Gestational exposure to organophosphate pesticides and longitudinally assessed behaviors related to ADHD and executive function

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Funding: RD 82670901, RD 83171001, and RD 83451301 from the U.S. Environmental Protection Agency (US EPA), and PO1 ES009605, RO1 ES015572, and R24 ES028529 from NIEHS.

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Conflict of interest: Dr. Bradman is a volunteer member of the Board of Trustees for The Organic Center, a non-profit organization addressing scientific issues about organic food and agriculture and is a member of the USDA National Organic Standards Board. Dr. Bradman also advises organic and conventional food growers and processors on pesticide-related issues. Other authors have no financial relationships or conflicts of interest relevant to this article to disclose.

Running head: Organophosphate pesticides and executive function

Abstract
The prefrontal cortex directs higher-order cognitive and behavioral processes 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. We enrolled pregnant women between 1999-2000 in a birth cohort drawn from an agricultural region of California. We measured dialkyl phosphate (DAP) metabolites of OP pesticides in maternal pregnancy urine (13 and 26 weeks) and estimated associations with behaviors related to attention deficit hyperactivity disorder and executive function, assessed longitudinally; n=351 provided outcome data at any point between ages 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, self-report). Higher gestational DAPs were consistently associated with behaviors related to attention deficit hyperactivity disorder and executive function. For example, a 10-fold increase in gestational DAPs was associated with poorer longitudinally assessed Behavior Rating Inventory of Executive Function scores, reported by mothers ($\beta=4.0; 95\%$ CI: 2.1, 5.8; higher score indicates more problems), and
Weschler Intelligence Scale for Children Working Memory scores (β=-3.8 point reduction (95% CI: -6.2, -1.3). Reducing gestational exposure to OP pesticides through public health policy is an important goal.

Key Words: Organophosphate pesticides, gestational exposure, executive function, attention, ADHD, neurodevelopment

Abbreviations: ADHD, Attention deficit hyperactivity disorder; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, Confidence interval; DAP, Dialkyl phosphate; DE, Diethyl phosphate; DM, Dimethyl phosphate; GEE, Generalized estimating equations; OP, Organophosphate

Organophosphate (OP) pesticides are commonly used in agriculture in California and in the U.S. (1). OPs are neurotoxicants which inhibit 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). Dialkyl phosphate (DAP) urinary metabolites, the most common biomarker of exposure to OPs, were detected in nearly all samples collected in a nationally representative U.S. study, indicating widespread exposure to OPs (18).

Previous studies report generally consistent associations of gestational exposure to OPs with adverse neurodevelopment in early childhood and at early school age, including poorer
intellectual development, 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 prefrontal cortex, these functions direct complex, higher-order cognitive and behavioral processes critical for planning, problem solving, sustaining attention, and inhibitory control, and 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, on children’s executive functioning, assessed longitudinally at ages 7, 9, 10.5, and 12 years, among children 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 1999-2000, we recruited pregnant women receiving prenatal care at community clinics serving the Salinas Valley’s farmworker population. Eligible women were ≥18 years old, <20 weeks gestation, Spanish- or English-speaking, qualified for low-income health insurance, and planned to deliver at the public hospital. Of 601 pregnant women who enrolled, 537 live born infants remained in the study at delivery. Gestational OP metabolite concentrations were available for 534 children, and 363 provided outcome data at any point between 7 and 12 years. We excluded
6 twins and 6 children with diagnosed developmental conditions (see Web Appendix 1) who could not complete all testing, leaving 351 children in the final analyses.

