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Early-life exposure to persistent organic pollutants (OCPs, PBDEs, PCBs, PFASs) and attention-deficit/hyperactivity disorder: A multi-pollutant analysis of a Norwegian birth cohort

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ABSTRACT

Background: Numerous ubiquitous environmental chemicals are established or suspected neurotoxicants, and infants are exposed to a mixture of these during the critical period of brain maturation. However, evidence for associations with the risk of attention-deficit/hyperactivity disorder (ADHD) is sparse. We investigated early-life chemical exposures in relation to ADHD.

Methods: We used a birth cohort of 2606 Norwegian mother–child pairs enrolled 2002–2009 (HUMIS), and studied a subset of 1199 pairs oversampled for child neurodevelopmental outcomes. Concentrations of 27 persistent organic pollutants (14 polychlorinated biphenyls, 5 organochlorine pesticides, 6 brominated flame retardants, and 2 perfluoroalkyl substances) were measured in breast milk, reflecting the child's early-life exposures. We estimated postnatal exposures in the first 2 years of life using a pharmacokinetic model. Fifty-five children had a clinical diagnosis of ADHD (hyperkinetic disorder) by 2016, at a median age of 13 years. We used elastic net penalized logistic regression models to identify associations while adjusting for co-exposure confounding, and subsequently used multivariable logistic regression models to obtain effect estimates for the selected exposures.

Results: Breast milk concentrations of perfluorooctane sulfonate (PFOS) and β-hexachlorocyclohexane (β-HCH) were associated with increased odds of ADHD: odds ratio (OR) = 1.77, 95% confidence interval (CI): 1.16, 2.72 and OR = 1.75, 95% CI: 1.22, 2.53, per interquartile range increase in ln-transformed concentrations, respectively. Stronger associations were observed among girls than boys for PFOS ($p_{interaction}$ = 0.025). *p,p′*-Dichlorodiphenyltrichloroethane (*p,p′*-DDT) levels were associated with lower odds of ADHD (OR = 0.64, 95% CI: 0.42, 0.97). Hexachlorobenzene (HCB) had a non-linear association with ADHD, with increasing risk in the low-level exposure range that switched to a decreasing risk at concentrations above 8 ng/g lipid. Postnatal exposures showed similar results, whereas effect estimates for other chemicals were weaker and imprecise.

Conclusions: In a multi-pollutant analysis of four classes of chemicals, early-life exposure to β-HCH and PFOS was associated with increased risk of ADHD, with suggestion of sex-specific effects for PFOS. The unexpected inverse associations between *p,p′*-DDT and higher HCB levels and ADHD could be due to live birth bias; alternatively, results may be due to chance findings.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by persistent inattention, hyperactivity and impulsivity. The prevalence of ADHD is 3.4–7% in children and slightly lower in adults (Polanczyk et al., 2014; Willcutt, 2012), although there is heterogeneity in prevalence estimates across studies and countries, partly attributable to differing diagnostic criteria

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and practices. Although ADHD is highly heritable, early-life environmental risk factors explain an estimated 10–40% of the variance in ADHD (Banerjee et al., 2007; Faraone et al., 2005; Larsson et al., 2014).

There is a growing body of evidence that early-life exposure to certain environmental contaminants impairs neuropsychological development. Hypothesized mechanisms include thyroid hormone insufficiency and disruption in early-life (Modesto et al., 2015), inhibition of acetylcholinesterase, dopaminergic dysfunction, disruption of calcium signaling and GABA signaling pathways, and gene-environment interactions (Braun, 2017; Grandjean and Landrigan, 2014). In humans, the evidence is most robust for several persistent pesticides and heavy metals, although the evidence base is scarce for most chemicals (de Cock et al., 2012; Polanska et al., 2013). A small number of studies have reported positive associations between persistent organic pollutants (POPs) and ADHD (Hoffman et al., 2010; Sagiv et al., 2010) or ADHD-related behaviors (Kalkbrenner et al., 2014; Sagiv et al., 2015b; Verner et al., 2015), while other studies have reported null or inconsistent results (Liew et al., 2015b). Many of the previous studies either investigated individual chemicals (or chemical classes), did not account for potential confounding from co-exposure to other chemicals or interactions between them, nor investigated both prenatal and postnatal exposure, or used a cross-sectional design, had a younger age of ADHD diagnosis, or used less sensitive tools to ascertain ADHD.

We investigated associations between POPs from four chemical classes and risk of ADHD diagnosis by around 13 years of age in a Norwegian birth cohort. We evaluated concentrations of chemicals measured in breast milk, which represent early breast milk exposure, and for the lipid-bound compounds are also a proxy of the child's *in utero* exposures (Vizcaino et al., 2014). We also modeled child chemical body burdens in the first 2 years of life because this is a critical window for neurodevelopment (Glantz et al., 2007), and intake through breastfeeding contributes to substantial exposures in this period (Haddad et al., 2015).

2. Methods

2.1. Study population

We used data from a prospective birth cohort, HUMIS (the Norwegian Human Milk Study, 2002–2009). The HUMIS cohort was established with the aim of measuring exposure to POPs in breast milk and investigating possible health effects. Briefly, new mothers were recruited in 2003–2009 by public health nurses during routine postnatal care home visits around 2 weeks postpartum in seven counties across Norway (Eggesbø et al., 2009). A subset of mothers were recruited in 2002–2005 by a pediatrician at the maternity ward in Østfold hospital in Southern Norway, two term births for every preterm birth (Eggesbø et al., 2009; Eggesbø et al., 2011). All mothers followed the same protocol and completed the same questionnaires, regardless of recruitment procedure. They were asked to collect 25 mL of breast milk each morning on 8 consecutive days before the child reached 2 months of age. Minor deviations in this sampling protocol, such as collection by breast pump, were accepted (see Supplemental material, Appendix S1 for additional details). Supplemental Table S1 shows a comparison of key characteristics from the general population of mothers giving birth in Norway, entire HUMIS cohort, and the subset analyzed in this study. Aside from preterm birth, other characteristics of this study population such as maternal age, primiparity, smoking at the start of pregnancy, birth weight and sex of the infant are all representative of the general population.

