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# Interactions of agricultural pesticide use near home during pregnancy and adverse childhood experiences on adolescent neurobehavioral development in the CHAMACOS study

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## ABSTRACT

**Background:** Studies have documented independent adverse associations between prenatal and early-life exposure to environmental chemicals and social adversity with child neurodevelopment; however, few have considered these exposures jointly. The objective of this analysis is to examine whether associations of pesticide mixtures and adolescent neurobehavioral development are modified by early-life adversity in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort.

**Methods:** We used linear mixed effects Bayesian Hierarchical Models (BHM) to examine the joint effect of applications of 11 agricultural pesticides within 1 km of maternal homes during pregnancy and youth-reported Adverse Childhood Experiences (ACEs) with maternal and youth-reported internalizing behaviors, hyperactivity, and attention problems assessed via the Behavior Assessment for Children (BASC) (mean = 50, standard deviation = 10) at ages 16 and 18 years ( $n = 458$ ).

**Results:** The median (25th-75th percentiles) of ACEs was 1 (0-3); 72.3% of participants had low ACEs (0-2 events) and 27.7% had ACEs (3+ events). Overall, there was little evidence of modification of exposure-outcome associations by ACEs. A two-fold increase in malathion use was associated with increased internalizing behaviors among those with high ACEs from both maternal- ( $\beta = 1.9$ ; 95% Credible Interval (CrI): 0.2, 3.7 for high ACEs vs.  $\beta = -0.1$ ; 95% CrI: 1.2, 0.9 for low ACEs) and youth-report ( $\beta = 2.1$ ; 95% CrI: 0.4, 3.8 for high ACEs vs.  $\beta = 0.2$ ; 95% CrI: 0.8, 1.2 for low ACEs). Applications of malathion and dimethoate were also associated with higher youth-reported hyperactivity and/or inattention among those with high ACEs.

**Conclusion:** We observed little evidence of effect modification of agricultural pesticide use near the home during pregnancy and adolescent behavioral problems by child ACEs. Future studies should examine critical windows of susceptibility of exposure to chemical and non-chemical stressors and should consider biomarker-based exposure assessment methods.

## 1. Introduction

Previous research has consistently shown that prenatal and early-life exposure to organophosphate (OP) pesticides is associated with poorer neurodevelopment, including cognitive function (Bouchard et al., 2011; Engel et al., 2011; Rauh et al., 2011; Gunier et al., 2017; Coker et al., 2017a; Rowe et al., 2016), traits related to autism spectrum disorder

(ASD) (Sagiv et al., 2018; Shelton Janie et al., 2014; Roberts et al., 2007; von Ehrenstein et al., 2019), and behavioral problems (Marks et al., 2010; Rauh et al., 2006; Fortenberry et al., 2014). Specifically, research has identified associations of OP pesticide exposure and increased hyperactivity/inattention (Marks et al., 2010; Rauh et al., 2006) and internalizing behaviors such as depression and anxiety (Suarez-Lopez et al., 2019, 2021; Furlong et al., 2014) during childhood and adolescence. Studies have also shown associations of early-life adversity, or

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### Abbreviations

ACE	Adverse Childhood Experience
ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autism Spectrum Disorder
BASC	Behavior Assessment System for Children
BHM	Bayesian Hierarchical Model
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas
CES-D	Center for Epidemiologic Studies Depression Scale
CrI	Credible Interval
DAP	Dialkylphosphate
DE	Diethylphosphate
DM	Dimethylphosphate
FSIQ	Full Scale Intelligence Quotient
HOME-SF	Home Observation Measurement of the Environment-Short Form
IQ	Intelligence Quotient
JAGS	Just Another Gibbs Sampler
MCMC	Markov Chain Monte Carlo
OP	Organophosphate

“toxic stress”, with poorer cognitive and neurobehavioral development (Hunt et al., 2017; Guinasso et al., 2016; Dennison et al., 2019; Navalta et al., 2018). However, studies to date have largely examined environmental and social exposures separately (Ruiz Jdel et al., 2016).

Growing evidence suggests that the detrimental effects of environmental neurotoxicants may be magnified by early-life adversity (Appleton et al., 2016; Cory-Slechta, 2005; Clougherty et al., 2014; Nilsen et al., 2020; Bellinger, 2000) and that these exposures are likely to co-occur (Horton et al., 2012; Tamayo et al., 2017), underscoring the importance of examining their joint effects. Research examining joint exposures to social adversity and environmental toxicants has shown synergistic associations on cognitive and behavioral outcomes. However, these studies have focused primarily on lead (Bellinger et al., 1988, 1990; Hubbs-Tait et al., 2009; Surkan et al., 2008; Tong et al., 2000; Xu et al., 2015), air pollutants (Cowell et al., 2015; Perera et al., 2013; Vishnevetsky et al., 2015), and environmental tobacco smoke (Hopson et al., 2016; Rauh et al., 2004). There are gaps in the literature on potential interactions of early-life adversity and other environmental neurotoxicants, such as pesticides. In previous analyses from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), we found that greater total adversity and domain-specific adversity (i.e., poor learning environment for boys and adverse parent-child interactions for girls) magnified associations between prenatal OP pesticide exposure – assessed via dialkylphosphate (DAP) metabolites – and decreased Intelligence Quotient (IQ) at age 7 years (Stein et al., 2016).

In addition to considering the joint impacts of chemical and non-chemical stressors, emerging evidence highlights the importance of employing statistical methods to efficiently evaluate the impacts of exposure to mixtures of highly correlated environmental chemicals (Tanner et al., 2020). In recent analyses, we employed Bayesian Hierarchical Modeling (BHM) to evaluate associations of applications of multiple agricultural pesticide within 1 km of the home during the prenatal and early childhood (ages 0–5) periods and maternal- and youth-reported internalizing and externalizing behaviors in CHAMACOS, a cohort of low-income Mexican-American youth living in the agricultural Salinas Valley, California. We observed modest associations of higher internalizing behaviors and attention problems in association with a two-fold increase in applications of OP pesticides such as chlorpyrifos, diazinon, and dimethoate near the home during the prenatal period. Here, we extend this analysis to examine potential interactions

of agricultural pesticide use with adverse childhood experiences (ACEs) and hypothesize that associations of pesticides with neurodevelopment are stronger among those experiencing more ACEs.

## 2. Methods

Information about participant recruitment and study procedures have been described previously (Eskenazi et al., 2004). Briefly, CHAMACOS is a longitudinal cohort study examining the health impacts of prenatal and early-life exposure to pesticides and environmental chemicals among children born in the agricultural Salinas Valley in Monterey County, California. We recruited pregnant women who met eligibility criteria ( $\geq 18$  years old,  $< 20$  weeks gestation, Spanish- or English-speaking, qualified for low-income health insurance, and planning to deliver at the county hospital) from community clinics serving low-income Latino patients in 1999–2000. Of the 601 women enrolled at baseline, 527 (88%) remained in the study through delivery of a live-born singleton and 337 (56%) remained in the study through the child’s 9-year assessment (referred to henceforth as CHAM1). We expanded the cohort in 2009–2011 and recruited an additional 305 9-year-old Salinas Valley residents whose mothers met eligibility criteria (were  $\geq 18$  years at delivery, Spanish- or English-speaking, qualified for low-income health insurance during pregnancy, delivered child in local hospital, and had sought prenatal care in the first trimester) (referred to henceforth as CHAM2). In total, 595 participants (CHAM1 and CHAM2) remained in the cohort through the 16-year study visit and 478 participants had also completed the 18-year study visit by March 2020, when data collection was paused due to the COVID-19 pandemic.