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

OP pesticide exposure assessment

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 (~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. We measured six DAP metabolites, including three dimethyl (DM) phosphate metabolites (dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate) and three diethyl (DE) phosphate metabolites (diethylphosphate, diethylthiophosphate, and diethyldithiophosphate), using gas chromatography-tandem mass spectrometry and isotope dilution calibration (30). We summed molar concentrations to yield total DM, total DE, and total DAP concentrations (nmoles/L) (31). For individuals with non-detectable 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, MD) 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 report (all time points), teacher report (age 7), and child self-report (age 10.5), using the Behavior Rating Inventory of Executive Function (32); the Conners’ ADHD/ Diagnostic and Statistical Manual of Mental Disorders Scales Fourth Edition Scales, Parent Version and Teacher Version (33); and the Behavior Assessment System for Children, 2nd edition Parent and Teacher Report and Self Report of Personality (34). In addition, we conducted neuropsychological assessments to assess child performance on aspects of ADHD and executive function, including the Wisconsin Card Sort Task-64: Computer Version 2- Research Edition (35); the Conners’ Continuous Performance Test II (36); and select scales of the Wechsler Intelligence Scale for Children - Fourth Edition (37). Details of test administration are described in Web Appendix 2. All neuropsychological assessments were conducted in a private room by bilingual, bicultural psychometricians, 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 (13 and 26 weeks gestation), shortly following delivery, and when children were 6 months, and 1, 2, 3.5, 5, 7, 9, 10.5, and 12 years old. All mothers were administered: the Peabody Picture Vocabulary Test (38), or its Spanish equivalent (39), to assess maternal receptive language at child age 6 months and 9 years; the Center for Epidemiologic Studies Depression Scale to assess maternal depressive symptoms (40) at child
age 1, 3, 7, and 9 years; and, the Home Observation for the Measurement of the Environment (HOME) -Short Form (41) to assess the home learning environment at age 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 impact neurodevelopment in CHAMACOS, and which may confound OP-related associations, including dichlorodiphenyltrichloroethane (DDT) (42, 43) and polybrominated diphenyl ether (PBDE) flame retardants (44, 45). We previously reported details about collection and measurement of these chemicals (42, 44).

Statistical analysis

All data management and analyses were conducted using Stata 15 (StataCorp. 2017, Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). We used Spearman correlations to examine consistency of scores over time and across raters (mothers, teachers, child self-report). We calculated mean total DM, DE, and DAP concentrations across the two pregnancy urine samples. We used linear regression to model log_{10}-transformed, specific gravity adjusted DAPs in relation to outcome measures and used generalized estimating equations (GEE) with robust standard errors to account for non-independence across repeated measures. We examined linearity of the dose-response function by running generalized additive models using 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 (continuous), years in the U.S. at delivery (continuous), education at delivery (categorical: <6th grade, 7–12th grade, completed high school), maternal receptive language at child age 9 years (continuous Peabody Picture Vocabulary Test score), average depressive symptom score at child age 7 and 9 years.
(continuous), and average Home Observation for Measurement of the Environment score from 7-12 years (continuous z-score). Though some of these variables come 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 (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 psychometrician who administered the test (categorical), language of testing, and video game usage (for the Conners’ Continuous Performance Test II and Wisconsin Card Sort Task 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 Observation for Measurement of the Environment score). We randomly imputed the remaining few covariate missing values (n=10, 6, and 6 observations for maternal depression, Home Observation for Measurement of the Environment score and video game usage, respectively).

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

In a sensitivity analysis, we re-ran all main models using inverse probability weighting (IPW) to explore possible bias resulting from differential loss-to-follow up in this cohort. We also re-ran key analyses excluding four 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 DAPs and neuropsychological data at any time between ages 7-12 years. Details on limits of detection and quality control for DAPs in CHAMACOS were published previously (17). Most mothers (87%) were born in Mexico, and most (74%) had resided in the United States for ten 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. DM metabolite concentrations (mean 95.9±3.1 nmol/L) exceeded DE concentrations (mean 20.0±3.0 nmol/L); total DAP concentrations (mean 130.3±2.7 nmol/L) therefore primarily reflect DM exposure. Web Table 1 compares sociodemographic and exposure characteristics of the original birth cohort with measured gestational DAPs (n=534) with 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 in the original cohort. Web Table 2 presents summary standardized scores on behavioral rating scales as well as child assessment scores 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, 4, and 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 Behavior Rating Inventory of Executive Function, Conners’ ADHD/ Diagnostic and Statistical Manual of Mental Disorders (DSM), Fourth Edition Scales, and Behavior Assessment System for Children, 2nd edition 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 were strongly correlated (0.70-0.89), maternal and teacher reports at age 7 were only weakly correlated (0.09-0.30). Web Table 4 shows that maternal report scale scores were moderately to strongly correlated across timepoints (0.54-0.69), children’s scores on the Weschler Intelligence Scale for Children, Fourth Edition scales were moderately correlated between ages 7 and 10½ (0.43-0.51), and children’s scores on Wisconsin Card Sort Task and Conners’ Continuous Performance Test II tasks were weakly correlated between ages 9 and 12 (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 (0.16-0.27). Child assessment scores were also weakly correlated with maternal, teacher, and child self-report scale scores.

