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Permalink

https://escholarship.org/uc/item/6wn0h8dg

Journal

Environmental Health Perspectives, 128(5)

ISSN

1542-4359

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Publication Date

2020-05-01

DOI

10.1289/ehp5444

Peer reviewed

Early Life Exposure to Perfluoroalkyl Substances (PFAS) and ADHD: A Meta-Analysis of Nine European Population-Based Studies

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INTRODUCTION: To date, the evidence for an association between perfluoroalkyl substances (PFAS) exposure and attention deficit and hyperactivity disorder (ADHD) is inconclusive.

OBJECTIVE: We investigated the association between early life exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), and ADHD in a collaborative study including nine European population-based studies, encompassing 4,826 mother–child pairs.

METHODS: Concentrations of PFOS and PFOA were measured in maternal serum/plasma during pregnancy, or in breast milk, with different timing of sample collection in each cohort. We used a validated pharmacokinetic model of pregnancy and lactation to estimate concentrations of PFOS and PFOA in children at birth and at 3, 6, 12, and 24 months of age. We classified ADHD using recommended cutoff points for each instrument used to derive symptoms scores. We used multiple imputation for missing covariates, logistic regression to model the association between PFAS exposure and ADHD in each study, and combined all adjusted study-specific effect estimates using random-effects meta-analysis.

RESULTS: A total of 399 children were classified as having ADHD, with a prevalence ranging from 2.3% to 7.3% in the studies. Early life exposure to PFOS or PFOA was not associated with ADHD during childhood [odds ratios (ORs) ranging from 0.96 (95% CI: 0.87, 1.06) to 1.02 (95% CI: 0.93, 1.11)]. Results from stratified models suggest potential differential effects of PFAS related to child sex and maternal education.

CONCLUSION: We did not identify an increased prevalence of ADHD in association with early life exposure to PFOS and PFOA. However, stratified analyses suggest that there may be an increased prevalence of ADHD in association with PFAS exposure in girls, in children from nulliparous women, and in children from low-educated mothers, all of which warrant further exploration. https://doi.org/10.1289/EHP5444

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder during childhood. The global

prevalence of ADHD in the population younger than 18 years of age has been estimated to have increased from 5.3% (Polanczyk et al. 2007) to 7.2% (Thomas et al. 2015). The use of ADHD medication among children in Asia, Australia, North America, and Europe has also increased (Raman et al. 2018). Whether ADHD is under- or overdiagnosed, however, remains under debate. Some environmental factors, as well as potential gene–environment interactions, may be related to the onset and contribute to an exacerbation of ADHD symptoms (Nigg et al. 2010; Polańska et al. 2012).

Perfluoroalkyl substances (PFASs) is a class of manufactured persistent organic chemicals with an extremely stable structure. These environmental pollutants are detected in human biological samples worldwide, with higher concentrations in populations in industrialized and urbanized areas (Houde et al. 2006) as well as in Nordic populations, including those in nonurbanized areas (Jørgensen et al. 2014). The most frequently detected PFASs in humans and biota are perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). Both compounds have a biological half-

life on the order of years in humans (Worley et al. 2017). Main sources for PFAS are contaminated drinking water (Sunderland et al. 2019), diet (particularly, fish consumption) (Papadopoulou et al. 2019), indoor air, dust, and consumer products including food packaging, outdoor gear, nonstick pan coatings, and fire extinguishers (Calafat et al. 2007). PFASs bind to serum proteins, particularly albumin (Han et al. 2003; Jones et al. 2003). PFASs may pass from mother to child through the placenta (Manzano-Salgado et al. 2015) and through breast milk (Mogensen et al. 2015).

PFASs are proposed developmental neurotoxicants (Grandjean and Landrigan 2014), yet the literature on PFAS exposure and ADHD is inconsistent (Liew et al. 2018). Some studies reported an association between higher PFAS concentrations and ADHD (Gump et al. 2011; Hoffman et al. 2010; Høyer et al. 2015; Stein and Savitz 2011) whereas some others did not find such associations (Lien et al. 2016; Liew et al. 2015; Ode et al. 2014; Strøm et al. 2014).

Moreover, a total of four studies reported sex-specific associations, with girls having higher prevalence of ADHD than boys in association with PFASs (Lenters et al. 2019; Oulhote et al. 2016; Quaak et al. 2016; Stein et al. 2014).

In summary, results suggestive of a higher prevalence of ADHD in association with PFAS exposure mostly come from cross-sectional studies (Gump et al. 2011; Hoffman et al. 2010) with the potential for reverse causation. The evidence from prospective studies is inconsistent, with some studies reporting positive (Høyer et al. 2015) and some null results (Lien et al. 2016). Thus, a large study providing variation in exposure range with exposure assessment during periods of brain development is needed. A large study population with a higher number of cases also allows for the study of the possible sex-specific associations reported in some of the previous studies. Therefore, we pooled data from nine European population-based studies to investigate the association between PFOS and PFOA levels from birth to 24 months of age and ADHD in childhood. Because biological samples used to assess exposure differed across studies in terms of sample type (maternal serum/plasma and breast milk) and timing of sample collection (first trimester, delivery), and because children's levels during the first 24 months of life were unavailable, we used a validated pharmacokinetic model of pregnancy and lactation to estimate pre- and postnatal concentrations of PFASs in children (Verner et al. 2016).