Study staff administered detailed questionnaires in either English or Spanish to mothers of CHAM1 participants at two time points during pregnancy, after delivery, and at multiple points throughout childhood. CHAM2 mothers were administered a comprehensive baseline interview when their children were enrolled at 9 years, and all mothers (CHAM1 and CHAM2) completed identical assessments when their children were 10.5, 12, 14, 16, and 18 years of age. CHAMACOS youth were interviewed directly starting at age 10.5 years. We limited the current analysis to participants with 1) a prenatal address that could be geocoded ( $n = 814$ ), 2) maternal- or youth-reported behavioral outcomes at the 16- or 18-year visit ( $n = 473$ ), and 3) childhood adversity reported retrospectively at the 18-year assessment ( $n = 466$ ). This left a total of 458 participants for the current analysis.

The University of California Berkeley Committee for the Protection of Human Subjects approved all study activities. We obtained written informed consent from all mothers at all study visits. Youth provided written assent at age 16 years and written consent at age 18 years.

### 2.1. Estimation of agricultural pesticide use near home

Exposure assessment procedures have been described elsewhere (Gunier et al., 2017; Hyland et al., 2021; Coker et al., 2017b). Briefly, we used California’s Pesticide Use Reporting (PUR) database to characterize wind-adjusted use of agricultural pesticides within 1 km of each participant’s residences during the prenatal period. In this analyses, we included the same 11 pesticides as in our original analysis examining associations of agricultural pesticide use within 1 km of the home and adolescent neurobehavioral outcomes (Hyland et al., 2021), which were selected based on the following criteria: 1) have evidence of neurotoxicity in humans or animals; 2) had more than 4500 kg applied in Monterey County during the prenatal period; and 3) were used within 1 km of the home of at least 50% of CHAMACOS participants during the prenatal period (see Table S1 for a list of pesticides and their classes). As in our previous analyses, we selected a 1 km buffer because this distance has been shown to be most strongly correlated with concentrations of agricultural pesticides in dust samples collected from homes in this region (Harnly et al., 2009; Gunier et al., 2011). We log<sub>2</sub>-transformed all pesticide use estimates and measures of association correspond to a

two-fold increase in pesticide use.

## 2.2. Behavioral Assessment

At the 16- and 18-year study visits, mothers were interviewed on the emotional and behavioral problems of their child using the Behavior Assessment for Children, second edition (BASC-2) (Reynolds, 2004). Youth independently completed the BASC-2 Self-Report of Personality (SRP). We considered maternal- and youth-reported scores from the internalizing problems composite scale, as well as the hyperactivity and inattention subscales. We examined BASC-2 scores as age- and sex-standardized T-scores ( $M = 50$ ,  $SD = 10$ ), with higher scores representing more symptomatic behaviors.

## 2.3. Adverse Childhood Experiences

At the 18-year visit, young adult participants completed an adaptation of the Centers for Disease Control and Prevention (CDC) Adverse

**Table 1**

Sociodemographic characteristics of CHAMACOS study participants with data on 16 or 18-year behavioral outcomes, agricultural pesticide use near home during prenatal period, and Adverse Childhood Experiences [ $n$  (%) or median (P25–P75)].

	All children ( $n = 458$ )	Low ACEs ( $n = 331$ )	High ACEs ( $n = 127$ )
<i>Maternal/household characteristics</i>			
Age at enrollment (years)	26 (22–30)	26 (22–30)	25 (22–29)
Country of birth			
Mexico or other	407 (88.9)	297 (89.7)	125 (98.4)
U.S.	51 (11.1)	34 (10.3)	2 (1.6)
Years in the U.S. at delivery			
≤5	222 (48.5)	167 (50.5)	55 (43.3)
>5, but not born in U.S.	196 (42.8)	135 (40.8)	61 (48.0)
Born in U.S.	40 (8.7)	29 (8.8)	11 (8.7)
Education at baseline			
≤6th grade	195 (42.6)	139 (42.0)	56 (40.1)
7th–12th grade	158 (34.5)	120 (36.3)	38 (29.9)
≥High school graduate	105 (22.9)	72 (21.8)	33 (26.0)
Marital status at baseline			
Not married/not living as married	81 (17.7)	52 (15.7)	29 (22.8)
Married/living as married	377 (82.3)	279 (84.3)	98 (77.2)
Maternal depression at 9-year visit ( $\geq 16$ CES-D score) <sup>a</sup>			
No	325 (71.0)	244 (73.7)	80 (63.0)
Yes	133 (29.0)	87 (26.3)	
Household income at 16-year assessment <sup>a</sup>			
At or below poverty level	258 (56.3)	178 (53.8)	80 (63.0)
Above poverty level	200 (43.7)	153 (46.2)	47 (37.0)
Language of 16-year maternal interview <sup>a</sup>			
English	56 (12.2)	35 (10.6)	21 (16.5)
Spanish	402 (87.8)	296 (89.4)	106 (83.5)
HOME z-score at 10.5-year assessment <sup>b</sup>	0.2 (−0.6, 0.6)	0.2 (−0.6, 1.0)	−0.2 (−0.9, 0.6)
<i>Child characteristics</i>			
ACEs	1 (0–3)	–	–
Low (0–2)	331 (72.3)	–	–
High (3+)	127 (27.7)	–	–
Child's sex			
Boy	216 (47.2)	169 (51.1)	47 (37.0)
Girl	242 (52.8)	162 (48.9)	80 (63.0)
Exact age at 16-year assessment	16.3 (16.1, 16.5)	16.3 (16.1, 16.5)	16.3 (16.1, 16.6)
Exact age at 18-year assessment	18.0 (18.0, 18.1)	18.0 (18.0, 18.1)	18.0 (18.0, 18.1)

<sup>a</sup> Missing data filled in from data collected at earlier or later time points.  $n = 40$  participants missing maternal depression at 9-year assessment; 7 missing poverty status at 16-year assessment; 16 missing maternal language of 16-year assessment.

<sup>b</sup> Missing data filled in from earlier or later assessments for 13 participants missing HOME z-score at 10.5-year assessment; filled in as median HOME z-score observed for population included in this analysis for one participant missing HOME z-score at all visits.

