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Prenatal and Childhood Exposure to Organophosphate Pesticides and Behavior Problems in Adolescents and Young Adults in the CHAMACOS Study

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Background: We previously reported associations of prenatal exposure to organophosphate (OP) pesticides with poorer neurodevelopment in early childhood and at school age, including poorer cognitive function and more behavioral problems, in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a birth cohort study in an agriculture community.

Objective: We investigated the extent to which early-life exposure to OP pesticides is associated with behavioral problems, including mental health, in youth during adolescence and early adulthood.

Methods: We measured urinary dialkylphosphates (DAPs), nonspecific OP metabolites, in urine samples collected from mothers twice during pregnancy (13 and 26 wk) and at five different times in their children (ages 6 months to 5 y). We assessed maternal report and youth report of externalizing and internalizing behavior problems using the Behavior Assessment System for Children, 2nd edition (BASC-2), when the youth were ages 14, 16, and 18 y. Because there was evidence of nonlinearity, we estimated associations across quartiles of DAPs and modeled repeated outcome measures using generalized estimating equations.

Results: There were 335 youths with prenatal maternal DAP measures and 14-. 16-, or 18-y BASC-2 scores. Prenatal maternal DAP concentrations (specific gravity–adjusted median, Q1–Q3 = 159.4, 78.7–350.4 nmol/L) were associated with higher T-scores (more behavior problems) from maternal report, including more hyperactivity [fourth vs. first quartile of exposure $\beta = 2.32$; 95% confidence interval (CI): 0.18, 4.45], aggression ($\beta = 1.90$; 95% CI: 0.15, 3.66), attention problems ($\beta = 2.78$; 95% CI: 0.26, 5.30), and depression ($\beta = 2.66$; 95% CI: 0.08, 5.24). Associations with youth report of externalizing problems were null, and associations with depression were suggestive (fourth vs. first quartile of exposure $\beta = 2.15$; 95% CI: −0.36, 4.67). Childhood DAP metabolites were not associated with behavioral problems.

Discussion: We found associations of prenatal, but not childhood, urinary DAP concentrations with adolescent/young adult externalizing and internalizing behavior problems. These findings are consistent with prior associations we have reported with neurodevelopmental outcomes measured earlier in childhood in CHAMACOS participants and suggests that prenatal exposure to OP pesticides may have lasting effects on the behavioral health of youth as they mature into adulthood, including their mental health. https://doi.org/10.1289/EHP11380

Introduction

Organophosphate (OP) pesticides are widely used agricultural pesticides. Although their use has declined in the last two decades, OP metabolites are universally detected in representative samples of the general U.S. population.[1–3] Diet, including pesticide residues in fruits and vegetables, is the predominant route of exposure to OP pesticides in the general population.[4,5] Among those living in agricultural communities, exposure may also occur from other sources, such as agricultural drift and drinking water, as well as through para-occupational exposures.[6–14]

OP pesticides act on insects and on humans at high doses by inhibiting acetylcholinesterase (AChE). Their mechanism of action in humans exposed at levels below which AChE inhibition is measurable is less clear, though there are several plausible noncholinergic mechanisms for their effects on brain development, such as alterations to axonal growth[15] and oxidative stress.[16,17] Epidemiological studies suggest that prenatal exposure to OP pesticides is associated with poorer cognitive and behavioral development in children.[23–31]

In the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), the cohort in which the current study is set, we have reported associations of prenatal maternal urinary concentrations of dialkylphosphate (DAP) metabolites, nonspecific biomarkers of OP pesticides, with poorer neurodevelopment, including poorer intellectual function at ages 1, 2, and 7 y,[23,32] more inattentive and hyperactive behaviors at ages 5 to 12 y.[28,30] and poorer executive function at ages 7 to 12 y.[28] We hypothesized that these consistent associations of DAPs with poorer neurodevelopment during childhood would be lasting and result in associations with downstream behavioral problems, including mental health problems, among CHAMACOS youth in adolescence and early adulthood. In the current study, we examined associations of prenatal maternal and early-childhood urinary DAP concentrations with maternal- and youth-reported internalizing and externalizing behavior problems assessed repeatedly from ages 14 to 18 y.

Methods

Study Recruitment and Population

Detailed descriptions of the CHAMACOS cohort have been reported elsewhere.[14,29] Briefly, we recruited pregnant women from six community clinics primarily serving Latino farmworker families in California's Salinas Valley between October 1999 and October 2000. Eligible women were ≥18 y of age, spoke Spanish or English, qualified for low-income health insurance (which was available to pregnant women regardless of immigration status),

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were <20 weeks' gestation, and were planning to deliver at a local county hospital. As shown in Figure S1, a total of 601 women were enrolled in the study, of whom 532 were followed to the birth of their 537 live-born infants (there were five sets of twins). Mother–child dyads were followed up for health and developmental assessments when the children were ∼ 6 months and 1, 2, 3.5, 5, 7, 9, 10.5, 12, 14, 16, and 18 y of age. We excluded four participants from the current analyses, including three participants with an autism spectrum disorder diagnosis and one participant with hydrocephaly.

