Title
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Residential Proximity to Agricultural Pesticide Use and Risk-Taking Behaviors in Young Adults from the CHAMACOS Study

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Abstract

Background: Prenatal pesticide exposure has been associated with poorer neurodevelopment during childhood, which could lead to greater risk-taking behaviors and delinquency in adolescence. This association may be augmented by adversity exposure.

Objectives: Evaluate the relationship between prenatal pesticide exposure and risk-taking behavior in young adults at 18-years of age. Assess whether adversity exposure modifies these associations.

Methods: Participants included mother-child dyads (n=467) enrolled in the Center for the Health Assessment of Mothers and Children Of Salinas (CHAMACOS) study, a longitudinal birth cohort set in the agricultural Salinas Valley of California. We estimated agricultural pesticide use within one km of maternal residences during pregnancy using a geographic information system, residential addresses, and California's Pesticide Use Reporting data. We used Bayesian hierarchical regression to evaluate associations of prenatal exposure to a mixture of 11 neurotoxic pesticides with self-reported police encounters, risk-taking behaviors, and unique types and frequency of delinquent acts. We also evaluated effect modification of these relationships by adversity exposure.

Results: We observed generally null associations of neurotoxic pesticide use with risk-taking behaviors. Prenatal residential proximity to chlorpyrifos use was associated with higher risk of a police encounter, a delinquent act, and higher incidence of both unique types of acts committed and total frequency of delinquent acts. Prenatal residential proximity to dimethoate use was associated with a higher incidence of police encounters and methomyl with a higher risk of committing a delinquent act. There were no consistent differences when stratified by the number of adverse childhood experiences.

Conclusions: We observed mostly null associations between prenatal residential proximity to agricultural pesticide use and risk-taking behaviors at age 18, with little evidence of effect modification by childhood adversity. There were suggestive associations for chlorpyrifos use with having any police encounter and with all measures of delinquent acts that warrant confirmation in other studies.

Keywords: pesticides, behavior, young adults, childhood adversity, Geographic information system (GIS) models, risk-taking, delinquency

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Human subjects

All research was approved by the University of California, Berkeley, Committee for the Protection of Human Subjects prior to commencement of the study. Written informed consent was obtained from all mothers and young adults at age 18.

Abbreviations

ACEs = Adverse Childhood Experiences

BHM = Bayesian Hierarchical Models

CHAMACOS = Center for the Health Assessment of Mothers and Children Of Salinas

CI = Confidence Interval

CrI = Credible Interval

DAP = Dialkylphosphate

HOME-SF = Home Observation for Measurement of the Environment-Short Form

IRR = Incidence Rate Ratio

IQ = Intelligence Quotient

OP = Organophosphate

PUR = Pesticide Use Report

RR = Relative Risk

1. Introduction

We have previously observed associations of prenatal concentrations of dialkylphosphates (DAPs), metabolites of organophosphate (OP) pesticides, and adverse neurodevelopment in participants of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, a prospective cohort of pregnant mothers and their children (Bouchard et al., 2011; Eskenazi et al., 2007; Marks et al., 2010). Although biomarkers such as DAP metabolites are an important tool to assess exposures to pesticides, several challenges limit their utility in epidemiologic analyses including a short half-life in the body (Bradman et al., 2013) and the lack of specific biomarkers available for many pesticides. In California, the uniquely comprehensive Pesticide Use Reporting (PUR) database provides information on all agricultural pesticide applications since 1990. Agricultural use involves a complex mixture of pesticides from different classes. Previous studies have demonstrated that PUR data correlate with pesticide levels in house dust (Gunier et al., 2011; Harnly et al., 2009) and community air samples (Harnly et al., 2005). Epidemiologic studies have also observed that higher nearby agricultural pesticide use is associated with adverse health outcomes, including Parkinson's disease (Costello et al., 2009; Wang et al., 2014), autism (Roberts et al., 2007; Shelton et al., 2014) and birth defects (Carmichael et al., 2014; Rull et al., 2006; Yang et al., 2014). In CHAMACOS, we reported that prenatal exposure to neurotoxic pesticides due to residential proximity to agricultural fields was associated with intelligence quotient (IQ) in children at 7-years of age using PUR data (Coker et al., 2017; Gunier et al., 2017).

Previous studies have observed relationships of lower IQ with higher delinquency (Lynam et al., 1993) and antisocial or criminal behaviors (Kandel et al., 1988). Maternal cigarette smoking during pregnancy (Lotfipour et al., 2014), exposure to airborne metals and particulate matter (Haynes et al., 2011), and exposure to lead (Dietrich et al., 2001; Mielke & Zahran, 2012; Nevin, 2000; Wright et al., 2008) have also been associated with risk-taking and delinquent behaviors in adolescence and early adulthood, but few studies have evaluated the relationship with pesticide exposure. In CHAMACOS, we have observed mostly null associations of prenatal urinary DAP concentrations with delinquency at 16-years of age (Vernet et al., 2021), and risk-taking or delinquent behaviors at 18-years of age (Sagiv et al., 2022).