The current study is based on the subset of 1199 mother–singleton child pairs for whom breast milk samples have been analyzed for at least one of the chemical classes (Fig. 1).

The birth cohort study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics and the Norwegian Data Inspectorate. Written informed consent was obtained from all participating mothers prior to enrolment.

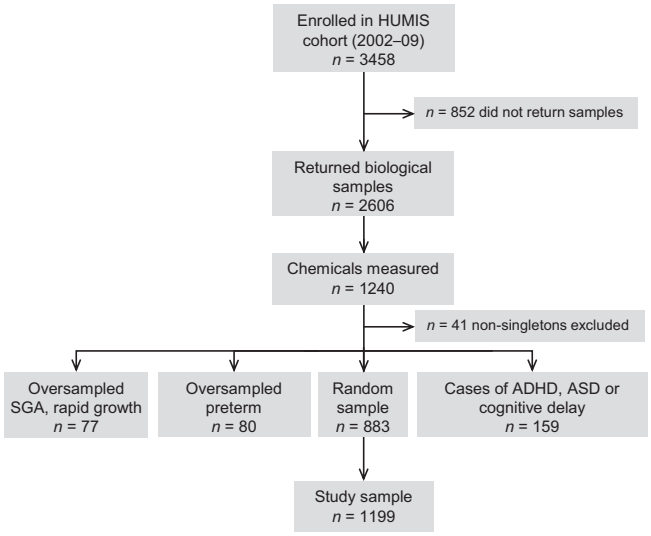

Fig. 1. Flow chart of study population selection within the HUMIS cohort. Due to financial constraints samples have been selected for chemical analysis dependent on the research question in the project that funded it. This has resulted in a study population oversampled for small for gestational age (SGA) and rapid growth (n = 77), and babies born preterm in Østfold county (n = 80). In addition, we analyzed chemicals for cases of neurodevelopmental disorders (ADHD, autism spectrum disorder (ASD), and cognitive delay cases) (n = 159).

2.2. Health outcomes

ADHD cases were identified by linkage to the nationwide Norwegian Patient Registry (https://helsedirektoratet.no/English) which covers specialist-confirmed diagnoses at hospitals and outpatient clinics. Cases were defined as International Classification of Diseases (ICD)-10 (WHO, 1993) codes F90.0, F90.1, F90.8 or F90.9 (hyperkinetic disorder), which corresponds to a narrower definition of ADHD than in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the of the American Psychiatric Association (2013), as symptoms of both inattentiveness and hyperactivity/impulsivity are required. There were no cases of F98.8 (which includes attention deficit disorder without hyperactivity), which is sometimes included in ADHD ascertainment (Oerbeck et al., 2017). The registry began collecting individual data in 2008, when the children were a median of 3.7 years of age, and data up until December 2016 was available at the time of linkage, when the children were a median of 12.7 years of age (range, 7.2–14.1).

2.3. Chemical exposure assessment

We assessed environmental chemicals commonly detected in breast milk, as these legacy pollutants are persistent and ubiquitous across the globe (Haug et al., 2018; van den Berg et al., 2017). Chemicals included polybrominated diphenyl ethers (PBDEs), and perfluoroalkyl acids of the class of poly- and perfluoroalkyl substances (PFAS), used respectively as brominated flame retardants and surfactants, which were not yet restricted at the time of the study; and industrial chemicals (polychlorinated biphenyls (PCBs)) and commercial organochlorine pesticides (OCPs), which although banned or restricted, are present in the environment. Chemicals were measured in individuals mother's pooled breast milk samples, which were collected at a median of 33 days postpartum. Due to financial constraints, samples have only been analyzed for a subset of women. Chemicals were measured in broadly two subsets: the first set was oversampled for preterm birth, small for gestational age, and rapid growth, and a second set was oversampled for

neurodevelopmental disorders, including ADHD, autism spectrum disorder, and cognitive delay (Fig. 1).

We restricted our study to the 27 chemicals that were measured in at least 800 samples (range: 882–1194) and detected in at least 50% of the samples: 14 PCBs, 5 OCPs, 2 PFASs, and 6 PBDEs. Four laboratories performed the chemical analyses, as previously described (Čechová et al., 2017a; Čechová et al., 2017b; Čechová et al., 2017c; Forns et al., 2015; Forns et al., 2016; Polder et al., 2009; Thomsen et al., 2010b): the Department of Environmental Exposure and Epidemiology, Norwegian Institute of Public Health (Oslo, Norway), the Department of Environmental Sciences, Norwegian University of Life Sciences (Ås, Norway), the Institute for Environmental Studies, Faculty of Earth and Life Sciences, VU University (Amsterdam, the Netherlands), and the Research Centre for Toxic Compounds in the Environment, Masaryk University (Brno, Czech Republic) (Supplemental material, Appendix S1).

Our primary exposure was the concentrations of chemicals in breast milk, which represent early breast milk exposure, and additionally for the lipid-bound compounds, *in utero* exposure. Since the critical window of neurodevelopment may be up to 2 years of age, and postnatal exposures can be substantial and variable, we estimated postnatal exposures for a secondary analysis. We modeled postnatal child blood levels for the 25 lipophilic chemicals using a two-compartment (mother and child lipid) pharmacokinetic model (Stigum et al., 2015). The model's equations use a number of input parameters including the measured chemical concentrations in breast milk; child's and mother's weight at birth, 3, 6, 12, and 24 months; the extrapolated fat mass of the child and mother; the maternal-reported duration of exclusive and partial breastfeeding; and the estimated quantity of breast milk consumed, all of which change over time. Compared with using a single measured concentration, or measured concentration * breastfeeding duration (lactation exposure model), the pharmacokinetic model yields the lowest measurement error (Stigum et al., 2015). Given the ethics of the alternative (multiple blood sampling for the child), modeling postnatal blood concentrations is the most suitable approach to capture the exposure profile of the infant during the first 2 years of life. We also modeled concentrations at birth to compare estimates of these with the measured concentrations. Full details of the model (Stigum et al., 2015) and validation (Forns et al., 2018) are available elsewhere. For the two protein-bound PFASs, we could not use the same model, and the secondary exposure was the product of breastfeeding duration and PFAS concentration.