Written informed consent was obtained from mothers at enrollment; children provided verbal assent starting at age 7 y and written consent starting at age 12 y. All activities were approved by the University of California, Berkeley Committee for the Protection of Human Subjects.

Assessment of Youth Behavior by Parent and Youth

Mothers (or the primary caregiver) completed the English ($n = 45$; 13% of mothers at 14-y visit; similar for subsequent visits) or Spanish ($n = 290$; 87%) version of the Behavior Assessment System for Children, 2nd edition (BASC-2)[33] at the 14-, 16-, and 18-y visits. Youths completed select subscales of the BASC-2 Self-Report of Personality (SRP) forms at age 14 y and completed the full SRP forms at ages 16 and 18 y. All youths completed these items independently and in English.

The BASC-2 asks parents to report on the frequency of their children's behaviors and emotional state across a range of domains, including adaptive skills, externalizing problems, internalizing problems, and school problems. For the self-report, youths report on their own perceived behaviors across these domains. For these analyses, we examined seven BASC-2 parent subscales (i.e., attention, hyperactivity, aggression, conduct disorder, anxiety, depression, and somatization) and five BASC-2 self-reported subscales (i.e., attention, hyperactivity, anxiety, depression, and somatization). The BASC-2 does not provide scores for the youth reports of aggression and conduct disorder. In addition, we examined two composite measures for the parent reports: Externalizing Problems, comprising hyperactivity, aggression, and conduct disorder subscales, and Internalizing Problems, comprising anxiety, depression, and somatization. For the BASC-2 self-report, we only report results for the Internalizing Problems composite; the Externalizing Problems composite is not available for youth self-reports. In addition, at the 14-y visit we asked youths a more limited set of questions that did not allow us to calculate an Internalizing Problems composite at this age. In our analyses, we used age and sex-standardized BASC-2 subscale and composite T-scores [mean ± standard deviation (SD): 50 ± 10].

Measurement of OP Metabolite Concentrations in Prenatal Maternal and Child Urine

We have presented detailed descriptions of urine collection and analysis elsewhere.[14] Briefly, we collected spot urine samples from mothers during pregnancy at ∼ 13 wk (Q1,Q3 = 10, 18 wk) and 26 wk (Q1,Q3 = 25, 27 wk) gestation, aliquoted samples, and stored them at −80°C. We shipped samples on dry ice to the U.S. Centers for Disease Control and Prevention (U.S. CDC), where they were analyzed using gas chromatography–tandem mass spectrometry (GC-MS/MS)[34] and quantified using isotope dilution calibration.[14] We quantified six dialkyl phosphate (DAP) metabolites, including three diethyl phosphate (DE) metabolites (diethylphosphate, diethyldithiophosphate, diethylthiophosphate) and three dimethyl phosphate (DM) metabolites (dimethylphosphate, dimethyldithiophosphate, dimethylthiophosphate). In CHAMACOS, DM metabolite concentrations greatly exceeded DE concentrations and were very similar to total DAP concentrations. We therefore conducted analyses with only total DAPs. We imputed metabolite values below the limit of detection (LOD) using random imputation based on a log-normal probability distribution and estimated with maximum likelihood estimation.[14,35,36] We quantified urine dilution by measuring the specific gravity of urine samples with a refractometer calibrated with deionized water at room temperature. We normalized DAP concentrations in prenatal maternal urine samples using specific gravity,[37] which we computed using the following formula[38]: Measurement × (1.024-1)/(specific gravity-1), where 1.024 is the mean specific gravity from a large reference sample.

We collected child urine samples at the 6-month, 1-y, 2-y, 3.5-y, and 5-y visits and analyzed them at the same U.S. CDC laboratory using the same methods as used with the prenatal maternal samples. We measured child urinary creatinine using a commercially available diagnostic enzyme method; we did not measure the specific gravity of child samples and thus normalized DAP concentrations in child urine samples using creatinine.

