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Original Contribution

Gestational Exposure to Organophosphate Pesticides and Longitudinally Assessed Behaviors Related to Attention-Deficit/Hyperactivity Disorder and Executive Function

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The brain's prefrontal cortex directs higher-order cognitive and behavioral processes that are important for attention, working memory, and inhibitory control. We investigated whether gestational exposure to organophosphate (OP) pesticides was associated with these abilities in childhood and early adolescence. Between 1999 and 2000, we enrolled pregnant women in a birth cohort drawn from an agricultural region of California. We measured dialkyl phosphate (DAP) metabolites of OP pesticides in maternal pregnancy urine samples (13 and 26 weeks) and estimated associations with behaviors related to attention-deficit/hyperactivity disorder and executive function, assessed longitudinally; 351 families provided neurodevelopmental outcome data at any point when the child was aged 7–12 years. We assessed function across multiple dimensions (e.g., working memory, attention), methods (e.g., behavior reports, child assessment), and reporters (e.g., mothers, teachers, child self-reports). Higher gestational DAP concentrations were consistently associated with behaviors related to attention-deficit/hyperactivity disorder and executive function. For example, a 10-fold increase in gestational DAP concentration was associated with poorer longitudinally assessed Behavior Rating Inventory of Executive Function scores, as reported by mothers ($\beta = 4.0$ (95% confidence interval: 2.1, 5.8); a higher score indicates more problems), and Weschler Intelligence Scale for Children—Fourth Edition Working Memory scores (a 3.8-point reduction; $\beta = -3.8$ (95% confidence interval: −6.2, −1.3)). Reducing gestational exposure to OP pesticides through public health policy is an important goal.

attention; attention-deficit/hyperactivity disorder; executive function; gestational exposure; neurodevelopment; organophosphate pesticides

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BASC-2, Behavior Assessment System for Children; BRIEF, Behavior Rating Inventory of Executive Function; CADS, Conners ADHD/DSM-IV Scales; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CHAM2, second wave of the CHAMACOS Study; CI, confidence interval; CPT II, Conners Continuous Performance Test II; DAP, dialkyl phosphate; GSD, geometric standard deviation; HOME, Home Observation for Measurement of the Environment; OP, organophosphate; WCST, Wisconsin Card Sorting Test; WISC-IV, Weschler Intelligence Scale for Children—Fourth Edition.

Organophosphate (OP) pesticides are commonly used in agriculture in California and throughout the United States (1). OPs are neurotoxicants which inhibit the action of acetylcholinesterase at high levels of exposure (2); however, less is known about the mechanisms by which low-level OP exposure affects the developing brain (3–14). Diet is a predominant route of exposure to OP pesticides (15), though ambient exposure among residents living in proximity to agricultural applications represents another important exposure pathway (16, 17). Urinary dialkyl phosphate (DAP) metabolites, the most common biomarker of exposure to OPs, were detected in nearly all samples collected in a nationally representative US study, indicating widespread exposure to OPs (18).

In previous studies, investigators reported generally consistent associations between gestational exposure to OPs and adverse neurodevelopment in early childhood and at early school age, including poorer intellectual development and poorer attention and motor skills (19–27). Less is known about the effects of gestational OP exposure on neurodevelopment in later childhood and adolescence, or specifically on behaviors related to attention or executive function at these ages. Subserved primarily by the brain's prefrontal cortex, these functions direct complex, higher-order cognitive and behavioral processes that are critical for planning, problem-solving, sustaining attention, and inhibitory control and that underlie goal-oriented behavior and emotional regulation (28). Problems with attention and executive function are also correlated with clinically diagnosed attention-deficit/hyperactivity disorder (ADHD) (29). Identification and intervention on early-life factors may have important implications for academic achievement, social behavior, and risky behavior.

In this analysis, we investigated associations of prenatal OP pesticide exposure, based on urinary DAP metabolite measurements, with children's executive functioning, assessed longitudinally at ages 7, 9, 10.5, and 12 years, in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study.

METHODS

Study sample

CHAMACOS is a birth cohort study from California's Salinas Valley. Between 1999 and 2000, we recruited pregnant women receiving prenatal care at community clinics serving the Salinas Valley's farmworker population. Eligible women were those who were at least 18 years of age, had pregnancies of less than 20 weeks' gestation, spoke Spanish or English, qualified for low-income health insurance, and planned to deliver at a public hospital. Of 601 pregnant women who enrolled, 537 liveborn infants remained in the study at delivery. Gestational OP metabolite concentrations were available for 534 children, and 363 families provided neurodevelopmental outcome data at any point between the child's ages 7 and 12 years. We excluded 6 twins and 6 children with diagnosed developmental conditions (see Web Appendix 1, available online at https://doi.org/10.1093/aje/kwab173) who could not complete all testing, which left 351 children in the final analyses.

We obtained written informed consent from all mothers and teachers. Children provided verbal assent at ages 7, 9, and 10.5 years and written assent at age 12 years. Study activities were approved by the University of California, Berkeley, Committee for the Protection of Human Subjects.

Assessment of OP pesticide exposure

We assessed OP pesticide exposure during pregnancy by measuring DAP metabolites in maternal urine samples. Details of our urine collection, analysis, and quality control procedures have been published elsewhere (17). Briefly, CHAMACOS mothers provided spot urine samples twice during pregnancy (at approximately 13 and 26 weeks' gestation). We aliquoted and stored samples at −80°C until shipment on dry ice to the Centers for Disease Control and Prevention (Atlanta, Georgia). We measured concentrations of 6 DAP metabolites, including 3 dimethyl metabolites (dimethyl phosphate, dimethyl thiophosphate, and dimethyl dithiophosphate) and 3 diethyl metabolites (diethyl phosphate, diethyl thiophosphate, and diethyl dithiophosphate), using gas chromatography–tandem mass spectrometry and isotope dilution calibration (30). We summed molar concentrations to obtain total dimethyl, total diethyl, and total DAP concentrations (nmol/L) (31). For individuals with nondetectable metabolite concentrations, we randomly imputed concentrations below the limit of detection based on a log-normal probability distribution (17). We accounted for urine dilution by measuring specific gravity using a hand-held refractometer (National Instrument Company, Inc., Baltimore, Maryland) and used specific-gravity–adjusted DAP metabolite concentrations in all analyses (31).