Examination of non-linearity using penalized splines revealed predominantly linear exposure-response relationships. We therefore 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 GEE (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 Behavior Rating Inventory of Executive Function scores. For example, a 10-fold increase in gestational DAP metabolite concentrations was associated with a 4.0 point (95% CI 2.1, 5.8) increase in T-scores for the Behavior Rating Inventory of Executive Function Global Executive Composite scale. Associations were similar for the Behavior Regulation and Metacognition Indices of the Behavior Rating Inventory of Executive Function. 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 Weschler Intelligence Scale for Children, Fourth Edition Working Memory Index scores (a 10-fold increase in DAPs was associated with a 3.8 point reduction; 95% CI: -6.2, -1.3), and to a lesser extent, Processing Speed Index. DAPs were also associated with poorer performance on the WSCT, e.g., 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), with suggestive associations with poorer teacher-reported Behavior Rating Inventory of Executive Function Metacognition Index (β=2.2; 95% CI: -0.4, 4.7), Conners’ ADHD/ Diagnostic and Statistical Manual of Mental Disorders (DSM), Fourth Edition Scales ADHD Index (β=2.9; 95% CI: 0.3, 5.6), and Behavior Assessment System for Children, 2nd edition Attention Problems (β=2.0; 95% CI: 0.2, 3.8), and child self-reported Behavior Assessment System for Children, 2nd edition Attention Problems (β=2.4; 95% CI: -0.5, 5.2).

Associations of gestational DAPs with executive function were somewhat stronger in boys than in girls (Table 2), particularly for parent-reported Behavior Rating Inventory of Executive Function scores, e.g., a 10-fold increase in DAPs was associated with a 5.7 point (95% CI 2.9, 8.6) increase in Global Executive Composite T-scores for boys and a 2.0 point increase for girls (95% CI: -0.2, 4.2) (p-value for interaction = 0.06). Sex differences were less pronounced or absent for the other outcome measures. Paradoxically, as shown in Table 3, gestational DAPs were more strongly related to poorer teacher-reported executive function and related behaviors for girls than boys, e.g., each 10-fold increase in DAP concentrations was associated with a 4.0 point (95% CI 0.7, 7.3) increase in Behavior Rating Inventory of Executive Function Global Executive Composite T-scores for girls and a 1.6 point (95% CI: -5.2, 2.0)
decrease for boys (p-value for interaction = 0.02). Sex differences for DAPs and self-reported behavior were neither strong nor consistent (Table 3).

DM and neurodevelopment associations closely mirrored those for total DAPs (Web Table 6), with strong adverse associations, particularly in boys, with parent-reported executive functioning, attention and working memory. By contrast, DE concentrations (Web Table 7) were not associated with any parent-reported outcomes but were associated with significantly poorer Wechsler Intelligence Scale for Children Processing Speed Index performance in boys (5.0 point decrease, 95% CI: -8.9, -1.2, per 10-fold increase in total DEs) but not girls (0.4; 95% CI -2.8,3.6; interaction p-value = 0.03). Higher DE exposure was also associated with more inconsistent performance (i.e., hit rate standard error, hit rate SE by block, and hit rate SE by inter-stimulus interval) for boys on the Conners’ Continuous Performance Test II.

The strong adverse associations of DAPs with parent-reported Behavior Rating Inventory of Executive Function 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 reported in Table 2. Associations with Conners’ Continuous Performance Test II performance, by contrast, were limited to age 9 years, and were not evident at age 12 years. Adjusting for polybrominated diphenyl ethers and dichlorodiphenyltrichloroethane in sensitivity analysis, excluding four children who used medications for attention problems, and inverse probability weighting (IPW) to account for differential loss to follow up did not materially change effect estimates.