Childhood Experiences (ACE) survey (Centers for Disease Contr, 2020), which inquires retrospectively about adverse events in the first 18 years of life (e.g., parent separation, experiencing violence or neglect, witnessing violence in the home or neighborhood), and has shown good predictive validity (Middlebrooks and Audage, 2008). Participants used Computer Assisted Personal Interviews (CAPIs) to confidentially answer questions about ACEs. The original ACE survey asks participants to indicate (yes/no) whether they experienced various events before age 18; we adapted this scale so that we could not disaggregate certain “reportable” events (e.g., sexual abuse) from non-reportable events. Our adapted ACE survey included two parts: in the first, we listed seven events and asked participants to report whether they had experienced 0, 1, 2, 3, 4 or 5+ of these events. These included emotional abuse, physical abuse, sexual abuse, parental separation, and either substance abuse, a mental health disorder, or incarceration of a household member. In the second part, we listed an additional seven questions that we later collapsed into the three remaining events of the ACEs scale (emotional neglect, physical neglect, or domestic violence). Participants responded to each of seven questions individually indicating whether they had experienced that event. We summed the number of events reported from the two parts and considered interactions with ACEs dichotomized as low as (0–2) or high (3+); these categories were selected based on the categorization used in previous analyses (Julian et al., 2018; Iob et al., 2020) and the distribution of ACEs reported in our study population. The adapted ACE survey is available in Appendix 1.

## 2.4. Covariate information

We collected detailed covariate information about the prenatal period and adjusted for the same confounders from our original analysis examining associations of agricultural pesticide use and adolescent neurobehavioral outcomes (Hyland et al., 2021), which were selected *a priori* using a directed acyclic graph (Greenland et al., 1999): maternal age (in years; continuous), maternal years spent in the US prior to delivery (categorical: ≤5 years, >5 years but not born in US, born in US), maternal education (categorical: ≤6th grade, 7th–12th grade, completed high school), and maternal marital status (dichotomous: not married/–not living as married vs. married/living as married). We also adjusted models for the following predictors of the outcomes selected *a priori*: maternal depression status at the 9-year assessment (categorical: yes vs. no) assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), child sex (biological sex assigned at birth based on parent report at delivery or 9Y enrollment; dichotomous), child exact age at assessment (years; continuous), Home Observation Measurement of the Environment-Short Form (HOME-SF) (Caldwell and Bradley, 1984) z-score at the 10.5-year visit (continuous) to assess enrichment and the quality of the child's home environment, household income at the time of assessment (categorical: at or below poverty line vs. above poverty line), and language of maternal interview for the BASC outcomes (English vs. Spanish).

## 2.5. Statistical analysis

We used a two-stage linear mixed effects BHM (Braun et al., 2014; De Roos et al., 2001; Kalkbrenner et al., 2010; White et al., 2016; Hamra et al., 2014; Buckley et al., 2016; Witte et al., 1994; Greenland, 1994) to examine associations of all 11 pesticides included simultaneously with BASC scores assessed at the 16- and 18-year study visits. Details of the analysis have been described previously (Hyland et al., 2021). Briefly, in the first stage, we regressed each BASC outcome on the exposures and covariates in a single linear mixed-effects model with a random subject-specific effect as:  $E[Y|X, W, u] = \alpha + X\beta + W\gamma + u$ ; where  $X$  is the vector of all pesticides,  $W$  is the vector of confounders, and  $u$  is a normally distributed subject-specific random effect. In the second stage, we modeled the exposure effects ( $\beta$ ) as a function of an exchangeability matrix  $Z$ , coefficient vector  $\pi$ , and residual error  $\delta$  (normally distributed

**Table 2**

Total pesticide use in Monterey County in 2000 and distribution of wind-adjusted agricultural pesticide applications within 1 km of maternal residence during prenatal period.

	Kilograms used (2000)	Kilograms used within 1 km of residence during pregnancy			
		P25	P50	P75	Max
<b>Organophosphate insecticides</b>					
Acephate	40,077	0.16	1.09	2.03	6.29
Chlorpyrifos	30,691	0.18	0.92	2.03	5.71
Diazinon	50,999	1.15	1.98	2.94	7.01
Malathion	30,490	0.00	0.31	1.42	5.51
Oxydemeton methyl	31,084	0.20	1.00	1.97	2.80
Dimethoate	20,259	0.12	0.59	1.54	3.63
<b>Carbamate insecticides</b>					
Methomyl	35,371	0.28	0.97	2.01	4.91
<b>Pyrethroid insecticides</b>					
Permethrin	11,869	0.12	0.48	1.16	4.12
<b>Neonicotinoid insecticides</b>					
Imidacloprid	8729	0.16	0.42	0.91	3.32
<b>Fungicides</b>					
Mn-fungicides	161,154	1.76	3.20	4.32	7.58
<b>Herbicides</b>					
Glyphosate	44,236	0.00	0.06	1.27	4.70

Notes: p25, 25th percentile; p50, 50th percentile; p75, 75th percentile; Max, Maximum.

with mean zero and precision  $\tau$ ) as:  $\beta = Z\pi + \delta$ . We incorporated a Z matrix with indicator variables (0/1) for the class to which each individual pesticide belongs (i.e., OPs, carbamates, pyrethroids,

**Table 3**

Adjusted<sup>a</sup> associations [ $\beta$  (95% CrI)] of interaction of two-fold increase in neurotoxic pesticide use within 1 km of residence during pregnancy and childhood ACEs<sup>b</sup> with maternal report of behavioral and emotional problems at age 16 and 18 years using Bayesian Hierarchical Modeling (BHM) (all participants:  $n = 458, k = 916$ ; low ACEs:  $n = 331, k = 662$ ; high ACEs:  $n = 127, k = 254$ ).