Neurodevelopmental assessment

We focused on behaviors related to ADHD and executive function problems assessed at ages 7, 9, 10.5, and 12 years. We obtained information on children's behavior from maternal reports (all time points), a teacher's report (age 7 years), and the child's self-report (age 10.5 years), using the following scales: the Behavior Rating Inventory of Executive Function (BRIEF) (32); the Conners ADHD/DSM-IV [*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*] Scales (CADS), Parent Version and Teacher Version (33); and the Behavior Assessment System for Children, Second Edition (BASC-2) Parent Rating Scales, Teacher Rating Scales, and Self-Report on Personality (34). In addition, we conducted neuropsychological assessments to measure child performance regarding aspects of ADHD and executive function, including the Wisconsin Card Sorting Test-64 (WCST) Computer Version 2 Research Edition (35); the Conners Continuous Performance Test II (CPT II) (36); and select subscales of the Wechsler Intelligence Scale for Children—Fourth Edition (37). Test administration is described in detail in Web Appendix 2. All neuropsychological assessments were conducted in a private room by bilingual, bicultural psychometricians who were trained and supervised by a clinical neuropsychologist. All study interviewers and psychometricians were blind to families' OP exposures.

Covariate assessment

We collected data on sociodemographic indicators at in-person visits. Study staff interviewed women twice during pregnancy (at 13 and 26 weeks' gestation), shortly following delivery, and when the children were 6 months and 1, 2, 3.5, 5, 7, 9, 10.5, and 12 years of age. All mothers were administered the Peabody Picture Vocabulary Test (38) or its Spanish equivalent (39) to assess maternal receptive language at child ages 6 months and 9 years; the Center

for Epidemiologic Studies Depression Scale to assess maternal depressive symptoms (40) at child ages 1, 3, 7, and 9 years; and the Home Observation for Measurement of the Environment (HOME)—Short Form (41) to assess the home learning environment at child ages 6 months and 1, 2, 3.5, 7, 9, 10.5, and 12 years. We also measured exposure to other chemicals during pregnancy that have been shown to affect neurodevelopment in CHAMACOS and which may confound OP-related associations, including exposure to dichlorodiphenyltrichloroethane (DDT) (42, 43) and polybrominated diphenyl ether (PBDE) flame retardants (44, 45). We previously reported details on data collection and measurement of these chemicals (42, 44).

Statistical analysis

All data management and analyses were conducted using Stata 15 (StataCorp LLC, College Station, Texas). We used Spearman correlations to examine consistency of scores over time and across raters (mothers, teachers, child self-reports). We calculated mean total dimethyl, diethyl, and DAP concentrations across the 2 pregnancy urine samples. We used linear regression to model $\log_{10}$-transformed, specific-gravity–adjusted DAP concentrations in relation to outcome measures and used generalized estimating equations with robust standard errors to account for nonindependence across repeated measures. We examined linearity of the dose-response function using generalized additive models with penalized splines (46).

We selected covariates a priori using causal diagrams (see Web Figure 1 for directed acyclic graph). All models included maternal age at delivery (years; continuous), maternal duration of residence in the United States at delivery (years; continuous), maternal educational level at delivery (categorical: <7th grade, 7–11th grade, completion of high school), maternal receptive language at child age 9 years (continuous Peabody Picture Vocabulary Test score), average maternal depressive symptom score at child ages 7 and 9 years (continuous), and average HOME score from ages 7 years to 12 years (continuous z score). Though some of these variables were measured after exposure (e.g., maternal receptive language), they are likely to be good representations of these important indicators prior to exposure. We also included child's age at assessment (years; continuous) and child's sex; while these variables are not associated with pesticide exposure, they explain variability in the outcome measures and may improve the precision of our estimates. We additionally adjusted for language of questionnaire administration in maternal report models. For child assessment models, we included covariates for the psychometrician who administered the test (categorical), language of testing, and video game usage (for the CPT II and WCST only).

For participants with missing values for covariates, we substituted participants' own values from an adjacent visit when possible and/or used an average score for a variable across visits (e.g., for HOME score). We randomly imputed the remaining few covariate missing values (n = 10, n = 6, and n = 6 observations for maternal depression, HOME score, and video game usage, respectively).

We examined differences by sex by including a term for interaction between DAP concentrations and sex in the main models and by computing sex-specific effect estimates. We computed a Wald P value for statistical interaction.

In a sensitivity analysis, we reran all main analyses using inverse probability weighting to explore possible bias resulting from differential loss to follow-up in this cohort. We also reran key analyses after excluding 4 children who were prescribed medication for attention problems at any point during this period.

RESULTS

Table 1 shows sociodemographic data and exposure levels for the 351 families with measured DAP concentrations and neuropsychological data collected at any time between the child's ages of 7 and 12 years. Details on limits of detection and quality control for DAPs in CHAMACOS were published previously (17). Most mothers (87%) had been born in Mexico, and most (74%) had resided in the United States for 10 years or less when their CHAMACOS child was born. Few mothers (20%) had completed high school, and many (46%) had a sixth-grade education or less. Total dimethyl metabolite concentrations (geometric mean = 95.9 (geometric standard deviation (GSD), 3.1) nmol/L) exceeded total diethyl concentrations (geometric mean = 20.0 (GSD, 3.0) nmol/L); therefore, total DAP concentrations (geometric mean = 130.3 (GSD, 2.7) nmol/L) primarily reflect total dimethyl exposure. Web Table 1 compares sociodemographic and exposure characteristics of the original birth cohort with measured gestational DAP concentrations (n = 534) with those of the 351 families included in these analyses, further divided by age point. DAP concentrations were slightly lower, on average, among families included in this analysis than among those in the original cohort. Web Table 2 presents summary standardized scores on behavioral rating scales as well as child assessment scores from evaluations completed at each age point. Average scores were largely consistent with those observed in the standardization sample for each scale or test.

