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Prenatal organophosphate ester exposure and executive function in Norwegian preschoolers

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Abstract

Background: Organophosphate esters (OPEs) are ubiquitous chemicals, used as flame retardants and plasticizers. OPE usage has increased over time as a substitute for other controlled compounds. This study investigates the impact of prenatal OPE exposure on executive function (EF) in preschoolers.

Methods: We selected 340 preschoolers from the Norwegian Mother, Father, and Child Cohort Study. Diphenyl-phosphate (DPhP), di-n-butyl-phosphate (DnBP), bis(2-butoxyethyl) phosphate (BBOEP), and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) were measured in maternal urine. EF was measured using the Behavior Rating Inventory of Executive Functioning-Preschool (BRIEF-P) and the Stanford-Binet fifth edition (SB-5). EF scores were scaled so a higher score indicated worse performance. We estimated exposure-outcome associations and evaluated modification by child sex using linear regression.

Results: Higher DnBP was associated with lower EF scores across multiple rater-based domains. Higher DPhP and BDCIPP were associated with lower SB-5 verbal working memory (β = 0.49, 95% CI = 0.12, 0.87; β = 0.53, 95% CI = 0.08, 1.02), and higher BBOEP was associated with lower teacher-rated inhibition (β = 0.34, 95% CI = 0.01, 0.63). DPhP was associated with lower parent-reported BRIEF-P measures in boys but not girls [inhibition: boys: 0.37 (95% CI = 0.03, 0.93); girls: –0.48 (95% CI = –1.27, 0.19); emotional control: boys: 0.44 (95% CI = –0.13, 1.26); girls: –0.83 (95% CI = –1.73, –0.00); working memory: boys: 0.49 (95% CI = 0.03, 1.08); girls: –0.40 (95% CI = –1.11, 0.36)]. Fewer sex interactions were observed for DnBP, BBOEP, and BDCIPP, with irregular patterns observed across EF domains.

Conclusions: We found some evidence prenatal OPE exposure may impact EF in preschoolers and variation in associations by sex.

Keywords: MoBa; MBRN; Organophosphate ester; Flame retardants; Neurodevelopment; Executive function; Behavior; DnBP; DPhP; BDCIPP; BBOEP; Inhibition; Emotional; Control; Working memory; Preschool; Norway

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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).

Description of the process by which someone could obtain the data and computing code: Data from the Norwegian Mother, Father and Child Cohort Study 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) and can be made available to researchers, provided approval from the Regional Committees for Medical and Health Research Ethics (REC), compliance with the EU 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 The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa Analytic code used for the present analysis may be obtained from the corresponding author.

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What this study adds

Organophosphate esters (OPEs) are flame retardants and/or plasticizers increasingly used as replacements for other chemicals. Studies have reported prenatal OPE exposure may be associated with a range of neurodevelopmental outcomes; however, no studies have evaluated executive function (EF) specifically. We evaluated overall- and sex-specific OPE-EF associations in preschoolers and found two OPEs, diphenyl-phosphate (DPhP) and di-n-butyl-phosphate (DnBP), were associated with lower EF scores across multiple domains both overall and, particularly, among boys. Strengths of our study include the high quality standardized clinical assessment that encompassed a range of EF measures, exposure biomarkers, and nesting within a well-characterized cohort.

Introduction

Organophosphate esters (OPEs) are a group of ubiquitous chemicals, primarily used as flame retardants and plasticizers, whose usage has increased over time as a substitute for other controlled compounds.[1] OPEs are found in the air and dust of many indoor settings and do not chemically bond with the products they are applied to.[1–8] Therefore, they are capable of leaching into the environment where, in indoor environments, they can accumulate over time leading to increased exposure.[1] As a result, urinary OPEs are widely detected in the general population.[9,10] In addition, OPEs can cross the placental barrier and have been detected in the placental tissue and amniotic fluid of pregnant women. Therefore, prenatal OPE exposure is of particular concern.[11–13]

The human health effects of OPEs are not well understood; however, both animal and human studies have found OPEs may contribute to adverse neurodevelopment.[14–27] Several biological mechanisms have been proposed to explain this relationship, including the potential for OPEs to affect the developing brain directly via developmental toxicity or indirectly through dysregulation of thyroid hormones.[28–30] Additionally, OPEs may also operate through sex-specific mechanisms, with female-only dysregulation of thyroid hormones having been observed for two OPEs: tris (1,3-dichloro-2-propyl) phosphate (TCDIPP) and triphenyl phosphate (TPhP).[31,32]

To date, few epidemiological studies have evaluated OPEs and neurodevelopment, most finding some evidence of association.[14,20–27] Higher di-n-butyl-phosphate (DnBP) and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) have been associated with increased odds of attention-deficit/hyperactivity disorder (ADHD) in preschoolers.[27] Higher diphenyl-phosphate (DPhP) and BDCIPP have been linked to increased risk of ADHD in children, and a spectrum of behavioral outcomes among preschoolers.[21,22] Additionally, higher prenatal DPhP exposure has been associated with decreased IQ, poorer WM, and increased attention problems.[14,21] Eight of these nine studies have also evaluated child sex as a potential modifier of the OPE- neurodevelopment relationship, with most of these studies finding some association.[14,21–27] However, observed sex-specific OPE-EF associations has differed in the literature with relation to both OPE and affected sex.[14,21–27]

