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Prenatal organophosphorus pesticide exposure and executive function in preschool-aged children in the Norwegian Mother, Father and Child Cohort Study (MoBa)

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ABSTRACT

Introduction: Prenatal exposure to organophosphorus pesticides (OPPs) has been associated with neurodevelopmental deficits in children, however evidence linking OPPs with specific cognitive mechanisms, such as executive function (EF), is limited.

Objective: This study aims to evaluate the association between prenatal exposure to OPPs with multiple measures of EF in preschool-aged children, while considering the role of variant alleles in OPP metabolism genes.

Methods: We included 262 children with preschool attention-deficit/hyperactivity disorder (ADHD), and 78 typically developing children, from the Preschool ADHD substudy of the Norwegian, Mother, Father, and Child Cohort Study. Participants who gave birth between 2004 and 2008 were invited to participate in an on-site clinical assessment when the child was approximately 3.5 years; measurements of EF included parent and teacher rating on Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P), and three performance-based assessments. We measured OPP metabolites in maternal urines collected at ~17 weeks' gestation to calculate total dimethyl- (ΣDMP) and diethyl phosphate (ΣDEP) metabolite concentrations. We estimated multivariable adjusted β's and 95% confidence intervals (CIs) corresponding to a change in z-score per unit increase in log-ΣDMP/DEP. We further characterized gene-OPP interactions for maternal variants in *PON1 (Q192R, M55L)*, *CYP1A2 (1548T > C)*, *CYP1A1 (IntG > A)* and *CYP2A6 (-47A > C)*.

Results: Prenatal OPP metabolite concentrations were associated with worse parent and teacher ratings of emotional control, inhibition, and working memory. A one log-$\sum$DMP increase was associated with poorer teacher ratings of EF on the BRIEF-P (e.g. emotional control domain: $\beta = 0.55$, 95% CI: 0.35, 0.74), when weighted to account for sampling procedures. We found less consistent associations with performance-based EF assessments. We found some evidence of modification for *PON1 Q192R* and *CYP2A6 -47A > C*. Association with other variants were inconsistent.

Conclusions: Biomarkers of prenatal OPP exposure were associated with more adverse teacher and parent ratings of EF in preschool-aged children.

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1. Introduction

Organophosphorus pesticides (OPPs) are a class of insecticides with widespread agricultural use throughout the world (Hertz-Picciotto et al., 2018a). OPPs irreversibly inhibit acetylcholinesterase causing nerve impulses to transmit indefinitely (Fukuto, 1990). OPPs also cause neurologic damage at lower doses (i.e. without overt symptoms) through oxidative stress and effects on proteins involved in fundamental neuronal processes (Slotkin and Seidler, 2007; Terry, 2012). Detoxification pathways include paraoxonase 1 (*PON1*) and the cytochrome P450 (*CYP*) superfamily of monooxygenases, which have common genetic variants that may modify expression and/or catalytic efficiency of their respective enzymes (Furlong, 2007; Kaur et al., 2017). Multiple OPPs are approved for use within the European Union/European Economic Community (EU/EEC), including chlorpyrifos (Bjørling-Poulsen et al., 2008). However globally, differences exist in regulations governing the use of OPPs, with some countries banning the use of multiple OPPs, while the same compounds may be permissible in others (Hertz-Picciotto et al., 2018b).

Multiple studies have demonstrated that consumption of conventionally-grown produce is an important route of exposure to OPPs (Oates et al., 2014; Papadopoulou et al., 2019; van den Dries et al., 2019). As such, human exposure may be affected by the import of agricultural products from countries where OPPs are approved for use. For example, a recent investigation of exposure in Norwegian women found that urinary concentrations of OPP metabolites were comparable to those measured in women residing in middle and southern Europe, despite the relatively limited use of OPPs in Norwegian agriculture (Haug et al., 2018), suggesting a role for imported foods as a mechanism of exposure for the Norwegian population (Ye et al., 2009).

Prenatal exposure to OPPs has been associated with a variety of neurodevelopmental deficits in children (Gonzalez-Alzaga et al., 2014), including reduced IQ (Bouchard et al., 2011; Coker et al., 2017; Engel et al., 2011, 2016; Gunier et al., 2017; Rauh et al., 2006, 2011; Rowe et al., 2016; Stein et al., 2018), developmental delay (Liu et al., 2016; Wang et al., 2017, 2020), impaired social responsivity (Furlong et al., 2014), and altered brain morphology (Rauh et al., 2012), microstructure (van den Dries et al., 2020), and activity (Binter et al., 2020). However, several studies have found no link between prenatal exposure and neurodevelopmental endpoints (Cartier et al., 2016; Donauer et al., 2016; Guo et al., 2019; van den Dries et al., 2019) or small and imprecise effects (Jusko et al., 2019; Ntantu Nkinsa et al., 2020). In particular, recent studies in the Generation R cohort in the Netherlands found that prenatal OPP exposure was not associated with children's nonverbal IQ (Jusko et al., 2019) or traits of attention-deficit hyperactive disorder (ADHD) and autism spectrum disorders (ASD) (van den Dries et al., 2019). Because most studies used non-specific biomarkers of OPP exposure, dimethyl- and diethyl phosphate metabolites, the lack of harmony in these results may arise from differences in the type or extent of OPP parent compound exposure as well as the route of exposure. These differences have implications with regard to the amount of exposure to the parent compound relative to nontoxic preformed OPP metabolites (Lu et al., 2005; Quirós-Alcalá et al., 2012).