Web Tables 3–5 present correlations between scores on the different rating scales and assessments. As shown in Web Table 3, while mothers' reports of their child's executive functioning and attention, as reported on the BRIEF, CADS, and BASC-2, were moderately to strongly correlated within each time point (r_s range, 0.46–0.83) and teachers' reports on the different scales at age 7 years were strongly correlated (r_s range, 0.70–0.89), maternal and teacher reports at age 7 years were only weakly correlated (r_s range, 0.09–0.30). Web Table 4 shows that maternal report scale scores were moderately to strongly correlated across time points (r_s range, 0.54–0.69), children's scores on the Weschler Intelligence Scale for Children—Fourth Edition (WISC-IV) scales were moderately correlated between ages 7 and 10½ years (r_s range, 0.43–0.51), and children's scores on WCST and CPT II tasks were weakly correlated between ages 9 and 12 years (r_s range, 0.17–0.38). Web Table 5 shows that children's self-reported hyperactivity and attention problems were weakly correlated with both maternal and teacher reports (r_s range, 0.16–0.27). Child assessment scores were

Table 1. Sociodemographic and Exposure Characteristics of Families (n = 351) Included in an Analysis of Associations Between Prenatal Organophosphate Pesticide Exposure and Children's Executive Functioning, by Exposure Level[a] and Outcome[b], CHAMACOS Study, 1999–2000

Characteristic	No. of Children	%	Maternal GM (GSD) ∑DAP Concentration During Pregnancy, nmol/L[c,d,e]	Child's Mean (SD) BRIEF GEC Score at Age 9 Years
Child sex				
Male	165	47	134.3 (2.3)	49.3 (11.3)
Female	186	53	126.8 (2.8)	49.2 (9.1)
Maternal country of birth				
United States	42	12	99.9 (2.6)	51.1 (10.7)
Mexico	305	87	135.7 (2.8)	48.9 (10.0)
Other	4	1	94.8 (1.6)	58.0 (20.7)
Maternal duration of US residence at child delivery, years				
≤1	78	22	131.5 (2.6)	48.4 (9.7)
2–5	95	27	146.8 (3.0)	49.8 (10.7)
6–10	87	25	127.1 (2.7)	48.4 (9.5)
≥11	56	16	132.9 (2.7)	49.4 (10.7)
Lifetime (born in United States)	35	10	95.0 (2.5)	51.3 (11.3)
Maternal age at child delivery, years				
18–24	145	41	138.1 (2.8)	50.9 (10.1)
25–29	116	33	121.0 (2.8)	48.4 (10.1)
30–34	56	16	138.4 (2.4)	47.2 (9.3)
35–45	34	10	118.3 (2.7)	48.6 (11.7)
Maternal education at child delivery				
<7th grade	160	46	128.9 (2.9)	48.1 (10.3)
7th–11th grade	121	34	129.0 (2.7)	50.4 (10.2)
Completion of high school	70	20	135.8 (2.5)	49.8 (10.1)
Maternal verbal IQ[f]				
≤74	75	21	147.9 (3.0)	46.4 (10.1)
75–99	121	34	149.4 (2.8)	50.9 (10.6)
≥100	151	43	106.9 (2.5)	49.2 (9.8)
Missing data	4	1		
Maternal smoking during pregnancy				
No	338	96	131.4 (2.7)	49.1 (10.2)
Yes	13	4	104.8 (2.9)	53.9 (10.1)
Duration of breastfeeding, months				
Never breastfed	16	5	118.4 (2.9)	51.3 (13.8)
≤1	46	13	116.3 (2.8)	49.1 (9.3)
2–6	118	34	121.7 (2.8)	48.7 (9.9)
7–12	75	21	145.9 (2.8)	50.8 (10.8)
>12	96	27	139.2 (2.6)	48.4 (10.0)
Mother depressed at age 7- and/or 9-year visit(s)				
No	217	62	128.1 (2.9)	46.9 (9.2)
Yes	124	35	126.4 (2.5)	53.4 (10.6)
Missing data	10	3		

Table continues

Table 1. Continued

Characteristic	No. of Children	%	Maternal GM (GSD) ∑DAP Concentration During Pregnancy, nmol/L[c,d,e]	Child's Mean (SD) BRIEF GEC Score at Age 9 Years
DAP urinary metabolites[c]				
No adjustment for specific gravity				
∑DEs	351		20.0 (3.0)	
∑DMs	351		95.9 (3.1)	
∑DAPs	351		130.3 (2.7)	
Adjustment for specific gravity				
∑DEs	351		26.1 (3.0)	
∑DMs	351		126.4 (3.2)	
∑DAPs	351		171.2 (2.9)	
Other chemicals (pregnancy serum concentration)[e]				
∑PBDEs[g]	331		25.6 (2.5)	
DDT	333		23.3 (5.3)	

Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; DAP, dialkyl phosphate; DDT, dichlorodiphenyltrichloroethane; DE, diethyl; DM, dimethyl; GEC, Global Executive Composite; GM, geometric mean; GSD, geometric standard deviation; IQ, intelligence quotient; N/A, not applicable; PBDE, polybrominated diphenyl ether; SD, standard deviation.

[a] Prenatal pesticide exposure was based on measurement of maternal urinary DAP metabolite concentrations.
[b] The outcome measure was the child's maternally reported BRIEF GEC score at age 9 years (*t* score).
[c] Urinary DAP metabolite concentrations based on the average concentration in 2 pregnancy urine samples.
[d] Unadjusted for specific gravity.
[e] Values for serum concentration are presented as ng/g of blood lipid.
[f] Maternal verbal IQ measured as receptive language using the Peabody Picture Vocabulary Test.
[g] Sum of PBDE congeners 47, 99, 100, and 153.

also weakly correlated with maternal, teacher, and child self-report scale scores.