	Internalizing problems			Hyperactivity			Attention problems		
	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs
<b>OPs</b>									
Acephate	0.0 (-1.7, 1.6)	0.0 (-1.8, 1.8)	0.0 (-2.7, 2.7)	-0.3 (-1.6, 1.0)	-0.4 (-1.8, 0.9)	0.0 (-2.1, 2.0)	-0.3 (-1.9, 1.2)	-0.3 (-1.9, 1.4)	-0.5 (-3.0, 1.9)
Chlorpyrifos	1.0 (-0.3, 2.3)	0.4 (-1.1, 1.8)	0.8 (-1.5, 3.1)	0.4 (-0.6, 1.4)	0.2 (-0.9, 1.3)	0.3 (-1.4, 2.1)	0.0 (-1.2, 1.1)	-0.2 (-1.5, 1.1)	0.0 (-2.1, 2.1)
Diazinon	-0.7 (-2.2, 0.9)	-0.4 (-2.0, 1.2)	-1.0 (-3.9, 1.9)	-0.3 (-1.5, 0.9)	-0.6 (-1.8, 0.7)	0.5 (-1.8, 2.6)	0.1 (-1.3, 1.5)	0.2 (-1.3, 1.7)	-0.6 (-3.3, 2.0)
Malathion	0.3 (-0.6, 1.3) <sup>c</sup>	-0.1 (-1.2, 0.9)	1.9 (0.2, 3.7)	-0.1 (-0.8, 0.6)	0.0 (-0.8, 0.8)	-0.2 (-1.5, 1.2)	0.2 (-0.7, 1.0)	0.3 (-0.7, 1.2)	0.0 (-1.6, 1.6)
Oxydemeton methyl	-0.1 (-2.5, 2.3)	0.5 (-2.0, 3.0)	-0.4 (-4.2, 3.3)	-0.3 (-2.2, 1.5)	-0.5 (-2.4, 1.4)	0.4 (-2.5, 3.2)	-0.1 (-2.3, 2.0)	-0.2 (-2.5, 2.1)	0.4 (-3.0, 3.8)
Dimethoate	0.2 (-1.9, 2.4)	0.2 (-2.1, 2.6)	0.8 (-2.7, 4.2)	0.4 (-1.3, 2.1)	0.5 (-1.3, 2.3)	0.3 (-2.3, 2.9)	1.4 (-0.6, 3.4)	1.2 (-1.0, 3.3)	2.0 (-1.1, 5.1)
<b>Carbamate</b>									
Methomyl	-0.2 (-1.6, 1.1)	0.0 (-1.4, 1.5)	-1.8 (-4.4, 0.8)	0.5 (-0.5, 1.6)	0.5 (-0.6, 1.6)	0.2 (-1.7, 2.1)	0.1 (-1.2, 1.3)	0.2 (-1.1, 1.6)	-0.7 (-3.0, 1.6)
<b>Pyrethroid</b>									
Permethrin	-0.7 (-3.5, 2.1)	-1.1 (-3.7, 1.5)	0.5 (-4.6, 5.5)	0.3 (-1.8, 2.4)	0.0 (-2.1, 2.0)	1.6 (-2.3, 5.4)	0.2 (-2.2, 2.8)	0.0 (-2.4, 2.4)	2.5 (-2.1, 7.2)
<b>Neonicotinoid</b>									
Imidacloprid	-0.8 (-4.2, 2.7)	-1.0 (-4.2, 2.2)	-1.9 (-7.6, 3.9)	-0.3 (-2.9, 2.3)	-0.5 (-2.9, 2.0)	-2.8 (-7.3, 1.6)	-2.9 (-6.0, 0.2)	-2.5 (-5.4, 0.4)	-6.3 (-11.5, -1.1)
<b>Fungicide</b>									
Mn-Fungicides	0.4 (-1.0, 1.8)	0.3 (-1.3, 1.8)	1.1 (-1.2, 3.4)	0.1 (-1.0, 1.2)	0.5 (-0.7, 1.6)	-0.4 (-2.1, 1.4)	0.1 (-1.2, 1.4)	0.2 (-1.2, 1.6)	0.5 (-1.7, 2.6)
<b>Herbicide</b>									
Glyphosate	0.3 (-0.6, 1.1)	0.1 (-0.7, 1.1)	0.6 (-1.2, 2.4)	0.3 (-0.3, 1.0)	0.3 (-0.4, 1.0)	0.6 (-0.8, 1.9)	0.3 (-0.5, 1.0)	0.2 (-0.6, 1.1)	0.1 (-1.5, 1.7)

Notes:  $n$ , number of participants with data for at least one time point;  $k$ , number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.

<sup>a</sup>Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, language of assessment, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.

<sup>b</sup>Low ACEs = 0–2 events; High ACEs = 3+ events.

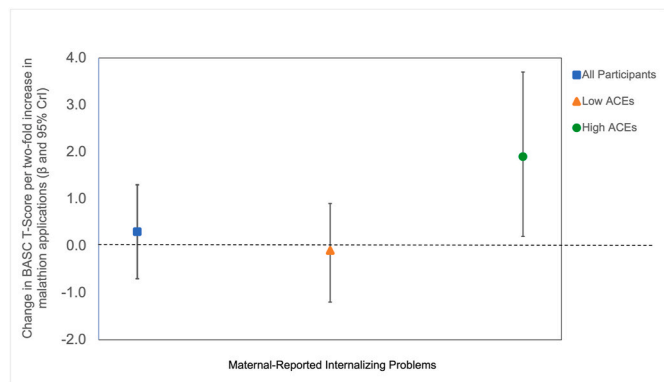
<sup>c</sup>95% CrI for product-interaction term of pesticides and ACEs did not cross the null (95% CrIs available in Table S3).

neonicotinoids, fungicides, and herbicides), asserting our *a priori* expectation that pesticides from the same class would have similar associations with the outcome (Table S1).

We extended our previous analyses examining associations of applications of these 11 pesticides within 1 km of the home during the prenatal period and neurobehavioral outcomes by considering interactions with ACEs. We included an interaction term between each pesticide (continuous) and the number of ACEs (categorized as 0–2 or 3+) in the first stage model. ACEs were reported by participants retrospectively at the 18-year assessment. We made the assumption that all ACEs occurred prior to age 16 years and thus preceded the outcome of interest (behavioral outcomes at ages 16 and 18 years). We considered there to be meaningful evidence of modification if the 95% credible intervals (CrIs) for the product-interaction term did not cross the null value, following similar criterion previously used in environmental BHM analyses (Buckley et al., 2016). We examined sex-specific effects by stratifying models by child sex.

We specified vague priors on nuisance parameters ( $\alpha, \gamma, \pi$ ) and pre-specified the precision for  $\delta$  (i.e.,  $\tau$ ) under the assumption that the  $\beta$  parameters would lie within  $\pm 0.5$  SD of the mean of the BASC outcome of interest in our population (i.e., from -5 to 5 in the normative sample). Models were specified in a Fully Bayesian framework (MacLehose and Hamra, 2014) and the posterior distribution of all model parameters was estimated via Markov Chain Monte Carlo (MCMC) sampling (Hamra et al., 2013). We used Gibbs sampling (Casella and George, 1992) from Just Another Gibbs Sampler (JAGS) (Plummer, 2003) to summarize the posterior distributions of these parameters and estimate the posterior median and 95% CrIs. We ran models with 50,000 iterations after an





**Fig. 1.** Adjusted association ( $\beta$  and 95% CrI) of two-fold increase in malathion applications within 1 km of the home during pregnancy using Bayesian Hierarchical Modeling (BHM) with maternal-reported internalizing behaviors, stratified by ACEs.

initial burn-in of 10,000. We assessed convergence graphically using trace plots, autocorrelation plots, and density plots (Hamra et al., 2013), and statistically using the Geweke test (Geweke, 2004) and Gelman-Rubin test statistic (Brooks and Gelman, 1998). All analyses were conducted using RStudio Version February 1, 1335. We present  $\beta$  coefficients and 95% CrIs predicted from the first-stage model.

**Table 4**

Adjusted<sup>a</sup> associations [ $\beta$  (95% CrI)] of interaction of two-fold increase in neurotoxic pesticide use within 1 km of residence during pregnancy and childhood ACEs<sup>b</sup> with youth report of behavioral and emotional problems at age 16 and 18 years using Bayesian Hierarchical Modeling (BHM) (all participants:  $n = 458$ ,  $k = 916$ ; low ACEs:  $n = 331$ ,  $k = 662$ ; high ACEs:  $n = 127$ ,  $k = 254$ ).