While multiple studies have found impacts of prenatal exposure to OPPs on general cognitive abilities (e.g. psychometric intelligence and mental development indices), there is little data examining more specific cognitive mechanisms. Executive function (EF) is an umbrella term for multiple categories of goal-directed, problem-solving behavior that emerge in the preschool period and continue to mature throughout childhood (Anderson, 2002). Research suggests there are three "core EFs": 1) inhibition, or self-control 2) working memory (WM), the ability to register, maintain and manipulate information, and 3) cognitive flexibility, also called shifting; higher order EFs, such as decision-making, goal setting, and planning are built from upon these core skills (Diamond, 2013). Deficits in EF are common among children diagnosed with neurodevelopmental disorders, such as ASD and ADHD (Margari et al., 2016). However, deficiencies in EF may also be found among individuals without developmental disabilities (Otterman et al., 2019).

A small number of previous studies have included measurements of EF in later childhood or adolescence (Furlong et al., 2017; Sagiv et al., 2019, 2021), and have found relationships between OPP exposure and EF in both positive and negative directions. Studies measuring WM have generally found reduced scores with increasing OPP exposure (Bouchard et al., 2011; Furlong et al., 2017; Rauh et al., 2011; Rowe et al., 2016; Stein et al., 2016). Many of these studies were performed in settings with high community exposure (i.e., communities exposed due to agricultural drift or residential pesticide application), which may not be reflective of contemporary exposure patterns in the general population. In addition, no prior study has assessed the effects OPP exposure on measurements of EF taken during preschool, which are critical for future educational achievement (Diamond, 2016).

The aim of the current study is to evaluate the association of prenatal exposure to OPPs with EF in preschool-aged children, while considering the potentially modifying role of OPP metabolism variants. To address these aims, we leverage a well characterized subset of the Norwegian, Mother, Father, and Child Cohort (MoBa).

2. Materials and methods

2.1. Study population

MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus et al., 2006, 2016). Pregnant women across Norway were recruited between 1999 and 2008 (Schreuder and Alsaker, 2014). An invitation was sent to women before a routine prenatal ultrasound, which 98% of pregnant women complete before the 20th week of gestation (Backe, 1997). Following enrollment and informed consent for each pregnancy, MoBa included 114,500 children, 95,200 mothers and 75,200 fathers, representing 41% of the invited pregnant women. Participating mothers contributed biospecimens and completed questionnaires throughout pregnancy and provided updates on their child's health and development longitudinally after birth (Paltiel et al., 2014). The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act.

The study population is nested within a substudy of the MoBa cohort, called the Preschool ADHD Substudy (Overgaard et al., 2014), which oversampled children exhibiting possible ADHD symptoms on the 36-month questionnaire. Selection criteria for the included children has been previously described (Choi et al., 2021). Briefly, children born between April 2004 and January 2008 whose mothers reported a high summed scores (>90th percentile) of ADHD-like symptoms (N = 2798), and a random sample of remaining children (N = 654), were invited to participate in an on-site clinical assessment of preschool ADHD. The enrollment groups were based on summed scores combining six items from the Child Behavior Checklist (Achenbach and Ruffle, 2000) and five items from the DSM-IV-TR criteria for ADHD (American Psychiatric Assocation, 2000). Of those invited, 1195 children (35%) aged 3–4 years (mean = 3.5) took part in a 1-day clinical assessment, of which 870 had an available maternal prenatal urine sample for the measurement of OPP metabolites (sFig. 1). Mothers of children who participated were slightly older, more highly educated, and had fewer children than those who chose not to participate (Skogan et al., 2015).

The analytic sample for this current analysis includes two clinical groups: 1) children with above/subthreshold symptoms of preschool ADHD based on DSM-IV-TR criteria (N = 262) using the Preschool Age Psychiatric Assessment (PAPA) (Egger and Angold, 2004), and 2) children randomly sampled from the eligible population who were subsequently found to have no clinical/subclinical symptoms of ADHD using

the PAPA, referred to as the typically developing group (N = 78). Further description of the diagnostic procedures for these children can be found in Kamai et al. (2021). Inverse sampling fractions (Richardson et al., 2007) are used to account for the oversampling of children symptomatic for preschool ADHD (further details in statistical analysis below).

2.2. Measurement of executive function

Parents and preschool teachers were asked to complete standardized inventories of child behavior before coming to the clinical assessment, which included neuropsychological tests and a semi-structured interview with the child. Methods and results from the preschool clinical assessment of neuropsychological functioning in MoBa have been previously described (Bendiksen et al., 2017; Biele et al., 2022; Overgaard et al., 2014, 2016, 2018a, 2018b, 2019, 2021, 2016, 2014; Rohrer--Baumgartner et al., 2014, 2016, 2016; Skogan et al., 2015, 2016). From parent and teacher assessments, we selected instruments related to EF (sTable 1). These included parent- and teacher ratings of the Behavior Rating Inventory of Executive Function - Preschool (BRIEF-P), subtests within the Stanford-Binet, 5th edition (SB-5), the A Developmental NEuro-PSYchological Assessment, 2nd edition (NEPSY-II), as well as the cookie delay task (CDT). Additional information on validation of Norwegian translations of the BRIEF-Preschool can be found in Skogan et al. (2016). Briefly, confirmatory factor analyses within the MoBa population supported the original 3-factor solution proposed by the BRIEF-P authors (Gioia et al., 2000). Additional information on neuropsychological testing can be found in Skogan et al. (2014). Briefly, tests were administered by a psychologist, or a trained graduate psychology student with special competence in child neuropsychology and supervised by a child psychologist or psychiatrist. All sessions were videotaped, and data from clinical assessments were reviewed by a child psychologist or psychiatrist and scored according to test algorithms. The SB-5 and NEPSY-II have been translated into Norwegian (Bayliss et al., 2005; Bull et al., 2008).