2.4. Covariates

Information on potential confounders was obtained from the Medical Birth Registry of Norway (child's sex, gestational age, birth weight, and maternal smoking during pregnancy), and from the questionnaires administered to the mothers at 6, 12, and 24 months postpartum.

2.5. Statistical analysis

2.5.1. Adjustment models

For the primary analysis, we assessed associations between measured breast milk concentrations of chemicals and ADHD. We defined two adjustment models based on a directed acyclic graph (DAG; see Fig. S1). The minimum sufficient adjustment set (M1) included: child age at linkage (continuous), maternal age (continuous), and maternal education ($\leq$12/ > 12 years completed). We also tested a model (M2) that was further adjusted for covariates for which evidence for an association with both the exposure and outcome is weaker: parity (primiparous/multiparous), smoking during pregnancy (yes/no), pre-pregnancy body mass index (BMI) (continuous), marital status (single/married or living with partner in the perinatal period), and maternal fatty fish consumption (servings/year) (Sciberras et al., 2017; Thapar et al., 2013), and variables related to oversampling: small for gestational age (SGA) (< 10th/$\geq$10th percentile of sex-specific Norwegian standards (Skjaerven et al., 2000)) and preterm birth (< 37/$\geq$37 weeks gestation). Estimates from M1 reflect the total effect estimates of chemical exposures and ADHD, but we cannot exclude selection bias due to the oversampling design. In the DAG, the study sample selection variable is not separated from the outcome or exposure and there is potential for selection bias in the odds ratio (OR) estimate for M1 (Greenland and Pearl, 2011). In M2, when we adjust for "SGA, preterm", we have adjusted for selection bias. However, since "SGA, preterm" is also a potential mediator for the effect of chemical exposures on ADHD, we may also have removed some of this effect in M2. In addition, although not commonly discussed, adjusting for preterm as a mediator may lead to collider bias (Wilcox et al., 2011).

Values below the sample- and chemical-specific limit of detection (LOD) were singly imputed using maximum likelihood estimation (Lubin et al., 2004), following a log-normal distribution and conditional on maternal age, parity, pre-pregnancy BMI, and child birth year. Twenty-four exposures had < 2% below the LOD, and the remaining exposures had 7% (PFOA), 10% (PBDE-28), and 28% (PBDE-154) of values below the LOD (see Table S2). We used multiple imputation by chained equations (Buuren and Groothuis-Oudshoorn, 2011) to impute missing exposure data (12–27% for 14 chemicals and $\leq$3.4% for the others) and missing covariate data ($\leq$3.2%) up to the full sample size of 1199. We imputed 100 datasets (see Supplemental methods). As a sensitivity analysis, we also ran complete case analyses.

2.5.2. Multi-pollutant variable selection and effect estimation

Due to the high number of correlated exposures from similar sources and potential for multicollinearity (Schisterman et al., 2017), we used a two-step approach to estimate the associations between the chemicals and ADHD. We first used elastic net logistic regression (Zou and Hastie, 2005), a variable selection method that adjusts for confounding due to correlated co-exposures and reduces the proportion of false positive results (Agier et al., 2016; Lenters et al., 2018; Sun et al., 2013). We repeated elastic net modeling in each of the 100 multiply imputed datasets, and considered exposures that were selected in more than half of the models as noteworthy (Wood et al., 2008). We also evaluated the *p*-values conditional on the selection for post-selection statistical inference, which reflects the strength of the associations (Lee et al., 2016; Taylor and Tibshirani, 2018; Tibshirani et al., 2017).

In the second step, we then refit the selected subset of chemicals in an ordinary multi-pollutant logistic regression model. For comparison, we also present the single-pollutant models adjusted for confounders and corrected for multiple comparisons with a false discovery rate controlled at < 5% (Benjamini and Hochberg, 1995).

We tested models using natural log (ln)-transformed exposure variables to reduce the influence of extreme values and improve model fit. Regression coefficients are presented for an interquartile range (IQR) increase in ln-exposure concentrations to render coefficients more comparable given the right-skewed distributions and highly variable exposure contrasts.

2.5.3. Secondary and sensitivity analyses

As a sensitivity analysis, we also tested models with untransformed exposure variables. We assessed potential effect measure modification by child sex, maternal education (a proxy of socioeconomic status and possible psychosocial adversity), maternal smoking (ever and also at the beginning of pregnancy), and parity (as multiparous may suffer from added residual confounding compared to primiparous).

For the most robustly-selected exposures from the primary analysis, we ran a number of additional sensitivity analyses: 1) maximum adjusted set of confounders, not including study sample selection variables; 2) excluding over-sampled SGA and preterm births; 3) excluding those recruited from Østfold county; and, 4) restricting to children aged 10 years and above (old enough to have likely been diagnosed with ADHD). We then conducted a secondary analysis using postnatal

estimates of the lipophilic chemical body burdens of the child at birth and at 3, 6, 12, 18, and 24 months of age to investigate if we could detect critical windows of exposure. These models were additionally adjusted for duration of any breastfeeding, which is a potential confounder in the postnatal exposure regression since longer duration of breastfeeding may influence both transfer of POPs and risk of ADHD. For the non-lipophilic PFASs, we assessed effect modification by total breastfeeding duration, as an indirect measure of postnatal exposure.