	Internalizing problems			Hyperactivity			Attention problems		
	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs	All participants	Low ACEs	High ACEs
<b>OPs</b>									
Acephate	0.2 (-1.5, 1.8)	0.3 (-1.4, 2.0)	-0.5 (-3.0, 2.1)	-0.2 (-1.7, 1.3)	0.2 (-1.3, 1.8)	-1.9 (-4.1, 0.5)	-0.1 (-1.5, 1.5)	-0.1 (-1.8, 1.5)	0.0 (-2.4, 2.4)
Chlorpyrifos	1.1 (-0.2, 2.4)	0.1 (-1.3, 1.5)	1.0 (-1.3, 3.2)	-0.4 (-1.6, 0.8)	-0.9 (-2.1, 0.4)	-1.0 (-3.1, 1.0)	0.1 (-1.0, 1.3)	-0.5 (-1.7, 0.8)	0.2 (-1.8, 2.3)
Diazinon	0.5 (-1.1, 2.0)	0.8 (-0.7, 2.4)	0.3 (-2.5, 3.0)	0.3 (-1.0, 1.8)	0.1 (-1.3, 1.6)	1.9 (-0.6, 4.6)	0.7 (-0.7, 2.1)	0.9 (-0.5, 2.4)	0.2 (-2.4, 2.8)
Malathion	0.6 (-0.4, 1.5) <sup>c</sup>	0.2 (-0.8, 1.2)	2.1 (0.4, 3.8)	-0.1 (-1.0, 0.7) <sup>c</sup>	-0.7 (-1.6, 0.3)	1.7 (0.1, 3.2)	0.0 (-0.9, 0.8)	-0.2 (-1.2, 0.7)	0.5 (-1.0, 2.0)
Oxydemeton methyl	-1.0 (-3.3, 1.4)	-0.2 (-2.7, 2.2)	-0.8 (-4.4, 2.8)	0.0 (-2.1, 2.2)	0.3 (-2.0, 2.5)	0.9 (-2.4, 4.1)	-0.9 (-3.1, 1.3)	-0.4 (-2.6, 1.9)	-1.4 (-4.7, 2.0)
Dimethoate	-0.6 (-2.8, 1.6)	-0.6 (-2.8, 1.6)	0.7 (-2.5, 4.0)	0.3 (-1.6, 2.3)	-0.1 (-2.1, 2.0)	2.9 (-0.1, 5.8)	1.5 (-0.5, 3.5) <sup>c</sup>	0.8 (-1.3, 3.0)	4.0 (0.9, 6.9)
<b>Carbamate</b>									
Methomyl	-0.4 (-1.7, 1.0)	-0.2 (-1.6, 1.1)	-1.6 (-4.0, 0.9)	0.3 (-0.9, 1.6)	0.4 (-0.9, 1.7)	-0.6 (-2.8, 1.6)	-0.4 (-1.6, 0.9)	-0.3 (-1.6, 1)	-0.6 (-2.9, 1.6)
<b>Pyrethroid</b>									
Permethrin	-0.5 (-3.2, 2.3)	-1.2 (-3.7, 1.3)	-1.4 (-6.2, 3.4)	-1.1 (-3.6, 1.4)	-1.9 (-4.2, 0.4)	-2.7 (-7.2, 1.8)	-1.7 (-4.2, 0.8)	-2.2 (-4.6, 0.1)	-1.4 (-6.1, 3.0)
<b>Neonicotinoid</b>									
Imidacloprid	-1.6 (-5.0, 1.7)	-1.7 (-4.7, 1.3)	-1.6 (-6.9, 3.9)	0.7 (-2.4, 3.8)	0.4 (-2.4, 3.2)	1.0 (-4.0, 6.0)	-1.9 (-5.0, 1.3)	-1.8 (-4.7, 1.0)	-2.5 (-7.6, 2.5)
<b>Fungicide</b>									
Mn-Fungicides	0.6 (-0.8, 2.0)	0.4 (-1.0, 1.8)	2.1 (-0.1, 4.3)	-0.2 (-1.5, 1.0)	0.2 (-1.1, 1.6)	-0.6 (-2.5, 1.4)	0.7 (-0.6, 2.0)	1.0 (-0.4, 2.3)	0.9 (-1.2, 2.9)
<b>Herbicide</b>									
Glyphosate	0.0 (-0.8, 0.8)	0.2 (-0.7, 1.0)	-0.9 (-2.5, 0.8)	0.4 (-0.3, 1.2)	0.7 (-0.1, 1.5)	-0.5 (-2.0, 1.1)	-0.2 (-0.9, 0.6)	0.0 (-0.8, 0.8)	-1.2 (-2.7, 0.4)

Notes:  $n$ , number of participants with data for at least one time point;  $k$ , number of observations from both time points. Higher BASC scores indicate more symptomatic behavior.

<sup>a</sup> Models adjusted for maternal age at delivery, years in the U.S., education at baseline, marital status at baseline, depression at 9Y assessment; child sex, child age at time of assessment, poverty status at time of assessment, HOME score at 10.5Y assessment.

<sup>b</sup> Low ACEs = 0–2 events; High ACEs = 3+ events.

<sup>c</sup> 95% CrI for product-interaction term of pesticides and ACEs did not cross the null (95% CrIs available in Table S3).

## 2.6. Sensitivity analysis

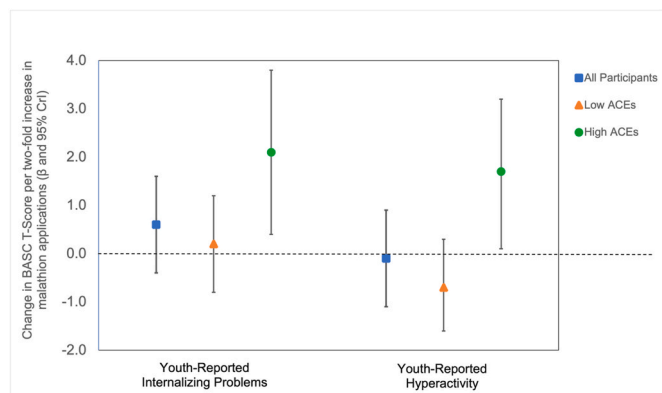
Because ACEs retrospectively reported at age 18 years may not have occurred prior to the 16-year assessment (and thus prior to the 16-year behavioral outcomes included in linear mixed effects models), we ran the same hierarchical models with 18-year outcome data only.

## 3. Results

Table 1 shows the sociodemographic characteristics of the participants included in this analysis ( $n = 458$ ). Mothers were predominantly born in Mexico (89%) and had low levels of education (43% had <6th grade education at baseline) and high household poverty levels (56% at or below federal poverty level at 16-year assessment). Maternal- and youth-report of internalizing behaviors, hyperactivity, and attention problems were similar across most sociodemographic characteristics (Table S2). Notably, participants with high ACEs tended to have higher (more symptomatic) scores for maternal- and youth-report of all outcomes compared to those with low ACEs (Table S2). The distribution of wind-adjusted applications of the 11 agricultural pesticides included in this analysis is shown in Table 2. All participants lived within 1 km of application of at least one pesticide. Spearman correlation coefficients for applications of the 11 pesticides ranged from 0.3 to 0.9 (Figure S1).