The BRIEF-P was developed to examine EF within the context of everyday environments in children aged 2–5 (Gioia et al., 1996). The 63-item instrument characterizes five domains of EF: emotional control, inhibition, WM, planning/organization, and shift (ability to move attention freely between tasks). Raters report whether a behavioral descriptor had been a problem for the child on a 3-point scales (never, sometimes, or often) during the past 6 months. The BRIEF-P was filled out by teachers and parents describing behavior in the school and home environment, respectively. For the analysis, we restricted to the emotional control, inhibition, and WM scales, because shift and plan/organize may not have reached a stable functional level of development at this age (Skogan et al., 2016). Raw scores were standardized by age and sex to calculate T scores.

Performance-based assessments were carried out by a psychologist with one parent present, as described previously (Rohrer-Baumgartner et al., 2014). The SB-5 (Roid and Pomplun, 2012) is a test battery used to measure nonverbal and verbal cognitive factors in all ages (2–85 years), including WM. Verbal WM was measured by asking participants to repeat sentences of increasing length. Nonverbal WM is measured with subtests: “delayed response”, where the child was asked to find an object hidden under one of three cups after a few seconds delay, and “block span”, where the child was asked to tap blocks in the same order as the administrator. NEPSY-II (Korkman et al., 1998) is a compendium of tests that examines attention/EF, language, sensorimotor, visuospatial, and memory/learning in children aged 3–12 years. A subtask measuring inhibition called the “Statue task”, where a child is asked to follow instructions to inhibit body movement, eye opening, and vocalization, under a series of increasing distractions. This test is believed to reflect poor inhibitory control and motor persistence (the ability to sustain an action in the absence of reinforcement). The CDT is an experimental task designed to evaluate children’s ability to delay a response to take a piece of cookie until an interval (of varying lengths) is up, signaled by the experimenter clapping their hands. Spearman correlation coefficients between measurements among our study participants are shown in sTable 2.

2.3. Measurement of OPP exposure

We estimated prenatal OPP exposure by measuring 3 dimethyl metabolites: dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), and 3 diethyl metabolites: diethyl phosphate (DEP), diethyl thiophosphate (DETP), and diethyl dithiophosphate (DEDTP), in maternal single spot urine samples collected at ~17 weeks’ gestation (sTable 3), using the ultra-performance liquid chromatography-time-of-flight system (UPLC-TOF) (Cequier et al., 2016). Laboratory quality control (QC) samples spiked at 5 and 50 ng/mL were included in each analytic batch, as well as 4–6 laboratory-blinded pooled QC samples. Average batch-specific coefficients of variation (CVs) for spiked QCs were generally between 5 and 8%. Average batch-specific CVs for laboratory blinded QCs were higher (9–20%), largely due to the lower mean concentrations among the pooled QC samples (means ranging between 0.4 ng/mL and 2.8 ng/mL, depending on the metabolite). Samples were randomly allocated across analytic batches. Specific gravity (SG) was measured using a pocket refractometer (PAL-10 S) from Atago to account for urinary dilution. Metabolites could not be quantified in one participant with above/subthreshold preschool ADHD, who was excluded from the analysis. OPP metabolite concentrations were adjusted for SG (Boeniger et al., 1993) by standardizing all measurements by the geometric mean of the analytic population ($OPP_{SG,\ i} = OPP_{raw,\ i} * (\mu_{SG}/(SGi - 1))$). Metabolite concentrations below the limit of detection (LOD) were imputed from a log-normal distribution bound by 0 and the LOD (Lubin et al., 2004). SG-adjusted concentrations of dimethyl- and diethyl metabolites were summed by molar weight to calculate total dimethyl- (ΣDMP) and total diethyl phosphate (ΣDEP) concentrations, and were subsequently log (natural) transformed. DEDTP was not included in ΣDEP because nearly 99% of values were below the LOD.

2.4. Measurement of covariates

We examined factors that could influence prenatal OPP exposure or preschool-aged EF as potential covariates. Maternal characteristics at enrollment were obtained from the baseline questionnaire (completed at ~17 weeks gestation): marital status (married, cohabitating, single/other), education (less than college completed, college completed, more than college, other), parity (nulliparous vs. parous), self-reported depression before pregnancy (i.e. history of depression; yes vs. no), self-reported pre-pregnancy weight and height to calculate pre-pregnancy body mass index (BMI) (kg/m^2), smoking and alcohol consumption during the first trimester of pregnancy (any vs. none). Financial problems in the previous 12 months (yes vs. no) was obtained from a questionnaire given at 30 weeks’ gestation. Maternal ADHD score were determined from the ADHD Self-Report Scale in the MoBa questionnaire completed when the child was 3 years old. Characteristics such as maternal age at birth, birth year, and child sex were obtained via data linkage with the Medical Birth Registry of Norway (MBRN) (Irgens, 2000), the national health registry containing information about all births in Norway.

Maternal dietary intake during pregnancy was captured using a food-frequency questionnaire completed by mothers at approximately 22 weeks’ gestation. For the current analysis, we used these dietary data to obtain information on frequency of fruit and raw vegetable consumption (servings/day) and choice of ecologically-grown, or “organic” produce (during pregnancy (seldom/never vs. sometimes/often/usually). In Norway, certification for labeling of organic produce went into effect in 2007 (https://debio.no/english/). Total fish intake (g/day) during pregnancy was also calculated from this questionnaire. To examine

potential non-dietary sources of OPP exposure, we obtained information on mother's self-reported contact with plant care substances (weed-killer, insecticides, and fungicides) in the six months before enrollment from the baseline questionnaire. Paternal use of plant care substances in the six months before wife became pregnant was obtained from the questionnaire administered to the father. We grouped dates of urine collection in June to August, September to November, December to February, and March to May, for seasons. Residence type (living on a farm vs. other) was additionally examined to look at potential agricultural exposure to OPPs and collected in the baseline questionnaire.