The existing literature on OPEs and neurodevelopment has thus far focused on neurodevelopmental outcomes that comprise a constellation of cognitive processes (e.g., attention span, vocabulary production, and assertiveness) or ADHD.[14,21–23,27] However, executive function (EF) has not been specifically studied in relation to OPEs. EF refers to a group of cognitive processes that measure planning, problem-solving, task completion, goal setting, and thought/behavior regulation.[33,34] EF starts developing early in life and deficits in EF can be found in the general population, having multiple negative downstream effects including lower academic achievement, engagement in risky behaviors, decreased treatment adherence, and poorer overall quality of life.[33,35–38] However, few promising interventions for executive dysfunction have been found. Furthermore, these interventions generally require the EF deficit to be consistently challenged.[39,40] As such, the identification of a modifiable risk for executive dysfunction has the potential to substantially impact public health by decreasing the overall burden of this pervasive adverse neurodevelopmental outcome.

Identification of a modifiable risk for adverse EF may have a substantial impact on public health by decreasing the number of related health complications.[33,36,37,41] Therefore, the purpose of this study is to evaluate prenatal OPE exposure on EF in preschoolers. As a secondary aim, we assess effect measure modification (EMM) of the evaluated OPE-EF relationships by child sex.

Methods

Study Population

The Norwegian Mother, Father, and Child Cohort Study (MoBa) is a large ongoing prospective population-based cohort of over 95,000 pregnant people (41% participation rate; 114,479 children) who were enrolled between 1999 and 2008.[42,43] Participants were recruited at their first ultrasound appointment, approximately 17 weeks' gestation, at which time blood and urine samples were collected.[42,43] Participants completed general health and behavior questionnaires at 17- and 30-weeks' gestation.[42,43] Data on pregnancy health, delivery procedures, and pregnancy outcomes were integrated from the Medical Birth Registry of Norway (MBRN), a comprehensive nation-wide birth registry in Norway.[42,43] Following delivery, children were followed-up periodically by questionnaires mailed to families at 6, 18, 22, and 36 months.[42,43]

Nested within MoBa is the Preschool ADHD Sub-study; this study focuses on participants enrolled between April 2004 and January 2008.[44–46] Children from singleton births who resided within close proximity to Oslo and had mothers that returned the 36-month questionnaire were considered for inclusion.[44–46] The 36-month questionnaire included a set of five questions formed from the symptom list for ADHD in the Diagnostic and Statistical Manual of Mental Disorders, Version 4, Text Revision and six questions from the Child Behavior Checklist/1.5-5 evaluation.[47,48] These 11 questions, referred to as the neurological screener, formed a quantitative index used to oversample children at higher risk for ADHD-like behaviors into an on-site clinical evaluation.[44] Children that scored at or above the 90th percentile (high sum score) on our neurological screener were automatically invited to participate in the on-site clinical assessment [minus a small subset that were recruited for the Autism Birth Cohort (ABC) Study] as well as a small random sample of the remaining population; these participants and those in the ABC Study were the only MoBa participants where measures of EF were obtained. A flow chart detailing study selection can be seen in Figure 1.

Our final study population included 262 children with clinically significant or subclinical symptoms of ADHD (determined utilizing the Preschool Age Psychiatric Assessment) and 78 typically developing controls, for a total of 340 children between the ages of 3.1 and 3.8 years.[46,49] To account for the oversampling of children based on our neurological screener, we utilized inverse probability of selection weights (IPSWs; Supplemental Proof; http://links.lww.com/EE/A223).

Measurement of OPE Metabolites

Urine collection, quality control (QC) methods, and details on OPE analysis have been previously published.[22,50,51] Briefly, maternal urine samples were collected at 17 weeks' gestation and shipped unrefrigerated overnight to the MoBa Biobank in