Evidence is emerging that early life adversity and environmental exposures often occur together, and that adversity modifies the effects of exposure to pollutants on neurodevelopment (Appleton et al., 2016). For example, a significant interaction was observed between prenatal exposure to environmental tobacco smoke and living in a poorer home learning environment on externalizing problems, with children having both exposures displaying more adverse behaviors (Hopson et al., 2016). Studies have also found that maternal stress potentiates the effects of both prenatal lead exposure on infant cognition (Tamayo Y Ortiz et al., 2017), and prenatal black carbon exposure on attention in boys (Cowell et al., 2015). In CHAMACOS, we observed stronger relationships between maternal prenatal urinary DAP concentrations and IQ at 7-years among children experiencing greater early childhood adversity (Stein et al., 2016).

To our knowledge, there are no previous studies evaluating prenatal residential proximity to agricultural pesticides and behavioral outcomes in adulthood like risk-taking behaviors and delinquent acts. Most epidemiologic studies have focused on individual pesticides or pesticide classes and this can lead to biased effect estimates due to confounding by other pesticides (Hamra & Buckley, 2018). In this study, we evaluate the relationship of prenatal residential proximity to agricultural use of a mixture of neurotoxic pesticides with risk-taking behaviors at 18-years of age using hierarchical regression models that incorporate multiple levels of information into a single analysis, providing a solution to multiple comparisons resulting from single pollutant models and effect estimates that are more accurate and plausible than conventional models (Witte et al., 2000). We also evaluate effect modification by childhood adversity.

2. Methods

2.1. Study population

We enrolled 601 pregnant women in the CHAMACOS study between October 1999 and October 2000. Women were eligible to participate if they were $\geq$ 18 years of age, <20 weeks pregnant, eligible for California's low-income health care program (MediCal), spoke English or Spanish, and were planning to deliver at the county hospital. We followed the women through the delivery of 537 live born children (referred to as CHAM1). We recruited and enrolled an additional 305 9-year old children and their mothers between 2009 and 2011 when CHAM1 children were 9 to 10-years old. New "CHAM2" children were eligible to participate if they met similar criteria as CHAM1. CHAM1 families completed multiple study visits on an approximately annual basis between pregnancy and child age 18. CHAM2 families completed the same study visits as CHAM1 families between child ages 9 and 18 years.

In the current study, we include young adults who completed the 18-year questionnaire on risk-taking behaviors (n=477), had prenatal residential history available for two or more trimesters of pregnancy (n=470), had all covariates (n=469) and who completed a questionnaire on childhood adversity at the 18-year assessment (n=467). Written informed consent was obtained from all mothers and young adults at age 18; all research was approved by the

University of California, Berkeley, Committee for the Protection of Human Subjects prior to commencement of the study.

2.2. Risk-taking behavior outcomes

At 18-years, young adult participants independently completed a computer-based questionnaire which includes general misbehavior and delinquency questions adapted from the Self-Reported Behavior and Self-Reported Delinquency (Elliott & Huizinga, 1983; Hinshaw et al., 2006; Van Hulle et al., 2007). Participants were presented with 49 acts ranging from mild delinquency (e.g., lying about age to see a movie) to felony offences (e.g. arson) and asked if they had ever committed each act. For each act endorsed, they were asked about the number of times they had completed the act in their entire lifetime. We created a binary variable for any delinquent act (yes to any act versus not to all acts), and created count variables representing the frequency of all acts endorsed and the number of different types of acts endorsed. To illustrate, a participant who reported shoplifting three times and running away from home one time would have a frequency count of four and a unique acts count of two. We asked the young adult if they had ever been arrested, picked up, stopped, or questioned by the police and the number of times this had occurred. We created a binary variable for any police encounter and a count variable that summed the total number of lifetime police encounters. Finally, we created a total risk-taking behavior count variable that summed any endorsement of the following at age 18: 1) any binge drinking in the last 30 days (4+ drinks for females, 5+ drinks for males), 2) ever used prescription drugs without a doctor's prescription or differently than instructed by a doctor, 3) ever used hard drugs (e.g. cocaine, heroin, methamphetamine, ecstasy, hallucinogens), 4) ever smoked and/or vaped nicotine, 5) any marijuana use in the last 30 days, 6) ever had sex before they turned 16-years old, 7) doesn't always use a condom during sex, 8) doesn't always use a seatbelt when riding or driving in a car, and 9) any police encounter.