Methods

Description of the European Population-Based Studies

We selected European population-based studies (hereafter referred to as studies) with available information on PFAS and ADHD, using two online inventories (https://www.enrieco.org and https://www.birthcohorts.net). Twelve of these studies agreed to participate: INUENDO-Greenland, INUENDO-Poland, and INUENDO-Ukraine (Toft et al. 2005); Duisburg (Germany) (Wittsiepe et al. 2008); polychorinated biphenyl (PCB) cohort (Slovakia) (Hertz-Picciotto et al. 2003); Human Milk Study (HUMIS; Norway) (Eggesbø et al. 2009); Danish National Birth Cohort 7-y cohort (DNBC), which is a random subset of all 1,400 children from the 7-y follow-up cohort (Fei and Olsen 2011); DNBC-FETOTOX (FETOTOX), a nested case–cohort sample that randomly selected 220 ADHD cases and 550 controls from the source population, and because of these random sampling procedures, 21 children from the DNBC were randomly selected again by chance in FETOTOX (20 controls and 1 ADHD case) (Liew et al. 2015); and Infancia y Medio Ambiente (INMA)-Valencia, INMA-Sabadell and INMA-Gipuzkoa (Spain) (Guxens et al. 2012).

The participants were restricted to live-born singleton births with data on concentrations of PFOS and/or PFOA, measured either in maternal serum/plasma or breast milk and available information on ADHD diagnosis or symptoms. The INUENDO-Poland cohort and the Duisburg cohort were originally included in the study but were excluded before statistical analysis owing to the low number of participants with complete information on ADHD and PFAS concentrations ($n = 69$ and 44, respectively). In total, the study sample encompassed 4,826 mother–child pairs from nine European population-based studies. Ethical approval was obtained from the local authorized institutional review boards. Informed consent was obtained from all participants.

Exposure Assessment

PFOS and PFOA concentrations were measured in maternal serum/plasma in INUENDO-Greenland, INUNEDO-Ukraine, INMA-Valencia, INMA-Sabadell, INMA-Gipuzkoa, DNBC, and FETOTOX and in breast milk in HUMIS and the PCB cohort (see Table S1). The percentage of values above the limit of detection (LOD)/quantification (LOQ) was 100% in almost all cohorts (see Table S1). We replaced concentrations below the LOD/LOQ (i.e., of PFOS in the PCB cohort and of PFOA in HUMIS and the PCB cohort) with a uniform randomly generated number between 0 and the analysis-specific limit reported from the laboratories.

We used a validated pharmacokinetic model to harmonize exposure metrics across studies and to generate estimates of postnatal PFOS and PFOA levels in the children at each month from birth until 24 months of age (Verner et al. 2016). Briefly, this two-compartment model (the mother and the fetus/child) allowed for simulation of lifetime exposure in the mother, placental transfer during pregnancy, and transfer through breastfeeding. Maternal doses were assumed to be fully absorbed and distributed based on estimated volumes of distribution. Placental transfer was parameterized based on published concentration ratios from paired maternal and cord serum measurements. Lactational transfer was calculated based on age- and body weight-dependent estimates of breast milk consumption and published milk:plasma partition coefficients. To simulate concentrations for each study dyad, the pharmacokinetic model used individual-specific information (child weight at each time point and sex, maternal age at delivery, pre-pregnancy maternal weight, duration of exclusive and total breastfeeding, sample type, and timing of sample collection) and measured PFOS and PFOA levels. Using this approach, the model was previously validated against longitudinal measurements from two studies not included in the current study (Fromme et al. 2010; Granum et al. 2013), and in regression models of simulated vs. measured children's levels at 6 and 36 months of age, the coefficients of determination (R^2) ranged from 0.50 to 0.62.

ADHD Assessment

The studies used health registries or questionnaires to assess ADHD (Table 1). In the HUMIS cohort, information on ADHD was obtained from the Norwegian Patient Registry (Surén et al. 2012), which contains diagnoses of ADHD up to August 2014, when the children's mean and median age was 10 y (range: 6–12 y). The FETOTOX sample identified ADHD cases from the Danish National Hospital Registry (Andersen et al. 1999) and the Danish Psychiatric Central Registry (Munk-Jørgensen et al. 1993) when the children's mean age was 10.7 y. The controls (440 boys and 110 girls) were randomly selected from the source population and frequency-matched to cases by sex. The source population was 42,737 boys and 40,652 girls in the DNBC with a prenatal blood sample available and mothers who had completed the first telephone interview (Liew et al. 2015).

Table 1. Outcome description in the study samples from the participating studies.

Study	Country	Test	Age of assessment (y)	Evaluator	Cases [n (%)]	Non-cases (n)	Years of cohort enrollment
INUENDO-Greenland	Greenland	SDQ	7–8	Parents	31 (6.0)	487	2002–2004
INUENDO-Ukraine	Ukraine	SDQ	7–8	Parents	26 (5.4)	459	2002–2004
PCB cohort	Slovakia	CBCL-ADHD	4	Parents	10 (5.4)	175	2000–2002
HUMIS	Norway	NPR	10	Medical doctor	23 (2.3)	966	2002–2009
DNBC	Denmark	SDQ	7	Parents	42 (4.6)	872	1996–2002
FETOTOX[a]	Denmark	DNHR, DPCR	11	Medical doctor	215 (28.3)	544	1996–2002
INMA-Valencia	Spain	ADHD-DSM-IV	4–5	Teachers	27 (7.3)	344	2004–2005
INMA-Sabadell	Spain	ADHD-DSM-IV	4–5	Teachers	18 (4.8)	360	2004–2007
INMA-Gipuzkoa	Spain	ADHD-DSM-IV	4–5	Teachers	7 (3.1)	220	2006–2008

Note: ADHD-DSM-IV, ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; CBC-ADHD, attention syndrome scale of the Child Behavior Checklist; DNBC, Danish National Birth Cohort; DNHR, Danish National Hospital Registry; DPCR, Danish Psychiatric Central Registry; HUMIS, Norwegian Human Milk Study; INMA, Infancia y Medio Ambiente; NPR, Norwegian patient register; PCB, polychorinated biphenyl; SDQ, Strengths and Difficulties Questionnaire.
[a]Observations in FETOTOX were selected using case–cohort sampling.