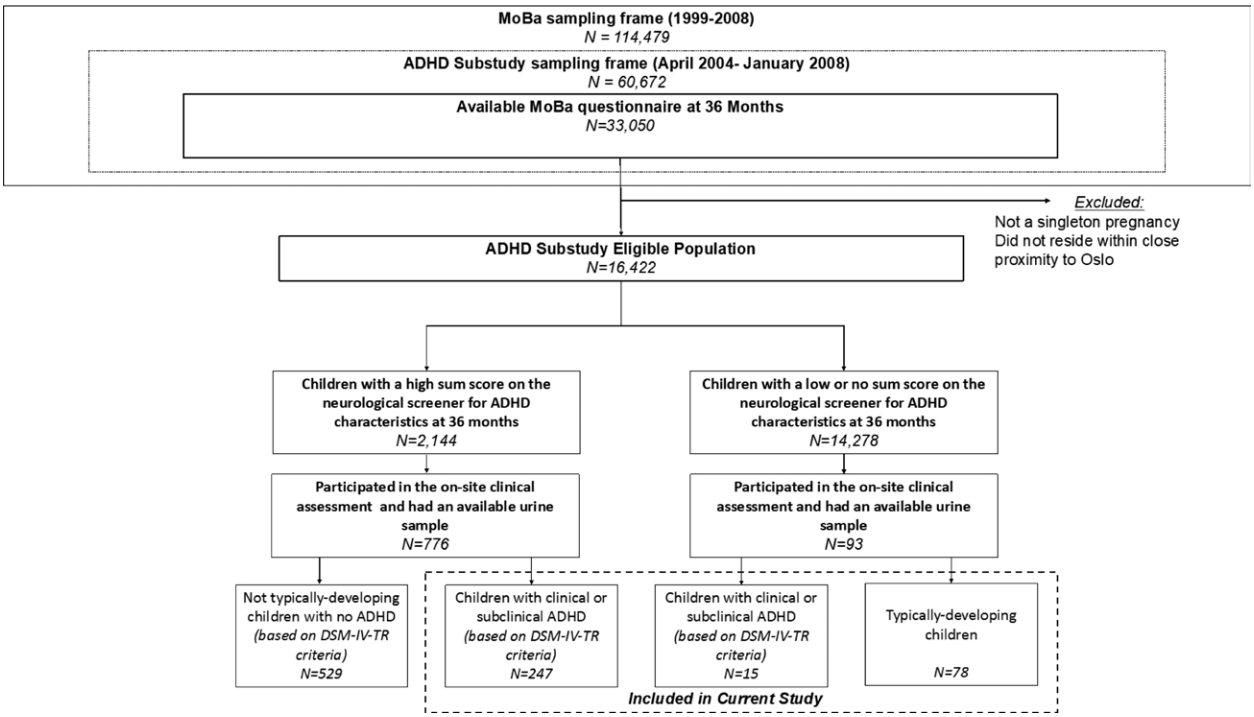

Figure 1. Study selection of children in this sub-study of the Norwegian Mother, Father, and Child Cohort Study.

Oslo, Norway (a central ISO-certified lab), where they were stored at −80°C.[50,51] Chlorhexidine was added to the samples during shipping to prevent bacterial growth; this method was found to be stable under multiple conditions including changes in temperature in a MoBa pilot study (UAP Vacutainers, BD, Franklin Lakes, NJ, USA).[50–52] Urine samples were randomized to batch, and each batch included laboratory blinded QC pooled urine samples, in-house control samples, and procedural blank samples.[50,51] Using ultra performance liquid chromatography (UPLC) coupled with quadrupole-time-of-flight, we measured four OPE metabolites: DPhP, DnBP, BBOEP, and BDCIPP.[53,54] These metabolites correspond to the parent compounds TPhP, tri-n-butyl-phosphate (TnBP), tris (2-butoxethly) phosphate (TBOEP), and TDCIPP, respectively. Coefficients of variation (CVs) for OPEs by batch using spiked samples (5 ng/mL) were approximately 15%.[54] Laboratory blinded QC pools exhibited more variability (CVs ranging from 32% to 70% excluding outliers), although the geometric mean of the OPE metabolites in the pooled QC samples were only slightly above the limit of detection (LOD), and orders of magnitude below the level of the spiked samples.[54] Specific gravity was measured for all urine samples using a pocket refractometer (PAL-10S), Atago.

Executive Function Measurement

We used both performance- and rating-based measures of EF. These measures include parent and teacher ratings from the Behavior Rating Inventory of Executive Functioning-Preschool (BRIEF-P) as well as subtests from the Developmental NEuroPSYchological Assessment II (NEPSY-II) and Stanford-Binet fifth edition (SB-5).[55–57] Approximately 90% of teachers returned the BRIEF and other required inventories.[58]

BRIEF-P is a validated 63-item questionnaire that evaluates EF in children 2–5 years and is comprised of five subscales: inhibition, emotional control (EC), working memory (WM), planning/organization, and shift.[55] Inhibition is the ability to regulate one's own behavior, EC is the ability to regulate one's own emotions, WM is the ability to recall, manipulate and use stored information, and shift is the ability to shift tasks or adapt to change.[55] Four weeks prior to the on-site clinical assessment, parents and teachers were requested to complete the BRIEF-P and return it at the clinical evaluation.[44–46] For our analyses, we used three BRIEF-P subscales: inhibition, EC, and WM. We excluded the planning/organization and shift scales due to concerns regarding their validity in our preschool-age study participants.[59] We calculated standardized age- and gender-specific T-scores from raw BRIEF-P scores in accordance with the BRIEF-P manual.[55]

The NEPSY-II and SB-5 were administered during the on-site clinical evaluation by a child psychologist.[56,57] NEPSY-II is a comprehensive diagnostic tool, consisting of 32 subtests, used to evaluate 6 domains of cognitive functioning, and has been validated for use in preschool-age children.[56,60] For our study, we used the NEPSY-II statue test, a subtest designed to evaluate response inhibition.[56] For the statue test, participants were asked to stand still with their eyes closed for 75 seconds. In 5 second intervals, a child was given a point if the child opened their eyes or moved (2 points if they opened their eyes and moved); a higher score was indicative of worse inhibition.[56] SB-5 is a clinical examination designed to assess a person's aptitude in knowledge, quantitative reasoning, fluid reasoning, visual-spatial processing, and WM.[57] For the current study, we used two subtests from the SB-5: nonverbal and verbal WM. Nonverbal WM was determined from a combination of two tasks: delayed response and block span.[57] For the delayed response assessment, a small toy was placed under one of three cups in front of the child; after a short time-delay, the child was asked to indicate under which cup the toy was.[57] The block span assessment was performed by the test administrator tapping a sequence on a series of blocks and having the child mimic the sequence.[57] Verbal WM was tested by having the child repeat sentences of increasing complexity.[57]

Potential Covariates

We identified potentially important covariates from the literature and used a directed acyclic graph (DAG) to identify potential confounders (Supplemental Figure 1; http://links.lww.com/