2.5. PON1 and CYP genotyping

To evaluate the role of variants in genes critical for OPP metabolism, we characterized single nucleotide polymorphisms (SNPs) in *PON1* and *CYP1A2, CYP1A1* and *CYP2A6*. DNA from maternal blood samples collected during pregnancy was extracted using FlexiGene, and candidate SNPs were measured using Sequenom IPLEX. We examined two SNPs in *PON1*: 1) rs662, "*Q192R*" and 2) rs854560, "*M55L*", and three across *CYP1A2, CYP1A1* and *CYP2A6*: 1) *CYP1A2* rs2470890, "*1548T > C*″, 2) *CYP1A1* rs4646421, "*IntG > A*″ and 3) *CYP2A6* rs28399433, "*-47A > C*" (sTable 4). PON1 variants examined are well-characterized (Dardiotis et al., 2019). Q192R is believed to affect substrate specificity, with the QQ genotype ("low-risk" allele) considered to have faster metabolism of toxic OPP forms (Garin et al., 1997) compared with QR/RR ("high-risk allele). 2) M55L is believe to reduce stability and enzyme concentrations (Humbert et al., 1993), although some studies have found conflicting evidence (Dardiotis et al., 2019); several studies have identified LL as the "high-risk" allele compared to MM/ML ("low-risk"). While *CYP* genes are also involved, less is known about the role of these variants in OPP metabolism; therefore, we examined a selection of SNPs in *CYP* genes with sufficient frequency of variants alleles in our study participants.

2.6. Statistical analysis

All outcome measures were converted to z-scores and standardized so higher scores correspond to worse (or more adverse) EF. We created a directed acyclic graph (DAG) to identify and select confounders (sFig. 2) (Hernan, 2002). A minimally sufficient set was identified using daggity (http://www.dagitty.net/). We also included a variable for child sex, which is highly associated with EF skills in preschool-aged children, and potential predictors of selection into the study, such as maternal parity, age, and education. For parsimony, we used backwards elimination to remove covariates that did not improve models fit (Weng et al., 2009), when examining the following response variables: 1) teacher and 2) parent ratings of emotional control on the BRIEF-P, and 3) non-verbal WM on the SB-5. Final models were adjusted for fruit consumption (servings/day), raw vegetable consumption (servings/day), age at childbirth, pre-pregnancy BMI, Maternal ADHD score, nulliparity, birth year, season of urine collection, and child sex.

We used multiple imputation with fully conditional specification for missingness in covariates and combined results using Rubin's rules implemented in PROC MIANALYZE. The imputation model included all covariates, log-ΣDMP/DEP, and the teacher BRIEF-P scales. We used multiple linear regression to estimate β′s and 95% confidence intervals (CI) corresponding to a change in z-score per unit increase in log-ΣDMP/DEP. To account for the sampling procedures, analyses were weighted to the population eligible for the ADHD substudy using sampling fractions estimated separately for enrollment groups (children with high summed scores of ADHD-like symptoms and random sample of remaining children). More details on these procedures and results of a simulation study examining different approaches to weighting can be found in Choi et al. (2021). To evaluate the potentially modifying role of SNPs in *PON1* and *CYP* genes, we used regression models with interaction terms for the continuous number of variant alleles present (0,1,2) to estimate change in β per allele substitution (Δβ). We determined the presence of modification based on Wald tests (p-value <0.05) for this parameter. For *PON1* genes, we used the genotype considered "low-risk" as the referent group, so Δβ′s correspond to change per "high-risk" allele. We performed sensitivity analyses removing weighting from models and stratifying by clinical group. All analyses were conducted using SAS 9.4 (Cary, NC).

3. Results

Mothers of study participants had an average age at childbirth of 30 years, most were nulliparous (no previous pregnancies) and had a college degree or higher education (Table 1). The proportion of mothers of above/subthreshold preschool ADHD children who were married (44% vs. 54%) and had completed college (35% vs. 24%), were lower compared to mothers of typically developing children. Participating mothers reported a median of ~2.5 servings of fruit and ~0.5 servings of raw vegetables a day during pregnancy, with around one third choosing ecologically-grown fruits (31%) and vegetables (33%) sometimes or more often (compared to seldom/never). Self-reported use of plant care substances (weedkiller, insecticides, and fungicides) in the six months before pregnancy was reported by 4.6% mothers. The proportion of mothers living on a farm (vs. other residence type) was low (2.2%). The median age at clinical assessment for children was 3.5 years. There were slightly more girls than boys in above/subthreshold preschool ADHD children (56%) and typically developing children (54%).

OPP metabolites were frequently detected in urine samples collected at ~17 weeks' gestation (sTable 3). DMTP and DEP were most frequently metabolites in both above/subthreshold preschool ADHD children (89% and 41%, respectively) and typically developing children (96% and 51%, respectively). There were no differences in metabolite concentrations between above/subthreshold preschool ADHD and typically developing children per the Wilcoxon ranked-sum test. The distribution of SG-adjusted ∑DMP and ∑DEP (summed by molar weight) is shown in Table 2.

Higher levels of prenatal ∑DMP and ∑DEP was associated with worse (higher z-scores) preschool-aged measurements of EF, particularly parent and teacher ratings on the BRIEF-P, when weighted to account for the study's sampling procedure (Fig. 1; sTable 5). A one unit increase in log-∑DMP was associated with nearly a half z-score increase in teacher ratings of emotional control (β = 0.55, 95% CI: 0.35, 0.74), inhibition (β = 0.48, 95% CI: 0.29, 0.67), and working memory (β = 0.50, 95% CI: 0.30, 0.69). In addition, a one unit increase in log-∑DEP and was associated with worse parent and teacher ratings on the BRIEF-P, with the largest magnitude of association for parent-rated emotional control (β = 0.47, 95% CI: 0.24, 0.70). Associations between OPP metabolite molar sums and changes in BRIEF-P T-scores are shown in sTable 6, with magnitudes of association mostly ranging from 3 to 6 points per log-unit increase in exposure.