### 3.1. Internalizing problems

The only pesticide for which we observed modification of exposure-



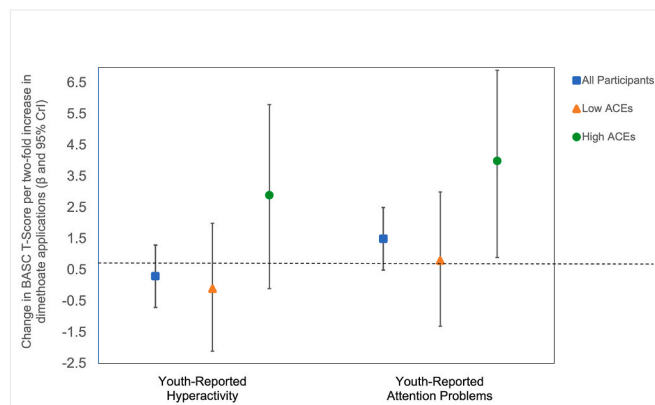
**Fig. 2.** Adjusted association ( $\beta$  and 95% CrI) of two-fold increase in malathion applications within 1 km of the home during pregnancy using Bayesian Hierarchical Modeling (BHM) with youth-reported internalizing behaviors and hyperactivity, stratified by ACEs.

outcome associations for internalizing problems was malathion (Table 3). Specifically, we found that a two-fold increase in malathion applications within 1 km of the home during pregnancy was associated with a 1.9-point increase (95% CrI: 0.2, 3.7) in maternal-report of internalizing problems among youth who experienced high ACEs (3+), compared with  $-0.1$  points (95% CrI:  $-1.2$ , 0.9) among youth who experienced low ACEs (0–2) (Fig. 1) (95% CrI for interaction term: 0.1, 4.0; Table S3). Malathion use was also associated with a 2.1-point increase (95% CrI: 0.4, 3.8) in youth-reported internalizing problems among those with high ACEs, compared with 0.2 points (95% CrI:  $-0.8$ , 1.2) among those with low ACEs (Table 4; Fig. 2) (95% CrI for interaction term: 0.1, 3.8; Table S3). Associations for both maternal- and youth-report were stronger among males (Table S4). For example, the effect of a two-fold increase in malathion applications with youth-reported internalizing problems was 1.2 (95% CrI: 0.0, 2.5) among males, compared to  $-0.1$  (95% CrI:  $-1.4$ , 1.3) among females (Table S4). This effect was even more pronounced when considering interactions with ACEs; for boys, malathion use near the home was associated with a 4.9-point increase (95% CrI: 1.9, 8.0) in self-reported internalizing problems among those with high ACEs, compared to a 0.8-point increase (95% CrI:  $-0.4$ , 2.1) among those with low ACEs. For girls, the effect was 1.4 (95% CrI:  $-0.8$ , 3.4) among those with high ACEs and  $-0.3$  (95% CrI:  $-1.8$ , 1.2) among those with low ACEs (Table S4).

In addition to malathion, a two-fold increase in Mn-containing fungicides within 1 km of the home during pregnancy was associated with increased youth report of internalizing problems among participants with high ACEs ( $\beta = 2.1$ ; 95% CrI:  $-0.1$ , 4.3), but not low ACEs ( $\beta = 0.4$ ; 95% CrI:  $-1.0$ , 1.8; Table 4); however, the 95% CrI for the interaction term included the null ( $-0.7$ , 4.1; Table S3). We did not observe evidence of modification by ACEs for associations of any other pesticides with maternal- or youth-reported internalizing problems.

### 3.2. Hyperactivity and attention problems

Results examining interactions of pesticide use near the home and childhood ACEs were largely null for maternal-reported hyperactivity and attention problems among all participants (Table 3) and in sex-stratified analyses (Tables S5 and S6). Notably, a two-fold increase in imidacloprid applications within 1 km of the home during pregnancy was associated with decreased maternal-reported attention problems



**Fig. 3.** Adjusted association ( $\beta$  and 95% CrI) of two-fold increase in dimethoate applications within 1 km of the home during pregnancy using Bayesian Hierarchical Modeling (BHM) with youth-reported hyperactivity and attention problems, stratified by ACEs.

among those with high ACEs ( $\beta = -6.3$ , 95% CrI:  $-11.5$ ,  $-1.1$ ), but not low ACEs ( $\beta = -2.5$ ; 95% CrI:  $-5.4$ , 0.4; Table 3); the 95% CrI for the interaction term included the null ( $-8.5$ , 0.8; Table S3). This inverse association of imidacloprid and ACEs on maternal-reported hyperactivity was stronger among girls than boys (Table S5). We did not observe associations of imidacloprid and youth-reported attention problems.

A two-fold increase in malathion applications was associated with increased youth-reported hyperactivity among those with high ACEs ( $\beta = 1.7$ ; 95% CrI: 0.1, 3.2), but not low ACEs ( $\beta = -0.7$ ; 95% CrI:  $-1.6$ , 0.3) (95% CrI for interaction term: 0.6, 4.0) (Table 4; Fig. 2). Additionally, a two-fold increase in dimethoate applications was associated with increased youth-reported hyperactivity and attention problems among those with high ACEs (Fig. 3). For hyperactivity, the effect was an increase of 2.9 points (95% CrI:  $-0.1$ , 5.8) among those with high ACEs and  $-0.1$  points (95% CrI:  $-2.1$ , 2.0) among those with low ACEs (Table 4); 95% CrI for interaction term:  $-0.1$ , 6.0 (Table S3). For attention problems, the effect was 4.0 points (95% CrI: 0.9, 6.9) among those with high ACEs and 0.8 points (95% CrI:  $-1.3$ , 3.0) among those with low ACEs (Table 4); 95% CrI for interaction term: 0.0, 6.2 (Table S3). There was not meaningful evidence of sex-specific effects for youth-reported hyperactivity (Table S5) or attention problems (Table S6).

### 3.3. Sensitivity analyses

Results from models in which we included only outcome data reported at the 18-year assessment, thus ensuring the ACEs occurred prior to the outcome, were similar to results from mixed-effects models including 16 and 18-year outcome data (Table S7 for maternal-reported outcomes; Table S8 for youth-reported outcomes); however, credible intervals from models employing just the 18-year outcome data were much wider given the smaller sample size. Overall, our interpretations were qualitatively similar.