Examination of nonlinearity using penalized splines revealed predominantly linear exposure-response relationships. Therefore, we report all exposure-outcome associations modeling exposure as a continuous variable using linear regression models. Table 2 presents adjusted associations of total gestational urinary DAP metabolites with outcomes assessed via maternal report and direct child assessment, modeled longitudinally using generalized estimating equations (multiple observations per child at ages 7, 9, 10.5, and/or 12 years). For all children, total DAP concentrations were associated with higher scores (more behavior problems) on all maternal report scales, with the strongest adverse associations observed for BRIEF scores. For example, a 10-fold increase in gestational DAP metabolite concentrations was associated with a 4.0-point increase (95% confidence interval (CI): 2.1, 5.8) in *t* scores for the BRIEF Global Executive Composite scale. Associations were similar for the Behavior Regulation and Metacognition Index scales of the BRIEF. We also found associations of DAPs with maternal report of behaviors related to ADHD, including inattention and hyperactivity. These findings were consistent with DAP-related associations with scores on tests completed by the child, including poorer WISC-IV Working Memory Index scores (a 10-fold increase in DAP concentrations was associated with a 3.8-point reduction (β = −3.8, 95% CI: −6.2, −1.3)) and, to a lesser extent, WISC-IV Processing Speed Index scores. DAP concentrations were also associated with poorer performance on the WCST—for example, more total errors (β = −3.6, 95% CI: −5.5, −1.7). Pregnancy DAP concentrations were more weakly related to teacher-reported and self-reported symptoms (Table 3); there were suggestive associations with poorer teacher-reported BRIEF Metacognition Index score (β = 2.2, 95% CI: −0.3, 4.7), CADS ADHD Index score (β = 3.0, 95% CI: 0.3, 5.7), and BASC-2 Attention Problems score (β = 2.0, 95% CI: 0.2, 3.8) and child's self-reported BASC-2 Attention Problems score (β = 2.4, 95% CI: −0.5, 5.2).

Associations of gestational DAP concentrations with executive function were somewhat stronger in boys than in girls (Table 2), particularly for parent-reported BRIEF scores; for example, a 10-fold increase in DAP concentration was associated with a 5.7-point increase (β = 5.7, 95% CI: 2.9, 8.6) in Global Executive Composite *t* scores for boys and a 2.0-point increase (β = 2.0, 95% CI: −0.2, 4.2) for girls (*P* for interaction = 0.06). Sex differences were less pronounced or absent for the other outcome measures. Paradoxically, as Table 3 shows, gestational DAP concentrations were more strongly related to poorer teacher-reported executive

Table 2. Change in Maternally Reported and Child-Assessed Neurodevelopmental Outcome Scores per 10-Fold Increase in Mean Total Gestational Urinary Dialkyl Phosphate Concentration (nmol/L) (From Repeated-Measures (Generalized Estimating Equations) Models), Overall and by Sex, CHAMACOS Study, 1999–2000

Assessment and Outcome	Orientation[a]	Child Ages at Assessment, years	Total				Boys				Girls				*P* for Interaction
			No. of Children	No. of Obs	β	95% CI	No. of Children	No. of Obs	β	95% CI	No. of Children	No. of Obs	β	95% CI	
Maternal report[b,c]															
BRIEF (*t* scores)[d]		7, 9, and 12													
Behavior Regulation Index	Higher		347	978	3.5	1.7, 5.3	163	460	5.7	2.9, 8.6	184	518	2.0	−0.2, 4.2	0.06
Metacognition Index	Higher		347	978	3.8	2.1, 5.6	163	460	5.4	2.8, 8.0	184	518	2.9	0.6, 5.1	0.19
Global Executive Composite	Higher		347	978	4.0	2.1, 5.8	163	460	6.0	3.3, 8.8	184	518	2.7	0.4, 4.9	0.10
CADS (*t* scores)[d]		7, 9, and 12													
ADHD Index	Higher		349	988	2.2	0.8, 3.6	163	464	2.1	0.1, 4.1	186	524	2.3	0.4, 4.3	0.77
DSM-IV Total Scale	Higher		349	988	2.1	0.5, 3.6	163	464	2.7	0.6, 4.9	186	524	1.7	−0.4, 3.9	0.58
Inattentive	Higher		349	988	2.0	0.7, 3.3	163	464	2.5	0.7, 4.4	186	524	1.8	−0.1, 3.6	0.64
Hyperactive/ Impulsive	Higher		349	988	1.9	0.2, 3.5	163	464	2.7	0.3, 5.1	186	524	1.3	−0.9, 3.6	0.45
BASC-2 (*t* scores)[d]		7 and 10.5													
Hyperactivity	Higher		335	634	1.8	0.4, 3.2	157	294	3.4	1.0, 5.8	178	340	0.8	−0.8, 2.4	0.12
Attention Problems	Higher		335	634	2.9	1.0, 4.8	157	294	2.5	−0.3, 5.3	178	340	3.0	0.5, 5.6	0.71
Child assessment[b,e]															
WISC-IV (standardized scores)[d]		7 and 10.5													
Processing Speed Index	Lower		334	605	−1.8	−4.2, 0.6	157	283	−2.9	−7.2, 1.5	177	322	−0.6	−3.4, 2.2	0.27
Working Memory Index	Lower		334	605	−3.8	−6.2, −1.3	157	283	−4.9	−8.8, −0.9	177	322	−2.4	−5.6, 0.7	0.48
WCST (*t* scores)[d]		9 and 12													
Errors	Lower		325	630	−3.6	−5.5, −1.7	153	295	−2.3	−5.3, 0.6	172	335	−3.7	−6.1, −1.2	0.58
Perseverative errors	Lower		325	630	−3.7	−6.3, −1.2	153	295	−2.8	−6.8, 1.3	172	335	−3.9	−7.1, −0.7	0.80
CPT II (*t* scores)[d]		9 and 12													
Errors of omission	Higher		325	634	1.8	−0.3, 3.9	153	297	2.1	−1.3, 5.6	172	337	1.3	−1.4, 4.0	0.32

