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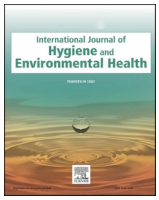

Gestational organophosphate ester exposure and preschool attention-deficit/hyperactivity disorder in the Norwegian Mother, Father, and Child cohort study

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ABSTRACT

Background: Attention-deficit/hyperactivity-disorder (ADHD) is a leading neurodevelopmental disorder in children worldwide; however, few modifiable risk factors have been identified. Organophosphate esters (OPEs) are ubiquitous chemical compounds that are increasingly prevalent as a replacement for other regulated chemicals. Current research has linked OPEs to neurodevelopmental deficits. The purpose of this study was to assess gestational OPE exposure on clinically-assessed ADHD in children at age 3 years.

Methods: In this nested case-control study within the Norwegian Mother, Father, and Child Cohort study, we evaluated the impact of OPE exposure at 17 weeks' gestation on preschool-age ADHD. Between 2007 and 2011, 260 ADHD cases were identified using the Preschool Age Psychiatric Assessment and compared to a birth-year-stratified control group of 549 children. We categorized bis(2-butoxyethyl) phosphate (BBOEP) and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) as values < limit of detection (LOD) (BBOEP N = 386, BDCIPP N = 632), ≥LOD but < limit of quantification (LOQ) (BBOEP N = 413; BDCIPP N = 75), or above LOQ (BBOEP N = 70; BDCIPP N = 102). Diphenyl phosphate (DPhP) and di-n-butyl phosphate (DnBP) were categorized as quartiles and also modeled with a log10 linear term. We estimated multivariable adjusted odds ratios (ORs) using logistic regression and examined modification by sex using an augmented product term approach.

Results: Mothers in the 3rd DnBP quartile had 1.71 times the odds of having a child with ADHD compared to the 1st quartile (95%CI: 1.13, 2.58); a similar trend was observed for log10 DnBP and ADHD. Mothers with BDCIPP ≥ LOD but < LOQ had 1.39 times the odds of having a child with ADHD compared to those with BDCIPP < LOD (95%CI: 0.83, 2.31). Girls had lower odds of ADHD with increasing BBOEP exposure (log10 OR: 0.55 (95%CI: 0.37, 0.93), however boys had a weakly increased odds (log10 OR: 1.25 (95%CI: 0.74, 2.11) p-interaction = 0.01].

Conclusions: We found modest increased odds of preschool ADHD with higher DnBP and BDCIPP exposure.

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Abbreviations

ADHD	Attention-deficit/hyperactivity-disorder
BBOEP	Bis(2-butoxyethyl) phosphate
BDCIPP	Bis(1,3-dichloro-2-propyl) phosphate
DnBP	Di-n-butyl phosphate
DPhP	Diphenyl phosphate
EMM	Effect measure modification
LOD	Limit of detection
LOQ	Limit of quantification
MoBa	The Norwegian Mother, Father, and Child Cohort Study
OPE	Organophosphate ester
PAPA	Preschool Age Psychiatric Assessment PBDEs Polybrominated diphenyl esters
PCBs	Polychlorinated biphenyls
TBOEP	Tris (2-butoxethly) phosphate
TDCIPP	Tris (1,3-dichloro-2-propyl) phosphate
TnBP	Tri-n-butyl phosphate
TPhP	Triphenyl phosphate

1. Introduction

Organophosphate esters (OPEs) are ubiquitous chemicals, generally used as flame retardants and/or plasticizers (van der Veen and de Boer, 2012), found in a multitude of everyday items such as household furniture (van der Veen and de Boer, 2012), electronics (van der Veen and de Boer, 2012), baby products (Stapleton et al., 2011), personal care products (Ingle et al., 2019a, 2020a), and nail polish (Ingle et al., 2019a, 2020a; Mendelsohn et al., 2016). OPE usage has substantially increased over time as a replacement for other regulated chemicals such as polybrominated diphenyl esters (PBDEs) and polychlorinated biphenyls (PCBs), that have been previously phased out due to their potential toxicity, ability to bioaccumulate, and environmental persistence (van der Veen and de Boer, 2012; Morelle, 2016; European Union (EU), 2001). Although OPEs do not bioaccumulate, they can leach into the surrounding environment where they are capable of entering the human body through inhalation, dermal absorption, and/or ingestion of contaminated food or water (van der Veen and de Boer, 2012).

There has been growing concern regarding OPEs due to their ubiquitous distribution and potential for adverse human health effects. Recent epidemiological studies have found associations between OPEs and adverse neurodevelopmental- (Lipscomb et al., 2017; Castorina et al., 2017; Doherty et al., 2018, 2019; Choi et al., 2021a), thyroid-based- (Hoffman et al., 2017; Preston et al., 2017), reproductive- (Carignan et al., 2018a; Meeker et al., 2009, 2013a), respiratory- (Bamai et al., 2018; Araki et al., 2014, 2018), and dermal- (Araki et al., 2018) endpoints; however, some studies have found no association (Deziel et al., 2018; Canbaz et al., 2016). OPE exposure during the gestational period is of significant interest because OPEs can cross the placental barrier (Ding et al., 2016; Wang et al., 2013) and may accumulate in the placenta (Ding et al., 2016) and/or amniotic fluid (Bai et al., 2019).