EE/A223).[61] Maternal age at delivery, birth year, and child sex were obtained via linkage with MBRN.[42,43] The questionnaire administered at enrollment (17 weeks' gestation) was used to determine marital status, parity, maternal education, financial difficulty in the past year, maternal smoking during the first or second trimester of pregnancy, and alcohol use during the first or second trimester of pregnancy.[42,43] We estimated maternal fish intake during the second trimester by summing daily, weekly, and monthly intake to calculate servings per day from the dietary questionnaire completed at 22 gestational weeks.[62] Maternal ADHD symptoms were determined from the 36-month postnatal questionnaire via the Adult ADHD Self-Report Scales.[63] A minimally sufficient adjustment set was derived using the DAG; this included birth year, maternal education, family income, maternal age at delivery, maternal fish intake (Supplemental Figure 1; http://links.lww.com/EE/A223). We also considered maternal ADHD symptoms as a potential confounder, but this was dropped from the final models for parsimony (did not significantly change effect estimates). Additionally, we included child sex in all models as sex is a strong determinant of EF.[64]

Statistical Analysis

OPE metabolite measures were standardized based on specific gravity to address urine dilution.[65,66] Both BBOEP and BDCIPP were infrequently detected [fewer than 50% of samples were above the LOD]. As a result, these metabolites were categorized as <LOD or ≥LOD. We scaled all outcome measures so a higher score was indicative of worse EF and standardized them to z-scores to facilitate comparisons across tests. Missing exposure and covariate data were imputed using multivariate imputation by chained equations (MICE). Biomarkers below the LOD were imputed from a log-normal distribution truncated at the LOD, conditional on exposures, outcomes, and covariates. We created 20 datasets with imputations under different random seeds, performed the full analysis on each of these datasets, and obtained summary estimates using Rubin's rules.[67–70]

To account for oversampling children with ADHD symptoms (i.e., a high sum score on the neurological screener), we created stabilized IPSWs (Supplemental Proof; http://links.lww.com/EE/A223).[71] Linear regression models were used to calculate the change in EF z-score per one log10-unit change in OPE, IPSW-weighted, and adjusted for covariates. Heteroscedasticity and normality were evaluated using fitted value plots and Q-Q plots, respectively. After imputation, DnBP and DPhP were log-transformed using a log10 transformation to address issues with homoscedasticity and normality in the final models. To account for the IPSWs in our variance estimates, we created 1,000 bootstrap samples and calculated variance estimates using the percentile method.[72,73] EMM between OPEs and sex was evaluated using an augmented product term approach; p-interactions<0.10 were considered indicative of significant heterogeneity.[74]

Potential copollutant confounding by another OPE was evaluated in a sensitivity analysis where models included one of the other three OPEs; this was performed for each OPE in turn. Effect estimates were then compared across models. Batch-effects were also evaluated by sequentially excluding individual batches and comparing estimates across exclusions. The present analyses are based on version 9 of the MoBa quality-assured data files. All analyses were conducted in SAS 9.4 (Cary, NC).

Results

Mothers in our final weighted population were generally 30 to 35 years old at delivery (37.4%), were nulliparous (56.7%), did not smoke (75.1%) or consume alcohol (89.6%) during the first 2 trimesters, did not experience financial difficulty (71.2%), consumed an average of 28.5 grams of fish per day, and were more likely to have male children (56.9%; Table 1). All covariates had fewer than 10% of observations missing before imputation.

DPhP and DnBP were frequently detected (~2% and 10% below the LOD respectively). BBOEP and BDCIPP were detected less frequently (54% and 76% below the LOD respectively; Table 2). We found DPhP and DnBP were weakly correlated (N=271; r_s=0.11) but BRIEF-P measures were moderately to highly correlated within rater (i.e., across EF subtype but within the same rater group [parent or teacher]; r=|0.49| to |0.77|) and weakly correlated across rater (i.e., across EF subtype and rater group [parent or teacher]; r=|0.05| to |0.35| Supplemental Table 1; http://links.lww.com/EE/A223). Additionally, all measures were weakly correlated across tests, even within the same subdomain (r=|0.01| to |0.37|). The distribution of EF measures for the IPSW-weighted population and subpopulations can be seen in Supplemental Table 2; http://links.lww.com/EE/A223.

Although we observed minimal evidence of association between DPhP and BRIEF-P domains in boys and girls combined, each log10 increase in DPhP was associated with approximately a half standard-deviation worsening of our calculated verbal WM z-score on the Stanford-Binet (β = 0.49, 95% CI: 0.12, 0.87; Figure 2; Supplemental Table 3; http://links.lww.com/EE/A223). Furthermore, higher DPhP exposure was associated with better nonverbal WM in girls but not boys [girls: β = –0.89 (95% CI = –1.93, –0.021); boys: β = –0.04 (95% CI = –0.60, 0.61); p-interaction<0.01]. We also observed consistent evidence of EMM by child sex for DPhP and all BRIEF-P parent measures (Figure 2; Supplemental Table 4; http://links.lww.com/EE/A223). In general, increased DPhP exposure was associated with poorer BRIEF-P EF ratings among boys, whereas among girls the opposite pattern was observed [inhibition: boys: β = 0.37 (95% CI = 0.03, 0.93); girls: β = –0.48 (95% CI = –1.27, 0.19); p-interaction<0.01; EC: boys: β = 0.44 (95% CI = –0.13, 1.26); girls: β = –0.83 (95% CI = –1.73, –0.00); p-interaction<0.01; WM: boys: β = 0.49 (95% CI = 0.03, 1.08); girls: β = 0.07 (95% CI = –1.11, 0.36); p-interaction<0.01]. However, there were few notable associations for teacher-rated EF, and, in general, the patterns across parent and teacher inventories were inconsistent.