Table continues

Table 2. Continued

Assessment and Outcome	Orientation[a]	Child Ages at Assessment, years	Total				Boys				Girls				*P* for Interaction
			No. of Children	No. of Obs	β	95% CI	No. of Children	No. of Obs	β	95% CI	No. of Children	No. of Obs	β	95% CI	
Errors of commission	Higher		325	634	1.6	−0.3, 3.4	153	297	−0.1	−3.3, 3.0	172	337	3.0	0.6, 5.3	0.07
Hit rate standard error															
Overall	Higher		325	634	1.5	−0.4, 3.4	153	297	1.9	−1.1, 4.9	172	337	1.2	−1.4, 3.7	0.86
By block	Higher		325	634	1.5	−0.5, 3.6	153	297	2.8	0.2, 5.5	172	337	1.1	−1.9, 4.1	0.56
By interstimulus interval	Higher		325	634	2.3	0.5, 4.1	153	297	2.4	0.0, 4.8	172	337	2.4	−0.1, 4.9	0.84
ADHD Confidence Index[f]	Higher		325	634	1.1	−2.5, 4.6	153	297	1.8	−3.8, 7.3	172	337	0.1	−4.6, 4.8	0.55

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BASC-2, Behavior Assessment System for Children, Second Edition; BRIEF, Behavior Rating Inventory of Executive Function; CADS, Conners ADHD/DSM-IV Scales; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; CPT II, Conners Continuous Performance Test II; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; Obs, observations; WISC-IV, Weschler Intelligence Scale for Children—Fourth Edition; WCST, Wisconsin Card Sorting Test.

[a] Higher scores indicate more symptomatic behavior; lower scores indicate poorer performance.

[b] All models adjusted for maternal age, duration of residence in the United States (years), education, receptive language, and average depression score at child's ages 7–9 years; average Home Observation Measurement of the Environment (HOME) score (child's ages 7–12 years); child's age at assessment; and child's sex.

[c] Parental report models additionally adjusted for language of questionnaire administration.

[d] BRIEF, CADS, BASC-2, WCST, and CPT II *t* scores are standardized to the mean score: 50 (standard deviation, 10); WISC-IV *t*-standardized scores are standardized to the mean WISC-IV score: 100 (standard deviation, 15).

[e] Child testing models additionally adjusted for psychometrician who administered the test, language of testing, and, for the CPT II and WCST models only, video game usage.

[f] The CPT II ADHD Confidence Index is not a *t* score but rather is produced by discriminant function analysis and represents the percentage of children with this performance profile who would be correctly classified as having ADHD.

Table 3. Change in Teacher-Reported and Child Self-Reported Neurodevelopmental Scores per 10-Fold Increase in Mean Total Gestational Urinary Dialkyl Phosphate Concentration (nmol/L), CHAMACOS Study, 1999–2000

Outcome	Orientation[a]	Teacher Report—Age 7 Years							Self-Report—Age 10.5 Years						
		No. of Children	Total		Boys		Girls		*P* for Interaction	No. of Children	Total		Boys		Girls		*P* for Interaction
			β	95% CI	β	95% CI	β	95% CI			β	95% CI	β	95% CI	β	95% CI	
BRIEF (*t* scores)[b,c]																	
Behavior Regulation Index	Higher	277	0.2	−2.1, 2.6	−2.6	−5.7, 0.5	2.4	−1.0, 5.8	0.03								
Metacognition Index	Higher	277	2.2	−0.3, 4.7	−0.7	−4.7, 3.4	4.4	1.2, 7.6	0.05								
Global Executive Composite	Higher	277	1.6	−0.9, 4.0	−1.6	−5.2, 2.0	4.0	0.7, 7.3	0.02								
CADS (*t* scores)[b,c]																	
ADHD Index	Higher	273	3.0	0.3, 5.7	0.5	−3.2, 4.3	4.6	0.8, 8.4	0.13								
DSM-IV Total Scale	Higher	272	1.4	−1.0, 3.7	−0.8	−4.2, 2.6	2.8	−0.4, 6.1	0.15								
Inattentive	Higher	276	1.6	−0.5, 3.7	0.4	−3.6, 4.3	2.5	0.1, 4.9	0.38								
Hyperactive/Impulsive	Higher	276	0.5	−1.9, 3.0	−2.3	−5.8, 1.1	2.4	−1.0, 5.8	0.06								
BASC-2 (*t* scores)[b,c]																	
Hyperactivity	Higher	277	−0.0	−2.4, 2.4	−3.7	−7.7, 0.2	2.8	0.1, 5.6	0.01	302	1.5	−1.0, 4.0	2.1	−2.0, 6.1	1.1	−2.2, 4.3	0.43
Attention Problems	Higher	277	2.0	0.2, 3.8	0.6	−2.3, 3.5	3.0	0.7, 5.3	0.16	295	2.4	−0.5, 5.2	0.7	−3.5, 4.9	3.5	−0.2, 7.1	0.42

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BASC-2, Behavior Assessment System for Children, Second Edition; BRIEF, Behavior Rating Inventory of Executive Function; Conners ADHD/DSM-IV Scales; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.

[a] Higher scores indicate more symptomatic behavior; lower scores indicate poorer performance.

[b] All models adjusted for maternal age, duration of residence in the United States (years), education, receptive language, and average depression score at child's ages 7–9 years; average Home Observation Measurement of the Environment (HOME) score (child's ages 7–12 years); child's age at assessment; and child's sex.

[c] BRIEF, CADS, and BASC-2 scores are standardized to the mean score: 50 (standard deviation, 10).

function and related behaviors for girls than for boys—for example, each 10-fold increase in DAP concentration was associated with a 4.0-point increase (β = 4.0, 95% CI: 0.7, 7.3) in BRIEF Global Executive Composite *t* scores for girls and a 1.6-point decrease (β = −1.6, 95% CI: −5.2, 2.0) for boys (*P* for interaction = 0.02). Sex differences for DAPs and self-reported behavior were neither strong nor consistent (Table 3).