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder commonly diagnosed in childhood, but symptoms of ADHD may emerge as early as the preschool period (AAo, 2019). Estimates of the persistence of ADHD from preschool through childhood vary (Overgaard et al., 2022a; Riddle et al., 2013; Lahey et al., 2016), however early identification and treatment of ADHD may have benefits, due to the substantial adverse individual (de Zeeuw et al., 2017; Galera et al., 2009; Rokeach and Wiener, 2018; Sarkis, 2014; Quintero et al., 2017; Lee et al., 2016a) and economic (Sciberras et al., 2017; Gupte-Singh et al., 2017; Le et al., 2014; Quintero et al., 2018; Cadman et al., 2012; Kotsopoulos et al., 2013) burdens associated with this disorder.

Several studies suggest gestational OPE exposure is associated with risk of ADHD or ADHD-like behaviors (Castorina et al., 2017; Doherty et al., 2019; Choi et al., 2021a). The only study to date to evaluate this association with ADHD as a clinical diagnosis was conducted by Choi (2021) et al. using a nested case-control study, also within the Norwegian Mother, Father, and Child cohort (MoBa) (Choi et al., 2021a). Choi et al. examined gestational OPE concentrations in relation to a diagnostic code registration of ADHD among children in the Norwegian National Patient Registry (NPR) (Choi et al., 2021a). Choi et al. reported that higher gestational concentrations of diphenyl phosphate (DPhP) and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) were associated with elevated risk of childhood ADHD registration. While preschool ADHD is correlated with childhood ADHD, it is not perfectly predictive (Overgaard et al., 2022a; Riddle et al., 2013; Lahey et al., 2016). Furthermore, diagnostic registrations of ADHD may be affected by variability in clinical practice, over-representation of more severe and disruptive cases, and an under-representation of girls. To date, all the studies we identified that evaluated associations of individual OPEs on ADHD, assessed and found evidence of an association between BDCIPP and ADHD or ADHD-like symptoms. Similarly, the majority of such studies have found evidence of associations with DPhP. Fewer consistent patterns exist for other OPEs, and, overall, there is a lack of agreement as to the existence of sex-specific effects (Castorina et al., 2017; Doherty et al., 2019; Choi et al., 2021a), with Choi et al. observing larger adverse associations among girls (Choi et al., 2021a) and three other studies observing no appreciable sex-related effect measure modification (EMM) (Castorina et al., 2017; Doherty et al., 2019). As such, the purpose of this study is to examine whether gestational OPE exposure may impact early manifestation of ADHD, specifically in relation to preschoolers.

A potential causal link between OPEs and ADHD could result in public health interventions with a meaningful impact through regulatory changes. As such, this study has the potential to identify or dismiss a modifiable cause of one of the leading neurodevelopmental disorders in preschoolers worldwide. To address this important question, we leverage a nested Preschool ADHD Substudy of MoBa, in which a high-quality standardized on-site clinical evaluation of all children was conducted, to determine the potential impact of OPEs on preschool ADHD. To evaluate potential sex differences in associations, we examined sex-related modification of the OPE-ADHD association in preschoolers.

2. Material and methods

2.1. Study population

MoBa is an ongoing, prospective population-based cohort study of pregnant Norwegian-speaking women enrolled between 1999 and 2008 (Magnus, 2007; Magnus et al., 2016). Women consented to participation at their first ultrasound appointment (~17 weeks' gestation) and, upon enrollment, blood and urine samples were collected. Questionnaires were completed by mothers at 17-, 22-, and 30-weeks' gestation as well as longitudinally after birth (Magnus et al., 2016). Of the original 227,702 pregnancies invited, 40.7% (N = 112,908 pregnancies; 95,200 women) agreed to participate, of which ~107,000 children are still actively enrolled (Magnus et al., 2016; Kamai et al., 2021).

This ADHD Substudy of MoBa consisted of children born between April 2004 and January 2008 that were the result of a singleton pregnancy, resided within close proximity to Oslo, did not meet criteria for the Autism Birth Cohort study (Stoltenberg et al., 2010), and with completed 36-month postnatal questionnaire (Engel et al., 2018a). Included in the 36-month questionnaire were 11 questions aimed at identifying children displaying ADHD-like behaviors (Overgaard et al., 2022b; Biele et al., 2022). These questions included 5 from the Diagnostic and Statistical Manual of Mental Disorders, Version 4, Text Revision (Association, 2000) (DSM-IV-TR; easily distracted, difficulty

waiting his/her turn, difficulty sustaining attention, talks excessively, and does not seem to listen) and 6 from the Child Behavior Checklist/1.5–5 (Achenbach and Rescorla, 2010) (can't concentrate, can't sit still, can't stand waiting, demands must be met immediately, gets into everything, and quickly shifts activities) (Biele et al., 2022). From these questions, we developed a quantitative index, referred to as the "sampling screener" (Biele et al., 2022). Children from the ADHD eligible population that scored in the 90th percentile or higher on this screener were automatically invited to participate in an on-site clinical evaluation (N = 2798) as well as a small random sample of children from the ADHD eligible population (N = 654). Of the original 3452 pregnancies invited, 1195 (34.6% participation rate) agreed to participate, 870 of which had a maternal urine sample available. This substudy of children that underwent clinical examination is referred to as the MoBa ADHD Substudy. Children that participated in the clinical evaluation were between 3.1 and 3.8 years of age (Ahmad and Warriner, 2001; Skogan et al., 2015). A flow diagram outlining selection into our current study can be viewed in Supplemental Fig. 1. The original study design was a case-cohort design, but we excluded cases from the referent sub-cohort in our study. As such, the current study design is a case-control design; control selection is discussed in more detail in the section 'selection of controls'.