We observed higher DnBP was often associated with worse EF, as measured by parent- and sometimes teacher-report on the BRIEF; however, estimates were sometimes imprecise, as indicated by wide confidence intervals. Furthermore, no patterns were observed within EF subdomains; for example, we did not always observe adverse associations across all measures of WM, etc. (Figure 2; Supplemental Table 3; http://links.lww.com/EE/A223). Although we did observed evidence of modification by child sex for DnBP and parent-reported and SB-5 verbal WM, directionality across these measures was inconsistent (worse in girls for the BRIEF, worse in boys for the SB-5).

We did not observe consistent associations within EF subdomains for BBOEP and BDCIPP (Figure 2; Supplemental Table 3, http://links.lww.com/EE/A223). However, BBOEP measures at or above the LOD were associated with approximately a third standard-deviation worsening of teacher-rated BRIEF-P inhibition (β = 0.34, 95% CI: 0.01, 1.02) compared to measures below the LOD, and BDCIPP measures at or above the LOD were associated with approximately a half standard-deviation worsening of verbal WM score on the SB-5 (β = 0.53, 95% CI: 0.08, 1.02) compared to measures below the LOD (Figure 2; Supplemental Table 3, http://links.lww.com/EE/A223). We also observed some sex interactions for BBOEP and BDCIPP. While BBOEP lacked consistency in the directionality of exposure-related associations by sex, both of the observed sex interactions for BDCIPP and EF were more adverse in girls [parent-reported BRIEF-P EC: girls: β = 0.47 (95% CI = –0.36, 1.42); boys: β = –0.71 (95% CI = –1.46, 0.34) p-interaction<0.01; parent-reported BRIEF-P WM: girls: β = 0.26 (95% CI = –0.43, 1.02); boys: β = –0.57 (95% CI = –1.25, 0.35) p-interaction<0.01; Figure 2; Supplemental Table 5; http://links.lww.com/EE/A223].

Table 1.

Characteristics of the Norwegian mother, father, and child cohort attention-deficit/hyperactivity disorder substudy, 2004–2008.[a]

	MoBa preschool ADHD group N (%) or mean ± SD	MoBa typically developing children N (%) or mean ± SD	Weighted population (%) or mean ± SD
Total N	262	78	
Maternal age at delivery (years)			
<30	122 (46.6)	26 (33.8)	(37.4)
30 to 34.99	110 (42.0)	31 (40.3)	(39.3)
≥ 35	30 (11.5)	20 (26.0)	(23.3)
Missing	0	1	
Child sex, N			
Male	146 (55.7)	42 (53.9)	(56.9)
Female	116 (44.3)	36 (46.2)	(43.1)
Missing	0	0	
Maternal education, N (%)			
Not a college graduate	92 (35.7)	19 (25.3)	(26.1)
College graduate	110 (42.6)	34 (45.3)	(48.5)
Post-college education	56 (21.7)	22 (29.3)	(25.4)
Missing	4	3	
Marital status			
Single/Co-habiting	147 (56.3)	36 (46.2)	(48.7)
Married	114 (43.7)	42 (53.9)	(51.3)
Missing	1	0	
Parity			
Nulliparous	157 (59.9)	43 (55.8)	(56.7)
Parous	105 (40.1)	34 (44.2)	(43.3)
Missing	0	1	
Maternal ADHD symptoms	33 (12.7)	5 (6.5)	(5.8)
Missing	3	1	
Maternal fish intake (g/day)	*26.1 (18.3)*	*28.5 (17.6)*	*28.5 (16.5)*
Missing	4	3	
Any smoking in 1st or 2nd trimester	61 (23.4)	16 (20.8)	(24.9)
Missing	1	1	
Any alcohol consumption in 1st or 2nd trimester	32 (13.3)	8 (11.0)	(10.4)
Missing	21	5	
Experienced financial difficulty in the past year[b]	68 (26.1)	20 (25.6)	(28.8)
Missing	1	0	
Year of birth			
2004	26 (9.9)	20 (25.6)	(22.0)
2005	63 (24.1)	30 (38.5)	(36.0)
2006	90 (34.4)	23 (29.5)	(33.3)
2007	83 (31.7)	5 (6.4)	(8.7)
Missing	0	0	

Weighted percentile sample size is 310.

Some percentiles may not equal 100 as a result of rounding.

[a]Study enrollment occurred through January 2008; however, no study participants in this subpopulation were enrolled in January 2008.

[b]Past year = year before enrollment (around 17 weeks' gestation).

MoBa indicates Norwegian Mother, Father, and Child Cohort Study; ADHD, attention-deficit/hyperactivity disorder; N, sample size; SD, standard deviation; g, grams.

Table 2.