Statistical Analyses

We examined the relationship of prenatal maternal and child urinary DAP metabolites with longitudinal (14-, 16-, and 18-y) parent- and youth-reported BASC-2 scores in longitudinal models using generalized estimating equations (GEE) for repeated outcomes, with an exchangeable correlation structure. We selected covariates based on previous studies of OP exposure and neurodevelopment in CHAMACOS.[28–30] Final models included the following: maternal age at delivery (continuous); maternal years spent in the United States prior to delivery (≤5 y, >5 y but not born in the United States, or born in the United States); maternal education at delivery (≤6th grade, 7th–12th grade, or high school graduate); maternal marital status at delivery (married or living as married vs. not married or not living as married); maternal risk for depression at the 9-y visit (<16 vs. ≥16) using the Center for Environmental Studies Depression Scale (CES-D;)[39] enrichment in the home at the 6-month visit (continuous z-score) using the Home Observation for Measurement of the Environment (HOME) Inventory[40]; household poverty status at the time of assessment (at or below poverty level, above poverty level); youth sex at birth; and age at the time of assessment. We modeled age at assessment and household poverty status at assessment as time-varying covariates in GEE models. Models for maternally reported outcomes also included the language of the maternal interview (Spanish or English). Missing covariate values (Table 1) were imputed using analogous questions from other visits conducted at the nearest time points. Finally, we adjusted models of childhood DAPs and behavior problems for prenatal maternal DAP concentrations.

We summed the six DAP metabolites and averaged the 13- and 26-wk maternal specific-gravity adjusted DAP metabolite concentrations. We summed the six DAP metabolites and calculated the area under the curve (AUC), as has been done in other studies of repeated exposures,[41,42] for the child creatinine-adjusted DAP metabolite concentrations from the 6-month, 1-y, 2-y, 3.5-y, and 5-y visits. In sensitivity analyses, we computed the mean across childhood DAP concentrations and examined mean DAP concentration in relation to behavioral outcomes; this analysis included a larger sample because children only needed one childhood sample to be included in these sensitivity analyses.

We assessed nonlinearity of exposure–outcome associations using generalized additive models (GAMs) with a three degrees of freedom cubic spline for the DAP concentrations (Figures S2–9). We found evidence of nonlinearity for several exposure–outcome relationships; thus we estimated associations across quartiles of DAPs in final models, with the lowest quartile as the reference group. Note that the imputation of values <LOD did not impact the

Table 1. Demographic characteristics of youth with prenatal maternal urinary DAPs and 14-. 16-, or 18-y BASC-2 scores, CHAMACOS ($n = 335$).

Characteristic	n (%) or mean ($\pm$ SD)
Maternal characteristics	
Age at delivery (y)	26.5 $\pm$ 5.2
Education at delivery	
≤6th grade	150 (44.8)
7th−12th grade	117 (34.9)
Completed high school	68 (20.3)
Years in the United States prior to delivery	
≤5 y	161 (48.1)
>5 y, nonnative	140 (41.8)
Born in the United States	34 (10.1)
Marital status at enrollment	
Married or living as married	278 (83.0)
Not married or living as married	57 (17.0)
Maternal risk for depression at 9-y visit (≥16 CES-D score)	
No	215 (73.6)
Yes	77 (26.4)
Missing	43
Household characteristics	
HOME z-score at 6-month visit	0.03 $\pm$ 1.1
Household income at 14-y visit	
At or below poverty level	225 (67.4)
Above poverty level	109 (32.6)
Missing	1
Household income at 16-y visit	
At or below poverty level	185 (55.2)
Above poverty level	150 (44.8)
Household income at 18-y visit	
At or below poverty level	129 (40.7)
Above poverty level	188 (59.3)
Missing	18
Youth characteristics	
Sex at birth	
Male	155 (46.3)
Female	180 (53.7)

Note: BASC-2, Behavior Assessment System for Children, 2nd edition; CES-D, Center for Environmental Studies Depression Scale; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; DAP, dialkylphosphate; HOME, Home Observation for Measurement of the Environment; SD, standard deviation.

quartile analysis because all values <LOD fell into this reference quartile. For each model, we also performed a test of trend across quartiles to assess whether there was statistically significant ($a = 0.05$) monotonicity of the exposure–outcome association.

We examined effect modification by sex using cross-product terms (DAP quartile multiplied by sex, with one interaction term for each quartile) in our GEE models. We assessed whether effect modification by sex was statistically significant using an overall Wald test for the three cross-product terms; a p-value <0.1 was interpreted as evidence of statistically significant effect modification by sex.

We conducted sensitivity analyses nested among participants with complete data on exposure at all time points to examine whether models that included exposures at different time periods among different subsets of participants impacted effect estimates.

All statistical analyses were performed with Stata (version 15.1; StataCorp) and R (version 3.6.3; R Development Core Team).