2.2. Selection of preschool ADHD cases

In contrast to the study by Choi et al. who used primarily childhood ADHD cases as the study outcome (i.e. children ages 6–11 years), we utilized children with preschool ADHD defined as children ages 2–5 years (all children in this study were 3 years old) (Choi et al., 2021a; Surén et al., 2012). Preschool ADHD differs from childhood ADHD in relation to symptom occurrence (proportion of hyperactive vs inattentive cases) and symptom severity, with both occurrence and severity declining between preschool and late childhood, particularly in relation to hyperactivity (Overgaard et al., 2022a; Lahey et al., 2005, 2016; Leopold et al., 2016; Curchack-Lichtin et al., 2014). As such, preschool ADHD is predictive but not perfectly correlated with childhood ADHD (Overgaard et al., 2022a; Riddle et al., 2013; Lahey et al., 2016).

In our study, preschool ADHD status was determined using the Preschool Age Psychiatric Assessment (PAPA) (Egger and Angold, 2004). PAPA is an interviewer-based psychiatric instrument, validated in children 2–5 years, and provides information on the magnitude and frequency of neurodevelopmental symptoms set forth in the DSM-IV-TR (Association, 2000; Egger and Angold, 2004; Egger et al., 2006). PAPA is not equivalent to a clinical diagnosis as this requires a more in-depth evaluation from multiple sources. In this study, trained graduate psychology students conducted standardized and structured psychiatric interviews using PAPA with a caregiver (generally the mother) under the supervision of a child psychologist or psychiatrist; all parents of children who participated in the 1-day clinical exam were interviewed with PAPA (Rohrer-Baumgartner et al., 2014). Preschool ADHD symptoms were counted as present if they persistent for 3-months or more across at least 2 settings (Egger and Angold, 2004). The inter-rater reliability of PAPA for preschool ADHD symptoms in our study was assessed by having a second blinded rater rescore the audiotapes of 79 interviews and found to be high (total preschool ADHD symptoms interclass correlation coefficient: 0.98) (Øvergaard et al., 2018). At the end of the ADHD section in PAPA, an impairment/impact section was also administered to participants who reported at least one ADHD symptom (Bendiksen et al., 2017). This section consisted of six functional domains (family relationships, friends, learning, play/leisure activities, child's quality of life, and family burden) (Bendiksen et al., 2017). Each functional domain was scored on a 4-point Likert scale (0, 1, 2, or 3 points) for a possible total of 18 points (Bendiksen et al., 2017). Impairment was considered present when the child scored 2 or higher overall (sum score) (Kamai et al., 2021).

In this study, a child was classified as meeting clinical criteria for ADHD if they had 6 or more symptoms (from a possible 9 symptoms) on PAPA and was also scored as having an impairment (Kamai et al., 2021; Egger and Angold, 2004). Children who presented with 6 or more preschool ADHD symptoms but no impairment or 3 to 5 preschool ADHD symptoms and an impairment were classified as having subclinical ADHD (Kamai et al., 2021). For this study, we considered children to have preschool ADHD if they score in the clinical (n = 114) or subclinical (n = 146) range on the PAPA for a total of 260 children hereafter referred to as "preschool ADHD cases" (Kamai et al., 2021; Egger and Angold, 2004).

2.3. Selection of controls

We selected a birth-year stratified random sample of participants, representative of the ADHD eligible population (i.e., representing the exposure distribution that gave rise to the cases), as a comparison group for the preschool ADHD cases (n = 556). This random sample was frequency matched to preschool ADHD cases on birth year and did not undergo clinical evaluation. Because only 7 preschool ADHD cases were also included in the random sample, we treated these children as preschool ADHD cases only, resulting in 549 children in the final control group.

2.4. Measurement of organophosphate ester (OPE) metabolites

Details regarding urine collection and analysis have been previously published (Choi et al., 2021a; Rønningen et al., 2006; Paltiel et al., 2014). Briefly, urine samples were collected ~17 weeks' gestation at which time they were shipped unrefrigerated overnight to the central biorepository in Oslo, Norway for immediate processing (Choi et al., 2021a; Rønningen et al., 2006; Paltiel et al., 2014). Bacterial growth was prevented during shipment through the inclusion of chlorhexidine (Hoppin et al., 2006). The majority of samples were received within one (66%) or two (10%) days of collection. All samples were processed the day of receipt and less than 1% underwent freeze-thaw cycles (Hoppin et al., 2006). Standard operating procedures were derived for comprehensive quality insurance. A laboratory information management system was used to prevent sample identity errors and track specimens.

In this study, we measured 4 OPE metabolites using ultra performance liquid chromatography (UPLC) coupled with quadrupole-time-of-flight (Cequier et al., 2014a; Choi et al., 2021b). These metabolites were di-n-butyl phosphate (DnBP), DPhP, BDCIPP, and bis (2-butoxyethyl) phosphate (BBOEP), which correspond with the parent compounds tri-n-butyl phosphate (TnBP), triphenyl phosphate (TPhP), tris (1,3-dichloro-2-propyl) phosphate (TDCIPP), and tris (2-butoxethly) phosphate (TBOEP) respectively.

Quality control procedures have been detailed previously (Choi et al., 2021b; Engel et al., 2018b). Briefly, 2 in-house control samples and 4–6 quality controlled pooled urine samples were included per analytic batch to assess assay precision and batch-batch variability respectively and cases and controls were randomized to batch. To account for urine dilution, we measured specific-gravity using a pocket refractometer (PAL-10S) from Atago.