## 4. Discussion

In previous analyses in this population, we observed some associations of OP pesticide use (i.e., chlorpyrifos, dimethoate, diazinon) near the home during pregnancy and modestly increased maternal- and youth-reported internalizing and externalizing problems at ages 16 and 18 years (Hyland et al. et al.). In this paper, we extend these analyses by

considering interactions of nearby agricultural pesticide use and ACEs experienced by youth. We observed little evidence of modification of associations between agricultural pesticide use near maternal homes during pregnancy and maternal- and youth-reported behavioral and emotional problems during adolescence by ACEs. For internalizing problems, only associations with malathion were modified by ACEs; results were consistent across maternal- and youth-report. There was some evidence of increased youth-, but not maternal-, reported hyperactivity and attention problems in association with malathion and dimethoate applications near the home among those with high ACEs. We did not observe meaningful evidence of modification by ACEs for any other pesticides.

Synergistic effects of early-life exposure to social stressors and environmental chemicals on neurodevelopment have been demonstrated in animal studies (Bolton et al., 2013; Cory-Slechta Deborah et al., 2004; Virgolini et al., 2006; Weston et al., 2014). These studies, which have largely focused on lead as an environmental exposure, suggest that mechanisms may include altered hypothalamic-pituitary-adrenal (HPA) axis function (Cory-Slechta et al., 2008; Virgolini et al., 2005), changes in levels of neurotransmitters and proteins in regions of the brain known to mediate learning/behavioral flexibility (Weston et al., 2014), and impaired hippocampal volume, functioning, and neurogenesis (Gilbert et al., 2005; Coe et al., 2003; Yu et al., 2016; Lemaire et al., 2006).

Epidemiologic studies have also shown that factors such as the child's home environment, maternal stress, psychological distress, and poor social support may amplify associations of environmental exposures such as lead, air pollution, environmental tobacco smoke, and heavy metals with childhood cognitive and behavioral outcomes (Bellinger, 2000; Bellinger et al., 1988, 1990; Hubbs-Tait et al., 2009; Surkan et al., 2008; Tong et al., 2000; Xu et al., 2015; Cowell et al., 2015; Perera et al., 2013; Vishnevetsky et al., 2015; Hopson et al., 2016; Rauh et al., 2004; Vreugdenhil et al., 2002). Nevertheless, only two previous studies to date have examined the joint effects of exposure to pesticides and social adversity (Horton et al., 2012; Stein et al., 2016). Previous analyses from our cohort indicate that the adverse effects of prenatal metabolites of OP pesticides, DAPs, and IQ at age 7 years were stronger among those with higher levels of total childhood adversity and domain-specific adversity (i.e., poor learning environment for boys and adverse parent-child relationships for girls) (Stein et al., 2016). In the only other previous study to investigate the impact of co-exposure to pesticides and social factors on neurobehavioral outcomes, investigators found that the child's home environment assessed at age 3 years did not modify the effects of prenatal chlorpyrifos exposure on working memory age at 7 years (Horton et al., 2012).

Information regarding the potential mechanisms of action of exposure to chemical and non-chemical stressors on human health outcomes, including neurodevelopment, remains limited. In particular, data gaps exist regarding whether environmental and psychosocial stressors may share common biological pathways, the impact of the specific timing of these exposures during pregnancy, childhood, and adolescence, and how exposure to multiple stressors may modify dose-response relationships (Lewis et al., 2011; Gee and Payne-Sturges, 2004). Exposure to chemical and non-chemical stressors are likely to co-occur in the same communities (Horton et al., 2012; Tamayo et al., 2017), exacerbating the impacts of racial and socioeconomic disparities (Gee and Payne-Sturges, 2004). Additional epidemiologic studies are needed examining how psychosocial stress and non-chemical stressors may increase susceptibility to environmental chemicals, including causal mechanisms (Clougherty et al., 2014; Ayer and Hudziak, 2009). It is also imperative to implement revised cumulative risk assessment frameworks

incorporating non-chemical stressors to develop effective regulatory actions and community interventions (Lewis et al., 2011; Rider et al., 2012) and address growing environmental justice disparities.

In this analysis, we observed that malathion use was associated with increased report of internalizing problems from both mothers and youth among participants experiencing high ACEs, and that effects were stronger among males. Previous studies have identified associations of occupational OP pesticide use and depression or depressive symptoms among farmworkers (Beseler et al., 2006; Beseler and Stallones, 2008; Beseler Cheryl et al., 2008; Wesseling et al., 2010; Beard et al., 2014; Saeedi Saravi et al., 2016; Malekirad et al., 2013; Meyer et al., 2010); fewer studies have examined the role of OP pesticide exposure and internalizing behaviors such as depression or anxiety among children or adolescents. In a previous longitudinal study of 141 children from the Mount Sinai Children's Environmental Health Center study, investigators reported that prenatal concentrations of dimethyl (DM) OPs, which include OPs such as malathion and dimethoate, were associated with parent-report of BASC internalizing problems at ages 4–9 years (Furlong et al., 2014). Additionally, a cross-sectional analysis of 529 adolescents ages 11–17 years living in a floricultural community in Ecuador found that lower acetylcholinesterase (AChE) activity, reflecting greater exposure to the cholinesterase-inhibiting pesticides OPs and carbamates, was associated with higher depression symptoms, particularly among girls (Suarez-Lopez et al., 2019). Notably, we observed that associations were much stronger among boys; however, credible intervals from sex-stratified analyses were quite wide given the smaller sample size. Surprisingly, we only observed associations with the pesticide malathion, which is one of the least toxic OP pesticides based on levels of AChE inhibition (United States Environment, 2006).

In addition to interactions of malathion and ACEs with maternal- and youth-reported internalizing problems, we observed that malathion and dimethoate were associated with increased youth-reported hyperactivity and attention problems, respectively, among participants with high ACEs; we did not observe interactions of any pesticides and ACEs for maternal-reported hyperactivity or attention problems. Notably, while adolescents tend to be more reliable reports or their own internalizing behaviors, mothers may be more reliable reporters of behaviors such as hyperactivity and inattention that can be more easily observed by others (Salbach-Andrae et al., 2009; Smith et al., 2000). One previous study found that prenatal biomarkers of exposure to chlorpyrifos, another OP pesticide, were associated with increased maternal report of hyperactivity and inattention at age 3 years among 354 inner-city children (Rauh et al., 2006). In previous analyses in our cohort, we also found that higher prenatal concentrations of DAPs, non-specific biomarkers of OP pesticide exposure, were associated adversely associated with attention ascertained via maternal report, psychometrician observation, and direct assessment at age 5 years, with stronger effects among boys (Marks et al., 2010). These results were largely driven by DMs (Marks et al., 2010).