Finally, we assessed whether associations for the selected exposures *a)* exhibited multiplicative interactions by introducing product terms between them; *b)* were non-linear, using generalized additive models (GAMs) fitted with a smoothing spline; and, c*)* whether exclusion of extreme exposure values or influential observations (based on Cook's distance for univariate outliers and Mahalanobis distances for multivariate outliers) affected the magnitude or shape of associations.

We used Stata (version 14.1; StataCorp LP, College Station, Texas) to model postnatal estimates and R software (version 3.3.2, including the packages *mice*, *glmnet*, and *selectiveInference*; R Foundation for Statistical Computing, Vienna, Austria) for all other statistical analyses.

3. Results

Characteristics of the mother–child pairs are displayed in Table 1. Mothers were a median of 30 years of age at delivery, 33% were overweight or obese prior to pregnancy, and 86% continued breastfeeding for > 6 months postpartum. A total of 55 children (4.6%) had been diagnosed with ADHD.

The distributions of chemicals in breast milk are shown in Fig. 2 (numerical values in Table S2). The highest breast milk concentrations within each of the four chemical classes were observed for BDE-47, PFOS, PCB-153, and dichlorodiphenyldicholorethylene (*p,p′*-DDE). There was clear clustering by chemical class with moderate to high correlations within chemical classes, and moderate correlations between PCBs and OCPs (see Fig. S2); 34% of pairwise Pearson correlations were $r_p > 0.5$ and 11% were $r_p > 0.8$. Concentrations of the modeled child body burdens peaked at the end of breastfeeding with median levels around 3 times higher at month 12 than at birth. Correlations between measured breast milk concentrations and the estimated postnatal child serum concentrations for the 25 lipophilic chemicals were high, but diverged with time; $r_p > 0.87$ for months 0 to 6 dropping to $r_p < 0.80$ for 14 exposures by 24 months (range $r_p = 0.69–1.00$) (Table S3).

Associations between covariates and ADHD, and between covariates and selected chemicals are shown in Table S4. Boys and children whose mothers smoked during pregnancy had an increased risk of ADHD. Maternal breast milk concentrations of chemicals generally increased with maternal age, earlier calendar year of sampling (child birth year), and maternal fish intake, and were reduced in multiparous women.

3.1. Associations with ADHD

Ten chemical exposures were predictive of ADHD in the majority of elastic net logistic regression models, across multiple imputation datasets, in the primary M1 minimal sufficient adjustment analysis: BDE-47 and 154, PFOA, PFOS, PCB-114, and β-HCH with an increased risk, and BDE-153, PCB-153, HCB, and *p,p′*-DDT with a decreased risk (Fig. 3 and Table S5). The most robust results were for PFOS, HCB, β-HCH, and *p,p′*-DDT (post-selection inference $p = 0.08$, 0.004, 0.09, and 0.06, respectively).

In a multi-pollutant logistic regression M1 model, the effect estimates were OR = 1.77 (95% CI: 1.16, 2.72) for an IQR increase in PFOS concentrations (IQR: 80.0–160.0 ng/L; a 100% increase in exposure), OR = 0.47 (95% CI: 0.29, 0.77) for HCB (IQR: 7.60–12.21 ng/g lipid; a 60% increase), OR = 1.79 (95% CI: 1.21, 2.65) for β-HCH (IQR: 2.92–6.47 ng/g lipid; a 122% increase), and OR = 0.59 (95% CI: 0.36, 0.99) for *p,p′*-DDT (IQR: 1.40–2.94 ng/g lipid; a 110% increase). For comparison purposes, these effects estimates are also presented per 1-ln-unit increase in the footnotes of Table S5.

Table 1
Study population characteristics [n (%)[a] or median (IQR)] by ADHD case status in the HUMIS cohort, Norway.

Characteristic	Cases (n = 55)	Controls (n = 1144)
Østfold[b]	10 (18)	295 (26)
Maternal characteristics		
Age at start of pregnancy (years)		
16–26	19 (35)	279 (24)
27–33	27 (49)	618 (54)
34–44	9 (16)	247 (22)
Education (years completed)		
≤12	21 (38)	246 (22)
> 12	32 (58)	883 (77)
Pre-pregnancy body mass index (kg/m^2)		
Underweight (< 18.5)	2 (4)	41 (4)
Normal weight (18.5–24.9)	27 (49)	694 (61)
Overweight (25–29.9)	11 (20)	272 (24)
Obese (≥30)	11 (20)	107 (9)
Parity		
1 (first child)	25 (45)	451 (39)
2	19 (35)	436 (38)
3–5	10 (18)	238 (21)
Single mother[c]	2 (4)	27 (2)
Smoked during pregnancy	15 (27)	117 (10)
Fatty fish consumption, (servings/year)	23 (9–42)	24 (10–49)
Timing of breast milk sampling		
< 2 months	23 (42)	666 (58)
2 months	21 (38)	324 (28)
> 2 months	6 (11)	101 (9)
Child characteristics		
Age at registry linkage (years)	12.5 (11.1–13.4)	12.7 (11.8–13.4)
Birth year		
2002–2003	27 (49)	465 (41)
2004–2005	21 (38)	514 (45)
2006–2009	7 (13)	165 (14)
Sex (boy)	44 (80)	611 (53)
Small-for-gestational age (< 10th percentile)	8 (15)	127 (11)
Preterm (< 37 weeks gestation)	8 (15)	96 (8)
Breastfeeding, any (months)	10 (7–14)	13 (9–16)

ADHD, attention-deficit/hyperactivity disorder; IQR, interquartile range.
There were missing values for education (n = 17), body mass index (34), parity (20), marital status (8), smoking (12), fish consumption (39), timing of breast milk sampling (58), child sex (2), and breastfeeding (20).
[a] Percentages may not add up to 100 due to rounding or missing values.
[b] Resident of Østfold county.
[c] Single, *versus* married or living together with partner in perinatal period.