2.5. Statistical analysis

Data analysis was based on version 9 of the quality-assured MoBa data files. We selected potential confounders *a priori* from the OPE-ADHD literature and assessed their relationship via direct acyclic graph (DAG) (Supplemental Fig. 2). (Pearl and Robins, 1995) From this DAG, we determined a minimally-sufficient adjustment set (MSS). The covariates in the MSS included maternal fish intake (Sala et al., 2022; Choi et al., 2022), birth year, child sex, family income, maternal age at delivery, and maternal education. From the Medical Birth Registry of Norway, we obtained maternal age at delivery, child sex (male/female), and birth year. We derived information on maternal education (<4-year

college degree, 4-year college degree, post-graduate degree or higher), marital status (married, single/co-habiting), parity (nulliparous/parous), financial difficulty in the past 6 months (yes/no), and maternal smoking during pregnancy (yes/no) and maternal drinking during pregnancy (yes/no) from the 17-gestational-weeks' questionnaire. We determined maternal fish intake from a semiquantitative food frequency questionnaire administered at 22-gestational-weeks' and calculated servings per day for total fish consumption by summing daily, weekly, and monthly intake (Brantsæter et al., 2008). Additionally, we derived a binary indicator of maternal ADHD symptoms via the Adult ADHD Self-Report Scales (ASRS), a validated assessment for adult ADHD symptoms that was completed as part of the 36-month questionnaire (Kessler et al., 2005). As maternal ADHD may confound the OPE-offspring ADHD relationship due to its high heritability (Banerjee et al., 2007; Silberg et al., 2015; Freitag et al., 2010; Faraone et al., 2005) and potential to affect OPE exposure levels through an unknown confounding pathway, we considered maternal ADHD for inclusion in our models in addition to covariates in the MSS. To address concerns regarding positivity, we removed variables that had a minimal impact on the final effect estimates and did not improve model fit for parsimony. Covariates in the final models included total fish consumption, maternal education, financial difficulty, maternal age, and child sex.

As BBOEP and BDCIPP both had more than 50% of their values below the limit of detection (LOD), we categorized these 2 OPEs as $<$ LOD, LOD to $<$ limit of quantification (LOQ), and $\geq$ LOQ because, imputation of these variables in a continuous form could potentially introduce bias (Lubin et al., 2004). Next, we adjusted OPE concentrations for urine dilution using specific-gravity as described by Hauser et al. (2004) et al. (Hauser et al., 2004) For other OPEs, we imputed exposure values below the LOD and missing covariate data from a log-normal distribution using a multivariate imputation by chained equation (MICE) approach ($m = 20$), with exposure data truncated at the LOD, and conditional on outcome, exposure, and other covariates. From this, we obtained summary estimates via Rubin's rules for imputation (Lubin et al., 2004; Rubin, 1987; Harel et al., 2018; Allison, 2001).

We calculated outcome-stratified Spearman correlations between non-imputed and imputed specific-gravity-corrected OPEs to determine correlations between exposure variables. We then determined optimal functional forms of OPEs and covariates from bivariate assessments and multivariable logistic regression models, with an emphasis on minimizing Akaike Information Criterion. Next, we created quartile cut-points for DPhP and DnBP concentrations based on the birth-year-stratified control group to represent the exposure distribution in the study base. We modeled DPhP and DnBP continuously using a log10 transformation and as quartiles to allow for nonlinear and/or non-monotonic trends. To estimate the association between each OPE and preschool ADHD, we calculated odds ratios (ORs) using logistic regression models, adjusted for covariates.

We assessed child sex as a potential effect measure modifier on the multiplicative scale using an augmented product term approach (Buckley et al., 2017). We considered EMM to be present if the p-value for the interaction term between child sex and OPE was at or below the *a priori* threshold of 0.10. All analyses were performed using SAS 9.4 (Cary, NC).

2.6. Sensitivity analyses

To assess the impact of imputing missing covariate data, we reran models without covariate imputation. To account for the potential influence of correlated OPE metabolites, we reran models co-adjusting for the other three main metabolites (one at a time). To investigate any potential batch-effects, we reran models excluding one batch at a time to determine if the exclusion of any single batch meaningfully impacted any of the final associations.

3. Results

Fifty-six percent of preschool ADHD cases were boys; however, child sex was equally distributed in our control group (Table 1). Mothers in our study averaged ~30 years of age at delivery. Mothers of children with preschool ADHD were less likely to be college educated (63% vs 74%) and more likely to be nulliparous (60% vs 49%), smoke during pregnancy (24% vs 14%), and report experiencing more financial difficulty (26% vs 14%) compared to mothers of children in the control group (Table 1). No covariate in our study had more than 10% missingness (Table 1).

DPhP and DnBP were usually detected, with greater than 90% of values above the LOD; as noted above, BBOEP and BDCIPP were less frequently detected (Table 2). Geometric means and percentiles for OPE metabolite measures were comparable between preschool ADHD cases and controls. OPE metabolites were minimally correlated, with Spearman correlations ranging from |0.020| to |0.345| for non-imputed measures (Supplemental Table 1A); imputation had little effect on these correlations (Supplemental Table 1B).

Mothers in the 3rd DnBP quartile had 1.71 times the odds (95%CI: 1.13, 2.58) of having a child with preschool ADHD compared to the 1st quartile; however, across quartiles of DnBP, the trend did not appear monotonic (Fig. 1; Supplemental Table 2). Similarly, increased log10

Table 1
Characteristics of a nested case-control study of preschool ADHD in MoBa, 2004–2007.