Three different questionnaires were used in the other participating cohorts: the Attention Syndrome Scale of the Child Behavior Checklist (CBCL-ADHD) (Achenbach and Rescorla 2000) was used in the PCB cohort (at 4 years of age); the Hyperactivity/Inattention Problems subscale of the Strengths and Difficulties Questionnaire (SDQ-Hyperactivity/Inattention) (Goodman 1997), was used in INUENDO-Greenland and INUENDO-Ukraine (at 7–8 years of age) and in the DNBC; and the ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (ADHD-DSM-IV) list (López-Ibor Aliño and Valdés Miyar 2002), was used in INMA-Valencia, INMA-Sabadell, and INMA-Gipuzkoa (at 4–5 years of age). Questionnaires were filled out by parents (INUENDO and PCB cohorts) or by teachers (INMA cohorts). We used recommended cutoffs for setting an ADHD diagnosis for the three questionnaires. The CBCL-ADHD questionnaire is based on the sum of six items (score range: 0–12). The raw scores were standardized within each individual in the PCB cohort (using a T-score distribution), and then a T-score >65 was used as cutoff score to classify children with ADHD (Achenbach and Rescorla 2000). The SDQ-hyperactivity/Inattention questionnaire is composed of five items (total scores obtainable ranges: 0–10). A score ≥7 points was used to classify children with abnormal hyperactivity/inattention (Goodman 1997) and suspected ADHD (Overgaard et al. 2019). Finally, the ADHD-DSM-IV questionnaire consists of 18 symptoms categorized into two separate groups: inattention (9 symptoms) and hyperactivity/impulsivity (9 symptoms). Each ADHD symptom is rated on a 4-point scale (0 = never or rarely, 1 = sometimes, 2 = often, or 3 = very often). Then, in the binary scoring method, the first two response options of the original responses (i.e., Options 0 and 1) are recoded as the symptom being absent (recoded as 0), whereas the next two response options (i.e., Options 2 and 3) are recoded as the symptom being present (recoded as 1). A score of ≥6 symptoms of inattention or hyperactivity was used as the cutoff for ADHD (López-Ibor Aliño and Valdés Miyar 2002). Our operational definition of ADHD was either a diagnosis recorded in a patient registry or symptoms above the aforementioned thresholds. Hereafter we refer to the outcome of the study as ADHD.

Other Variables

We identified eight potential confounders *a priori* using directed acyclic graphs (DAGs) (see Figure S1); maternal prepregnancy body mass index (BMI, continuous), maternal age at delivery (years, continuous), maternal education (cohort-specific categories were recategorized as low, medium, and high (see Table S2), maternal smoking during pregnancy (yes/no) except in INUENDO cohorts for which we included maternal smoking prior to pregnancy, maternal parity (nulliparous yes/no), duration of total

breastfeeding (months, continuous) and child sex (male/female). Models of prenatal PFAS exposure were not adjusted by duration of breastfeeding.

Statistical Analyses

We imputed missing covariate data separately by cohort, using multiple imputation by chained equations assuming data to be missing at random (Rubin 1987; van Buuren 2007) using a preselected list of covariates such as maternal education, sex, parity, gestational age, duration of breastfeeding, and child weight after pregnancy. Thus, we estimated children's concentrations of PFOS and PFOA using the pharmacokinetic model for each imputation set ($n = 5$). We used a two-stage approach to assess the association between children's PFAS levels and ADHD. First, associations were analyzed separately for each study. We used logistic regression models to assess the association between PFOS and PFOA at birth and at 3, 6, 12, and 24 months of age and ADHD in all studies individually, except for the FETOTOX study. Because the FETOTOX study sample was derived using a case–cohort sampling strategy, we employed generalized linear models (log-binomial) and accounted for the sampling fractions of cases and controls to estimate risk ratios and 95% confidence intervals (CIs) for PFOS and PFOA exposures and ADHD as previously described (Liew et al. 2015). All models were adjusted for the identified confounders listed above. Second, the study-specific effect estimates from the logistic regression models and generalized linear models in FETOTOX were combined using random-effects meta-analysis. We assessed heterogeneity in the estimates using the Q test and the I^2 statistic. When a cohort contributed five or fewer cases in any of the analysis, that cohort was excluded only for this specific analysis.

Due to differences in ADHD prevalence in males and females (Polanczyk et al. 2007), as well as the differential associations by sex of PFAS with behavioral problems and ADHD observed in previous studies (Oulhote et al. 2016; Quaak et al. 2016; Stein et al. 2014), we additionally presented the estimates stratified by sex. By using pooled analyses of individual-level data, we added an interaction term for sex (cutoff for significance was $p < 0.10$) to evaluate possible effect–modification by sex. Sampling weights were also applied, and cohort was included as fixed-effect.

As a sensitivity analysis, we repeated the main analysis leaving out one study at a time in order to determine the influence of a particular study. In addition, because duration of total breastfeeding was used to estimate the exposure, we decided *a priori* to run a sensitivity analysis excluding it from the set of covariates in the multivariable model. Finally, we also repeated the analyses stratified by parity, which is associated with PFASs levels (Ode et al. 2013), and also by maternal education, which has been suggested as a potential effect modifier in the association between

persistent pollutants and ADHD (Lenters et al. 2019). We added an interaction term for parity and maternal education (cutoff for significance was $p < 0.10$) to evaluate possible effect–modification by parity and maternal education. Sampling weights were also applied, and cohort was included as fixed-effect. Finally, postnatal models were also adjusted for child birthweight.