DISCUSSION

We found that pregnancy urinary DAPs were associated with behaviors related to ADHD
and executive function problems in children age 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 show 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, though in range, of those observed in a representative sample of the general U.S. population (17, 18).

The associations we present in this analysis are relatively consistent with other prospective cohort studies. A study of a multiethnic population enrolled during pregnancy in New York City found associations of DAPs, particularly DE, with the Working Memory index of the Weschler Intelligence Scale for Children, Fourth Edition at age 7 to 9 years (22), and with working memory in factor analysis (47). Another New York City study that examined the OP insecticide chlorpyrifos (which metabolizes to DE) in cord blood from African-American and Dominican mothers also reported associations with poorer Working Memory index of the Weschler Intelligence Scale for Children, Fourth Edition at age 7 years (25), particularly among boys (48). In the current study, we report associations of Weschler Intelligence Scale for Children, Fourth Edition Working Memory index primarily with DMs; though we did find weak associations of DEs 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 across 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 disorder scale on the
Child Behavior Checklist at 24 months, poorer attention, and increased traits related to Autism
Spectrum Disorders using the Social Responsiveness Scale-2 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 (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 measures. In this neuroimaging study, we used
functional near-infrared spectroscopy (fNIRS) 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 reported associations of gestational
chlorpyrifos exposure with volumetric differences in a subset of participants (n=40) across a
number of brain regions in the frontal lobes, including reduced cortical thickness in the
prefrontal cortex (51), the primary brain region for executive function.

A strength of this study is the rich array of outcome measures, including parent report,
teacher report, child self-report, and child neuropsychological assessment scores. With the
exception of child self-reports of hyperactivity or attention problems, which were not associated
with gestational DAPs, 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 DAPs and maternal Behavior Rating Inventory of Executive Function executive function scores, which though observable in both boys and girls are particularly pronounced in boys. In contrast, to the extent that any association between DAPS and teacher-reported executive function and attention outcomes are observable, they are 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 though 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 assessed performance. Although the magnitude of correlations between adult-reported behaviors and child-reported or assessed skills were only weak or modest, the consistency of the DAP-related associations was notable.

The specific biological mechanism for organophosphate neurotoxicity on non-cholinergic pathways is unclear. While the mechanisms linking OPs with acetylcholinesterase inhibition are well established, OP exposure in the general population (including CHAMACOS) are 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 Ca^{2+} homeostasis (4); and 5) epigenetic modifications (7, 10). Animal studies have also reported OP-related changes in behavior, including hyperactivity, short-term memory, and social behavior (5, 8, 9, 12, 13).

Our study has some limitations. DAPs are non-specific metabolites making inference to a specific OP pesticide or source of exposure difficult. DAPs in urine may also reflect exposure to metabolites preformed in the environment and not parent pesticide exposure, therefore
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 having two DAP measurements during pregnancy. We did not have data on teacher characteristics or parent ADHD/executive function. Attrition in the CHAMACOS cohort across time was not negligible. The 351 children included in these analyses represent 66% of the initial cohort with gestational DAP measures (n=534). Characteristics for these groups were similar (with minor exceptions), and sensitivity analyses which included inverse probability weighting suggest 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 have 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 continues into early adulthood, and executive functions in particular, postnatal exposure could be important and should be considered in future work.

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 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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Acknowledgements: We thank the CHAMACOS staff, students, and community partners who made this study possible, as well as the biorepository staff for their assistance in specimen management.

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Table 1. Sociodemographic and exposure characteristics of CHAMACOS families (n=351) included in this analysis by exposure and outcome (maternal BRIEF GEC scores at 9y): CHAMACOS study population, enrolled 1999-2000 in Salinas Valley, California