	Preschool ADHD group *Mean (SD)* or N (%)	Controls[a] *Mean (SD)* or N (%)
Total N	260	549
Maternal age at delivery (years)	*30.0 (4.05)*	*30.9 (4.23)*
Missing	0 (0.0)	2 (0.4)
Child sex, N		
Male	145 (55.8)	275 (50.1)
Female	115 (44.2)	274 (49.9)
Missing	0 (0.0)	0 (0.0)
Maternal education, N (%)		
Not a college graduate	92 (35.4)	121 (22.0)
College graduate	108 (41.5)	237 (43.2)
Post-college education	56 (21.5)	168 (30.6)
Missing	4 (1.5)	23 (4.2)
Marital status		
Single/Co-inhabiting	146 (56.2)	257 (46.8)
Married	113 (43.5)	287 (52.3)
Missing	1 (0.4)	5 (0.9)
Parity		
Nulliparous	156 (60.0)	270 (49.2)
Parous	104 (40.0)	277 (50.5)
Missing	0 (0.0)	2 (0.4)
Maternal ADHD symptoms	33 (12.7)	21 (3.8)
Missing	2 (0.8)	12 (2.2)
Maternal fish intake (g/day)	*26.2 (18.33)*	*27.4 (19.05)*
Missing	4 (1.5)	7 (1.3)
Any smoking in 1st or 2nd trimester	62 (23.8)	76 (13.8)
Missing	1 (0.4)	6 (1.1)
Any alcohol consumption in 1st or 2nd trimester	32 (12.3)	65 (11.8)
Missing	21 (8.1)	44 (8.0)
Experienced financial difficulty in the past year[b]	67 (25.8)	75 (13.7)
Missing	1 (0.4)	2 (0.4)
Birth year		
2004	26 (10.0)	55 (10.0)
2005	62 (23.9)	131 (23.9)
2006	90 (34.6)	190 (34.6)
2007	82 (31.5)	173 (31.5)
Missing	0 (0.0)	0 (0.0)

[a] Controls are birth-year-stratified to account for changes in exposure or outcome frequency attributable to birth year.
[b] Past year refers to the year before enrollment (around 17 weeks' gestation).

Table 2
Gestational specific gravity-corrected OPE metabolite distribution in a nested case-control study of preschool ADHD in MoBa, 2004–2007.

Exposure	Geometric Mean[a]	Geometric SD[a]	Min	25%	50%	75%	Max	LOD[b]	% ≥ LOD[b]	LOQ[c]	% ≥ LOQ[c]
DPhP (ng/mL)								0.03		0.10	
Preschool ADHD (N = 260)	0.48	2.95	<LOD	0.29	0.49	0.93	37.22		96.5%		92.3%
Controls[d] (N = 549)	0.46	2.93	<LOD	0.26	0.48	0.88	11.16		96.5%		93.4%
DnBP (ng/mL)								0.07		0.20	
Preschool ADHD (N = 260)	0.26	2.18	<LOD	0.17	0.25	0.37	10.93		95.4%		66.5%
Controls[d] (N = 549)	0.25	2.36	<LOD	0.15	0.23	0.38	25.59		92.7%		58.5%
BBOEP (ng/mL)	–	–						0.07		0.20	
Preschool ADHD (N = 260)	0.08	2.01	<LOD	<LOD	<LOD	0.13	0.84		44.2%		12.3%
Controls[d] (N = 549)	0.09	2.13	<LOD	<LOD	<LOD	0.13	3.40		43.7%		14.6%
BDCIPP (ng/mL)								0.17		0.50	
Preschool ADHD (N = 260)	0.17	2.40	<LOD	<LOD	<LOD	<LOD	16.83		20.4%		10.8%
Controls[d] (N = 549)	0.18	2.72	<LOD	<LOD	<LOD	<LOD	96.92		19.5%		12.2%

[a] Values below the limit of detection (LOD) were imputed using LOD/ $\sqrt{2}$ for the geometric mean and standard deviation.
[b] Limit of detection.
[c] Limit of quantification.
[d] Controls are birth-year-stratified to account for changes in exposure or outcome frequency attributable to birth year.