2.3. Geographic-based estimates of agricultural pesticide use

We used California's PUR database to estimate potential exposure to agricultural pesticides near each CHAMACOS mother's residence during pregnancy from 1999-2001, as has been described previously (Gunier et al. 2017). The PUR data include the amount of active ingredient applied in kilograms, application date, and location to a one-square mile section defined by the Public Land Survey System. We selected 11 pesticides for analysis based on the following criteria: evidence of neurotoxicity in humans or animals, more than 4,500 kg applied in Monterey County from 1999-2001, and used within 1 km of the home for at least 50% of CHAMACOS participants (Hyland et al., 2021). For pregnancy addresses, we used the latitude and longitude coordinates from geocoded residential addresses, which were recorded prospectively at study visits for CHAM1 participants, retrospectively at the 9-year visit for CHAM2 participants, and confirmed retrospectively for all at the 16-year visit. We estimated pesticide use during pregnancy for participants with residential location available for greater than or equal to 75% of the prenatal period. For each residence, we estimated the total amount of each pesticide applied within a 1 km radius buffer because this distance has been shown to optimize the correlation between agricultural pesticide applications and concentrations measured in nearby house dust samples (Gunier et al., 2011; Harnly et al., 2009). The equations and methods that we used to calculate nearby pesticide use have been published previously in more detail (Gunier et al., 2017). We also obtained data on wind direction to account for potential downwind transport of pesticides from the application site. The closest meteorological stations were located in Arroyo Seco, Castroville, King City, Salinas North, Salinas South, and Pajaro (California

Irrigation Management Information System (CIMIS), 2022). We used the daily proportion of time the wind blew from eight directions to calculate wind frequency. We employed a GIS to determine the direction of each Public Land Survey Section centroid in relation to the residences and weighted pesticide use (kg) in a section by the proportion of time that the wind blew from each direction.

2.4. Assessment of childhood adversity

At age 18, as part of their confidential self-completed questionnaire, young adult participants completed an adapted version of the Adverse Childhood Experiences (ACEs) survey (CDC, 2021), about adverse experiences in the first 18 years of life. In the first part of our adapted survey, we asked participants whether they had experienced 0, 1, 2, 3, 4 or 5+ of these events listed seven events, so that we could not disaggregate reportable events (e.g. abuse) from non-reportable events. Events included, for example, parent separation, household member with a mental health disorder, household member incarceration, and questions about emotional, physical, and sexual abuse. In the second part of our adapted survey, participants answered specific multi-part questions about three additional ACEs (emotional neglect, physical neglect, witnessing domestic violence). We summed the number of events reported from the two parts and created a binary variable for low (0 – 2 events) and high (3+ events) ACEs based on the distribution in our population and categories used in previous analyses (Iob et al., 2020). Our adapted ACEs survey is included as Appendix A.

2.5. Covariate data

Bilingual interviewers conducted maternal interviews in Spanish or English twice during pregnancy (~13 and 26 weeks gestation), after delivery, and when the children were 6 months, and 1, 2, 3.5, 5, 7, 9, 10.5, 12, 14, 16, and 18 years of age. Interviewers collected demographic information including maternal age, education, country of birth, number of years lived in the United States, marital status, and family income. At the 10.5-year visit, we asked mothers questions form the HOME-SF (Home Observation for Measurement of the Environment-Short Form) scale to assess enrichment in the home environment (e.g. access to books, extracurricular activities, family meals) (Caldwell & Bradley, 1984; U.S. Bureau of Labor Statistics, 2002).

2.6. Statistical analysis

We compared demographic covariates for participants who were included in our analyses to those who were not included in our analyses using chi-squared tests for categorical variables and t-tests for continuous variables. We log2-transformed all pesticide use estimates (after adding 1 to eliminate 0 values) to reduce the influence of outliers and to improve the linear fit of the models. We selected the following covariates for inclusion in all models based on a directed acyclic graph: maternal country of birth (Mexico, U.S./Other), maternal age at delivery (continuous in years); maternal years in U.S. (≤ 5 years, > 5 years, born in the US), maternal education (≤ 6^{th} grade, 7^{th} grade or more); marital status at 18y visit (married/living as married, not married); family income at the 18 year visit (< federal poverty level, ≥ federal poverty level); HOME-SF z-score at the 10.5 year visit (continuous); and youth sex and age (continuous) at the 18 year visit.

We used semi-Bayesian Hierarchical regression models (BHM), fit by two-stage least squares, to calculate more stable parameter estimates while dealing with issues of collinearity and multiple comparisons (Witte et al., 1998, 2000). We used Poisson regression (Zou, 2004) for binary outcomes (any police encounter, any delinquent act) to estimate relative risk (RR) and negative binomial models for count outcomes (number of police encounters, number of different delinquent acts, frequency of delinquent acts, count of risk-taking behaviors) to estimate incidence rate ratios (IRR). We ran one model that included all 11 pesticides for each outcome. Our results reflect the RR or IRR for the outcome with a two-fold increase in use of each pesticide, adjusted for the other ten pesticides. In the first stage, we regressed each risk-taking outcome on the pesticide exposures and covariates in a single model. In the second stage, we specified a model for the set of exposure coefficients from the first stage (β) with a linear weighted-least squares regression model that is a function of the exposure coefficient vector and residual error (Witte et al., 2000). We prespecified the variance based on results from the generalized linear models described below and prior experience with these exposures. We selected a variance (τ=0.21) that assumed the RR and IRR would lie within 0.67 to 1.5. We present RR and IRR and 95% credible intervals (CrI) from the first stage model. We evaluated these associations among all participants and in sub-group analyses stratified by high (3+ adverse events) vs. low (<3 adverse events) ACEs to assess effect modification by childhood adversity. We conducted the BHM analyses using R version 3.6.1.