Prenatal ∑DMP metabolites were not associated with performance-based assessments of EF (Fig. 1, sTable 5), An association between log-∑DEP and poorer non-verbal WM on the SB-5 (β = 0.45, 95% CI: 0.13, 0.78) was observed, however associations with the remaining performance EF assessments were less consistent with this finding.

In sensitivity analyses, we removed weighting by sampling fraction (sTable 7), and stratified models according to clinical group (sTable 8). Associations between OPP metabolites and preschool-aged measurements of EF were attenuated in unweighted analyses, a population that overrepresents children with above/subthreshold preschool ADHD (sTable 7). The association between log-∑DMP and higher z-scores of teacher ratings on the BRIEF-P was reduced in magnitude by around half (e.g. emotional control domain: β = 0.27, 95% CI: 0.05, 0.50). When analyses were stratified by clinical group, some associations between ∑DMP/∑DEP and z-scores of preschool-aged EF measurements were stronger in typically developing children compared to those with above/subthreshold preschool ADHD (sTable 8).

Table 1
Characteristics of the study population nested in the preschool ADHD study of the Norwegian Mother, Father and Child Cohort Study, 2004–2008.

Maternal characteristics[a]	Above/subthreshold Preschool ADHD, n = 262		Typically developing, n = 78		Weighted[b], n = 340	
	Median or N	IQR or (%)	Median or N	IQR or (%)	Median or N	IQR or (%)
Age at childbirth (years)	30	27–33	30	28–35	30	27–34
Missing			1			
Marital status						
Single/other	15	(5.7)	3	(3.8)	(3.4)	
Cohabitating	132	(51)	33	(42)	(45)	
Married	114	(44)	42	(54)	(51)	
Missing	1					
Education						
Less than college completed	92	(35)	19	(24)	(25)	
College completed	110	(42)	34	(44)	(47)	
More than college	56	(22)	22	(28)	(24)	
Other	3	(1.1)	3	(3.8)	(3.1)	
Missing	1					
Financial problems in last 12 months, yes vs. no	66	(26)	20	(26)	(29)	
Missing	7		1			
Pre-pregnancy BMI (kg/m^2)	23.4	21.1–26.0	23.5	20.8–25.7	23.7	20.9–26.0
Missing	8		1			
Nulliparous, yes vs. no	157	(60)	43	(56)	(57)	
Missing			1			
Self-reported depression before pregnancy, yes vs. no	28	(11)	7	(9.0)	(8.7)	
Maternal ADHD score[c]	1	0–3	1	0–2	1	0–2
Missing	3		1			
Smoking in first trimester, any vs. none	61	(23)	16	(20)	(25)	
Missing	1		1			
Alcohol consumption in first trimester, any vs. none	32	(13)	8	(11)	(10)	
Missing	21		5			
Fish consumption during pregnancy (g/day)	24	14–36	27	17–36	26	17–37
Missing	4		3			
Factors associated with OPP exposure						
Contact with plant care substances[d], yes vs. no	15	(5.9)	3	(3.9)	(4.6)	
Missing	14		2			
Paternal contact with plant care substances[e], yes vs. no	12	(5.3)	10	(14)	(12)	
Missing	36		7			
Living on a farm (vs. other residence type)	7	(2.7)	2	(2.6)	(2.2)	
Missing	2					
Fruit consumption during pregnancy (servings/day)	2.5	1.0–2.5	2.5	1.0–2.5	2.5	1.0–2.5
Missing	6		4			
Raw vegetable consumption during pregnancy (servings/day)	0.5	0.2–0.8	0.5	0.2–1.0	0.5	0.2–1.0
Missing	6		4			
Use of ecologically-grown fruits during pregnancy (seldom/never vs. sometimes/often/usually))	69	(27)	25	(33)	(31)	
Missing	9		3			
Use of ecologically-grown vegetables during pregnancy (seldom/never vs. sometimes/often/usually)	93	(37)	27	(36)	(33)	
Missing	10		3			
Season of urine collection						
Summer	68	(26)	15	(19)	(22)	
Fall	56	(21)	12	(15)	(14)	
Winter	73	(28)	25	(32)	(32)	
Spring	65	(25)	26	(33)	(32)	
Child characteristics						
Child age (month)	41.7	40.7–42.4	41.6	40.6–42.4	41.5	40.6–42.4
Missing	2		1			
Child sex						
Boy	116	(44)	36	(46)	(43)	
Girls	146	(56)	42	(54)	(57)	
Child birth year						
2004	26	(9.9)	20	(26)	(22)	
2005	63	(24)	30	(38)	(36)	
2006	90	(34)	23	(29)	(33)	
2007	83	(32)	5	(6.4)	(8.7)	

N; number Med; Median; ADHD, attention-deficit/hyperactive disorder; BMI, body mass index; IQR, interquartile range, OPP, organophosphorus pesticide.

[a] Maternal characteristics are at the time of enrollment (~15 weeks gestation) unless otherwise stated.

[b] To account for the sampling procedures, we performed analysis weighted to the population eligible for the ADHD substudy using sampling fractions. Proportions based on the weighted population.

[c] Maternal ADHD score was from the ADHD Self-Report Scale in the MoBa questionnaire completed when the child was 3 years old.

[d] Mothers were asked about contact weedkiller, insecticides, and fungicides during the six months since enrollment.