Results

Study Population

Among the youths with a prenatal maternal urinary DAP measure ($n = 535$), 335 also had a maternally reported BASC score from the 14-, 16-, or 18-y visit, and 331 had a self-reported BASC score at any of those visits (Figure S1). Among youths with a child urinary DAP measure ($n = 463$), 255 also had a maternally reported BASC score from the 14-, 16-, or 18-y visit and 252 had a self-reported BASC score at any of those visits (Figure S1). For 335 youths with a prenatal maternal urinary DAP measure and a maternally reported BASC-2 score from the 14-, 16-, or 18-y visit, most mothers were born outside of the United States ($n = 301$, 89.9%); $n = 290$ were born in Mexico, and about half ($n = 161$, 48.1%) had been in the United States for 5 y or less at the time of delivery (Table 1). Nearly half of mothers ($n = 150$, 44.8%) had less than a 7th-grade education, and only 68 (20.3%) had completed high school. About a quarter of the mothers ($n = 77$, 26.4%) showed signs of depression at the time of the 9-y visit. Approximately two-thirds of households were at or below the poverty level at the 14-y visit, with the percentage living in poverty decreasing for later visits.

In comparison with CHAMACOS mothers who did not complete a 14-, 16-, or 18-y visit, mothers included in the study sample were older and had lived in the United States longer prior to delivery (Table S1). Children also had marginally lower HOME scores at 6 months and were more likely to be female. We report descriptive statistics of BASC-2 scores, as reported by the mothers and youths at 14-, 16-, and 18-y visits, in Table 2. Correlations of maternal report with self-report of BASC-2 behaviors ranged from 0.19 for attention to 0.28 for somatization. Correlations within reporter between outcome measures at different time points ranged, depending on the time point and BASC outcome, from 0.50 for attention at the 14- and 16-y visits to 0.71 for depression at the 16- and 18-y visits for maternal reports and from 0.25 for somatization at the 14- and 16-y visits to 0.55 for anxiety at the 16- and 18-y visits for youth self-reports.

Table 3 shows concentrations of prenatal maternal DAPs, specific-gravity adjusted and averaged across the early pregnancy (13-wk) and mid-pregnancy (26-wk) visits. In addition, we show concentrations of childhood DAPs, creatinine adjusted, and the mean and AUC. A subset of the 326 participants with a childhood DAP measurement at any time had enough values to compute the AUC ($n = 255$). Correlations between pregnancy and childhood DAPs were very low, reflecting levels from very recent exposure and rapid metabolism of OPs in the body; correlation coefficients ranged from as low as −0.0001 for prenatal and 12-month DAPs to 0.14 for 12-month and 24-month DAPs.

Prenatal Maternal DAPs and Externalizing Behaviors and Attention Problems

Mean prenatal maternal DAP concentrations were associated with more externalizing problems and more attention problems in youth, as reported longitudinally by mothers at the 14-, 16-, and 18-y visits (Figure 1; Table S2). A trend of increasing BASC-2 scores (indicating more problem behavior) across quartiles of prenatal maternal DAPs was most apparent for the hyperactivity (fourth vs. first quartile $\beta = 2.32$; 95% CI: 0.18, 4.45), aggression (fourth vs. first quartile $\beta = 1.90$; 95% CI: 0.15, 3.66), and attention problems (fourth vs. first quartile $\beta = 2.78$; 95% CI: 0.26, 5.30) subscales, as well as the Externalizing Problems Composite (fourth vs. first quartile $\beta = 1.63$; 95% CI: −0.45, 3.71). These trends were statistically significant with p-values for trend (all <0.05), indicating monotonicity, though there did appear to be a leveling off for the Externalizing Problems subscales between the third and fourth quartile. We did not observe this threshold for attention, for which there was a strictly monotonic exposure–response association across DAP quartiles. Associations of prenatal maternal DAPs with maternal report of youth conduct disorder and youth self-report of hyperactivity and attention were all null (see Figure 1 and Table S3).

We did not observe statistically significant effect modification by sex for any of the associations of prenatal maternal DAPs and maternal or youth self-report of externalizing behaviors or attention problems (Table S4). However, we did observe suggestively stronger associations of prenatal maternal DAPs with more

Table 2. Descriptive statistics of scores on the Behavioral Assessment Scale for Children, 2nd edition (BASC-2) as reported by mother and youth at 14-, 16-, and 18-y visits, CHAMACOS.

	Maternal report			Youth report		
BASC-2 outcome	14 y ($n=327$) M ± SD	16 y ($n=317$) M ± SD	18 y ($n=314$) M ± SD	14 y ($n=318$) M ± SD	16 y ($n=311$) M ± SD	18 y ($n=309$) M ± SD
Externalizing composite	45.7 (7.5)	45.6 (8.8)	49.6 (11.2)	NA	NA	NA
Hyperactivity	45.7 (8.2)	46.5 (9.5)	44.8 (8.3)	NA	47.8 (9.9)	46.4 (9.9)
Aggression	45.1 (7.0)	44.5 (7.3)	43.7 (6.5)	NA	NA	NA
Conduct disorder	47.6 (7.6)	47.1 (9.2)	46.4 (8.3)	NA	NA	NA
Attention subscale	49.2 (9.7)	50.2 (10.0)	50.1 (11.8)	NA	49.1 (9.9)	48.7 (9.8)
Internalizing composite	49.4 (9.6)	50.1 (10.0)	49.2 (10.3)	NA	49.0 (10.5)	49.5 (11.7)
Anxiety	49.3 (10.0)	49.2 (9.7)	50.0 (10.6)	49.2 (9.5)	50.7 (11.5)	52.2 (12.1)
Depression	49.7 (8.8)	50.6 (10.4)	49.1 (10.1)	48.1 (9.5)	47.8 (9.9)	49.6 (11.7)
Somatization	49.5 (10.7)	50.4 (10.0)	46.9 (6.8)	47.7 (8.4)	49.5 (9.9)	49.5 (10.4)