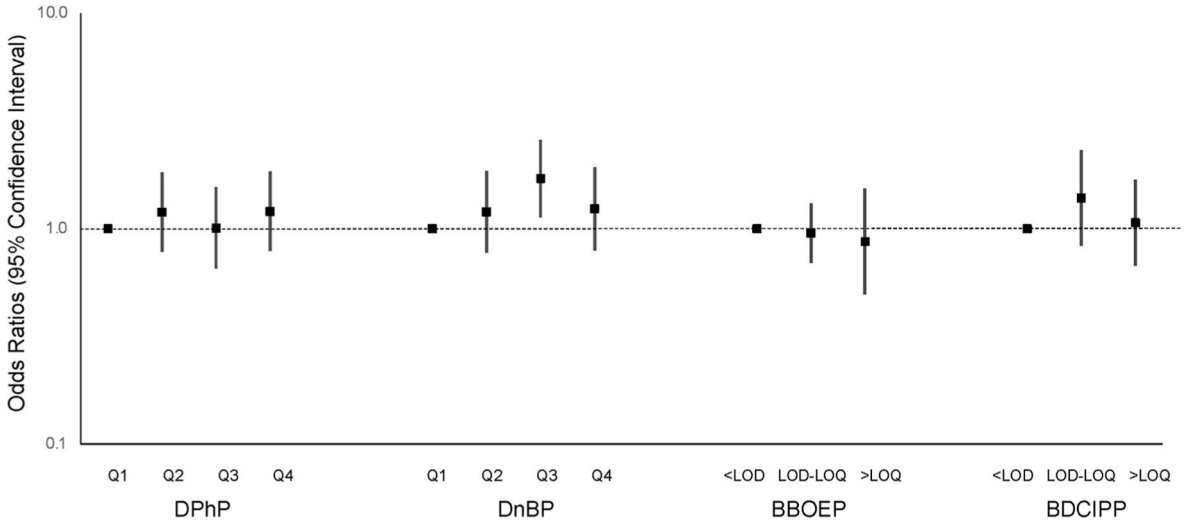

Fig. 1. Associations between quartiles of DPhP and DnBP and categorized measures of BBOEP and BDCIPP, based on their limits of detection and quantification respectively, in relation to preschool ADHD in a nested case-control study of preschool ADHD in MoBa, 2004–2007 (N = 809). All models are from an imputed logistic regression model adjusted for total fish consumption, maternal education, financial difficulty, and maternal age.

DnBP exposure was also association with higher odds of ADHD [OR: 1.30; 95%CI: 0.86, 1.97); Table 3]. Some quantile- or category-specific ORs were elevated, for example BDCIPP measures ≥ LOD but < LOQ had 1.39 times the odds (95%CI: 0.83, 2.31) of having a child with preschool ADHD compared to those with BDCIPP measures < LOD (Fig. 1; Supplemental Table 2). However, we did not observe monotonic patterns of association for any OPE. Results from multiply-imputed models were consistent with those from a complete case analysis (Supplemental Table 2). Furthermore, associations were not meaningfully affected by mutual adjustment for any other OPE metabolite (Supplemental Table 3), and no batch-effects were observed (Supplemental Figs. 3A–3D).

A product term between BBOEP and child sex was statistically significant, suggesting multiplicative EMM (p-interaction 0.01; Table 3). Specifically, girls had lower conditional odds of preschool ADHD with BBOEP exposure above the LOD, whereas the result for boys suggested associations that were null or in the opposite direction. [Girls: log10 OR: 0.55 (95%CI: 0.37, 0.93); Boys: log10 OR: 1.25 (95%CI: 0.74, 2.11); p = 0.01]. No notable EMM was observed for any other OPE.

4. Discussion

Using a nested case-control subset of MoBa, we examined the relationship between gestational OPE exposure and preschool ADHD. We found some evidence that gestational exposure to DnBP and BDCIPP may be associated with increased odds of ADHD, although associations were modest in magnitude and did not follow a monotonic exposure-response trend. We observed evidence of heterogeneity by child sex for BBOEP and preschool ADHD, with girls having lower odds of preschool ADHD with increased exposure, while boys trending in the opposite direction. However, no other OPE association evidenced modification by child sex.

There is a very limited epidemiological literature on gestational exposure to OPEs and child neurodevelopment; however, substantial concern exists for their potential impact on human neurodevelopment due to their ubiquitous distribution and potential to disrupt neurological process (Dishaw et al., 2011; Gu et al., 2018). Studies on PC12 human cells have found OPEs may inhibit DNA synthesis (Dishaw et al., 2011) and/or total acetylcholinesterase activity (Gu et al., 2018), disrupt cell proliferation (Gu et al., 2018), and increase neurodifferentiation into cholinergic and/or dopaminergic phenotypes (Dishaw et al., 2011).

Four epidemiological studies have assessed OPE exposure and ADHD

Table 3
Assessment of multiplicative effect measure modification by child sex for the relationship between gestational OPEs and preschool ADHD in a nested case-control study of preschool ADHD in MoBa, 2004–2007.

Exposure	Combined[a,b,c]	Boys[d,e]	Girls[d,f]	P-value[h]
	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	
Log10 exposure				
DPhP	1.07 (0.77, 1.48)	0.95 (0.61, 1.49)	1.23 (0.76, 2.00)	0.45
DnBP	1.30 (0.86, 1.97)	1.47 (0.84, 2.57)	1.12 (0.60, 2.11)	0.54
Exposure ≥ LOD[g]				
BBOEP	0.94 (0.69, 1.28)	1.31 (0.86, 2.00)	0.58 (0.37, 0.93)	0.01
BDCIPP	1.19 (0.83, 1.71)	1.25 (0.74, 2.11)	1.07 (0.63, 1.80)	0.67

[h]P-value is derived from organophosphate ester*sex interaction·

[a] Refers to full model without the incorporation of interaction terms.

[b] Combined model contains 260 Preschool ADHD cases and 549 birth-year-stratified controls.

[c] All models are derived from an imputed logistic regression model adjusted for total fish consumption, maternal education, financial difficulty, maternal age, and sex.

[d] Stratum-specific estimates are derived from models that additionally include interaction terms for each included variable using an augmented product term approach to assess effect measure modification by sex.

[e] Model for boys contains 145 Preschool ADHD cases and 275 birth-year-stratified controls.

[f] Model for girls contains 115 Preschool ADHD cases and 274 birth-year-stratified controls.