Results

Table 1 shows the outcome distribution across the included study samples. The proportion of ADHD ranged from 2.3% in HUMIS to 7.3% in INMA-Valencia. In the FETOTOX sample, the proportion of ADHD was 28.3% due to a case–cohort design with oversampling of cases. Table 2 summarizes the characteristics of each study sample. The percentage of males was slightly above 50% in most of the study samples, except in the PCB cohort, which had only 43.2% males, whereas the FETOTOX study included >80% males because of matching on child sex. Mothers from some study samples (INUENDO-Greenland, INUENDO-Ukraine, and the PCB cohort) were less educated, whereas studies such as HUMIS, DNBC, and INMA-Gipuzkoa included more highly educated women (>50%). Maternal age at delivery was around 30 y in most studies, with INUENDO-Greenland, INUENDO-Ukraine, and the PCB cohort including the youngest mothers, with a mean age at delivery of 27, 25, and 26 y, respectively. HUMIS was the study with the longest mean duration of total breastfeeding (12 months) and INMA-Valencia was the study with the shortest mean duration (5 months). The percentage of nulliparous women ranged between 37% in the PCB cohort and 80% in INUENDO-Ukraine. PFAS concentrations measured in original matrixes according to child and maternal characteristics are included in Tables S3 and S4. Overall, males or children of mothers with low education had higher PFAS concentrations than females or children of higher-educated mothers, although this was not observed for PFOS and PFOA in the Slovakian and Norwegian cohort, for which PFAS were measured in breast milk.

Tables S5 and S6 respectively show the distributions of measured and of estimated PFOS and PFOA levels in the children. Among the studies with PFOS and PFOA levels measured in maternal serum or plasma, DNBC, FETOTOX, and INUENDO-Greenland had the highest median concentration of both compounds, and INUENDO-Ukraine had the lowest median concentration. The two cohorts with PFOS and PFOA levels measured in breast milk, HUMIS and the PCB cohort, had the lowest measured values.

Figure 1 and Table S7 show the association between estimated PFAS levels at different time points and ADHD. The results of the meta-analysis showed no association between PFOS or PFOA and ADHD at any time point, with ORs close to 1 ranging from 0.96 (95% CI: 0.87, 1.06) to 1.02 (95% CI: 0.93, 1.11). Some individual studies such as INUENDO-Ukraine, the PCB cohort, HUMIS, INMA-Valencia, and INMA-Gipuzkoa showed ORs above 1 for the association between PFOS and ADHD, whereas FETOTOX showed ORs consistently below 1 for both toxicants at all time points.

When we removed one study at a time, pooled estimates did not change, with two exceptions: *a*) when FETOTOX was excluded, which contributed with 215 of the 399 ADHD cases, the ORs for PFOS ranged from 1.07 (95% CI: 0.94, 1.20) to 1.10 (95% CI: 0.95, 1.28) (see Table S8) as opposed to ORs consistently slightly below and close to the null in all other models; and *b*) when we removed DNBC, the ORs for PFOA that were slightly above 1, became slightly below 1, although in both cases, they were close to the null (see Table S9).

When we stratified the meta-analysis by child sex, we observed ORs above 1 in girls, ranging from 1.12 (95% CI: 0.87, 1.06) to 1.30

(95% CI: 0.98, 1.73), and most ORs below 1 in boys ranging from 0.92 (95% CI: 0.81, 1.03) to 1.03 (95% CI: 0.85, 1.25) (Figure 2; Tables S10 and S11). This indication of an effect modification by sex was most pronounced for PFOS. Furthermore, the ORs were more precise in the models stratifying on boys, than for girls, owing to the differences in the number of cases (306 cases in boys vs. 82 cases in girls). The ORs were consistently above 1 for girls and below 1 for boys in FETOTOX and DNBC, which contributed the highest proportion of cases (more than 60% of cases). In addition, the interaction term assessed on an additive scale was not significant in any of the models tested ($p = 0.55–0.99$) (Figure 2).

When we repeated the analysis excluding duration of total breastfeeding from the model, the estimates did not change (see Table S12). Stratifying by parity, we observed a tendency toward a higher prevalence of ADHD in association with PFOS in children from nulliparous compared with multiparous mothers. This was most evident, with significant interaction terms, in the models testing the association between exposure and ADHD at birth and when assessed on an additive scale (see Figure S2 and Tables S13 and S14). Stratifying by maternal education, we observed a higher prevalence of ADHD in association with PFOS and PFOA only in children from low-educated mothers. Although children from medium-educated mothers had ORs close to the null and children from high-educated mothers had ORs below 1 in models for PFOS, this trend was different in the models for PFOA (see Figure S3 and Tables S15 and S16). The interaction term, assessed on an additive scale, was significant in all the models tested. These results are influenced by FETOTOX, the study contributing the highest number of cases that showed an OR above 1 in the low-education stratum and ORs below 1 in the medium- and high-education strata. In the low-education stratum, only four studies were included, INUENDO cohorts (INUENDO-Greenland and INUENDO-Ukraine), FETOTOX, and INMA-Valencia, with FETOTOX being the study showing the highest ORs. In the high-education stratum, only four studies were included: HUMIS, DNBC, FETOTOX, and INMA-Sabadell. Finally, when we added child birthweight in the postnatal models, the results did not change (see Table S17).

