South-Eastern Health Region, G&PJ Sorensen Fund for Scientific Research, and from the Norwegian Resource Centre for ADHD, Tourette syndrome and Narcolepsy. The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research, NIH, and National Institute of Neurological Disorders and Stroke (NINDS) (grant no.1 UO1 NS 047537-01 and grant no.2 UO1 NS 047537-06A1). We are grateful to all the participating families in Norway who take part in this on-going cohort study, and to the staff of the ADHD Study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.10.003.

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