Total dimethyl and neurodevelopment associations closely mirrored those for total DAPs (Web Table 6), with strong adverse associations with parent-reported executive functioning, attention, and working memory, particularly in boys. By contrast, total diethyl concentrations (Web Table 7) were not associated with any parent-reported outcomes but were associated with significantly poorer WISC-IV Processing Speed Index performance in boys (a 5.0-point decrease (β = −5.0, 95% CI: −8.9, −1.2) per 10-fold increase in total diethyl concentrations) but not girls (a 0.4-point increase (β = 0.4, 95% CI: −2.8, 3.6); *P* for interaction = 0.03). Higher diethyl exposure was also associated with more inconsistent performance (i.e., hit-rate standard error, hit-rate standard error by block, and hit-rate standard error by interstimulus interval) for boys on the CPT II.

The strong adverse associations of DAPs with parent-reported BRIEF scores appeared relatively stable across age (7, 9, and 12 years) (Web Table 8). This was true for most of the other outcome measures as well, though precision was lower than for the repeated-measures analyses shown in Table 2. Associations with CPT II performance, by contrast, were limited to age 9 years and were not evident at age 12 years. Adjustment for exposure to polybrominated diphenyl ether and dichlorodiphenyltrichloroethane in sensitivity analysis, exclusion of the 4 children who used medications for attention problems, and use of inverse probability weighting to account for differential loss to follow-up did not materially change effect estimates.

DISCUSSION

We found that urinary DAP concentrations during pregnancy were associated with behaviors related to ADHD and executive function problems in children aged 7–12 years. These findings extend previously reported associations in CHAMACOS of OPs with neurodevelopment, including attention problems at age 5 years (24). Notably, we showed that OP-related associations with neurodevelopment persist in children as they age and extend to other challenges in executive function, including cognitive flexibility, working memory, and behavioral inhibition. DAP concentrations in CHAMACOS were higher than, though within range of, those observed in a representative sample of the general US population (17, 18).

The associations we present in this analysis are relatively consistent with those of other prospective cohort studies. In a study of a multiethnic population enrolled during pregnancy in New York City, researchers found associations of DAPs, particularly diethyls, with the Working Memory Index of the WISC-IV at ages 7–9 years (22) and with working memory in factor analysis (47). In another New York City study that examined the OP insecticide chlorpyrifos (which metabolizes to diethyls) in umbilical cord blood from African-American and Dominican mothers, investigators also reported associations with poorer WISC-IV Working Memory Index score at age 7 years (25), particularly among boys (48). In the current study, we report associations of WISC-IV Working Memory Index score primarily with total dimethyls, though we did find weak associations of total diethyls with working memory, also among boys only (Web Tables 6 and 7).

To our knowledge, this is the first study to show associations of OP pesticides with executive function in early adolescence. We observed associations with several dimensions of executive function across time, including cognitive flexibility, working memory, response inhibition, and behavioral regulation. We also observed associations with related traits that overlap with ADHD, including inattention and hyperactivity. These extend previously reported associations of gestational DAPs with other outcomes related to executive function in CHAMACOS, including higher risk scores on the Pervasive Developmental Problems scale of the Child Behavior Checklist at 24 months, poorer attention, and increased numbers of traits related to autism spectrum disorder (assessed using the Social Responsiveness Scale, Second Edition) at age 14 years (23, 24, 49).

Our findings are supported by a study of neural activity assessed in a subset of 95 participants enrolled in the second wave of the CHAMACOS cohort study (CHAM2) (50). We did not include CHAM2 participants in the current study because these children were recruited at age 9 years and therefore did not have gestational DAP measurements. In this neuroimaging study, we used functional near-infrared spectroscopy to measure cortical activation in the prefrontal cortex during tasks of executive function (among other tasks) (50). We found that residential proximity to OP use during pregnancy, estimated using California's Pesticide Use Reporting database, was associated with altered brain activation during tasks of executive function that targeted cognitive flexibility, visuospatial working memory, and letter working memory. In another neuroimaging study, a New York City cohort study, Rauh et al. (51) reported associations between gestational chlorpyrifos exposure and volumetric differences across a number of brain regions in the frontal lobes in a subset of participants (n = 40), including reduced cortical thickness in the prefrontal cortex, the primary brain region for executive function.

A strength of this study is the rich array of outcome measures, including parent reports, teacher reports, child self-reports, and child neuropsychological assessment scores. With the exception of child self-reports of hyperactivity or attention problems, which were not associated with gestational DAP concentrations, we observed some degree of adverse association between gestational OP exposure and each of our outcome measures.

This rich array of outcome measures also gave rise to some puzzling inconsistencies. The most striking associations we present are between gestational DAP concentrations and maternal BRIEF executive function scores, which, though observable in both boys and girls, were particularly pronounced in boys. In contrast, to the extent that any associations between DAP concentrations and teacher-reported

executive function and attention outcomes are observable, they were observed among girls only (Table 3). Inconsistencies between parent and teacher ratings of children's behavior is a common finding in previous studies (52), and our data suggest that although mothers' and teachers' observations were only weakly correlated with one another within this cohort, both were about equally correlated with children's self-reported hyperactivity and attention problems and children's performance on neuropsychological assessments. Although the magnitudes of correlations between adult-reported behaviors and child-reported or neuropsychologically assessed skills were only weak or modest, the consistency of the DAP-related associations was notable.

The specific biological mechanism for an effect of OP neurotoxicity on noncholinergic pathways is unclear. While the mechanisms linking OPs with acetylcholinesterase inhibition are well established, OP exposure in the general population (including CHAMACOS participants) is likely to be too low to target this pathway. Potential pathways related to low-dose OP exposure include 1) disruption of neurotransmitter systems including dopamine and serotonin, which modulate prefrontal cortical function; 2) inhibition of axonal growth (6, 14); 3) increased oxidative stress or inflammatory mediators (3, 11); 4) imbalanced intracellular calcium ion (Ca^{2+}) homeostasis (4); and 5) epigenetic modifications (7, 10). Researchers in animal studies have also observed OP-related changes in behavior, including hyperactivity, short-term memory, and social behavior (5, 8, 9, 12, 13).