2.7. Sensitivity analysis

For sensitivity analyses, we used generalized linear models with robust standard errors for our outcomes. We used Poisson regression (binary outcomes) to the RR and 95% confidence intervals (CI), and negative binomial models (count outcomes) to estimate the IRR and 95% CI. As with the BHM models, our results reflect the RR or IRR for the outcome with a two-fold increase in use of each pesticide, adjusted for the other ten pesticides, and we stratified by high and low ACEs to assess effect modification by childhood adversity. We conducted the sensitivity analyses using Stata Version 15.1.

3. Results

3.1. Demographics, outcomes, and exposures

Demographic characteristics of CHAMACOS participants included in our analyses (n=467) are provided in Table 1. Most mothers of the young adult participants were born in Mexico (87.4%), were 30-years old or younger at delivery (73.3%), and were married or living as married at the time of enrollment (81.4%). Slightly less than half of the mothers had a 6th grade education or less (42.6%) and had been in the U.S. 5 years or less at the time of delivery (47.6%), and more than half of the households were living below the poverty level at the 18-year visit (57.0%). High ACEs (3+ events) were reported by 27.8% of the youth. Mothers of young adults included in our analyses were more likely ($p<0.05$) to be older at delivery and to have lived in the U.S. longer than the mothers of youth that were not included in these analyses; otherwise the two populations were similar demographically.

At the 18-year visit, 24.2% of the youth reported any police encounter, 66.8% endorsed at least one risk-taking behavior and 68.1% had committed at least one delinquent act (Table 2). The median (IQR) reported values were 1 (0 – 2) for risk-taking behavior count, 2 (0 – 6) for the number of unique types of delinquent acts and 6 (0 – 31) for the frequency of delinquent acts. The percentage of participants with any applications of the 11 pesticides within 1 km of their residences during the prenatal period ranged from 49.9% for glyphosate to 96.8% for diazinon (Table 2). Imidacloprid had the lowest mean wind-adjusted use 0.7 kg and maneb had the highest mean use at 15.3 kg. For all pesticides examined, the distribution of use within 1 km of the residences was right-skewed and spanned several orders of magnitude. Pesticide applications during the prenatal period were positively and significantly correlated with each other. Spearman correlation coefficients ranged from weakly correlated ($r_s=0.21$) for glyphosate and malathion, to strongly correlated ($r_s=0.90$) for acephate and oxydemeton-methyl (Supplemental Table 1).

3.2. Associations between proximity to pesticide use and risk-taking behaviors

We didn't observe any notable patterns of associations between pesticide use near the home during pregnancy and our delinquency and risk-taking outcomes. However, we did observe some suggestive associations. In BHM models, we found that each two-fold increase in chlorpyrifos (RR=1.17, 95% Credible Interval (CrI): 0.98, 1.40) was associated with an increased risk of at least one police encounter and for dimethoate (IRR=1.36, 95% CrI: 1.00, 1.85) an increased number of police encounters (Table 3). We also observed associations for two-fold increase in chlorpyrifos use with an increased risk of at least one delinquent act (RR=1.14, 95% CrI: 1.04, 1.24), with an increased number of types of delinquent acts (IRR=1.23, 95% CrI: 1.07, 1.40) (Table 4) and frequency of delinquent acts (IRR=1.25, 95% CrI: 1.04, 1.49) (Table 5). In addition, a two-fold increase in methomyl use was associated with a higher risk (RR=1.16, 95% CrI: 1.07, 1.25) for at least one delinquent act (Table 4). For oxydemeton-methyl and maneb, we observed associations in the opposite direction, with a reduced risk for at least one delinquent act (RR=0.84, 95% CrI: 0.71, 0.99) with higher oxydemeton-methyl for any delinquent act (Table 4) and at least one police encounter (RR=0.84, 95% CrI: 0.68, 1.02), respectively (Tables 3 and 4).

3.3. Effect modification by childhood adversity

In BHM models stratified by high and low ACEs, we observed that dimethoate use was only associated among those with high ACEs with a higher rate of police encounters (IRR=1.63, 95% CrI: 1.14, 2.32), and higher rates of unique types of delinquent acts (IRR=1.27, 95% CrI: 1.00, 1.61) and frequency of delinquent acts (IRR=1.38, 95% CrI: 1.03, 1.85) (Tables 3-5). Among those with high ACEs, malathion use was associated with higher rates of unique types of delinquent acts (IRR=1.16, 95% CrI: 1.03, 1.31) and frequency of delinquent acts (IRR=1.30, 95% CrI: 1.11, 1.51). Conversely, we observed elevated IRR with chlorpyrifos and glyphosate use only among those with low ACEs for both the number of unique types of delinquent acts (IRR=1.26, 95% CrI: 1.08, 1.49) and (IRR=1.19, 95% CrI: 1.06, 1.34) respectively, and the frequency of delinquent acts (IRR=1.33, 95% CrI: 1.09, 1.62) and (IRR=1.29, 95% CrI: 1.12, 1.49) respectively. Methomyl use was also related to an elevated risk of reporting at least one delinquent act only among those with low ACEs (RR=1.21, 95% CrI: 1.09, 1.39).