Discussion

This is the largest collaborative effort to assess the association between PFASs and ADHD, pooling data from nine European population-based studies and using a validated pharmacokinetic model to estimate concentrations of these toxicants in children. Overall, our results did not suggest an increased prevalence of ADHD in association with either exposure PFOS or PFOA.

Overall, the results of the meta-analyses were consistently null. The combined OR point estimates for the association between PFOS and PFOA exposure and ADHD during childhood were close to 1 in all the different tests performed. Our results concur with three longitudinal studies that reported no association between prenatal exposure to PFOS and PFOA and ADHD during childhood (Lien et al. 2016; Ode et al. 2014; Strøm et al. 2014), although one reported increased ADHD symptoms in association with prenatal exposure to PFNA (Lien et al. 2016). Our results differ from three cross-sectional studies that reported positive association between PFAS and ADHD (Gump et al. 2011; Hoffman et al. 2010; Stein and Savitz 2011). Two cross-sectional studies reported an association between higher PFAS concentrations measured in serum samples from children, including PFOS, PFOA, perfluorohexane sulfate (PFHxS), and perfluorononanoic acid (PFNA), and ADHD in children 9–15 years of age (Gump et al. 2011; Hoffman et al. 2010). A third cross-sectional study reported a higher prevalence of ADHD in children 5–18 years of age, with higher PFOS and PFHxS measured in their serum but a marked lower prevalence in the highest exposure concentrations of PFOA (Stein and Savitz 2011).

Table 2. Distribution of exposure and covariables of interest across participating studies.

Exposure and covariables of interest	INUENDO-Greenland ($n = 518$)	INUENDO-Ukraine ($n = 485$)	PCB cohort ($n = 185$)	HUMIS ($n = 989$)	DNBC ($n = 914$)	FETOTOX[a] ($n = 759$)	INMA-Valencia ($n = 371$)	INMA-Sabadell ($n = 378$)	INMA-Gipuzkoa ($n = 227$)
Measured PFOS concentrations [ng/mL [median (range)]][a]	20.19 (4.1–87.3)	5.01 (0.8–18.1)	0.03 (0.0–0.7)	0.11 (0.0–0.5)	33.55 (6.4–106.7)	26.90 (3.9–103.8)	6.20 (0.8–18.5)	6.39 (0.3–38.6)	5.30 (1.2–17.5)
Measured PFOA concentrations {ng/mL [median (range)]}[b]	1.83 (0.5–5.1)	0.96 (0.2–9.8)	0.03 (0.0–0.2)	0.04 (0.0–0.2)	5.26 (0.5–41.5)	4.00 (0.5–17.7)	2.39 (0.3–10.1)	2.87 (0.3–31.6)	1.66 (0.4–8.1)
Child sex (% male)	53.5	52.8	43.2	54.2	50.3	80.4	51.8	51.9	50.2
Child birth weight [kg (mean ± SD)]	3,602 ± 588	3,270 ± 419	3,324 ± 486	3,535 ± 652	3,636 ± 527	3,591 ± 585	3,203 ± 506	3,263 ± 411	3,316 ± 455
Maternal educational level (%)									
Low	56.8	60.6	46.5	8.4	2.6	4.6	26.1	23.7	10.2
Medium	41.7	39.4	50.3	13.7	30.5	37.4	45.0	44.4	37.2
High	1.5	0.0	3.2	77.9	66.9	58.0	28.8	31.9	52.7
Maternal age at delivery [y (mean ± SD)]	27.3 ± 6.3	25.1 ± 4.8	26.1 ± 4.9	30.3 ± 4.7	30.4 ± 4.3	29.6 ± 4.4	31.8 ± 4.0	31.8 ± 4.2	33.0 ± 3.3
Maternal prepregnancy BMI [kg/m² (mean ± SD)]	27.2 ± 3.9	24.4 ± 3.1	22.3 ± 4.2	24.3 ± 4.6	23.7 ± 4.2	23.9 ± 4.3	23.8 ± 4.6	24.0 ± 4.7	22.9 ± 3.3
Prenatal maternal smoking (% smokers)[c]	87.4	31.0	17.6	7.8	20.8	28.6	39.1	26.7	22.7
Parity (% nulliparous)	31.9	80.0	36.8	37.8	45.1	47.5	57.4	59.0	55.5
Duration of total breastfeeding [months (mean ± SD)]	9.3 ± 4.1	7.7 ± 3.9	9.8 ± 9.8	12.4 ± 5.2	8.0 ± 4.7	6.7 ± 4.8	5.3 ± 4.4	6.4 ± 4.5	7.0 ± 4.6
Sample time from birth [months (mean ± SD)]	−3.2 ± 2.7	−3.7 ± 2.9	0.1 ± 0.0	1.2 ± 0.6	−7.3 ± 0.5	−7.0 ± 1.1	−6.2 ± 0.4	−6.0 ± 0.5	−6.0 ± 0.5

Note: BMI, body mass index; DNBC, Danish National Birth Cohort; HUMIS, Norwegian Human Milk Study; INMA, Infancia y Medio Ambiente; PCB, polychorinated biphenyl; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; SD, standard deviation.

[a]Observations in FETOTOX were selected using case-cohort sampling.

[b]PFAS concentrations were measured in maternal serum/plasma in INUENDO-Greenland, INUENDO-Ukraine, DNBC, FETOTOX, INMA-Valencia, INMA-Sabadell, and INMA-Gipuzkoa and in breast milk in HUMIS and the PCB cohort. Specific details on chemical-analytical methods and detection/quantification limits in each study are included in Table S1.