Note: BASC-2, Behavior Assessment System for Children, 2nd edition; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; M, mean; NA, not applicable (either because not asked or the subscale measure does not exist); SD, standard deviation.

attention problems among girls than boys [fourth vs. first quartile $\beta=4.72$ (95% CI: 1.40, 8.04) for girls vs. $\beta=0.18$ (95% CI: −3.55, 3.92) for boys; p- for interaction = 0.28].

Prenatal Maternal DAPs and Internalizing Problems

Mean prenatal maternal DAP concentrations were also associated with more internalizing problems, as reported longitudinally by mothers at the 14-, 16-, and 18-y visits (Figure 2; Table S3). Like externalizing problems, associations with internalizing behaviors also showed a leveling off at the third quartile, with a more pronounced dip in strength of association at the fourth quartile of DAPs. For example, for depression we saw stronger associations for the third vs. first quartile ($\beta=3.28$; 95% CI: 0.68, 5.87) in comparison with the fourth vs. first quartile ($\beta=2.66$; 95% CI: 0.08, 5.24). Unlike externalizing behaviors, however, associations were also found for prenatal maternal DAPs and depression self-reported by the youths, with the same trend of the strongest associations in the third quartile of prenatal maternal DAPs exposure with a dip toward the null at the fourth quartile (depression third vs. first quartile $\beta=3.68$; 95% CI: 1.14, 6.21 and fourth vs. first quartile $\beta=2.15$; 95% CI: −0.36, 4.67). Trends across quartiles were not significant for youth report of anxiety, somatization, or internalizing composite score.

We observed no statistically significant effect modification by sex for either maternal or youth report of youth internalizing behaviors (Table S5).

Postnatal DAPs and Behavior Problems

We found no pattern of associations for child DAP concentrations using the AUC from age 6 months to 5 y, with either externalizing behaviors, attention problems, or internalizing symptoms, reported by mothers or self-reported by youths (Tables S6 and S7). Results were essentially the same (all null) when we examined associations in relation to mean childhood DAP concentrations in sensitivity analyses.

Sensitivity Analysis

Tables S8 and S9 present a comparison of estimates of prenatal maternal and childhood urinary DAPs in relation to externalizing and internalizing problems (Tables S3, S4, S7, and S8) with models nested among those with complete data on exposure at all time points. Estimates from these nested models were generally farther from the null and less precise because of the substantially smaller subset of participants with data for all time points. These nested models did not lead to different conclusions, however.

Discussion

Our results show associations of prenatal maternal urinary DAP concentrations with maternal report of both externalizing and internalizing behavior problems in CHAMACOS youths ages 14–18 y, including more hyperactivity, aggression, attention problems, and depression. We also found associations of prenatal maternal DAPs with youth reports of internalizing problems, most strongly with depression. We found null associations of early-childhood urinary DAP concentrations with these behaviors.

These findings are consistent with associations reported for prenatal exposure to OPs and neurodevelopment among younger children in other cohorts[25,27,31,43,44] as well as in CHAMACOS. In CHAMACOS, we have also found associations of prenatal maternal DAP concentrations with behavioral problems at earlier ages that may be related to, or on the pathway to, the behavior

Table 3. Summary statistics for pregnancy and childhood DAP concentrations among CHAMACOS participants with a 14-, 16-, or 18-y BASC-2 outcome.