Prenatal specific-gravity-corrected organophosphate ester metabolite distribution in the nested study population within the Norwegian mother, father, and child cohort study, 2004–2008.[a]

Exposure	Geometric mean (SD)[b]	Min	25%	50%	75%	Max	LOD	%≥LOD	LOQ	%≥LOQ
DPhP (ng/mL)							0.03		0.10	
Preschool ADHD (N = 262)	0.49 (2.94)	<LOD	0.30	0.50	0.95	38.14		96.6%		92.4%
Typically developing (N = 78)	0.45 (3.45)	<LOD	0.20	0.44	0.82	16.17		97.4%		93.6%
Weighted population (N = 310)	0.45 (3.24)	<LOD	0.21	0.44	0.82	38.14		97.8%		92.5%
DnBP (ng/mL)							0.07		0.20	
Preschool ADHD (N = 262)	0.27 (2.18)	<LOD	0.18	0.26	0.38	11.20		95.4%		67.6%
Typically developing (N = 78)	0.20 (2.06)	<LOD	0.14	0.22	0.35	0.67		87.2%		53.9%
Weighted population (N = 310)	0.23 (2.06)	<LOD	0.15	0.23	0.37	11.20		89.5%		59.5%
BBOEP (ng/mL)							0.07		0.20	
Preschool ADHD (N = 262)	0.08 (2.00)	<LOD	<LOD	<LOD	0.14	0.86		44.7%		13.0%
Typically developing (N = 78)	0.09 (2.17)	<LOD	<LOD	<LOD	0.15	1.07		47.4%		19.2%
Weighted population (N = 310)	0.09 (2.08)	<LOD	<LOD	<LOD	0.15	1.07		46.2%		17.03%
BDCIPP (ng/mL)							0.17		0.50	
Preschool ADHD (N = 262)	0.17 (2.42)	<LOD	<LOD	<LOD	<LOD	17.24		21.0%		11.1%
Typically developing (N = 78)	0.17 (2.00)	<LOD	<LOD	<LOD	0.18	2.67		25.6%		10.3%
Weighted population (N = 310)	0.16 (1.91)	<LOD	<LOD	<LOD	<LOD	17.24		23.6%		9.75%

Concentrations were expressed to three significant digits.

Weighted population was created using inverse probability of selection weights to account for oversampling of ADHD cases.

[a]Study enrollment occurred through January 2008; however, no study participants in this subpopulation were enrolled in January 2008.

[b]Variables below the LOD were imputed using LOD/s.

min indicates minimum; max, maximum; ng/mL, nanograms per milliliter.