| Characteristic                                      | No.   | (%)    | \(\sum\) DAPs (nmol/L)\(^{a,b}\) | BRIEF GEC at 9y\(^{c}\) mean (SD) |
|-----------------------------------------------------|-------|--------|---------------------------------|-----------------------------------|
| **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**                       |       |        |                                 |                                   |
| U.S.                                                | 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 years in US at child delivery**          |       |        |                                 |                                   |
| <=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)                       |
| Entire Life                                         | 35    | (10)   | 95.0 (2.5)                      | 51.3 (11.3)                       |
| **Maternal age at child delivery**                  |       |        |                                 |                                   |
| 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**            |       |        |                                 |                                   |
| <6th grade                                          | 160   | (46)   | 128.9 (2.9)                     | 48.1 (10.3)                       |
| 7th-12th grade                                      | 121   | (34)   | 129.0 (2.7)                     | 50.4 (10.2)                       |
| Completed high school                               | 70    | (20)   | 135.8 (2.5)                     | 49.8 (10.1)                       |
| **Maternal Verbal IQ\(^d\)**                       |       |        |                                 |                                   |
| \(\leq74\)                                         | 75    | (21)   | 147.9 (3.0)                     | 46.4 (10.1)                       |
| 75-99                                               | 121   | (34)   | 149.4 (2.8)                     | 50.9 (10.6)                       |
| \(\geq100\)                                        | 151   | (43)   | 106.9 (2.5)                     | 49.2 (9.8)                        |
| missing                                             | 4     | (1)    | 331.1 (2.4)                     | also missing                      |
| **Maternal smoking during pregnancy**               |       |        |                                 |                                   |
| Duration of breastfeeding | Never breastfed | ≤1 month | 2-6 months | 7-12 months | >12 months |
|--------------------------|-----------------|----------|------------|-------------|-----------|
| No                       | 338 (96)        | 16 (5)   | 46 (13)    | 118 (34)    | 75 (21)   |
| Yes                      | 13 (4)          | 104.8 (2.9) | 49.1 (10.1) | 48.7 (9.9)  | 50.8 (10.8) |

| Mother depressed at 7 and/or 9 year visits | No | Yes | missing |
|-------------------------------------------|----|-----|---------|
| 217 (62)                                  | 124 (35) | 10 (3) |

| DAP urinary metabolites in pregnancy\(a\) | \(\Sigma\)DEs unadjusted for specific gravity | \(\Sigma\)DMs unadjusted for specific gravity | \(\Sigma\)DAPs unadjusted for specific gravity | \(\Sigma\)DEs adjusted for specific gravity | \(\Sigma\)DMs adjusted for specific gravity | \(\Sigma\)DAPs adjusted for specific gravity |
|------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| 351                                      | 20.0 (3.0)                                   | 95.9 (3.1)                                   | 130.3 (2.7)                                   | 26.1 (3.0)                                   | 126.4 (3.2)                                   | 171.2 (2.9)                                   |

| Serum concentration during pregnancy     | \(\Sigma\)PBDEs (47,99,100,153) | DDT |
|------------------------------------------|---------------------------------|-----|
| 331                                      | 25.6 (2.5) ng/lipid             | 23.3 (5.3) ng/lipid |

Abbreviations: BRIEF GEC, Behavior Rating Inventory of Executive Function Global Executive Composite; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; DAP, dialkyl phosphate; DDT, dichlorodiphenyltrichloroethane; DE, diethyl phosphate; DM, dimethyl phosphate; GM, geometric mean; GSD, geometric standard deviation; PBDE, polybrominated diphenyl ether; SD, standard deviation.

\(a\) Urinary DAP metabolite concentrations based on the average concentration in two pregnancy urine samples.

\(b\) Unadjusted for specific gravity.

\(c\) BRIEF GEC from maternal report at child age 9 years; t-score.

\(d\) Maternal Verbal IQ measured as receptive language using the Peabody Picture Vocabulary Test.

\(e\) BRIEF GEC scores only available for one family missing maternal depression at 7y and 9y; SD does not apply.
Table 2. Change in maternal report and child-assessed outcome scores per 10-fold increases in mean total gestational urinary DAP concentrations (nmol/L) using repeated measures (GEE) models, overall and stratified by sex, in the CHAMACOS study population, enrolled 1999–2000 in Salinas Valley, California.