3.4. Sensitivity analyses

Results from GLM with all participants, and among those with low and high ACEs, were generally similar in direction and magnitude to the BHM estimates with slightly wider confidence intervals (Supplemental Tables 2-4). Exceptions were dimethoate, where the rate of police encounters was much higher (IRR=2.07; 95% CrI: 1.25, 3.43), and methomyl use where the rates were much higher for both the unique types and frequency of delinquent acts.

4. Discussion

We generally observed null associations between prenatal residential proximity to potentially neurotoxic pesticides we assessed and risk-taking behaviors or delinquency at 18-years of age. The only consistent association was with prenatal proximity to chlorpyrifos use, which was related to an increased risk of at least one police encounter, endorsing at least one delinquent act, number of unique types of delinquent acts, and frequency of committing delinquent acts. We did not find consistently stronger associations between potential pesticide exposure and risk-taking behaviors among young adults who reported more adverse childhood experiences. To our knowledge, this is the first study to evaluate prenatal residential proximity to pesticide use, childhood adversity, and high risk-taking behaviors or delinquency outcomes in young adulthood.

In previous studies in the CHAMACOS cohort, we found that residential proximity during the prenatal period to higher use of these same potentially neurotoxic pesticides was associated with lower Full-Scale and Verbal IQ scores at age 7 in CHAMACOS children (Coker et al., 2017; Gunier et al., 2017). We also observed associations between prenatal urinary concentrations of DAPs with child mental development and pervasive developmental problems at 24 months of age (Eskenazi et al., 2007), attention at 3.5 and 5 years of age (Marks et al., 2010), IQ at age 7 (Bouchard et al., 2011), traits related to autism spectrum disorder from 7-14 years of age (Sagiv et al., 2018), attention-deficit/hyperactivity disorder and executive function from ages 7-12 years (Sagiv et al., 2021). However, these associations were generally stronger with urinary metabolites of dimethyl dialkylphosphates, rather than diethyl dialkylphosphate, the metabolite for chlorpyrifos. We did not find consistent evidence for associations between prenatal urinary DAP concentrations and delinquency at 16-years of age (Vernet et al., 2021) or similar risk-taking behaviors at 18-years of age in CHAMACOS (Sagiv et al., 2022).

Although we generally did not find effect modification of the exposure-outcome relationships by childhood adversity, adversity can be assessed using different methods other than ACEs. In CHAMACOS, we observed stronger associations between prenatal urinary DAPs and child IQ at 7-years of age among children with more early life adversity, adversity was measured differently in that analysis, in a way that cannot be replicated for CHAM2 children who were enrolled at age 9 (Stein et al., 2016). We also observed associations between prenatal residential proximity to OP and carbamate pesticides and both household- and neighborhood-level poverty, however, the interaction terms for pesticide exposure and poverty level were not significant (Rowe et al., 2016). We did not find evidence on effect modification by ACEs (measured the same as in this analysis) on the limited associations we observed between prenatal urinary DAPs and risk-taking behaviors at age 18 (Sagiv et al., 2022). We observed mostly null associations of residential proximity to use of neurotoxic pesticides with behavioral or emotional problems assessed at 16 and 18-years of age (Hyland et al., 2021), and there was little evidence of modification of these exposure-outcome associations by ACEs (Hyland et al., 2022).

To our knowledge, CHAMACOS is the only study to have evaluated the relationship between pesticide exposure and risk-taking or delinquent behaviors. However, other environmental exposures have been associated with these outcomes including maternal cigarette smoking during pregnancy (Lotfipour et al., 2014), exposure to airborne metals and particulate matter (Haynes et al., 2011), and exposure to lead (Dietrich et al., 2001; Mielke & Zahran, 2012; Nevin, 2000; Wright et al., 2008). Previous studies have also observed effect modification of delinquency and risk-taking behaviors with greater childhood adversity. For example, significant interactions have been observed between prenatal exposure to environmental tobacco smoke and living in a poorer home learning environment (Hopson et al., 2016), prenatal exposure to lead and maternal stress during pregnancy (Tamayo Y Ortiz et al., 2017), and prenatal exposure to black carbon with maternal stress during pregnancy (Cowell et al., 2015). We selected ACEs as a measure of childhood adversity *a priori*, however future studies should consider other measures of childhood adversity.

Our study had some limitations. We used residential proximity to agricultural pesticide use as a proxy for pesticide exposure, although previous studies have shown that PUR data and environmental pesticide concentrations are correlated (Gunier et al., 2011; Harnly et al., 2005, 2009), suggesting PUR data provides a meaningful indicator of pesticide exposure. Nonetheless, it is not a complete indicator of pesticide exposure. We did not assess pesticide exposure from other sources including home use, diet, and occupational exposures from mother’s own farm work during pregnancy or her co-residence with other farmworkers. In addition, we only assessed proximity to agricultural pesticide use at the maternal residence, not other locations where the mother spent time. Further limitations are that the risk-taking and delinquency outcomes were self-reported, and we assessed adverse childhood experiences retrospectively at the 18-year visit. In general, these limitations would likely bias our results towards the null. Our power was somewhat limited to detect interactions in the analyses that we stratified by high and low adverse childhood experiences.