Our study had some limitations. DAPs are nonspecific metabolites, making inference to a specific OP pesticide or source of exposure difficult. DAP concentrations in urine may also reflect exposure to metabolites that were preformed in the environment and not parental pesticide exposure, thereby overestimating pesticide exposure. In addition, rapid metabolism of OPs is a central limiting factor in our DAP measures, resulting in exposure measurement error; this was ameliorated somewhat by taking 2 urinary DAP measurements during pregnancy. We did not have data on teacher characteristics or parental ADHD/executive function. Attrition in the CHAMACOS cohort across time was not negligible. The 351 children included in these analyses represented 66% of the initial cohort with gestational DAP measurements (n = 534). Characteristics of these groups were similar (with minor exceptions), and sensitivity analyses which included inverse probability weighting suggested that differential attrition did not substantially affect the associations we report. Finally, we did not account for postnatal OP pesticide exposure. Early childhood exposure to DAPs has been shown to have weak or null associations with neurodevelopmental outcomes at age 7 years or younger in CHAMACOS (20, 24); however, given that brain development (executive functions in particular) continues into early adulthood, postnatal exposure could be important and should be considered in future work.

In conclusion, we found that gestational OP exposure was associated with behaviors related to ADHD and poorer executive function across multiple ages, domains, and types of neuropsychological assessments. These results, taken together with a growing body of previous literature showing adverse effects of OP pesticides on the developing brain, provide compelling support for the neurotoxicity of these chemicals at levels present in agricultural and possibly other populations. Public health intervention and policy reforms, such those outlined in a recent review of the evidence on early-life exposure to OP pesticides and neurodevelopment (53), are important for reducing exposure to these chemicals during the gestational period.

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REFERENCES

1. Grube A, Donaldson D, Kiely T, et al. *Pesticides Industry Sales and Usage: 2006 and 2007 Market Estimates*. Washington, DC: Environmental Protection Agency; 2011. https://www.epa.gov/sites/production/files/2015-10/documents/market_estimates2007.pdf. Accessed May 28, 2021.
2. Sultatos LG. Mammalian toxicology of organophosphorus pesticides. *J Toxicol Environ Health*. 1994;43(3):271–289.
3. Crumpton TL, Seidler FJ, Slotkin TA. Is oxidative stress involved in the developmental neurotoxicity of chlorpyrifos? *Brain Res Dev Brain Res*. 2000;121(2):189–195.
4. Giordano G, Afsharinejad Z, Guizzetti M, et al. Organophosphorus insecticides chlorpyrifos and diazinon and oxidative stress in neuronal cells in a genetic model of glutathione deficiency. *Toxicol Appl Pharmacol*. 2007; 219(2-3):181–189.
5. Grabovska S, Salyha Y. ADHD-like behaviour in the offspring of female rats exposed to low chlorpyrifos doses

before pregnancy. *Arh Hig Rada Toksikol*. 2015;66(2):121–127.
6. Howard AS, Bucelli R, Jett DA, et al. Chlorpyrifos exerts opposing effects on axonal and dendritic growth in primary neuronal cultures. *Toxicol Appl Pharmacol*. 2005;207(2):112–124.
7. Kim HY, Wegner SH, Van Ness KP, et al. Differential epigenetic effects of chlorpyrifos and arsenic in proliferating and differentiating human neural progenitor cells. *Reprod Toxicol*. 2016;65:212–223.
8. Lan A, Stein D, Portillo M, et al. Impaired innate and conditioned social behavior in adult C57Bl6/J mice prenatally exposed to chlorpyrifos. *Behav Brain Funct*. 2019;15(1):Article 2.
9. Levin ED, Addy N, Baruah A, et al. Prenatal chlorpyrifos exposure in rats causes persistent behavioral alterations. *Neurotoxicol Teratol*. 2002;24(6):733–741.
10. Shin HS, Seo JH, Jeong SH, et al. Effect on the H19 gene methylation of sperm and organs of offspring after chlorpyrifos-methyl exposure during organogenesis period. *Environ Toxicol*. 2015;30(12):1355–1363.
11. Slotkin TA, Seidler FJ. Oxidative stress from diverse developmental neurotoxicants: antioxidants protect against lipid peroxidation without preventing cell loss. *Neurotoxicol Teratol*. 2010;32(2):124–131.
12. Terry AV Jr, Gearhart DA, Beck WD Jr, et al. Chronic, intermittent exposure to chlorpyrifos in rats: protracted effects on axonal transport, neurotrophin receptors, cholinergic markers, and information processing. *J Pharmacol Exp Ther*. 2007;322(3):1117–1128.
13. Terry AV Jr, Stone JD, Buccafusco JJ, et al. Repeated exposures to subthreshold doses of chlorpyrifos in rats: hippocampal damage, impaired axonal transport and deficits in spatial learning. *J Pharmacol Exp Ther*. 2003;305(1):375–384.
14. Yang D, Howard A, Bruun D, et al. Chlorpyrifos and chlorpyrifos-oxon inhibit axonal growth by interfering with the morphogenic activity of acetylcholinesterase. *Toxicol Appl Pharmacol*. 2008;228(1):32–41.
15. Bradman A, Quiros-Alcala L, Castorina R, et al. Effect of organic diet intervention on pesticide exposures in young children living in low-income urban and agricultural communities. *Environ Health Perspect*. 2015;123(10):1086–1093.
16. Bradman A, Castorina R, Barr DB, et al. Determinants of organophosphorus pesticide urinary metabolite levels in young children living in an agricultural community. *Int J Environ Res Public Health*. 2011;8(4):1061–1083.
17. Bradman A, Eskenazi B, Barr DB, et al. Organophosphate urinary metabolite levels during pregnancy and after delivery in women living in an agricultural community. *Environ Health Perspect*. 2005;113(12):1802–1807.
18. Barr DB, Wong LY, Bravo R, et al. Urinary concentrations of dialkylphosphate metabolites of organophosphorus pesticides: National Health and Nutrition Examination Survey 1999–2004. *Int J Environ Res Public Health*. 2011;8(8):3063–3098.
19. Bouchard MF, Bellinger DC, Wright RO, et al. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. *Pediatrics*. 2010;125(6):e1270–e1277.
20. Bouchard MF, Chevrier J, Harley KG, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ Health Perspect*. 2011;119(8):1189–1195.
21. Engel SM, Berkowitz GS, Barr DB, et al. Prenatal organophosphate metabolite and organochlorine levels and performance on the Brazelton Neonatal Behavioral Assessment Scale in a multiethnic pregnancy cohort. *Am J Epidemiol*. 2007;165(12):1397–1404.
22. Engel SM, Wetmur J, Chen J, et al. Prenatal exposure to organophosphates, paraoxonase 1 and cognitive development in childhood. *Environ Health Perspect*. 2011;119(8):1182–1188.
23. Eskenazi B, Marks AR, Bradman A, et al. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. *Environ Health Perspect*. 2007;115(5):792–798.
24. Marks AR, Harley K, Bradman A, et al. Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS Study. *Environ Health Perspect*. 2010;118(12):1768–1774.
25. Rauh V, Arunajadai S, Horton M, et al. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos a common agricultural pesticide. *Environ Health Perspect*. 2011;119(8):1196–1201.
26. Rauh VA, Garfinkel R, Perera FP, et al. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics*. 2006;118(6):e1845–e1859.
27. Young JG, Eskenazi B, Gladstone EA, et al. Association between in utero organophosphate pesticide exposure and abnormal reflexes in neonates. *Neurotoxicology*. 2005;26(2):199–209.
28. Miyake A, Friedman NP. The nature and organization of individual differences in executive functions: four general conclusions. *Curr Dir Psychol Sci*. 2012;21(1):8–14.
29. Silverstein MJ, Faraone SV, Leon TL, et al. The relationship between executive function deficits and DSM-5-defined ADHD symptoms. *J Atten Disord*. 2020;24(1):41–51.
30. Bravo R, Driskell WJ, Whitehead RD Jr, et al. Quantitation of dialkyl phosphate metabolites of organophosphate pesticides in human urine using GC-MS-MS with isotopic internal standards. *J Anal Toxicol*. 2002;26(5):245–252.
31. Elkins HB, Pagnotto LD. The specific gravity adjustment in urinalysis. *Arch Environ Health*. 1969;18(6):996–1001.
32. Gioia GA. *Behavioral Rating Inventory of Executive Function (BRIEF)*. Lutz, FL: Psychological Assessment Resources, Inc.; 2000.
33. Conners CK. *Conners' Rating Scales—Revised (CSR-R) Technical Manual (Includes Auxiliary Scales: CADS-P and CADS-T)*. North Towanda, NY: Multi-Health Systems, Inc.; 2001.
34. Reynolds CR, Kamphaus RW. *Behavior Assessment System for Children, Second Edition (BASC-2)*. Circle Pines, MN: AGS Publishing; 2004.
35. Heaton RK. *WCST-64: Computer Version 2 Research Edition*. Odessa, FL: Psychological Assessment Resources, Inc.; 2000.
36. Conners CK. *Conners Continuous Performance Test (CPT II)*. North Towanda, NY: Multi-Health Systems, Inc.; 2000.
37. Wechsler D. *WISC-IV Administration and Scoring Manual*. San Antonio, TX: Harcourt Assessment, Inc.; 2003.
38. Dunn LM. *Examiner's Manual for the Peabody Picture Vocabulary Test*. 3rd ed. Circle Pines, MN: American Guidance Service; 1997.
39. Dunn LPE, Lugo D, Dunn L. *Test de Vocabulario en Imagenes Peabody: Adaptacion Hispanoamericana [Peabody Picture Vocabulary Test: Hispanic-American Adaptation]*. Circle Pines, MN: Dunn Educational Services, Inc.; 1986.