[c]In INUENDO maternal smoking was assessed prior to pregnancy.
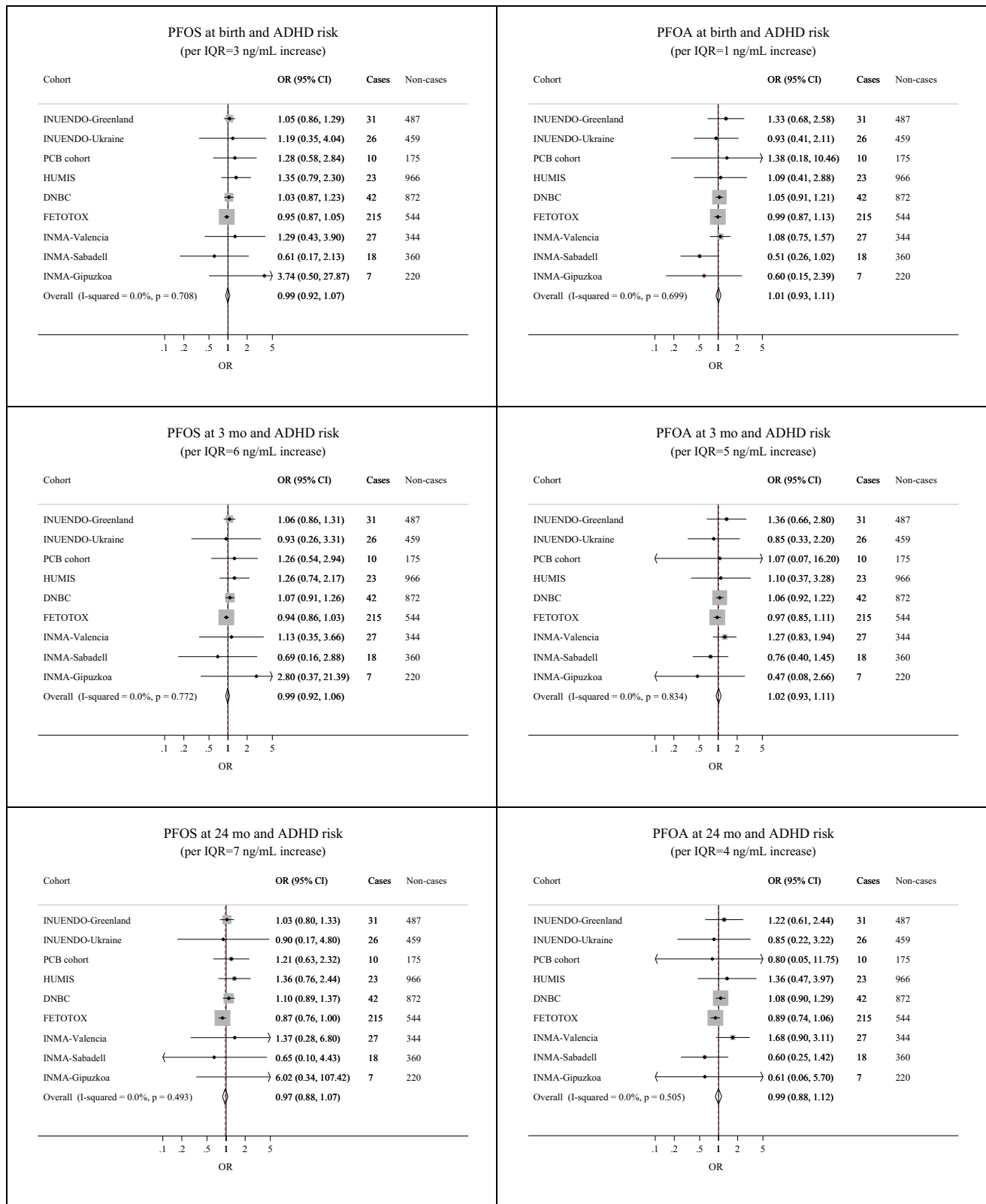
Figure 1. Adjusted cohort-specific and combined associations between exposure to estimated PFOS and PFOA levels in children and ADHD. Combined OR and 95% CI were estimated by random-effects meta-analysis by cohort. Models applied to each cohort were adjusted for maternal age at delivery, maternal smoking during pregnancy, maternal education, parity, prepregnancy BMI, duration of all breastfeeding, and child sex. ORs were estimated using logistic regression for all cohorts except FETOTOX, where log-binomial models that accounted for sampling fractions were used to estimate RRs. ORs were based on an IQR increase of PFOS and PFOA. The size of the squares is proportional to the weight. Note: ADHD, attention deficit and hyperactivity disorder; BMI, body mass index; CI, confidence interval; DNBC, Danish National Birth Cohort; HUMIS, Norwegian Human Milk Study; INMA, Infancia y Medio Ambiente; IQR, interquartile range; I^2, percentage of the total variability due to between-areas heterogeneity; mo, months; OR, odds ratio; PCB, polychorinated biphenyl; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; RR, risk ratio.
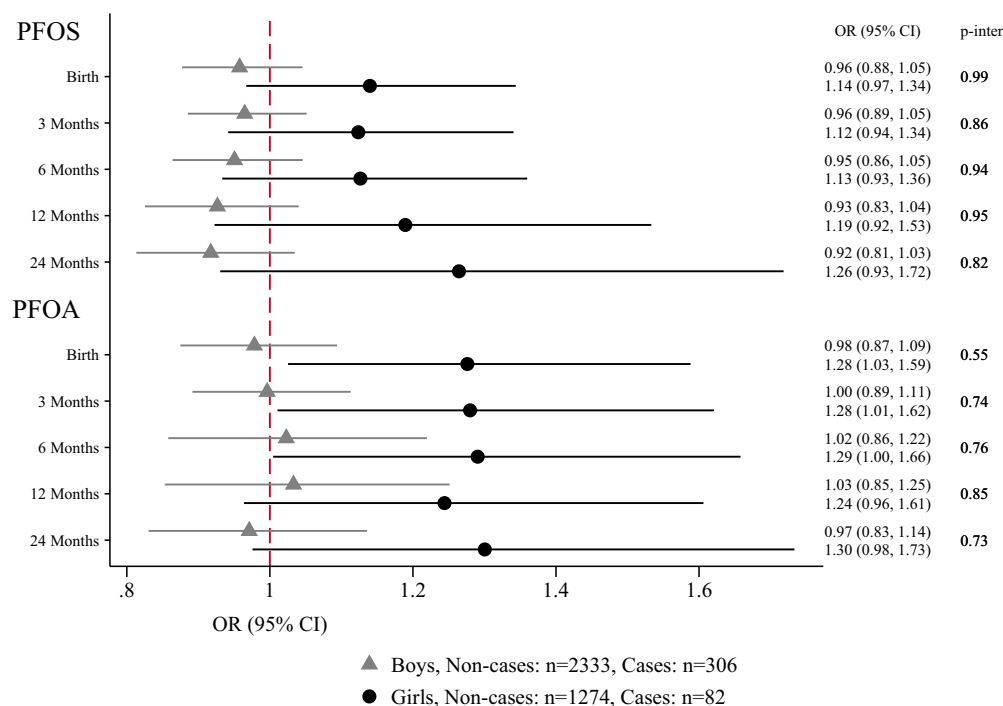
Figure 2. Adjusted combined associations between exposure to estimated PFOS and PFOA levels in children and ADHD stratified by child sex. Numeric data are provided in Tables S14 and S15. ORs based on an IQR increase of PFOS and PFOA. ORs and 95% CIs were estimated by random-effects meta-analysis by area. Models were adjusted for maternal age at delivery, maternal smoking during pregnancy, maternal education, parity, prepregnancy BMI, and duration of all breastfeeding. By using pooled analyses of individual-level data, we added an interaction term for sex (cutoff for significance was $p < 0.10$) to evaluate possible effect–modification by sex. Sampling weights were also applied, and cohort was included as fixed-effect. Note: ADHD, attention deficit and hyperactivity disorder; BMI, body mass index; CI, confidence interval; IQR, interquartile range; OR, odds ratio; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; p-inter, p value for interaction.