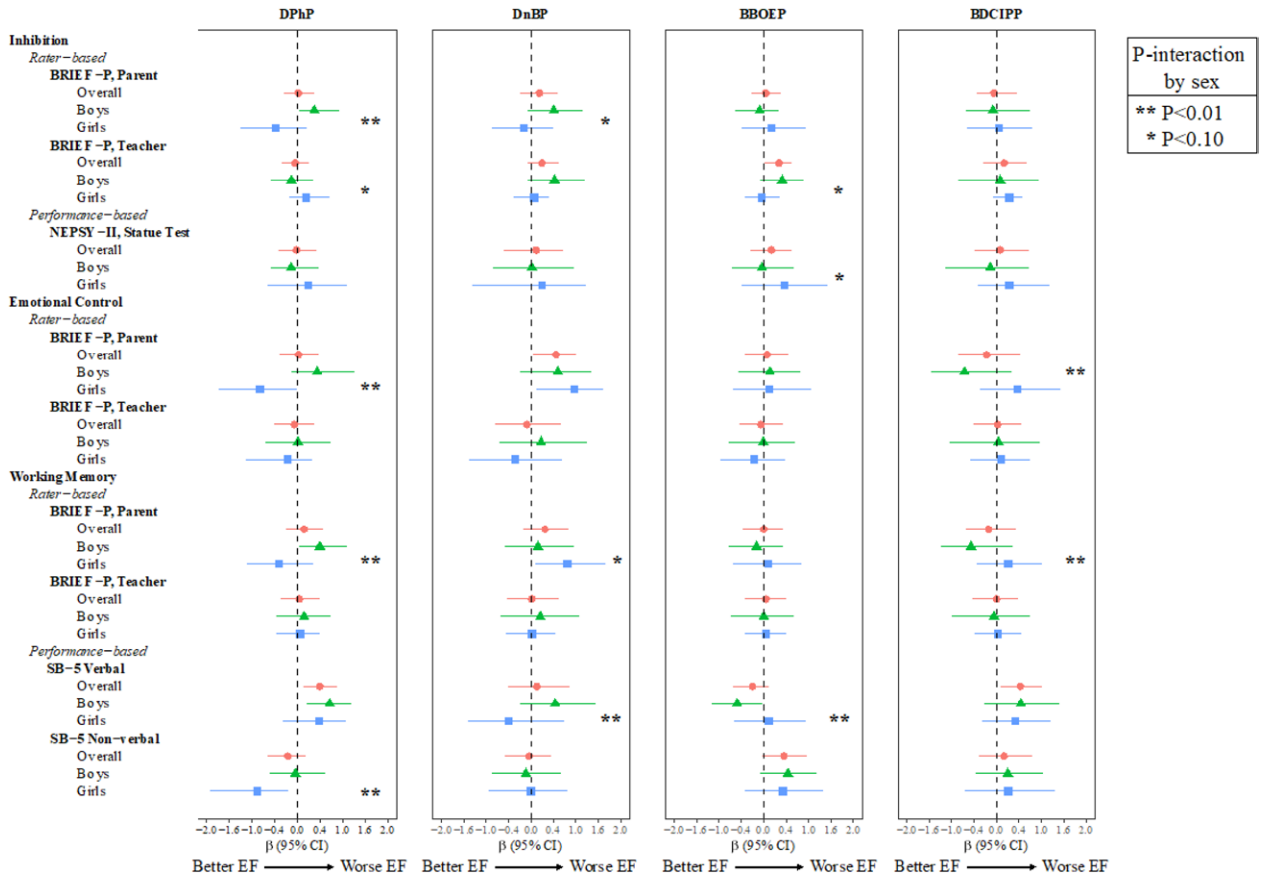

Figure 2. Main and sex-specific associations of organophosphate esters and measures of executive function in an IPSW-weighted study population within the Norwegian Mother, Father, and Child Cohort, 2004–2008 (N = 310). DPhP and DnBP were analyzed using a log10 term and BDCIPP and BBOEP are categorized as <LOD and ≥LOD. All models are adjusted for birth year, total fish consumption, maternal education, financial difficulty, maternal age, and child sex. 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 child sex. Outcome measures are standardized to z-scores with a mean of 0 and standard deviation of 1. Performance-based outcome measures were reversed so higher scores were indicative of worse executive functioning for all measures. P-interactions were derived from the interaction term using an augmented product term approach.

Neither copollutant confounding by another measured OPE nor batch-specific effects were detected (Supplemental Figures 2A–D and 3A–D; http://links.lww.com/EE/A223).

Discussion

Using a nested study within MoBa that included an on-site clinical assessment of neuropsychological functioning in the preschool period, we observed some association between OPEs and EF. Higher prenatal DnBP was often associated with more adverse EF overall (in boys and girls combined), although no patterns were observed across specific EF subdomains. Additionally, higher DPhP or BDCIPP was associated with adverse overall SB-5 verbal WM, and higher BBOEP was associated with worse teacher-rated inhibition. Higher DPhP was also associated with worse parent-rated measures of EF, but only among boys. Fewer sex interactions were observed for DnBP, BBOEP and BDCIPP, with irregular patterns of association across EF subdomains.

To date, nine studies have examined the association between OPEs and neurodevelopment.[14,20–27] These studies have evaluated a broad range of neurodevelopmental outcomes including general cognitive, psychomotor, and behavioral effects, social behaviors, and ADHD, with no studies assessing EF specifically.[14,20–27] The study most similar to ours was conducted by Doherty (2019a) et al.[21] This study evaluated DPhP and BDCIPP in relation to behavioral outcomes in preschoolers, but did not measure DnBP or BBOEP.[21] Doherty et al found higher prenatal DPhP and BDCIPP concentrations were associated with more adverse scores on the Externalizing Problems and Behavioral Symptoms Index composites using parent-ratings from the Behavioral Assessment System for Children, second edition (BASC-2).[21] In this study, we found that higher prenatal DPhP and BDCIPP were both associated with adverse verbal WM on the SB-5, and worse parent-rated measures of EF among boys.

The association between higher DnBP and worse EF as measured by parent- and sometimes teacher- report on the BRIEF-P in our study was consistent with previous research in preschoolers but inconsistent with 2 other studies in children.[22,26,27] Hall et al observed that higher DnBP exposure may be associated with increased odds of ADHD in preschoolers using a nested case-control study of ADHD in MoBa; however, this trend did not appear monotonic and confidence intervals were wide.[27] In contrast, Choi et al did not observe any association with DnBP and childhood ADHD diagnosis using a nested case-control study of ADHD in MoBa.[22] Still, this study found that higher DPhP was associated with increased ADHD risk in children, although stronger associations were found among girls, whereas in our study associations were found mostly among boys.[22] Additionally, Percy (2021) et al found individual OPEs, including DnBP, DPhP, and BDCIPP, and joint effects of OPEs as a mixture (bis(2-chloroethyl) phosphate, DnBP, DPhP, and BDCIPP) were not associated with child IQ at 8 years in longitudinal cohort study.[26]

The literature on prenatal OPE exposure and child brain development is sparse and has utilized a diverse array of developmental assessment approaches, making it somewhat difficult to synthesize findings.[14,20–27] The BASC and BRIEF-P are distinct but well-validated rating-based measures of behavior and EF,

and there is a high degree of correlation across summary indices.[75] However, differences in OPE associations across studies that utilize different approaches for measuring brain development is not surprising. For example, performance- and rater-based EF measures are known to be weakly correlated, perhaps indicating that they represent distinct underlying cognitive constructs.[76,77] Additionally, prior research has also found weak correlations across raters and tests.[14,20,76–78] This may be the result of differences in the environments in which the child is evaluated (natural [i.e., school, home/community] vs. controlled [i.e., standardized testing environment such as a clinic]).[14,20,76–78] It may also be that some raters are more able or qualified to assess specific domains.[79] Our study included a standardized clinical assessment inclusive of parent- and teacher-rating-based scales as well as performance-based metrics designed to characterize the child's behavior in multiple environments and under both natural and controlled conditions. This enabled us to examine OPE associations within a single EF subdomain (inhibition, EC, or WM) across multiple raters and evaluation approaches. And yet, on only a limited number of occasions, associations were confirmed across raters and assessment type. As such, inconsistencies across findings within an EF subgroup (e.g. across measures of WM) could be due to differences between the underlying constructs being measured, between rater- and performance-based measures, and/or within rater-based measures (i.e. differences between raters).