The main strengths of this study are the use of PUR data, which provides the amount of active ingredients and location for all agricultural pesticide applications, and the use of BHM to evaluate pesticide mixtures. PUR data allowed us to examine multiple pesticides in an efficient, unbiased manner, including pesticides that do not have biomarkers. The use of BHM enabled us to assess pesticide mixtures in single models accounting for correlation between these exposures while providing effect estimates that are more accurate and plausible than conventional models. We also had extensive follow up over 18 years including information on potential confounders from the prospective CHAMACOS cohort study.

5. Conclusion

We observed mostly null associations between prenatal residential proximity to agricultural pesticide use and risk-taking behaviors at age 18, with the exception of proximity to chlorpyrifos use, which was associated with having at least one police encounter and all measures of delinquent acts. Further studies are needed to evaluate the long-term effects of prenatal exposure to chlorpyrifos. There was little evidence of interactions between prenatal residential proximity to pesticide use and childhood adversity assessed with ACEs on risk-taking and delinquent behaviors in young adulthood.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Robert Gunier has consulted for law firms in cases involving pesticide exposure and human health. The other authors declare they have no actual or potential competing financial interests.

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Table 1. Characteristics of CHAMACOS cohort participants (n=467).

Cohort Characteristic	n (%)
Maternal Country of Birth	
Mexico	408 (87.4)
United States and other	59 (12.6)
Maternal Age at Delivery	
18 - 24	196 (42.0)
25 - 29	16 (31.3)
30 - 34	78 (16.7)
35 - 45	47 (10.1)
Maternal Years in US	
<=5 years	227 (48.6)
>5 years, non-native	198 (42.4)
Born in the US	42 (9.0)
Maternal Education	
≤ 6th grade	199 (42.6)
7th grade or more	2678(57.4)
Marital Status at enrollment	
Married/Living as married	380 (81.4)
Not married	87 (18.6)
Family income at 18y	
< Poverty level	266 (57.0)
≥ Poverty level	201 (43.0)
Sex	
Female	245 (52.5)
Male	222 (47.5)
Adverse Childhood Experiences (ACES)	
Low (0 – 2 events)	337 (72.2)
High (3+ events)	130 (27.8)

Table 2. Distributions of 18-year risk taking outcomes and wind-adjusted pesticide use (kg) within 1 km of prenatal residences (n=467).

Outcomes	**Any n (%)**	**Mean (SD)**	**p25**	**p50**	**p75**	**Max**
Police encounters	113 (24.2)	0.8 (2.2)	0	0	0	15
Risk count	312 (66.8)	1.6 (1.7)	0	1	2	7
Delinquency – number of acts	318 (68.1)	4.5 (5.8)	0	2	6	35
Delinquency - frequency of acts	318 (68.1)	31.2 (71.5)	0	6	31	769
Pesticide						
Acephate	396 (84.8)	3.2 (6.8)	0.1	1.2	3.1	77.3
Chlorpyrifos	403 (86.3)	3.0 (5.6)	0.1	0.9	3.1	51.4
Diazinon	452 (96.8)	6.5 (11.7)	1.2	2.9	6.7	128.0
Dimethoate	428 (91.6)	1.6 (2.8)	0.1	0.5	1.9	31.3
Glyphosate	233 (49.9)	1.9 (4.1)	0	0	1.3	25.1
Imidacloprid	450 (96.4)	0.7 (0.9)	0.1	0.3	0.9	9.0
Malathion	314 (67.2)	2.1 (5.0)	0	0.2	1.7	44.5
Maneb	447 (95.7)	15.3 (22.4)	2.4	8.2	19.0	191.0
Methomyl	430 (92.1)	2.5 (4.1)	0.2	1.0	3.2	29.1
Oxydemeton-methyl	412 (88.2)	2.7 (5.0)	0.2	1.0	2.9	53.6
Permethrin	439 (94.0)	1.0 (1.8)	0.1	0.4	1.2	16.4

Table 3. Adjusted[a] associations of interaction for two-fold increase in wind-adjusted neurotoxic pesticide use (kg) within 1 km of residence during pregnancy and childhood ACEs with police encounters at age 18 years using Bayesian Hierarchical Modeling (n=467 all; 337 low ACES; 130 high ACES).