[e] Fathers were asked about contact with weedkiller, insecticides, and fungicides in the six months before wife became pregnant.

Table 2
Distribution of total dimethylphosphate and diethylphosphate metabolites in urines collected at ~17 weeks' gestation.

OPP metabolite level (nmol/L)	N	Geometric Mean	Geometric SD	Min	25%	50%	75%	Max
∑DMP[a]								
Above/subthreshold preschool ADHD	261	5.76	1.63	3.1	25.6	56.7	113.9	1362
Typically developing	78	6.06	1.58	6.6	28.2	61.2	125.9	594
Weighted[b]	339	6.09	1.57	3.1	27.8	64.7	136.7	1362
∑DEP[a]								
Above/subthreshold preschool ADHD	261	3.59	1.48	2.0	10.1	18.2	34.2	241
Typically developing	78	3.81	1.43	2.9	11.1	21.7	38.0	126
Weighted[b]	339	3.81	1.43	2.0	11.5	22.5	38.5	241

OPP, organophosphorous pesticide, DMP, dimethylphosphate, DEP, diethylphosphate; ADHD, attention-deficit/hyperactivity disorder; SD, standard deviation.
[a] Dimethyl and diethyl metabolite concentrations were adjusted for specific gravity (SG) by standardizing to the geometric mean. Concentrations below the limit of detection were imputed from a log-normal distribution. Metabolites were summed by molar weight (ΣDEP, ΣDMP). DEDTP was not included in ΣDEP as 99% of values were below the limit of detection. Concentrations were measured maternal spot urines collected at ~17 weeks' gestation.
[b] Weighted to the population eligible for the ADHD substudy using sampling fractions.

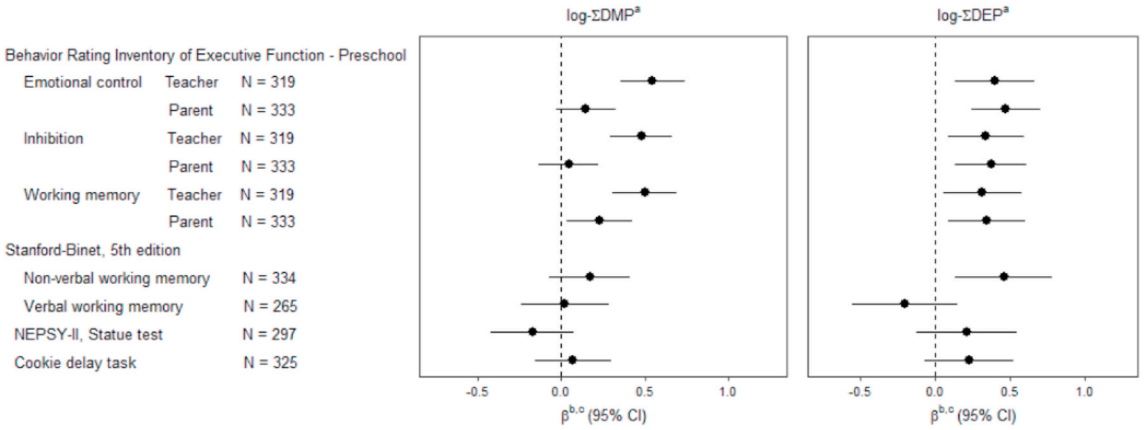

Fig. 1. Association of log-∑DMP and log-∑DEP with preschool-aged measurements of executive function in regression analysis with weighting by sampling fractions.
CI, confidence interval; DMP, dimethylphosphate, DEP, diethylphosphate, NEPSY, A Developmental NEuro-PSYchological Assessment.
a. Dimethyl- and diethyl phosphate metabolites concentrations were adjusted for specific gravity (SG) by standardizing to the geometric mean. Concentrations below the limit of detection were imputed from a log-normal distribution. Metabolites were summed by molar weight (ΣDEP, ΣDMP), and log (natural) transformed. DEDTP was not included in ΣDEP as 99% of values were below the limit of detection. Samples were measured maternal spot urines collected at ~17 weeks' gestation.
b. β for change in z-score per unit increase in log-∑DMP/DEP standardized so higher scores correspond to worse executive function. Weighted to the population eligible for the ADHD substudy using sampling fractions.
c. Adjusted for fruit consumption (servings/day), raw vegetable consumption (servings/day), age at childbirth, pre-pregnancy body mass index (kg/m2), maternal ADHD score, nulliparity, birth year, season of urine collection, and child sex.

To evaluate the potential modifying role of common variants in *PON1*, we estimated the change in the association between log-∑DMP and log-∑DEP and teacher ratings on the BRIEF-P, per *Q192R* and *M55L* substitution in maternal genotype (sTable 9). For *Q192R*, the adverse associations between log-∑DMP and multiple teacher ratings of EF among mothers with the QQ genotype was attenuated for those with QR/RR (e.g. Inhibit: Δβ per R substitution = −0.40, 95% CI: −0.75, −0.05), however we did not see patterns of modification of ∑DEP by *Q192R*. No consistent patterns of association were seen for *M55L* substitutions in *PON1*.

We similarly evaluated SNPs in *CYP1A2, CYP1A1, and CYP2A6* (sTable 10). The most consistent evidence of effect measure modification was found for the *-47A > C* allele in *CYP2A6*. Specifically, the associations of log-∑DEP with poorer teacher ratings of emotional control, inhibition and WM, were attenuated for mothers with C alleles (e.g. emotional control: Δβ per C allele = −0.80, 95% CI: −1.38, −0.22), although there was less consistency for ∑DMP. Among the other CYP genotypes measured, patterns of effect measure modification varied and were not consistently statistically significant.