In addition to the use of different assessment approaches, differences between our results and those in other studies may be the result of different levels of exposure. For example, participants in the studies by Doherty et al had substantially lower exposure to DPhP and BDCIPP compared to those in the Norwegian MoBa study population (~70% lower median of DPhP and ~90% lower median of BDCIPP; concentrations for all prenatal OPE-neurodevelopmental studies are provided in Supplemental Table 6; http://links.lww.com/EE/A223).[21] Other plausible explanations for these differences include differences due to the timing of urine collection (MoBa: ~17 weeks' gestation; Doherty: 24–29 weeks' gestation), or residual uncontrolled confounding in either study.[21] Additionally, because Doherty et al evaluated behavioral problems using only parent-rated behavior, we are not able to compare results across raters.[21]

While several studies have reported interactions between OPEs and child sex, including ours, there is a disagreement regarding the most negatively affected sex across, and sometimes within, studies.[14,21–23] Doherty et al, Castorina (2017) et al, and Percy (2022) et al did not observed sex interactions for DPhP or BDCIPP.[14,21,23,25] Hall et al observed inverse associations between BBOEP and ADHD in preschool-age girls but not boys but did not observe evidence of EMM for DnBP, DPhP, or BDCIPP.[27] Choi et al found some evidence that the adverse association between DPhP and ADHD was stronger for girls but did not find evidence of sex interactions for DnBP, BDCIPP, or BBOEP.[22] Liu et al observed stronger inverse associations between prenatal BDCIPP and psychomotor- and mental- development in 2-year-olds, not observing modification for DPhP or BBOEP.[24] Percy (2021) et al reported significant interaction for DPhP and child sex (sex-specific estimates were not provided) with relation to a DPhP-WM association but did not observe evidence for sex interactions for DnBP and BDCIPP.[26] We observed multiple sex interactions for DPhP and parent-rated BRIEF-P measures. In girls, unexpectedly, higher exposure was associated with better parent-rated inhibition, emotional control, and WM, as well as SB-5 nonverbal WM, although similar patterns were not found for teacher ratings. Fewer sex interactions were observed for DnBP, BBOEP and BDCIPP, with a lack of directional consistency and irregular patterns across a subdomain. Low statistical power to detect interactions may, in part, explain differences among studies with respect to reporting of sex-specific associations. To resolve these differences, larger studies will be needed with careful attention to the potential for sex-specific confounding pathways.[74]

Our study has many strengths. Our study contained detailed covariate information that permitted us to control for many plausible confounders such as prenatal fish intake and financial difficulty. To our knowledge, this is the only study to focus on OPEs and EF. In doing so, we leveraged a detailed evaluation of preschool neuropsychiatric development, inclusive of parent- and teacher- reported measures and performance-based assessments and utilized multiple measures of EF to better understand the underlying cognitive processes potentially impacted by OPEs. Additionally, we evaluated the potential for copollutant confounding of another measured OPE in a sensitivity analysis, finding no evidence.

We also acknowledge some limitations. OPEs have short half-lives, lasting only a few hours for parent compounds and a few days for metabolites.[80,81] As such, OPE metabolites have low to moderate reliability when assessed over the course of a trimester (Supplemental Table 4; http://links.lww.com/EE/A223).[4,82–85] Our study only had access to a single spot urine sample, measured at 17 weeks' gestation. Therefore, results from this study cannot be generalized outside the 2nd trimester and may not validly estimate OPE exposure during the entirety of the 2nd trimester. Future studies should consider using multiple urine samples to more validly estimate OPE exposure during pregnancy. In addition, although DPhP is the recognized urinary biomarker for TPhP, it is a nonspecific metabolite and may reflect exposure to other parent compounds with potentially different toxicities.[1] Because OPE exposure has increased over time, temporal confounding was a concern in our study.[1] To address this, we included birth year as an adjustment term in our models; however, we acknowledge that residual confounding may still be present. Additionally, although we utilized stabilized IPSWs to account for over-selection of children with ADHD-like behaviors, these weights do not address differences between our eligible population and the wider MoBa cohort, many of whom were not eligible for the Preschool ADHD Sub-study due to birth year or geographic location.[86] MoBa itself is a selected population which has been shown to under-represent young mothers, mothers living alone, and mothers with three or more previous births, and/or mothers with a history of stillbirth; however, biases in large prospective cohorts are expected to be small.[86,87] Furthermore, those who scored high on the neurological screener but did not have symptoms of preschool ADHD at the on-site clinical assessment were not selected into our final study population; as such, our results cannot make inferences about this population. Although outcomes at age 3 are uncertain, this exclusion may limit the generalizability of our study.[78] Finally, as the children in this study were preschool-aged, higher order EF processes such as planning/organization and shift could not be reliability assessed.

Poor EF has been associated with several adverse endpoints including decreased quality of life, engagement in risky behaviors, and decreased treatment adherence.[33,35–38] Additionally, research has demonstrated that poor EF correlates with multiple comorbidities including ADHD, depression, anxiety, dissociation, dyslexia, and autism.[88–95] Although early EF measurements can be age and/or task dependent, these measurements show a high correlation into childhood when assessing measurement invariance. Furthermore, deficits in EF are known to be pervasive and can have multiple downstream effects.[33,35–38,88–96] To date, few modifiable risk factors or effective long-term interventions have been identified, with most interventions requiring consistent participation to maintain progress.[39,40] Our results suggest a possible modest association between higher OPE exposure and EF, however larger studies are needed to confirm these results, ideally with more measures of exposure in pregnancy. Nonetheless, given the limited existing literature and the widespread use of these chemicals, this study is an important

step forward in the potential identification of a modifiable risk factor for EF.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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