3.2. Secondary and sensitivity analyses

Using elastic net modeling, a somewhat smaller set of exposures was selected in the further adjusted M2 model (7 compared to 10), with BDE-154, PFOA, and PCB-114 no longer selected; however, the mutually adjusted M2 effect estimates were generally similar in magnitude and precision in comparison to the M1 effect estimates (Table S5). For comparison, we evaluated the more conventional single-pollutant associations, unadjusted for co-exposures, and details of these associations are shown in Table S6. In single-pollutant models with untransformed exposures, PFOS, PFOA, and HCB were significant. For the most robustly-selected exposures, testing the maximum adjusted set of confounders excluding study sample selection variables, excluding those over-sampled for SGA and preterm, excluding those who lived in Østfold county, or restricting to those who were aged > 10 years, did not alter the interpretation of our results (Table S7). Effect estimates were similar for the analysis based on multiple imputation compared to complete case analysis (Table S8).

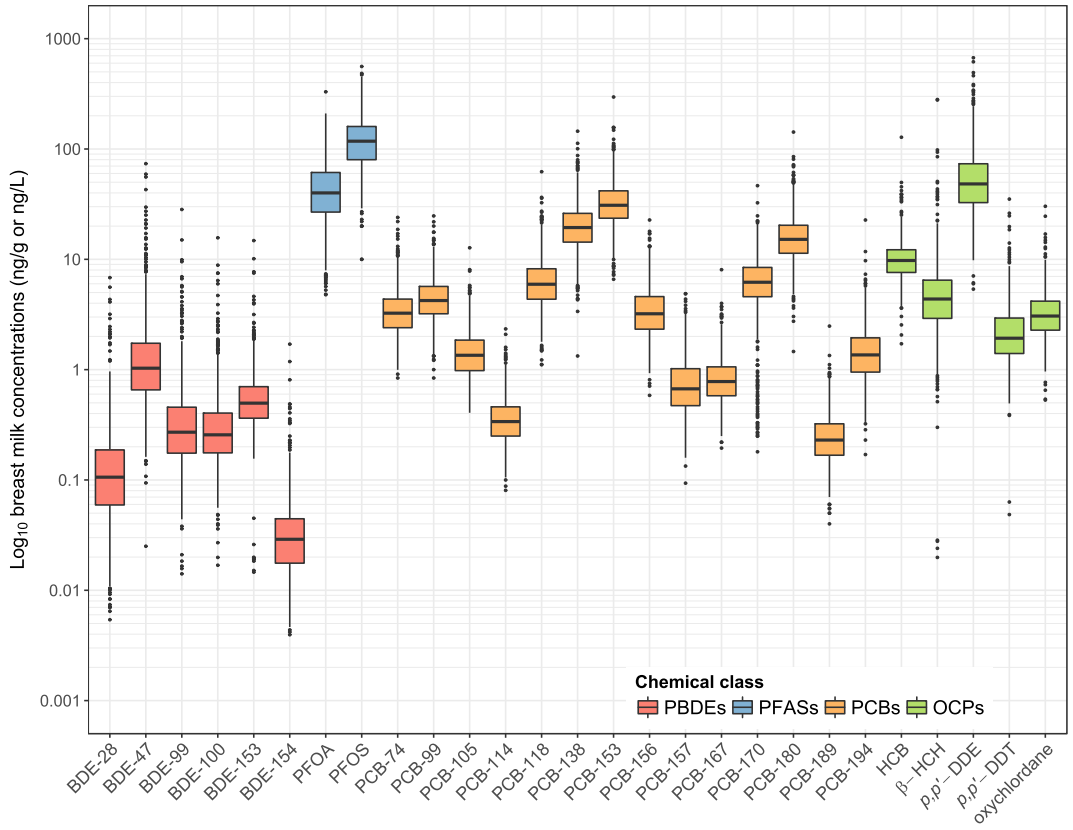

Fig. 2. Boxplot distributions of the breast milk concentrations of the 27 chemicals. Horizontal lines correspond to medians, and boxes to the 25th–75th percentiles; whiskers extend to data within the interquartile range times 1.5, and data beyond this are plotted as dots. Wet weight concentrations are presented for PFASs (ng/L) and lipid adjusted concentrations for all other chemicals (ng/g lipid). See Table S2 for numerical values.
Abbreviations: (P)BDE, (poly)brominated diphenyl ether; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; OCPs, organochlorine pesticides; PFASs, poly- and perfluoroalkyl substances; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate.

Analyses based on modeled lipophilic exposures at birth and at five postnatal periods in the first 2 years of life yielded effect estimates that were similar in magnitude and precision for measured HCB, β-HCH, and *p,p′*-DDT except for small, non-significant increased estimates at 24 months (Table S9). For non-lipophilic PFOS, we did not observe effect modification by duration of any breastfeeding, a proxy for postnatal exposure (data not shown).

For the subset of four robustly selected exposures, there were no two-way interactions between exposures. There were also no clear outliers. Removal of the three most influential observations had a negligible effect on the effect estimates (data not shown). The associations for PFOS, β-HCH, and *p,p′*-DDT were clearly linear, whereas the association for HCB exhibited an inverted U-shaped curve, with an inflection point at around 8.0 ng/g lipid (Fig. S3). There was evidence of effect modification by maternal education and child sex for PFOS but not for maternal smoking and parity. Higher odds of ADHD diagnosis with increasing PFOS levels was observed only for higher educated mothers [OR = 2.38 (95% CI: 1.39, 4.06) *vs.* lower educated: OR = 1.00 (95% CI: 0.50, 2.02); $p_{interaction}$ = 0.049] and a stronger association was observed for girls [OR = 5.21 (95% CI: 1.75, 15.48) *vs.* boys: OR = 1.32 (95% CI: 0.82, 2.13); $p_{interaction}$ = 0.025]. No effect modification was observed for HCB, β-HCH, and *p,p′*-DDT for any of the tested factors.