Our results suggest a potential differential effect of PFASs related to child sex with a possible increased prevalence of ADHD in girls that is associated with exposure to PFOS and PFOA. A sex-specific association of PFAS on ADHD has been reported in four studies, suggesting that girls are at higher prevalence of ADHD than boys in association with PFAS. One longitudinal study conducted in the United States observed that an increase in PFOA levels measured in child serum was associated with fewer ADHD-like behaviors among boys and more ADHD-like behaviors in girls 6–12 years of age (Stein et al. 2014). In a small Dutch study ($n = 59$ mother–child pairs), increases in PFOS and PFOA levels measured in cord plasma were associated with more externalizing behavior in girls, but not in boys, at 18 months of age (Quaak et al. 2016). Similarly, a cross-sectional study of 656 Faroese children observed that increases in PFOS, PFNA, and PFHxS measured in the serum of girls at 7 years of age were associated with higher behavioral problems, including ADHD, and no associations for boys (Oulhote et al. 2016). In the same study, the authors reported no association between the same PFASs measured in maternal serum during pregnancy and ADHD, indicating that postnatal exposure may be more important than prenatal exposure. Our study lends some support to these results. When we stratified by child sex, we observed a consistent increased prevalence of ADHD in girls with ORs ranging between 1.12 (95% CI: 0.87, 1.06) and 1.02 (95% CI: 0.93, 1.11) and in boys, with ORs ranging between 0.92 (95% CI: 0.81, 1.03) and 1.03 (95% CI: 0.85, 1.25). However, these results did not clearly differ, as indicated by the p-values of interaction. Estimates were imprecise, particularly in girls, owing to the low number of ADHD cases (82 and 306 cases in girls and boys, respectively). In addition, the results observed might be highly influenced by individual results observed in FETOTOX and

DNBC studies having the highest proportion of cases. In any case, the association is worth further exploration in large studies owing to the low number of cases of ADHD in girls.

Early life exposure to environmental toxicants might be associated with differential health effects for males and females (Weiss 2011), supporting a sex-specific association between PFASs and ADHD. The mechanisms underlying the potential predisposition of females having a higher prevalence of ADHD than males in association with PFAS are unclear. One hypothesis may be that because males are more prone to ADHD, any possible harmful effects of PFAS are overshadowed by other susceptibility factors in males that are more strongly associated with ADHD such as genetic factors, hormonal mechanisms, or a less-stimulating family environment. Another explanation is related to the mounting evidence that a potential endocrine-disrupting effect of PFASs may interfere with estrogen homeostasis (Sonthithai et al. 2016). The role of estrogens and androgens in brain development and its relationship with neurodevelopmental disorders has been debated in the last decades. Estrogen has been suggested as a critical protective factor in females in diseases that are more prevalent in men, such as Parkinson's disease or ADHD, all involving midbrain dopaminergic systems. Conversely, the decline of estrogen produced after menopause reduces this advantage of females and results in a higher prevalence in females for some diseases later in life, such as Alzheimer's disease (Gillies and McArthur 2010b). The role of androgens has been also discussed in relation to brain development (Collaer and Hines 1995) and ADHD. Prenatal and early postnatal exposure to androgens (specifically testosterone) exert organizational effects on ADHD by influencing dopaminergic neural circuitry (Martel et al. 2009). However, in *in vivo* and *in vitro* animal studies, the exposure to PFAS might disrupt the function of nuclear hormone receptors, interfering with steroidogenesis and altering

the expression of endocrine-related genes (Du et al. 2013). Thus, the endocrine-disrupting effect of PFASs on estrogen signaling may cause different effects in males and females, emerging as different vulnerabilities to some disorders, such as ADHD (Ballesteros et al. 2017; Gillies and McArthur 2010a).