Sample period	*N*	% >LOD	GM	GSD	Min	P10	P25	P50	P75	P90	Max
Pregnancy [specific gravity-corrected (nmol/L)]											
13-wk	334	86.8	131.8	4.5	4.4	18.0	43.6	127.6	416.7	1,058.2	9,065.5
26-wk	314	100.0	124.4	2.6	6.1	39.1	69.7	121.6	234.6	443.7	2,366.1
Pregnancy mean	335	99.7	167.1	2.8	10.1	49.2	78.7	159.4	350.4	694.4	4,628.3
Childhood [creatinine-adjusted (nmol/g)]											
6-month	293	99.0	209.6	4.9	2.0	26.0	74.5	185.9	656.3	1,693.2	78,234.6
1-y	304	95.1	221.6	4.6	3.6	36.4	80.4	214.8	630.2	1,608.3	10,551.8
2-y	299	96.3	221.6	4.4	2.9	26.8	89.4	228.3	568.5	1,388.6	5,942.5
3.5-y	244	93.4	194.3	4.8	1.9	20.0	50.3	170.2	443.6	929.1	9,240.2
5-y	288	89.0	132.1	4.9	0.9	19.4	49.6	147.2	345.0	840.3	10,084.5
Childhood mean	326	100.0	185.4	2.4	19.1	59.7	109.1	177.6	342.1	584.3	2,376.3
Childhood area under the curve (AUC)	255	100.0	1,648.2	2.5	147.6	558.2	844.1	1,615.5	2,880.8	6,278.5	18,926.4

Note: BASC-2, Behavior Assessment System for Children, 2nd edition; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; DAP, dialkylphosphate; GM, geometric mean; GSD, geometric standard deviation; Max, maximum; Min, minimum; P10, 10th percentile; P25, 25th percentile; P50, 50th percentile; P75, 75th percentile; P90, 90th percentile.

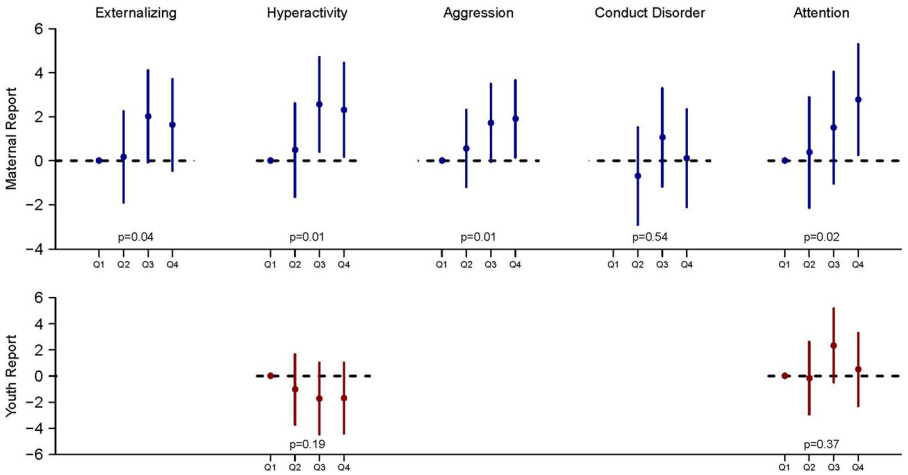

Figure 1. Adjusted associations estimated from multivariable linear regression models using generalized estimating equations (GEE) for repeated outcomes of quartile of mean prenatal maternal urinary DAP concentrations (*x*-axis) and mean difference (β and corresponding 95% confidence interval; *y*-axis) in BASC-2 Externalizing Problems Composite, externalizing behaviors subscales (hyperactivity, aggression, conduct disorder), and the attention subscale, as reported by mothers and youth at ages 14, 16, or 18 y, and *p*-for-trend, CHAMACOS ($n = 958$ observations for 335 participants for maternal report of outcomes; for youth report, there were $n = 619$ observations for 323 participants for attention and 618 observations for 323 participants for hyperactivity). DAP quartile ranges (specific gravity-corrected, nmol/L) are Q1: 10.1–78.67; Q2: 78.74–159.4; Q3: 161.6–350.4; Q4: 354.1–4,628.3. Models are adjusted for maternal age, education, marital status, and years living in the United States prior to delivery; maternal depression at 9 y; HOME Inventory *z*-score at 6 months; child sex; and child age and household poverty at the time of assessment. Models with maternal report of outcomes also included the language in which the questionnaire was administered. All effect estimates for this figure can be found in Table S3. Note: BASC-2, Behavior Assessment System for Children, 2nd edition; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; DAP, dialkylphosphate; HOME, Home Observation for Measurement of the Environment; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

problems we report in the current study. These include more inattentive and hyperactive behaviors at age 3.5 and 5 y,[30] poorer executive function at ages 7–12 y,[28] and poorer social cognition at age 14 y.[45] These findings suggest that earlier associations may be sustained over time in adolescence and potentially persist into early adulthood. Our findings also raise concerns about how these behaviors could manifest over time; although we have not observed associations of DAP concentrations with more frank risk-taking behavior, such as substance abuse, delinquency, or violent acts by age 16 and 18 y,[46,47] it may be important to continue to observe these young adults to see whether these concerning behaviors have more long-lasting effects on well-being and mental health into adulthood.