4. Discussion

Leveraging a comprehensive, on-site preschool-aged neuropsychological assessment, we examined the relationship between prenatal OPP exposure and preschool-aged EF in a well-characterized subset of the MoBa study. We found that ∑DMP and ∑DEP biomarkers of OPP exposure were associated with higher z-scores of teacher and parent ratings of EF, indicating that elevated prenatal exposure levels are related to poorer EF in the child. For example, a one log-∑DMP increase was associated with poorer teacher ratings of EF on the BRIEF-P, corresponding to ~3 to 6 points on the original BRIEF-P scale (T-scores). Increasing ∑DEP was also associated with poorer teacher and parent ratings on the BRIEF-P. No consistent pattern between ∑DMP and performance-based assessments was found, however we observed an association between ∑DEP and worse non-verbal WM on the SB-5. In unweighted analyses, the associations between ∑DMP and ∑DEP and BRIEF-P ratings were attenuated, and when stratifying by clinical group, we found stronger adverse associations in typically developing children compared to children with clinically significant or subthreshold preschool ADHD. We evaluated the potential modifying role of variant alleles and found some evidence of significant modification for *Q192R* in *PON1* and *-47A > C in CYP2A6*, however patterns of association with

other variants were not consistent.

The overall results of this study are in agreement with the majority of the previous OPP literature, which finds deficits in neurodevelopment associated with increasing exposure (Gonzalez-Alzaga et al., 2014). However, there are few papers that have focused specifically on EF, and among them, results are inconsistent. A 2017 study by Furlong et al. (2017) in an urban birth cohort in New York (Mount Sinai cohort), found that higher concentrations of ∑DMP in third trimester urine samples was associated with an improved "EF factor", comprised primarily of parent-reported BRIEF domains among children 6–9 years of age. Sagiv et al. (2021) leveraged multiple rater and performance-based assessments of EF in the agricultural CHAMACOS cohort (Sagiv et al., 2021), finding associations between DMP and DEP metabolites and poorer teacher and parent ratings on the BRIEF between 7 and 12 years of age. In this study, DMP and DEP were most strongly associated with the mother's BRIEF ratings, compared to maternal reporting on the Connors ADHD/DSM-IV (CADS) and Behavior Assessment System for Children, 2nd ed (BASC-2). Our study results are more closely aligned with those of Sagiv et al. (2021), although our study participants likely received much lower and more indirect exposure to OPPs, primarily via dietary intake of conventionally grown fruits and vegetables (Ye et al., 2009). However, comparisons of DMP and DEP biomarker-based associations across studies is complicated in populations with differing routes of OPP exposure, and thus differing profiles of exposure to parent compounds. It should be noted that DMP and DEP metabolites are non-specific biomarkers of multiple parent compounds whose toxicities vary widely (Sudakin and Stone, 2011). As such, differences in associations across studies may in part relate to differences in the composition of parent compounds to which any specific population is exposed. Direct exposure to pesticides through residential insecticide applications, occupational exposures, or secondary to agricultural drift, is likely to result in a higher magnitude of exposure to the parent compound, and relatively less exposure to preformed DMP and DEP metabolites (Quirós-Alcalá et al., 2012; Sudakin and Stone, 2011). However dietary exposure to OPPs is likely to a mix of parent compound and preformed metabolites (Lu et al., 2005), the latter of which are non-toxic and indistinguishable from parent-compound exposure when measuring diethyl and dimethyl-phosphate metabolites in urine.

Although we found consistent adverse associations with parent and teacher rated EF domains, we found less consistent evidence of association with performance-based measures. Previous research has shown limited correlation between EF assessments as measured by rater-based and performance measures, indicating that different underlying cognitive constructs are being tapped by these tools (Isquith et al., 2005, 2013; Toplak et al., 2013). We also found limited correlations across performance and rater-based methods (sTable 2). In the preschool period, performance-based assessments of EF may be less precise than in older children, since EFs are not fully developed until adult age. In addition, performance tasks are administered under ideal experimental conditions, in an environment that is highly structured, and with the goals of the assessment clearly defined (Toplak et al., 2013). In contrast, ratings-based assessments ask parents and teachers to reflect on usual behaviors in a typical environment (school or home) that may vary in terms of structure. Therefore, the lack of overlap in our findings is not entirely unexpected.

Metabolism of OPPs is a two-step process where parent compounds are activated to their toxic "oxon" form by *CYP* genes, then detoxified primarily through hydrolysis by *PON1* (Furlong, 2007; Kaur et al., 2017). Variants (i.e. polymorphisms) in these genes may alter their enzymatic activity resulting in exposure to toxic metabolites forms. *PON1* has several well characterized variants that affect enzymatic activity and/or serum concentrations, including *Q192R* and *M55L* (Dardiotis et al., 2019). Prior studies evaluating modification of OPP associations by *Q192R* have produced mixed findings. Engel et al. (2011) found that relationships between prenatal DMP and DEP and the mental development index (MDI) of the Bayley Scales of Infant Development-II (BSID-II) measured at 12 months were stronger for mothers with 192QR and RR genotypes, considered slow metabolizers (i.e. "high-risk"), particularly among Black and Hispanic mother-child pairs, but found stronger relationships between prenatal DMP and perceptual reasoning at 6–9 years old for those with the QQ genotype (Engel et al., 2011), who are expected to have faster metabolism and clearance of toxic OPP forms. A pooled analysis of four U.S. birth cohorts additionally found more adverse associations between DEP and the MDI of the BSID at 24 months among mothers with the QQ genotype (Engel et al., 2016). Wang et al. similarly found stronger relationships between DEP and several domains on the Gesell Developmental Scales at 12 months for children of mothers with the QQ genotype in Shandong province, China (Wang et al., 2020). We found some evidence that adverse associations between ∑DMP and teacher ratings of preschool-aged EF were strongest among mothers with the QQ genotype, but no consistent patterns for ∑DEP. Several studies in US cohorts (Eskenazi et al., 2014; Millenson et al., 2017) and a study in Generation R (Jusko et al., 2019) which have assessed neurodevelopment later in childhood (ages 5–9 years) reported no evidence of modification by *Q192R*. Only one prior study of prenatal OPP exposure has evaluated the *M55L*, which is believed to reduce stability and enzyme concentrations of *PON1*; Jusko et al. (2019) found no evidence of modification by *M55L* for the associations of DMP and DEP with nonverbal IQ measured at 6 years in Generation R (Jusko et al., 2019). Overall, the literature on *PON1*-mediated modification is inconclusive, potentially due to the lack of specificity in the exposure biomarker, and thus their utility as a marker of susceptibility to OPPs may be limited (Dardiotis et al., 2019).