Pesticide	**Any Police Encounter**			**Number of Police Encounters**		
	All RR (95% CrI)	**Low ACEs RR (95% CrI)**	**High ACEs RR (95% CrI)**	**All IRR (95% CrI)**	**Low ACEs IRR (95% CrI)**	**High ACEs IRR (95% CrI)**
Acephate	1.10 (0.88, 1.37)	1.00 (0.78, 1.29)	1.15 (0.89, 1.50)	1.15 (0.89, 1.49)	1.07 (0.79, 1.43)	1.25 (0.94, 1.67)
Chlorpyrifos	1.17 (0.98, 1.40)	1.17 (0.95, 1.44)	1.09 (0.84, 1.40)	1.04 (0.83, 1.32)	1.18 (0.93, 1.50)	1.08 (0.84, 1.40)
Diazinon	1.01 (0.82, 1.25)	1.07 (0.84, 1.37)	1.00 (0.77, 1.30)	0.96 (0.75, 1.23)	1.10 (0.86, 1.41)	1.07 (0.77, 1.49)
Dimethoate	1.22 (0.93, 1.59)	1.19 (0.88, 1.61)	1.24 (0.90, 1.70)	1.36 (1.00, 1.85)*	1.21 (0.86, 1.70)	1.63 (1.14, 2.32)*
Glyphosate	0.99 (0.87, 1.14)	1.00 (0.85, 1.19)	0.99 (0.81, 1.19)	1.02 (0.85, 1.24)	1.04 (0.87, 1.25)	0.81 (0.60, 1.08)
Imidacloprid	0.99 (0.71, 1.39)	1.03 (0.71, 1.49)	0.92 (0.63, 1.35)	0.96 (0.65, 1.41)	0.95 (0.64, 1.43)	0.76 (0.47, 1.22)
Malathion	1.02 (0.88, 1.19)	1.03 (0.86, 1.24)	1.08 (0.89, 1.32)	1.12 (0.95, 1.33)	1.14 (0.94, 1.38)	1.24 (0.93, 1.64)
Maneb	0.84 (0.68, 1.02)	0.87 (0.68, 1.11)	0.82 (0.63, 1.07)	0.83 (0.63, 1.08)	0.73 (0.55, 0.95)*	0.74 (0.51, 1.07)
Methomyl	1.01 (0.83, 1.22)	0.99 (0.79, 1.26)	0.96 (0.75, 1.24)	0.98 (0.79, 1.21)	1.05 (0.84, 1.32)	0.70 (0.52, 0.94)*
Oxydemeton-methyl	0.96 (0.73, 1.27)	1.02 (0.75, 1.39)	1.02 (0.75, 1.39)	0.90 (0.66, 1.22)	0.98 (0.70, 1.36)	1.26 (0.89, 1.79)
Permethrin	0.96 (0.71, 1.29)	0.97 (0.69, 1.36)	0.93 (0.63, 1.36)	1.04 (0.75, 1.43)	0.95 (0.68, 1.33)	0.72 (0.47, 1.10)

[a] Models adjusted for youth sex, age at 18y visit, maternal age at delivery, maternal education, maternal years in the U.S., maternal marital status at 18y, household poverty category at 18y, and HOME z-score at 10.5y.

Abbreviations: ACEs=adverse childhood experiences; CrI=credible interval; IRR=incidence rate ratio; RR=relative risk.

* 95% CrI does not include the null hypotheses (1.0).

Table 4. Adjusted[a] associations of interaction for two-fold increase in wind-adjusted neurotoxic pesticide use (kg) within 1 km of residence during pregnancy and childhood ACEs with delinquent acts at age 18 years using Bayesian Hierarchical Modeling (n=467 all; 337 low ACES; 130 high ACES).

Pesticide	**Any Delinquent Act**			**Number of Unique Delinquent Acts**		
	All	**Low ACEs**	**High ACEs**	**All**	**Low ACEs**	**High ACEs**
	RR (95% CrI)	**RR (95% CrI)**	**RR (95% CrI)**	**IRR (95% CrI)**	**IRR (95% CrI)**	**IRR (95% CrI)**
Acephate	0.96 (0.86, 1.07)	0.94 (0.81, 1.09)	0.96 (0.85, 1.08)	1.02 (0.86, 1.21)	0.92 (0.74, 1.14)	1.14 (0.94, 1.38)
Chlorpyrifos	1.14 (1.04, 1.24)*	1.10 (0.98, 1.22)	1.11 (1.00, 1.22)*	1.23 (1.07, 1.40)*	1.26 (1.08, 1.49)*	1.09 (0.93, 1.27)
Diazinon	1.06 (0.95, 1.18)	1.09 (0.95, 1.24)	1.02 (0.91, 1.13)	1.03 (0.87, 1.21)	1.10 (0.89, 1.35)	0.88 (0.72, 1.09)
Dimethoate	0.96 (0.83, 1.11)	0.94 (0.78, 1.13)	1.04 (0.88, 1.22)	1.09 (0.87, 1.36)	1.06 (0.82, 1.36)	1.27 (1.00, 1.61)*
Glyphosate	1.00 (0.94, 1.06)	1.02 (0.95, 1.10)	0.96 (0.88, 1.04)	1.02 (0.92, 1.13)	1.19 (1.06, 1.34)*	0.81 (0.70, 0.93)*
Imidacloprid	0.98 (0.79, 1.20)	1.04 (0.81, 1.32)	0.85 (0.66, 1.11)	0.94 (0.71, 1.25)	0.96 (0.71, 1.31)	0.88 (0.63, 1.22)
Malathion	0.96 (0.90, 1.02)	0.92 (0.85, 1.00)	1.05 (0.98, 1.12)	1.01 (0.90, 1.13)	0.91 (0.80, 1.03)	1.16 (1.03, 1.31)*
Maneb	0.96 (0.87, 1.05)	0.93 (0.82, 1.05)	1.03 (0.93, 1.13)	0.88 (0.74, 1.03)	0.84 (0.68, 1.03)	1.04 (0.86, 1.25)
Methomyl	1.16 (1.07, 1.25)*	1.21 (1.09, 1.34)*	1.05 (0.93, 1.17)	1.05 (0.92, 1.20)	1.12 (0.96, 1.32)	0.92 (0.76, 1.11)
Oxydemeton-methyl	0.84 (0.71, 0.99)*	0.87 (0.70, 1.07)	0.90 (0.76, 1.06)	0.88 (0.68, 1.14)	0.93 (0.71, 1.21)	0.88 (0.68, 1.13)
Permethrin	0.98 (0.81, 1.18)	0.97 (0.78, 1.21)	0.98 (0.77, 1.25)	0.97 (0.75, 1.25)	0.94 (0.72, 1.23)	0.89 (0.64, 1.23)