In an exploratory *a posteriori* analysis, we found that fish intake was significantly predictive of PFOS, β-HCH, HCB, and *p,p′*-DDT levels with a 4–7% increase in median concentrations for the four chemicals per IQR in fish intake (equivalent to 89 servings/year; see also Table S4). Fatty fish was a more important predictor of β-HCH, HCB, and *p,p′*-DDT levels, whereas lean fish was a more important predictor of PFOS levels (data not shown).

4. Discussion

In this prospective Norwegian cohort study, early-life exposure to four environmental chemicals was associated with the odds of ADHD diagnosis in childhood. PFOS and β-HCH were associated with an increased risk, and *p,p′*-DDT with a decreased risk, and HCB showed a non-linear exposure–response relationship. These results were robust to adjustment for other persistent chemical exposures and relevant confounders. The other 23 chemical exposures were less consistently associated or associations were close to null.

PFOS, HCB, β-HCH, and *p,p′*-DDT are persistent organic pollutants (UNEP, 2015) and body burdens of these compounds will remain substantial in the coming years because of their long half-lives and environmental persistence (Bu et al., 2015; Jung et al., 1997; Olsen et al., 2007; Ritter et al., 2009; To-Figueras et al., 2000). Fish intake was significantly predictive of PFOS, β-HCH, HCB, and *p,p′*-DDT levels in this study population. This is in agreement with previous studies demonstrating that fish intake is the most important dietary source of exposure for these four POPs (Haug et al., 2010; Xu et al., 2017).

4.1. Comparisons with other studies

We observed a positive association between breast milk concentrations of PFOS (median 117 ng/L in breast milk) and ADHD that was sex-specific: stronger and only statistically significant in girls. This finding should be interpreted cautiously due to the small number of female cases in our study (n = 10). However, other studies have also

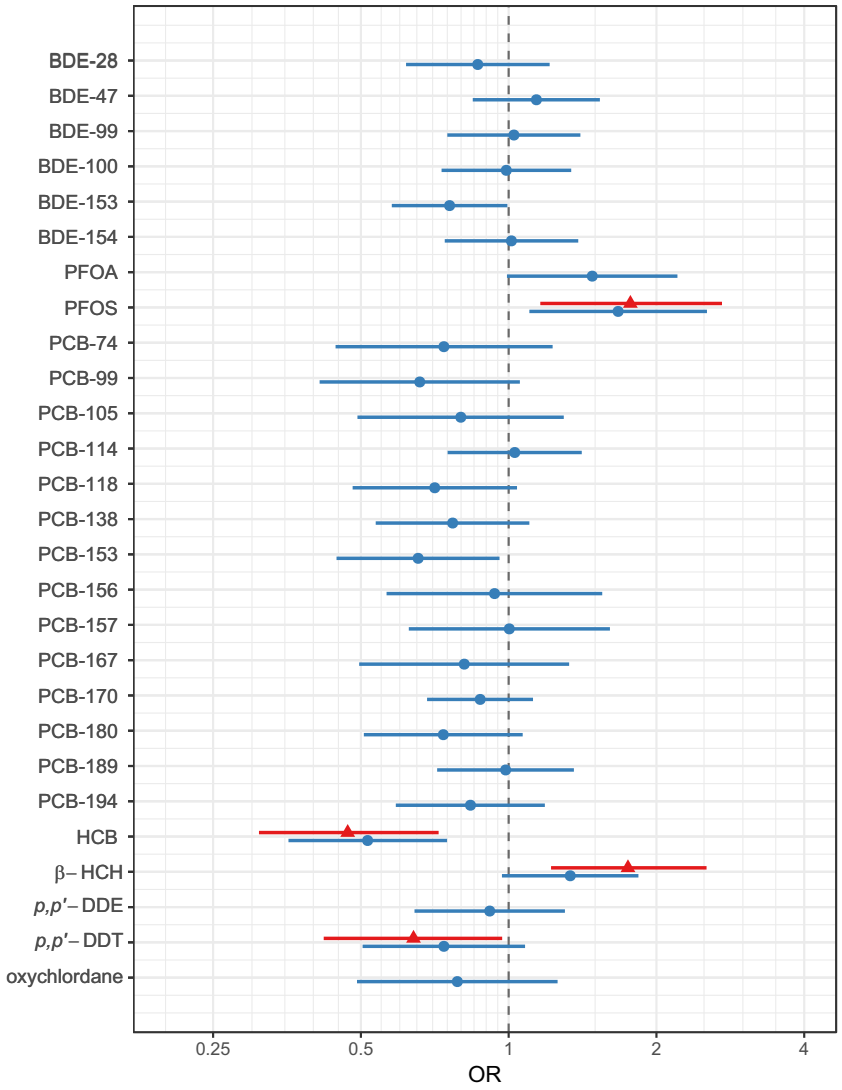

Fig. 3. Odds ratios (OR) and 95% confidence intervals for attention-deficit/hyperactivity disorder (ADHD) per interquartile range increase in ln-transformed exposure concentrations. Coefficients from single-exposure logistic regression models (blue circles); and the elastic net logistic regression-selected subset of chemicals remodeled in a multiple-exposure unpenalized logistic regression model (red triangles) are presented. Models were adjusted for child age at linkage, maternal age, and maternal education. Coefficients were similar upon further adjustment for parity, small for gestational age, preterm birth, smoking during pregnancy, pre-pregnancy BMI, cohabitation or marital status, and maternal fatty fish consumption around pregnancy. Missing data was multiply imputed. In elastic net models, exposures selected in the majority of imputed datasets and which were significant ($p < 0.10$) were considered most robust; selection within each imputed dataset was determined by minimization of 10-fold cross-validation binomial deviance (Friedman et al., 2010). See Tables S5–S6 for numerical results. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reported adverse associations between prenatal or child serum concentrations of PFOS or PFOA and behavioral or ADHD symptoms in girls, and not in boys (Goudarzi et al., 2016; Oulhote et al., 2016; Stein et al., 2014). An effect of PFOS on females only is plausible, since estrogen plays a critical role in brain programming (Bale et al., 2010), while PFOS is an estrogen receptor agonist in a number of experimental models (Benninghoff et al., 2011; Du et al., 2013). However, a large, prospective nested case-control study in the Danish National Birth Cohort with median maternal serum PFOS concentrations of 27.4 ng/mL did not find these sex differences, or any other consistent associations between prenatal PFAS exposures and registry-based ADHD (Liew et al., 2015b). Other prospective studies of prenatal PFAS exposure and child neurodevelopment have largely been inconsistent or null (Fei and Olsen, 2011; Ode et al., 2014; Oulhote et al., 2016; Strøm et al., 2014), as was breast milk exposure in this cohort at a younger age (Forns et al., 2015). Cross-sectional childhood exposure has been associated with increased odds of ADHD in NHANES (median child serum PFOS concentrations of 22.6 μg/L) (Hoffman et al., 2010), although the association was only apparent for perfluorohexane sulfonate, and not PFOS or PFOA, in the highly contaminated C8 communities in Ohio (Stein and Savitz, 2011).