The results of the present study also suggest a differential effect of PFAS related to maternal education, with an increased prevalence of ADHD in association with PFOS and PFOA among children from low-educated mothers only. The increased prevalence of ADHD in children from low-educated mothers has been previously reported (Sagiv et al. 2013), although whether maternal education may modify the association between PFAS and ADHD is still under debate. In addition, our results showed an increased prevalence of ADHD in children from nulliparous women in association with PFOS and PFOA. It is well known that that parous women have lower concentrations of persistent toxicants than nulliparous women (Berg et al. 2014; Richterová et al. 2018). Interactions across different classes of persistent toxicants are plausible and could explain this finding. Further exploration in large studies, including a higher number of cases of ADHD and a multipollutant model where interactions with other toxicants may be explored, is warranted.

The present study has a number of strengths, including the large sample size, assessment of ADHD during childhood using validated questionnaires and registry-based diagnosis, early life PFAS exposure assessment with a wide range of exposure timing, and centralized statistical analysis. To reduce confounding, we adjusted for several potential confounders. We also tested the associations among first parity only because prior parity may introduce unknown confounders, especially the duration of exclusive and partial breastfeeding of prior children, which again is related to many maternal characteristics (e.g., age, BMI, smoking, education, income, healthy lifestyle). Finally, we also tested the possible effect–modification of maternal education.

However, the results of the present study must also be evaluated in view of its potential limitations. Although our study included 4,826 children, it was not adequately powered to detect small effect sizes due to the low prevalence of ADHD in all the studies apart from FETOTOX). The participating studies were not established using the same protocol, and therefore the data collection differed in the biological matrices in which PFAS were measured, the timing of the matrix collection, and the timing and the method used to evaluate ADHD. The ADHD measurement is one of the major limitations of the study. Only in the studies conducted in Norway and Denmark was a physician diagnosis was made. In the remaining countries, different questionnaires with different validity and different evaluators were used to assess ADHD symptomatology. In addition, the age of assessment was different between the different studies. Although we have used recommended cutoffs for setting an ADHD diagnosis, it is uncertain whether the threshold used approximates the standard ADHD diagnosis defined by the DSM-V (American Psychiatric Association 2013), which requires having symptoms present before 12 years of age; symptoms present in two or more settings; symptoms interfering or reducing the quality of social, school, or work functioning; and, symptoms not better explained by another mental disorder. Therefore, in the present study, the ADHD outcome should be considered as a proxy for the ADHD diagnosis in all countries but in Norway and Denmark. However, the results at the study level (e.g., different trends between the different INMA cohorts that used the same questionnaire) did not suggest that these differences in outcome ascertainment explain the null results. In addition, we were not able to explore subtypes of ADHD (i.e., inattentive, hyperactive, or mixed). This could be relevant to understand the differences between boys and girls. In addition, the results of the present study might be negatively confounded by the inclusion of maternal education as covariate of adjustment, particularly in HUMIS and the PCB cohort, where PFAS was measured in breast milk. In these studies, maternal education is associated with a lower prevalence of ADHD but also with higher levels of exposure (Braun and Gray 2017).

We employed a pharmacokinetic model to estimate children's PFAS concentrations at birth through the first 2 y of life. This approach allowed us to evaluate associations during multiple potential windows of vulnerability, a substantial improvement over the traditional exposure assessments, which are limited to measurements in available blood samples (typically, ethical considerations limit blood samples obtained from infants). However, with estimated model precision ranging from 50% to 62% in a previous validation study, model error is likely to have biased the exposure–outcome associations toward the null. In addition, the differences in the timing of PFAS measurement can introduce some bias because it has been observed that PFAS levels measured late in pregnancy may be lower due to some physiological processes that depend on the BMI of the mother (Mamsen et al. 2019). Further, pharmacokinetic modeling of children's PFAS levels was based on breast milk levels in HUMIS and the PCB cohort. This raises the possibility of selection bias if breastfeeding duration is reduced by maternal PFAS exposure, as suggested by a previous study (Romano et al. 2016). However, we believe the risk of bias is low given that most women were still breastfeeding at the time of sample collection in HUMIS study (99%) and the PCB cohort (98%). We could not adjust our models by year of mother's enrollment in the different studies, and because there are temporal trends in PFAS concentrations and in awareness of ADHD among parents and teachers, this might confound the results of the present study. Finally, we could not control for confounding by kidney function, which can be related to PFAS excretion and child health.

In summary, we found no increased prevalence of ADHD in association with early life exposure to PFOS and PFOA in a sample of almost 5,000 children from nine European population-based studies. However, stratified analyses suggest that there may be an increased prevalence of ADHD in association with PFAS exposure in girls, in children from nulliparous women, and in children from low-educated mothers, all of which warrant further exploration.

Acknowledgments

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