Consistent with our findings from previous analyses examining associations of pesticide use near the home during pregnancy with adolescent emotional and behavioral problems (Hyland et al., 2021) (without interactions by ACEs), we observed that imidacloprid applications were associated with fewer maternal-reported attention problems among participants with high ACEs, particularly among girls. Notably, neonicotinoid insecticides are commonly applied as seed treatments (Jeschke et al., 2011; Tomizawa and Casida, 2005), as opposed to more dispersive application methods used for many pesticides (Weppner et al., 2006), which could result in less aerial drift to nearby homes. It is well documented that residential proximity to pesticide-treated fields is associated with increased concentrations of OP



pesticides in both environmental and urine samples (Lu et al., 2000; Ward et al., 2006; Curl et al., 2002; Coronado et al., 2011), and previous studies have shown high correlations between PUR data and OP concentrations in homes in this study region (Harnly et al., 2005, 2009). However, data gaps exist regarding how well PUR data may approximate exposure to pesticides such as neonicotinoids. While relying on PUR data alone does not capture all sources and routes of exposure to any of the pesticides included in this analysis, agricultural pesticide use data may be less reliable to characterize exposure to neonicotinoids due to their modes of application and physio-chemical properties (Wood and Goulson, 2017; Simon-Delso et al., 2015; Thompson et al., 2020; Lu et al., 2018), including low volatility (Bonmatin et al., 2015; Borsuah et al., 2020), which may affect their transport to nearby homes. Neonicotinoids are the most widely used class of insecticides worldwide (Simon-Delso et al., 2015; Zhang et al., 2019) and additional epidemiologic studies, potentially including more integrative exposure assessment approaches, are needed to better understand their potential impacts of neurodevelopment.

Findings from this study should be interpreted in light of some limitations. First, we did not collect data regarding all specific ACEs participants experienced or the age at which each event occurred, but rather asked participants to retrospectively report the number of ACEs prior to the 18-year study visit. Previous studies suggest that adverse events experienced earlier in childhood (e.g., ages 0–5 years (National Research Council, 2000)) may have stronger effects on behavioral outcomes than events occurring later in childhood or adolescence. Moreover, it is possible that the retrospective assessment of ACEs at age 18 could have resulted in measurement error, particularly for events occurring earlier in childhood. Additionally, we cannot say with certainty that the ACEs reported at age 18 occurred prior to the 16-year behavioral outcomes. However, results from sensitivity analyses in which we included only 18-year outcome data were similar to results from main analyses. Second, as discussed in previous analyses (Marks et al., 2010), use of nearby agricultural pesticide use to characterize potential pesticide exposure may result in exposure misclassification. Although several studies show significant relationships between nearby use of some agricultural pesticides and residential contamination (Harnly et al., 2009; Gunier et al., 2011), the physical-chemical properties of individual pesticides, wind speed and direction during applications, precipitation, and other factors will affect the likelihood of actual human exposure (Cryer and van Wesenbeeck, 2011; Cryer, 2005; van Wesenbeeck et al., 2011). Future studies should consider interactions of exposures to pesticides and adversity using more accurate methods of exposure assessment, such as repeated biomarker measurements. Third, we did not examine interactions with pesticide use near the home during early childhood, which we may consider in future analyses. Finally, we only considered pesticide use within 1 km of the home, and future investigations should consider additional buffer distances.

This study also has notable strengths and builds upon the literature in a number of ways. Previously, we examined associations between applications of mixtures of agricultural pesticides near the home during pregnancy and maternal- and youth-reported internalizing and externalizing behavior during adolescence; here we extend these analyses by considering interactions with childhood adversity. CHAMACOS is a large, well-characterized cohort with rich collection of exposure, covariate, and outcome data assessed longitudinally. We collected behavioral measures from two reporters (i.e., mothers and youth) and adversity measures from youth using validated scales. While some

previous studies have evaluated interactions of chemical and non-chemical stressors using frequentist methods, we are the first to examine potential exposure to mixtures of pesticides (assessed via agricultural pesticide use near the home) and social adversity. We employed BHM in order to estimate associations for specific pesticides while mutually adjusting for all other pesticide exposure variables in the same model. By facilitating a “borrowing” of information across similar exposures, BHM results in estimates with lower mean squared error and interval estimate coverage closer to the nominal level, even in the presence of highly correlated exposures (Greenland, 1994; MacLehose et al., 2007; Greenland and Poole, 1994), and also reduced the potential for extreme exposure-outcome associations, addressing concerns regarding multiple comparisons (Braun et al., 2014; Greenland, 1992, 1994, 2007). While we presented a large number of associations, we attempted to focus results on trends observed for particular pesticides and consistencies in associations observed across maternal- and youth-report. Finally, this study is the first to examine interactions of environmental neurotoxicants and adversity on behavioral outcomes measured longitudinally into adolescence and young adulthood.

## 5. Conclusion

We observed little evidence of interactions between applications of agricultural pesticides near the home during the prenatal period and childhood adversity, assessed via ACEs, with maternal- or youth-reported behavioral and emotional outcomes among CHAMACOS participants at ages 16 and 18 years. There is increasing consensus regarding the need to examine the joint neurodevelopmental impact of environmental toxicants and social factors, as these exposures are likely to co-occur (Horton et al., 2012; Tamayo et al., 2017), and failure to account for potential effect modification may underestimate the impact of environmental neurotoxicants (Bellinger, 2008). Future studies should consider examining interactions of chemical and non-chemical stressors using biomarker-based exposure assessment methods.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Asa 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 also a member of the USDA National Organic Standards Board. The other authors declare they have no actual or potential competing financial interests.

## Acknowledgements

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## Appendix A

1. Many children experience stressful life events while they are growing up, during their first 18 years of life. Please read the **seven** statements below. Count the number of statements that apply to you.

While you were growing up, during your first 18 years of life:

- A parent or other adult in the household **often** swore at you, insulted you, put you down, humiliated you, or acted in a way that made you afraid that you might be physically hurt.
- A parent or other adult in the household **often** pushed, grabbed, slapped, or threw something at you or **ever** hit you so hard that you had marks or were injured.
- An adult or person at least 5 years older than you **ever** touched or fondled you, had you touch their body in a sexual way, or attempted or actually had oral, anal, or vaginal intercourse with you.
- Your parents were **ever** separated or divorced.
- You lived with someone who was a problem drinker or alcoholic or who used street drugs.
- A household member was depressed, mentally ill, or attempted suicide.
- A household member went to prison.

How many of these statements apply to you?

- 0
- 1
- 2
- 3
- 4
- 5 or more

While you were growing up, during your first 18 years of life:

2 A. Did you **often** feel that no one in your family loved you or thought you were important or special?

- No
- Yes [SKIP TO 3 A]

2 B. Did you **often** feel that your family didn't look out for each other, feel close to each other, or support each other?

- No
- Yes

3 A. Did you **often** feel that you didn't have enough to eat, had to wear dirty clothes, and had no one to protect you?

- No
- Yes [SKIP TO 4 A]

3 B. Did you **often** feel that your parents were too drunk or high to take care of you or take you to the doctor if you needed it?

- No
- Yes

4 A. Was your mother or stepmother **often** pushed, grabbed, slapped, or had something thrown at her?

- No
- Yes [SKIP TO END]

4 B. Was your mother or stepmother **sometimes or often** kicked, bitten, hit with a fist, or hit with something hard?

- No
- Yes [SKIP TO END]

4C. Was your mother or stepmother **ever** repeatedly hit at least a few minutes or threatened with a gun or knife?

- No
- Yes

END.

**Appendix B. Supplementary data**Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2021.111908>.**References**

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