We identified a reduced odds of ADHD diagnosis in association with early-life *p,p′*-DDT exposure, in contrast to our *a priori* hypothesis that environmental chemical exposures are detrimental to neuropsychological development. Most previous studies assessed *p,p′*-DDE, the primary metabolite of *p,p′*-DDT, in relation to ADHD or related conditions, and the association for *p,p′*-DDE (median breast milk levels: 48.3 ng/g lipid) was null in this study. Prenatal *p,p′*-DDE was associated with total difficulties (Strengths and Difficulties Questionnaire), including conduct problems and hyperactivity, at 5–9 years in the INUENDO (Greenland and Ukraine) cohort (Rosenquist et al., 2017). Other studies have generally reported null or near-null associations (Grandjean et al., 2012; Strøm et al., 2014), including the largest study to date on *p,p′*-DDE and ADHD, a European pooled analysis in 4437 mother-child pairs in which the average of the cohorts' median estimated child blood levels at birth was 156.7 ng/g lipid (Forns et al., 2018).

HCB had a non-linear association with ADHD: we observed increasing risk in the low-level exposure range, which switched to a decreasing risk at concentrations above 8 ng/g lipid in a non-parametric GAM analysis. Experimental evidence supports that HCB is neurotoxic; *e.g.*, HCB affected neuronal differentiation and inhibited neurite development in GABAergic neurons in a mouse model (Addae et al., 2013). Previously, prenatal HCB exposure has been associated with an increased risk of poor social competence and teacher-reported ADHD-related scores at 4 years in Spain (Ribas-Fito et al., 2007), and deficits in child cognition (but not hyperactivity and inattention) at 4 years in Greece (Kyriklaki et al., 2016). However, the recently published European pooled analysis of HCB (in which the average of the cohorts' median estimated child blood levels at birth was 41.0 ng/g lipid) found

no association with risk of ADHD (Forns et al., 2018). We hypothesize that the decrease in risk observed at higher concentrations could be related to live-birth bias (Liew et al., 2015a). If higher HCB exposures cause increased pregnancy loss, as previously observed in a contaminated population (Jarrell et al., 1998), and as indicated by its association with SGA (Eggesbø et al., 2009), this competing risk coupled with unmeasured confounding could bias HCB–ADHD associations towards null or induce an apparent protective association due to collider stratification bias. This could also apply to the inverse association observed between *p,p′*-DDT and ADHD, as *p,p′*-DDE exposure has also been associated with pregnancy loss (Longnecker et al., 2005). However, this is speculative, and the potential for bias debatable (Basso, 2016; Schisterman and Sjaarda, 2016), especially since other studies report no associations between pregnancy loss and these compounds (Weselak et al., 2008).

We also observed a novel and robust association between breast milk concentrations of β-HCH and increased ADHD. The epidemiologic evidence for the effects of β-HCH, a compound structurally similar to HCB, on neuropsychological development is limited. In a cross-sectional analysis of a U.S. cohort (NHANES; $n = 2546$), urinary 2,4,6-trichlorophenol, a metabolite of certain OCPs including HCB and HCHs, was associated with parent-reported ADHD (Xu et al., 2011). Our findings suggest that this compound should be further investigated for neurotoxicity.

We did not find clear associations for PCBs in relation to ADHD diagnosis. Most previous studies have reported null or near-null associations for PCBs (Strøm et al., 2014), although the sample sizes have often been small (Neugebauer et al., 2015). One study near a PCB-contaminated harbor in New Bedford, Massachusetts, USA ($n = 573$) reported associations between PCB-153 (cord serum levels, median 38 ng/g lipid) and teacher-reported ADHD-behaviors and tests reflecting inattention and impulsivity around 8 years of age (Sagiv et al., 2010; Sagiv et al., 2012), with stronger associations observed for prenatal compared to postnatal exposure estimates (Verner et al., 2015). However, the European pooled analysis of PCB-153 (in which the average of the cohorts' median estimated child blood levels at birth was 47.9 ng/g lipid) found no association with risk of ADHD (Forns et al., 2018). The differences between the New Bedford and European studies could be due to study sample size or a different underlying mix of PCB congeners.

We also did not find clear evidence that PBDEs were associated with ADHD. We found suggestive evidence that BDE-47 was associated with an increased risk of ADHD and BDE-153 with a decreased risk. Several smaller studies ($n = 62$–285) reported associations between prenatal and postnatal PBDE exposures and inattention and hyperactivity in young school-aged children (Chen et al., 2014; Gascon et al., 2011; Hoffman et al., 2012; Roze et al., 2009). In the CHAMACOS cohort in California, prenatal ΣPBDE exposure was associated with various measures of attention and executive functioning at ages 9, 10.5, and 12 years (Sagiv et al., 2015b). A potential explanation for the discrepancy with our results might be that the exposure–outcome association exhibits a threshold, and the U.S. populations generally have higher PBDE exposure due to stringent furniture and product flammability regulations; for example, the median prenatal PBDE-47 concentration was 15.0 ng/g in maternal serum in the CHAMACOS study population, compared to a median concentration of 1.03 ng/g lipid in breast milk in the present Norwegian study population, approximately equivalent to 0.7 ng/g in maternal serum (Mannetje et al., 2012). Furthermore, sub- or pre-clinical continuous measures of ADHD-related behaviors or traits may have increased statistical power to detect associations compared to case-control analyses (Sagiv et al., 2015a).