We recently reported mostly null or modest associations of applications of OP pesticides within 1 km of the home with these same BASC outcomes in CHAMACOS.[48] Specifically,

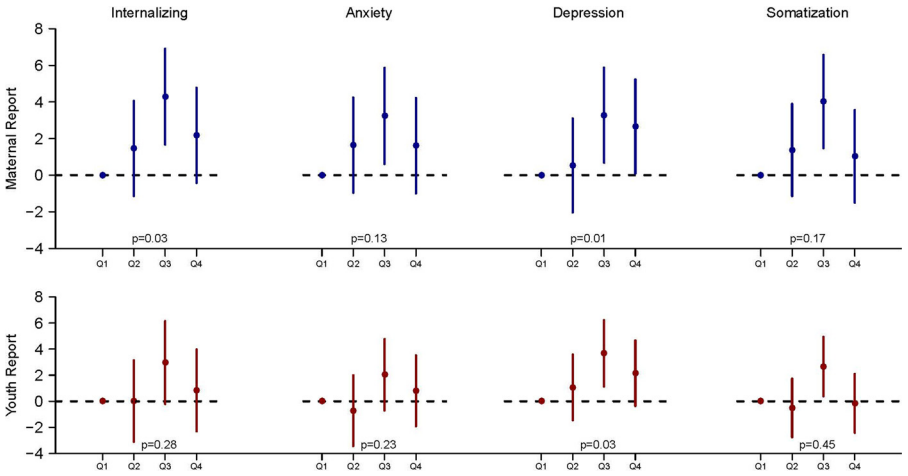

Figure 2. Adjusted associations estimated from multivariable linear regression models using generalized estimating equations (GEE) for repeated outcomes of quartile of mean prenatal maternal urinary DAP concentrations (*x*-axis) and mean difference (β and corresponding 95% confidence interval; *y*-axis) in BASC-2 Internalizing Problems Composite and internalizing behaviors subscales (anxiety, depression, somatization), as reported by mothers and youth at ages 14, 16, or 18 y, and *p*-for-trend, CHAMACOS ($n = 958$ observations for 335 participants for maternal report; for youth report, there were $n = 617$ observations for 323 participants for Internalizing Problems Composite, 936 observations for 331 participants for anxiety, 936 observations for 331 participants for depression, and 928 observations for 331 participants for somatization). DAP quartile ranges (specific gravity-corrected, nmol/L) are Q1: 10.1–78.67; Q2: 78.74–159.4; Q3: 161.6–350.4; Q4: 354.1–4,628.3. Models are adjusted for maternal age, education, marital status, and years living in the United States prior to delivery; maternal depression at 9 y; HOME Inventory *z*-score at 6 months; child sex; and child age and household poverty at the time of assessment. Models with maternal report of outcomes also included the language in which the questionnaire was administered. All effect estimates for this figure can be found in Table S4. Note: BASC-2, Behavior Assessment System for Children, 2nd edition; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; DAP, dialkylphosphate; HOME, Home Observation for Measurement of the Environment; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

we observed suggestive associations of applications of chlorpyrifos, an OP pesticide, during pregnancy with maternal and youth reports of depression ($\beta = 1.0$; 95% CI: −0.2, 2.1 and $\beta = 1.1$; 95% CI: −0.1, 2.3, respectively, per 2-fold increase in pesticide use within 1 km of residence) and diazinon and dimethoate, other OP pesticides, with youth reports of attention problems ($\beta = 1.2$; 95% CI: 0.0, 2.5 and $\beta = 1.9$; 95% CI: 0.0, 3.6, respectively, per 2-fold increase in pesticide use within 1 km of residence). However, we did not observe associations of OP pesticide applications near the home during pregnancy with the maternal or youth reports of externalizing problems that we observed for prenatal maternal DAPs in the current study. DAPs are nonspecific OP metabolites, which preclude us from making any direct comparisons with this previous study that examined individual OP pesticides. In addition, DAPs reflect exposure not only from nearby applications but also from dietary intake.[49]

Although there is literature showing associations of OP poisoning with depression among farmworkers,[50–54] there are few studies that have investigated associations of early-life exposure to OP pesticides, and exposure at lower levels, with mental health. Aside from our current findings showing associations of depression with prenatal maternal DAP concentrations—and our previous study showing suggestive associations with proximity to OP use during pregnancy[48]—we identified only two other studies that examined developmental exposure to OPs and mental health. A New York City birth cohort study reported associations of prenatal dimethyl phosphate metabolite concentrations and maternal report of BASC internalizing behaviors using factor analysis among 141 children ages 6–9 y.[55] Another study of 529 adolescents ages 11–17 y living in proximity to agriculture in the Ecuadorian Andes found that lower acetylcholinesterase activity, measured in a finger stick sample, a biomarker indicator higher childhood exposure to cholinesterase inhibitors (e.g., OP pesticides), was associated with more depressive symptoms, especially among adolescent girls.[56] Examining mental health consequences of early-life exposure to environmental chemicals is an area where further research is warranted as existing prospective birth cohorts age into adolescence and early adulthood.[57]