Despite the role of CYPs in OPP metabolism (Kaur et al., 2017), there has been less attention paid to the potential for common variants to modify the association of prenatal OPP exposure on neurodevelopment. Individual CYPs have different affinities for parent OPP compounds, which change depending on concentration (reviewed in Kaur et al., 2017). While multiple *CYPs* are involved in OPP metabolism, *CYP3A4* has been most consistently demonstrated as a major metabolizer of OPPs (Croom et al., 2010; Kaur et al., 2017). Our study participants lacked sufficient variability in variant frequency to evaluate the *IntG > A* change in *CYP3A4*. As such, we evaluated the potential modifying role of SNPs in *CYP* genes involved in xenobiotic metabolism with sufficient variant frequencies in population. While no patterns were seen for *1548T > C* in *CYP1A2* and *IntG > A* in *CYP1A1*, we found attenuated associations for *-47A > C* allele changes in *CYP2A6,* which is believed reduce its enzymatic activity. However, we could find no other published studies that have linked this allele change in *CYP2A6* to metabolism of OPPs. Our study extends this literature by examining variants in multiple SNPs in *CYP* genes for their potential to modify associations to chronic, low dose exposure OPPs during pregnancy and preschool-aged EF.

Strength of this study include the use of a comprehensive battery of EF tests, with concurrent parent and teacher ratings and performance-based assessments, to better characterize the nature of any associations with EF outcomes. Consistency in associations across parent and teacher ratings provides further evidence of the reliability of our findings. This study was nested within the well-characterized MoBa cohort, which collected detailed covariate information on child and maternal characteristics, including dietary patterns during pregnancy. These data allowed us to account for important confounders, like dietary intake of fruits and vegetables, and maternal symptoms of ADHD, which have not been considered in a number of previous investigations. While EFs vary in the general population, children with ADHD tend to have lower scores across a range of EF-related outcomes as compared to typically developing children (Barkley, 1997). Thus, over-sampling children with non-normative EF may have selected for a uniquely susceptible population. Contrary to our expectations, DMP and DEPs were somewhat more strongly associated with EF in typically developing children, which may indicate that other pathways are more prominently related to EF in the setting of ADHD, including heritable pathways. Nonetheless,

our design allowed us to explore these questions while accounting for the oversampling of those symptomatic for preschool ADHD. Finally, there has been limited research focused on cognitive effects in the preschool period, however identifying deficits in this period can have important consequences for the child. Previous research has demonstrated the utility of interventions for EF at this age (Sasser et al., 2017; Traverso et al., 2015), with improvements being critical for educational success later in life (Jacobson et al., 2011; Willoughby et al., 2012).

Our study also has several limitations. We were limited to a single spot urine collection at mid-pregnancy to assess prenatal exposure to OPPs. OPPs are rapidly metabolized and a single measurement during pregnancy may not adequately reflect patterns of exposure over the entire period (Spaan et al., 2015). It is possible that our study sample, which leveraged an on-site standardized assessment of Preschool ADHD nested within the large and well characterized MoBa cohort, is impacted by self-selection in relation to factors that influenced a mother's willingness to bring her child in for a long assessment. We attempted to address this by using selection weighing approaches, and included in our multivariable adjusted models, covariates that may additionally predict participation in the clinical exam, such as maternal education, age, parity and maternal symptoms of ADHD. Finally, while we used a standardized clinical inventory of psychiatric symptoms validated for the preschool period to ascertain ADHD symptoms relative to DSM-IV criteria, this assessment is not equivalent to a diagnostic interview, which would include multiple sources of information and informants for a clinical diagnosis of ADHD. A previous study by Overgaard et al. (2021) in the MoBA, found that these criteria collected at ~3 years identified around half of children with persistent elevation of ADHD symptoms approximately 2 years later (Overgaard et al., 2021).

5. Conclusions

In a study nested in a Norwegian, population-based birth cohort, we found that higher prenatal concentrations of OPP metabolites were associated with worse EF, such as emotional control, inhibition, and working memory, in preschool-aged children, measured using parent and teacher ratings on the BRIEF-P. OPP usage has reduced in recent decades due to regulations in the Europe, the US, and across the globe (Hertz-Picciotto et al., 2018b). As such, levels of exposure measured among women in this current study may be higher than exposure in pregnant women today. Nonetheless, dietary exposure to OPPs remains widespread even in countries with limited OPP usage, such as Norway, due to importation of agricultural products. Our study adds to the evidence that argues for more aggressive global regulation of OPPs in order to limit exposure during pregnancy.

Ethics

The current study is based on version 9 of the quality-assured data files released for research in preschool ADHD. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry. The current study was approved by the Regional Committee for Medical Research Ethics in Norway and reviewed and determined to be exempt from further review by the Office of Human Research Ethics at the University of North Carolina at Chapel Hill.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113555.

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