[g] Limit of detection.

or ADHD-like symptoms, all observing associations with some OPE metabolites (Lipscomb et al., 2017; Castorina et al., 2017; Doherty et al., 2019; Choi et al., 2021a). The only study to investigate behavioral symptoms in the preschool period was by Doherty et al. (2019) et al. (Doherty et al., 2019) They found higher gestational DPhP and BDCIPP exposure was related to more behavioral and externalizing problems in 3 year-old children in North Carolina, with both DPhP and BDCIPP associated with more attention problems and BDCIPP related to greater hyperactivity (Doherty et al., 2019). However, our results were not entirely consistent with their study. We found little evidence of association with DPhP exposure, and only slightly elevated odds of ADHD in relation to BDCIPP; Doherty et al. did not evaluate DnBP or BBOEP so comparisons could not be made for these OPEs. Differences between our study and Doherty et al. may be attributed to differences between time of exposure collection or differences in OPE levels between our study populations. For example, Doherty et al. collected urine samples later in pregnancy, specifically around 27 weeks' gestation, whereas urine samples in MoBa were collected at approximately 17 weeks' gestation. OPEs have low to moderate reliability when measured ~10 weeks' apart (Percy et al., 2020; Carignan et al., 2018b; Zhao et al., 2019; Kuiper et al., 2020; Ingle et al., 2019b, 2020b; Meeker et al., 2013b; Romano et al., 2017), therefore it could be that associations vary due to differences in an underlying susceptible window (de Graaf-Peters and Hadders-Algra, 2006). Furthermore, in general, exposure levels in our study were somewhat lower than Doherty et al., which would likely have impacted our precision and statistical power for tests of association.

Our results should also be interpreted in conjunction with those of Choi (2021) et al., who also used a nested substudy of MoBa but leveraged the NPR for registered ADHD diagnoses mostly in childhood (i.e. ages 6–11 years; 12 preschool ADHD cases in this study overlapped with NPR registered ADHD cases in the Choi et al. study) (Choi et al., 2021a; Surén et al., 2012). Similar to ours, Choi et al. found a weak trend between higher BDCIPP exposure and greater ADHD risk, but no association with BBOEP (Choi et al., 2021a). Choi et al. also observed greater than medium DPhP exposure was associated with higher ADHD risk, although found no associations for DnBP exposure (Choi et al., 2021a). However, it is important to note that the cases included their study were ADHD registrations in the NPR. Because a gold standard for ADHD diagnosis does not exist, medical registry cases may be affected by provider-level differences in diagnostic procedures. Additionally, as children had to be referred to a specialist provider for evaluation, more severe or more disruptive ADHD cases are likely to be referred, whereas primarily inattentive cases, found more often among girls, may be under-represented. As such, the Choi et al. study had fewer ADHD cases among girls as compared to our study [Choi et al.: 28% ADHD cases were girls; our study: 44% ADHD cases were girls]. It is also important to note that while the demographic and behavioral risk factors commonly associated with ADHD in childhood (prenatal smoking, young maternal age, low maternal education, skewed toward male sex) were also found to be over-represented among our preschool ADHD cases, preschool ADHD symptoms do not always persist into childhood (Riddle et al., 2013; Lahey et al., 2016). It has been suggested that the persistence of the preschool ADHD phenotype is ~90% over the course of childhood and adolescence (Riddle et al., 2013; Lahey et al., 2016). Therefore, differences between our results and those of Choi et al. may be attributable to etiological differences between preschool ADHD and childhood ADHD.

Sexually dimorphic differences of the relationship between OPEs and ADHD have been observed in humans, with female-only dysregulation of thyroid hormones(Xu et al., 2015; Liu et al., 2016), and through androgen-based mechanisms (Kojima et al., 2013, 2016; Ren et al., 2018; Reers et al., 2016). The epidemiological findings on EMM of the OPE-ADHD relationship by child sex have been mixed with one study finding larger adverse effects in girls compared to boys (Choi et al., 2021a) and two studies generally observing no associations (Castorina et al., 2017; Doherty et al., 2019). However, all studies to date (including ours) have had low statistical power to assess EMM, which could result in the observed study differences. Although we found a statistically significant sex-related EMM for BBOEP in our study, odds of ADHD were lower with higher exposure to BBOEP among girls, with the opposite pattern found among boys. This was consistent with the only other study on OPEs and ADHD (Choi et al., 2021a) but inconsistent with two other OPE studies evaluating ADHD -related symptoms that observed no appreciable sex-specific effects (Castorina et al., 2017; Doherty et al., 2019). As such, there is a lack of consensus overall as to the presence of sex-related heterogeneity.

Some study limitations should be noted. In our study, OPE exposure was measured using a single spot urine collection at 17 weeks' gestation. This is not ideal as OPEs have relatively short half-lives lasting only 1–5 days (Hou et al., 2016; Lynn et al., 1981) and have been found to have low (DnBP (Percy et al., 2020), DPhP (Percy et al., 2020; Zhao et al., 2019; Kuiper et al., 2020; Ingle et al., 2019b, 2020b; Meeker et al., 2013b; Romano et al., 2017; Hoffman et al., 2014)) to moderate (BDCIPP (Percy et al., 2020; Carignan et al., 2018b; Kuiper et al., 2020; Ingle et al., 2019b; Ingle et al., 2020b; Meeker et al., 2013b; Romano et al., 2017; Hoffman et al., 2014)) reliability when assessed 2–3 months apart (no epidemiological studies on reliability were found for BBOEP). As such, the OPE metabolite measurements in our study may not reflect OPE exposure throughout pregnancy. Although the pregnancy period of susceptibility for OPEs and neurodevelopment is unknown, the second trimester is a particularly sensitive window for brain growth and development, where adverse exposures could be more salient in terms of long-term neurological effects (Vohr et al., 2017; Selevan et al., 2000). However, DPhP is a non-specific metabolite of TPhP and can be produced by several other parent compounds including resorcinol bis (diphenyl phosphate) (Ballesteros-Gomez et al., 2015a), ethyl-hexyldiphenyl phosphate (Ballesteros-Gomez et al., 2015b), and tert-butylphenyl diphenyl phosphate (Heitkamp et al., 1985). Therefore, DPhP concentrations in our study may in part reflect exposure to another parent compound that could have a different toxicity compared