[a] Models adjusted for youth sex, age at 18y visit, maternal age at delivery, maternal education, maternal years in the U.S., maternal marital status at 18y, household poverty category at 18y, and HOME z-score at 10.5y.

Abbreviations: ACEs=adverse childhood experiences; CrI=credible interval; IRR=incidence rate ratio; RR=relative risk.

* 95% CrI does not include the null hypotheses (1.0).

Table 5. Adjusted[a] associations of interaction for two-fold increase in wind-adjusted neurotoxic pesticide use (kg) within 1 km of residence during pregnancy and childhood ACEs with counts of risk taking behaviors and delinquent acts at age 18 years using Bayesian Hierarchical Modeling (n=467 all; 337 low ACES; 130 high ACES).

Pesticide	Risk Count			Frequency of Delinquent Acts		
	All IRR (95% CrI)	Low ACEs IRR (95% CrI)	High ACEs IRR (95% CrI)	All IRR (95% CrI)	Low ACEs IRR (95% CrI)	High ACEs IRR (95% CrI)
Acephate	1.03 (0.87, 1.22)	0.96 (0.79, 1.16)	1.12 (0.91, 1.38)	1.12 (0.91, 1.38)	1.01 (0.78, 1.30)	1.27 (1.00, 1.60)*
Chlorpyrifos	1.03 (0.91, 1.17)	1.04 (0.90, 1.20)	0.88 (0.74, 1.05)	1.25 (1.04, 1.49)	1.33 (1.09, 1.62)*	1.06 (0.86, 1.31)
Diazinon	0.94 (0.80, 1.11)	1.06 (0.89, 1.28)	0.83 (0.65, 1.05)	1.05 (0.86, 1.28)	1.21 (0.97, 1.51)	0.91 (0.70, 1.19)
Dimethoate	1.15 (0.93, 1.42)	1.09 (0.86, 1.39)	1.18 (0.92, 1.51)	1.15 (0.89, 1.50)	1.10 (0.83, 1.48)	1.38 (1.03, 1.85)*
Glyphosate	1.05 (0.96, 1.15)	1.09 (0.98, 1.20)	0.96 (0.83, 1.10)	1.06 (0.93, 1.21)	1.29 (1.12, 1.49)*	0.85 (0.69, 1.04)
Imidacloprid	0.89 (0.68, 1.16)	0.89 (0.66, 1.19)	0.96 (0.69, 1.33)	0.92 (0.67, 1.27)	0.76 (0.55, 1.05)	0.80 (0.55, 1.17)
Malathion	1.00 (0.90, 1.11)	1.00 (0.89, 1.12)	1.03 (0.90, 1.18)	1.05 (0.92, 1.20)	0.97 (0.83, 1.14)	1.30 (1.11, 1.51)*
Maneb	0.90 (0.76, 1.07)	0.84 (0.71, 1.00)	1.03 (0.83, 1.27)	0.78 (0.63, 0.98)	0.72 (0.54, 0.96)*	0.98 (0.76, 1.27)
Methomyl	1.03 (0.90, 1.18)	1.00 (0.85, 1.18)	1.11 (0.92, 1.34)	0.95 (0.81, 1.12)	0.99 (0.82, 1.19)	0.71 (0.56, 0.89)*
Oxydemeton-methyl	0.99 (0.79, 1.24)	1.12 (0.88, 1.43)	0.92 (0.70, 1.21)	0.93 (0.68, 1.26)	0.97 (0.72, 1.31)	0.85 (0.64, 1.14)
Permethrin	1.18 (0.94, 1.47)	1.19 (0.94, 1.51)	1.06 (0.76, 1.48)	0.91 (0.68, 1.21)	0.91 (0.67, 1.24)	0.79 (0.56, 1.10)

[a] Models adjusted for youth sex, age at 18y visit, maternal age at delivery, maternal education, maternal years in the U.S., maternal marital status at 18y, household poverty category at 18y, and HOME z-score at 10.5y.

Abbreviations: ACEs=adverse childhood experiences; CrI=credible interval; IRR=incidence rate ratio; RR=relative risk.

* 95% CrI does not include the null hypotheses (1.0).