A notable strength of this study was analysis of data from multiple informants, including maternal and self-report of behaviors. This approach may have allowed for a more comprehensive picture of child behaviors; however, it also led to some contradictory results. For example, we found associations of prenatal maternal DAPs with maternal reports of hyperactivity that were absent when we looked at youth self-reports. Youths have been shown to be poor reporters of attention-deficit/hyperactivity disorder (ADHD) symptoms, such as hyperactivity, which would result in random error from nondifferential outcome misclassification that could explain null findings for self-reports.[58] In addition, previous studies have generally shown fairly low correlation of behavioral ratings across multiple informants.[59] Rather than calling into question the reliability of these differing behavioral accounts, however, there has been justification for keeping data from multiple informants separate, as we have in our analysis, because the different informants each contribute important information about youth behavior.[59] We did observe some consistency for prenatal maternal DAP concentrations and internalizing problems, and in particular, depression, across maternal and youth reports.

We examined different windows of susceptibility to OP pesticide exposure, including the prenatal period and the early-childhood period. Both are periods of rapid brain development when exposure to environmental insult could potentially interfere with neurodevelopment.[60] We found that behavioral problems were associated with prenatal maternal DAP concentrations but not child DAP concentrations. This finding is consistent with previous CHAMACOS analyses, where we reported associations of prenatal maternal DAP concentrations with lower IQ at age 7 y and poorer attention at ages 3.5 and 5 y but no association of childhood DAPs with these outcomes.[23,30]

We observed nonlinear associations for prenatal maternal DAPs and both externalizing and internalizing behavior problems (Figures 1 and 2) with, in most cases, the strongest associations for the third quartile. This pattern was particularly pronounced for youth reports of internalizing behaviors (Figure 2), where associations were strongest in the third quartile but approached the null for the fourth quartile. Threshold effects are not uncommon in environmental epidemiology,[61] though it is difficult to explain biologically why there would be an inverse U-shaped relationship, with null associations at the highest exposure levels.

The specific mechanism by which OP pesticides exert their effect on the developing brain remains uncertain, because OP exposure in CHAMACOS and other human population-based studies are too low to result in measurable inhibition of acetylcholinesterase. OP-related effects on hyperactivity, short-term memory, and social behavior have been shown in rodent models.[18,62–66] Mechanisms that could underlie associations of OPs with behavior problems among humans include neurotransmitter disruption,[21,22] axonal growth inhibition,[19] alterations in Ca^{2+} homeostasis and oxidative stress,[16–18] and epigenetic modifications.[15,20]

Estimating exposure to OP pesticides by measuring urinary DAP metabolite concentrations has some limitations. DAPs are nonspecific OP metabolites, making it difficult to pinpoint whether associations may be attributed to a specific OP pesticide (e.g., chlorpyrifos or diazinon). In addition, DAPs reflect exposure to preformed metabolites as well as their parent pesticides, and a recent study shows that preformed DAPs may be the primary driver of urinary DAPs in urban populations.[49] Participants of CHAMACOS live in proximity to agriculture and likely derive some of their exposure from local pesticide use, as is reflected in their high DAP levels[8,14]; however, DAP levels resulting from dietary intake may indeed result in an overestimate of exposure to parent OPs. Finally, rapid metabolism of OPs in the body likely results in exposure measurement error, because a single spot urine fails to reflect longer-term exposure. We mediated this problem to some degree by collecting urine at multiple times during pregnancy and early childhood and examining associations with average or cumulative (AUC) levels, but it is likely that exposure misclassification was still present, which most likely attenuated effect estimates. In addition, looking at cumulative or average childhood DAP exposure over a 5-y period may have masked associations that might be present if there is a more vulnerable window of exposure during childhood. This trade-off between specificity of exposure window and exposure measurement error (as well as issues with multiple comparisons if we were to look at associations with DAPs measured at each time point in childhood individually) limits our interpretation of these childhood DAP exposure results.

Attrition in the early years of the CHAMACOS cohort was considerable. Of the 533 eligible children with gestational DAP measures, only 335 (63%) had data on behavior from the 14-, 16-, or 18-y visits. These participants had slightly older mothers and mothers who lived in the United States longer prior to giving birth (Table S1) (variables we adjusted for in our multivariable analyses) but otherwise closely resembled the cohort initially recruited. In addition, we have shown in previous work that analyses accounting for differential attrition (inverse probability weighting) do not change effect estimates.[28]

In summary, we found that prenatal, but not childhood, urinary OP metabolite concentrations were associated with both externalizing and internalizing behavior problems in youth ages 14–18 y. These lasting effects beyond childhood and into adulthood, including effects on mental health, supports the need to mitigate exposure to OP pesticides during pregnancy.

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