to TPhP. However, DPhP is the field standard biomarker for TPhP, and most previous studies observed an association between gestational DPhP exposure and ADHD or ADHD-like symptoms (Doherty et al., 2019; Choi et al., 2021a). Additionally, because OPE exposure occurs as a mixture rather than in isolation, the potential for co-pollutant confounding, synergistic and/or antagonistic interactions, and/or cumulative (i.e. joint) effects cannot be dismissed, although it is unlikely that our findings represent underestimation of real effects due to these phenomena (Braun, 2017). In our study we found low correlations between our 4 measured OPEs, and, in a sensitivity analysis, mutual adjustment for other OPEs did not impact any of our estimates. Furthermore, although preschool ADHD is a valid measure (AAo, 2019), it has low continuity with childhood ADHD and is difficult to diagnose as many of the symptoms associated with preschool ADHD are considered normative for this age-group (Overgaard et al., 2022a; Frick and Nigg, 2012). This study attempts to minimize the potential for misclassification of ADHD in the preschool period by only assessing these outcomes using a validated instrument specifically designed for preschoolers, PAPA, consisting of an in-person in-depth standardized interview conducted by trained personnel. As a result, these measures provide us greater confidence in their accuracy compared to the use of other methods such as diagnostic codes. Regardless, outcome misclassification for ADHD would not likely strongly impact effect estimates as the misclassification is not expected to be differential by exposure. Finally, there is the possibility that selection bias may affect our results given that only the cases were assessed via an in-person assessment whereas non-cases were not (Hernán et al., 2004).

Our study has several important strengths. This case-control study was nested within the large and well characterized Norwegian Mother, Father, and Child cohort (MoBa). Our preschool ADHD cases were identified using a high-quality and validated clinical assessment tool for the preschool period, the Preschool Aged Psychiatric Assessment. The clinical assessment was found to have high inter-rater reliability and was conducted under the supervision of a child psychologist or psychiatrist (Overgaard et al., 2018). As a result, this study is less likely to suffer from outcome misclassification compared to studies relying on self-report (Frick and Nigg, 2012). This study also utilized biomarkers of OPEs rather than reliance on external measures such as household dust. Biomarkers inherently integrate exposure from all sources, thus accounting for the diverse potential sources of OPE exposure including cars (Brommer et al., 2012; Zhou et al., 2017), residential housing (Meeker et al., 2013a; Zhou et al., 2017; Ali et al., 2012; Cequier et al., 2014b; He et al., 2016), and office spaces (Brommer et al., 2012; Zhou et al., 2017; He et al., 2016), as well as potential exposure from food (Zhang et al., 2016a; Li et al., 2019; Ding et al., 2018) and water (Li et al., 2014; Kim and Kannan, 2018; Lee et al., 2016b). Therefore, utilization of biomarkers in our study rather than external measures has the potential to contribute to greater exposure validity. Additionally, this study also has a good representation of girls (44%) allowing for greater statistical power to assess EMM of the OPE-ADHD relationship by child sex. Our study also fills an important research gap on the OPEs DnBP and BBOEP as TBOEP and TnBP are frequently reported as two of the highest OPE concentrations in dust (particularly in Europe) and have been found to be associated with developmental toxicity and dysregulation of thyroid hormones (Chupeau et al., 2020; Zhang et al., 2016b; Liu et al., 2017).

5. Conclusions

OPEs are ubiquitous (van der Veen and de Boer, 2012; Stapleton et al., 2011; Ingle et al., 2020a; Ingle et al., 2019a; Mendelsohn et al., 2016) and increasing in usage (van der Veen and de Boer, 2012), although there is a paucity of research on their safety. Our results support a modest and imprecise association between DnBP and BDCIPP with preschool ADHD. Preschool ADHD is a prevalent neurodevelopmental disorder (Lavigne et al., 2009; Wichstrom et al., 2012; Willcutt, 2012) with substantial adverse individual (Mariani and Barkley, 1997; McGoey KEEckert and VanBrakle, 2001) and economic (Sciberras et al., 2017; Gupte-Singh et al., 2017; Le et al., 2014; Quintero et al., 2018; Cadman et al., 2012; Kotsopoulos et al., 2013) consequences. As such, identification of potentially-modifiable risk factors for this common and impactful neurodevelopment disorder is critically needed.

Ethics

The MoBa study was conducted with a license from the Norwegian Data Protection Agency in accordance with guidelines from the Declaration of Helsinki. The MoBa study is currently regulated by the Norwegian Health Registry Act. The Preschool ADHD study was approved by the Regional Committee for Medical and Health Research Ethics South East Norway (ref. nu. 2011/179). Written informed consent was required and obtained for all participants in MoBa. Similarly, additional approval and written informed consent of participants for the clinical evaluation was required and obtained by the Regional Committee for Medical Research Ethics (ref. nu. 2012/985). Data analyses were performed with approval of the UNC Office of Human Research Ethics (ref. nu. 20–2462).

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Data statement

Data from MoBa and the Medical Birth Registry of Norway used in this study are managed by the national health register holders in Norway (Norwegian Institute of Public Health; NIPH) and can be made available to researchers, provided approval from the Regional Committees for Medical and Health Research Ethics (REC), compliance with the European Union General Data Protection Regulation (GDPR) and approval from the data owners. The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should apply through helsedata.no. Access to data sets requires approval from REC in Norway and an agreement with MoBa Analytic code used for the present analysis may be obtained from the corresponding author.

Declarations of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2022.114078.

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