4.2. Strengths and limitations

Our study had several strengths, including the prospective design, a relatively large sample size, information on a large number of potential confounders, and objective registry linkage for detection of ADHD cases. We simultaneously assessed the largest number of chemical exposures in breast milk to date in relation to ADHD diagnosis, reducing the potential for confounding bias by correlated co-exposures or detection of false positive associations for correlated yet not-causally associated exposures (Agier et al., 2016). We did not detect substantial correlations between chemical classes, and the co-adjustment model showed little confounding by other chemicals classes for this outcome. This finding could aid the interpretation of other studies that focused on only one chemical class.

We were able to assess early breast milk exposure, which for the lipophilic compounds is a good proxy for *in utero* exposure, and is corroborated by the results of our modeled child blood concentrations at birth. Furthermore, for the lipophilic compounds, we modeled postnatal exposure to 2 years of age, finding no additional effects from exposure during this period. Postnatal exposures are important due to the high rate of neurogenesis and synaptic pruning in the first 2 years of life, and, due to breastfeeding, the infant's concentrations can reach 6 times higher than the mother's (Haddad et al., 2015). The model assumes that all chemicals have the same half-life, ignoring potential differences in partitioning kinetics between serum and breast milk (Mannetje et al., 2012), nevertheless, it substantially improved postnatal exposure assessment in a validation study. For three chemicals (PCB-153, HCB and *p,p′*-DDE), correlations between modeled and measured levels in the child at 6 and 16 months of age were high ($r_s = 0.75$–0.82) (Forns et al., 2018), and performance is expected to be better in this study population with more detailed breastfeeding and weight change data than the Slovak population used for the validation study. However, for PFASs, our early breast milk concentrations do not represent *in utero* exposure, as the composition and concentration in breast milk is substantially different to that in maternal serum (Kärrman et al., 2007). PFASs measured in maternal serum would thus be required to fully disentangle possible prenatal and/or postnatal exposure effects of these chemicals.

Our study had several limitations. As with any epidemiological study, we cannot exclude residual confounding bias or bias amplification due to unmeasured or mismeasured covariates, or misspecification of the causal structure (Pearl, 2011). Adjusting for the study sample selection variables, also mediators, in M2, could have led to collider bias, although there was little evidence of this when comparing the results from the two adjustment models. We did not include several chemical classes of concern, including heavy metals, pyrethroids, and organophosphate pesticides (Marks et al., 2010); however, since the exposure sources and pharmacokinetics differ, the correlations between measured and unmeasured chemical classes are expected to be low, with minimal confounding bias. There is evidence that some micronutrients play a role in the etiology of ADHD (Sonuga-Barke et al., 2013), and may also share dietary exposure sources with the chemicals in lipid-rich foods such as dairy and fish (Caspersen et al., 2016). This could theoretically introduce a negative bias, leading to a reduced risk of POPs on ADHD. However, adjustment for maternal fatty fish intake did not materially influence our results, suggesting limited residual confounding from this source. Statistical power differed between chemicals due to a differing number of samples measured for some chemicals, in part due to the oversampling design. We also cannot rule out differential measurement error of the exposure data, however, we found limited evidence of batch effects across chemical analysis laboratories. Furthermore, differing analytical precision for each chemical could contribute to non-differential measurement error (and variable statistical power in multi-pollutant models), nevertheless, the precision was comparable across the chemical classes (Forns et al., 2016; Thomsen et al., 2010a). Imputing missing exposures had a negligible effect on the estimates as the complete case results were not materially different from those obtained using multiply imputed exposures.

There may have been an incomplete ascertainment of ADHD cases

in the study population. If a child was diagnosed before 2008 (children in this cohort would have been six years or younger), and had no further contact with a specialist, this diagnosis would not be registered in the National Patient Registry, although this is expected to be rare. It is possible that some children presenting symptomatology suggestive of ADHD had not yet received a diagnosis at the time of linkage. The mean age at first diagnosis registered in the National Patient Registry was 8.38 years in a general population sample of children born 2000–2008 (Oerbeck et al., 2017). 119 children (10%) were under the age of 10 years at the time of linkage in the present study population, and restricting analyses to children 10 years of age and older did not materially affect our results. The cumulative incidence of ADHD reached 4.3% for those 14 years of age (at linkage in 2014) in the Norwegian Mother and Child Cohort Study (MoBa, $n = 104{,}846$ children) (Gustavson et al., 2017), compared to 2.1% in the entire HUMIS cohort or 4.6% in the present (oversampled) study population. We were not able to evaluate different subtypes of ADHD, such as the hyperactive *versus* inattentive dimensions.

Finally, we examined a large number of exposure–outcome associations, and these results should be interpreted with caution given the potential for chance findings.

5. Conclusions

In a detailed assessment of 27 environmental chemicals in breast milk, early-life exposure to certain persistent organic pollutants was associated with risk of ADHD. Specifically, we report a novel association with β-HCH that requires replication, and, additional evidence of an effect of PFOS in females only. Protective effects from *p,p′*-DDE and HCB may be due to live birth bias, unmeasured residual confounding or chance findings. Further studies, including those designed to detect potential sex-specific effects, and pooled analysis of cohorts to obtain large enough sample sizes, are warranted to explore the potential neurotoxicity of a broader array of the chemical space.

Competing financial interests

The authors declare that they have no actual or potential competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.01.020.

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