| Outcome | age (yrs) at assessment | Overall | Boys | Girls | p-value interaction |
|---------|-------------------------|---------|------|-------|---------------------|
| Maternal Report<sup>bc</sup> |            |        |      |       |                     |
| Behavior Rating Inventory of Executive Function (T-scores)<sup>a</sup> | 7, 9, 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 (2.3,8.0) | 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 |
| Conners ADHD/DSM-IV Scales (T-scores)<sup>a</sup> | 7, 9, 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 |
| Behavior Assessment System for Children-2 (T-scores)<sup>a</sup> | 7, 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<sup>bc</sup> |            |        |      |       |                     |
| Weschler Intelligence Scales for Children (standardized scores)<sup>a</sup> | 7, 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 |
| Wisconsin Card Sort Test (T-scores)<sup>a</sup> | 9, 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 |
| Conners’ Continuous Performance Test II (T-scores)<sup>a</sup> | 9, 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 |
| 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 |
|                                |        |        |        |        |        |        |        |        |
|--------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
|                                |        |        |        |        |        |        |        |        |
| Hit rate standard error 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 |        |        |        |        |        |        |        |
| Hit rate standard error by inter-stimulus 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 Indexf 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; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; DAP, dialkyl phosphate; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GEE, generalized estimating equations; obs., observations.

a higher scores indicate more symptomatic behavior; lower scores indicate poorer performance.

b All models adjusted for maternal age, years in U.S., education, receptive language, and average depression score (7-9y); average Home Observation for the Measurement of the Environment score (7-12y); child age at assessment; and child sex.

c Parent report models additionally adjusted for language of questionnaire administration.

d Behavior Rating Inventory of Executive Function, Conners’ ADHD/ Diagnostic and Statistical Manual of Mental Disorders Scales, Behavior Assessment System for Children, Wisconsin Card Sort Task, and Conners’ Continuous Performance Test T-scores are standardized to mean ± SD = 50 ± 10; Wechsler Intelligence Scale for Children T-standardized scores are standardized to mean ± SD = 100 ± 15.

e Child testing models additionally adjusted for psychometrician who administered test, language of testing, and, for Conners’ Continuous Performance Test and Wisconsin Card Sort Task models only, video game usage.

f The Conners’ Continuous Performance Test ADHD Confidence Index is not a T-score but is rather 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 scores per 10-fold increases in mean total gestational urinary DAP concentrations (nmol/gL) in the CHAMACOS study population, enrolled 1999-2000 in Salinas Valley, California.

| Outcome | Teacher Report - Age 7 Years | Self-Report - Age 10.5 Years |
|---------|-----------------------------|-----------------------------|
|         | Orientation \(^a\) | No. | \(\beta\) (95% CI) | \(\beta\) (95% CI) | \(\beta\) (95% CI) | p-value | No. | \(\beta\) (95% CI) | \(\beta\) (95% CI) | \(\beta\) (95% CI) | p-value |
| Behavior Rating Inventory of Executive Function (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 | 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 | 277 | 1.6 (-0.9,4.0) | -1.6 (-5.2,2.0) | 4.0 (0.7,7.3) | 0.02 |
| 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 | 277 | 1.6 (-0.9,4.0) | -1.6 (-5.2,2.0) | 4.0 (0.7,7.3) | 0.02 |
| Conners ADHD/DSM-IV Scales (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 | 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 | 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 | 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 | 276 | 0.5 (-1.9,3.0) | -2.3 (-5.8,1.1) | 2.4 (-1.0,5.8) | 0.06 |
| Behavior Assessment System for Children-2 (T-scores)\(^b,c\) | | | | | | | | | | | | |
| Hyperactivity | higher | 277 | -0.0 (-2.4,2.4) | -3.7 (-7.7,0.2) | 2.8 (0.3,5.6) | 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; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; DAP, dialkyl phosphate; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GEE, generalized estimating equations.

\(^a\) (+) higher scores indicate more symptomatic behavior/poorer performance; (-) lower scores indicate poorer performance.

\(^b\) All models adjusted for maternal age, years in U.S., education, receptive language, and average depression score (7-9y); average Home Observation for the Measurement of the Environment score (7-12y); child age at assessment; and child sex.

\(^c\) Behavior Rating Inventory of Executive Function, Conners’ ADHD/ Diagnostic and Statistical Manual of Mental Disorders Scales, and Behavior Assessment System for Children scores are standardized to mean ± SD = 50 ± 10.