40. Radoff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):85–401.
41. Caldwell B, Bradley R. *Home Observation for Measurement of the Environment—Revised Edition*. Little Rock, AR: University of Arkansas; 1984.
42. Eskenazi B, Marks AR, Bradman A, et al. In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children. *Pediatrics*. 2006;118(1):233–241.
43. Gaspar FW, Harley KG, Kogut K, et al. Prenatal DDT and DDE exposure and child IQ in the CHAMACOS cohort. *Environ Int*. 2015;85:206–212.
44. Eskenazi B, Chevrier J, Rauch SA, et al. In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS Study. *Environ Health Perspect*. 2013;121(2):257–262.
45. Sagiv SK, Kogut K, Gaspar FW, et al. Prenatal and childhood polybrominated diphenyl ether (PBDE) exposure and attention and executive function at 9–12 years of age. *Neurotoxicol Teratol*. 2015;52(B):151–161.
46. Peng RD, Dominici F. *Statistical Methods for Environmental Epidemiology With R: A Case Study in Air Pollution and Health*. New York, NY: Springer Science+Business Media; 2008.
47. Furlong MA, Herring A, Buckley JP, et al. Prenatal exposure to organophosphorus pesticides and childhood neurodevelopmental phenotypes. *Environ Res*. 2017;158: 737–747.
48. Horton MK, Kahn LG, Perera F, et al. Does the home environment and the sex of the child modify the adverse effects of prenatal exposure to chlorpyrifos on child working memory? *Neurotoxicol Teratol.* 2012;34(5): 534–541.
49. Sagiv SK, Harris MH, Gunier RB, et al. Prenatal organophosphate pesticide exposure and traits related to autism spectrum disorders in a population living in proximity to agriculture. *Environ Health Perspect*. 2018; 126(4):047012.
50. Sagiv SK, Bruno JL, Baker JM, et al. Prenatal exposure to organophosphate pesticides and functional neuroimaging in adolescents living in proximity to pesticide application. *Proc Natl Acad Sci U S A*. 2019;116(37):18347–18356.
51. Rauh VA, Perera FP, Horton MK, et al. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proc Natl Acad Sci U S A*. 2012;109(20): 7871–7876.
52. Lawson GM, Nissley-Tsiopinis J, Nahmias A, et al. Do parent and teacher report of ADHD symptoms in children differ by SES and racial status? *J Psychopathol Behav Assess*. 2017;39(1):426–440.
53. Hertz-Picciotto I, Sass JB, Engel S, et al. Organophosphate exposures during pregnancy and child neurodevelopment: recommendations for essential policy reforms. *PLoS Med*. 2018;15(10):e1002671.