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Original Contribution

Preconception and first trimester exposure to pesticides and associations with stillbirth

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Abstract

Associations of pesticide exposures during preconception with stillbirth have not been well explored. We linked Arizona pesticide use records with birth certificates from 2006 to 2020 and estimated associations of living within 500 m of any pyrethroid, organophosphate (OP), or carbamate pesticide applications during a 90-day preconception window or the first trimester, with stillbirth. We considered a binary measure of exposure (any exposure), as well as log-pounds and log-acres applied within 500 m, in a negative control exposure framework with log-binomial regression. We included 1 237 750 births, 2290 stillbirths, and 27 pesticides. During preconception, any exposure to pesticides was associated with stillbirth, including cyfluthrin (risk ratio [RR] = 1.97; 95% CI, 1.17-3.32); zeta-cypermethrin (RR = 1.81; 95% CI, 1.20-2.74); OPs as a class (RR = 1.60; 95% CI, 1.16-2.19); malathion (RR = 2.02; 95% CI, 1.26-3.24); carbaryl (RR = 6.39; 95% CI, 2.07-19.74); and propamocarb hydrochloride (RR = 7.72; 95% CI, 1.10-54.20). During the first trimester, fenpropathrin (RR = 4.36; 95% CI, 1.09-17.50); permethrin (RR = 1.57; 95% CI, 1.02-2.42); OPs as a class (RR = 1.50; 95% CI, 1.11-2.01); acephate (RR = 2.31; 95% CI, 1.22-4.40); and formetanate hydrochloride (RR = 7.22; 95% CI, 1.03-50.58) were associated with stillbirth. Interpretations were consistent when using continuous measures of pounds or acres of exposure. Pesticide exposures during preconception and first trimester may be associated with stillbirth.

This article is part of a Special Collection on Environmental Epidemiology.

Key words: pesticides; stillbirth; fetal death; organophosphate pesticides; pyrethroid pesticides; carbamate pesticides; environmental exposures; miscarriage.

Introduction

The potential public health burden of pesticides is high because pesticides are designed for toxicity. Exposures to pesticides are ubiquitous, mostly through diet,[1-7] but also through household use, agricultural drift, occupational exposures, and para-occupational residue on shoes and clothes.[8] The prenatal period is a particularly susceptible window of exposure because environmental exposures during this period affect lifelong health through fetal programming. Prenatal exposure to different classes of insecticides has been associated with several adverse birth and childhood outcomes.[9-16]

Stillbirth, fetal death, and miscarriage present major physical and psychological health burdens for pregnant women.[17] Stillbirth and miscarriages are types of fetal death, but stillbirths occur after gestational week 20 and miscarriages occur at or before week 20. Stillbirth occurs in approximately 4-5 births per 1000[18] in developed countries, and the rate is up to 3% of births in low- and middle-income countries.[19] Stillbirth has been associated with some environmental exposures, including ambient temperature,[20-22] air pollution,[23,24] and pesticides.[25-28] However, epidemiologic studies of pesticide exposures and stillbirth in the United States have not been published in the past 2 decades, a period that has seen dramatic changes in pesticide use compared with the 20th century.

The health effects of pesticides are usually studied with metabolite-based measures of exposure in prospective cohort studies. However, the rarity of stillbirth makes it difficult to study in the general population when using this approach, and biomarkers also are not typically available in a preconception setting. For organophosphate (OP) pesticides and pyrethroids, we generally also have used summary class measures, such as summed dialkylphosphates, which capture exposure to 75% of OP pesticides,[29] or common metabolites like 3-phenoxybenzoic acid, which represents exposure to several pyrethroid pesticides but cannot identify the effects of a specific active ingredient. Finally,

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in a study of OP residues on fruits and vegetables, up to 60% of the OP residues were the metabolites, not the parent pesticide,[30] so biomarkers reflect ingestion of both preformed metabolites and exposure to the parent ingredient.

One alternative to biomarker-based assessment includes the use of pesticide use registries (PURs). Although PURs do not capture the full range of pesticide exposures from personal behaviors (eg, diet), occupational use, tracked-in residue (hereafter referred to as track-in), or residential use, the ambient metric of pesticide exposure and the association with health outcomes is mostly unbiased by personal-level factors.[31] Because some bias due to unmeasured confounding may remain from using these time-series data, we adopted a negative control exposure (NCE) framework, which has been successfully used in prior studies to account for residual bias.[32-37] The NCE is often operationalized by controlling for an exposure estimate that is a good proxy for the exposure but that cannot causally be associated with the outcome. One recommendation for such a variable in spatial and time-series data is to use exposures after the outcome has occurred. Here, we operationalize the NCE by controlling for exposure after the outcome (birth).

An additional advantage of using PURs instead of biomarkers is that it allows us to examine the preconception period as a susceptible window of exposure. This window is mostly unexplored in relation to pesticides, despite recent studies showing that other environmental exposures during this period may, indeed, affect fetal and child health.[38-46] Here, we used our unique study design to incorporate preconception pesticides into this study of stillbirth.

When PURs are combined with state-wide databases (eg, on reproductive outcomes), the result is enhanced power to study rare outcomes. Therefore, we evaluated associations of pyrethroids, OPs, and carbamate insecticides with stillbirth, using data from the Arizona Pregnant Women's Environment and Reproductive Outcomes Study (Az-PEARS), a project that links Arizona's PUR with birth certificates in the state of Arizona from 2006 to 2020. In Arizona, stillbirths are recorded on birth certificates.

Methods

Data were collected as part of the Az-PEARS, which links existing health data across multiple sources to enable population-wide epidemiologic analyses. Study protocols and data procedures were approved by the University of Arizona's Institutional Review Board.

Birth certificates and study population

Arizona's Department of Health Services provided geocoded birth certificates from 2006 to 2020. We restricted these to birth certificates that indicated maternal residential street address at birth in the state of Arizona that could be geocoded (eg, we excluded those that listed post office boxes or mile markers; $n = 25\,796$), and we also excluded mothers older than 50 years ($n = 1448$), due to the probability of adoption or surrogacy. We extracted covariate, demographic, and outcome information from birth certificates, including maternal education, race/ethnicity, age, child sex, and fetal death/stillbirth. The state of Arizona requires that birth certificates be issued for stillbirths/fetal deaths for fetuses of more than 20-week gestations, and the birth certificates record these deaths. Hereafter, these outcomes are referred to as stillbirths.

Exposures

The state of Arizona requires that all commercial agricultural pesticide applications, including all aerial applications, be reported to the state. In addition, growers and applicators must report all soil-applied applications of pesticides on the Arizona Department of Environmental Quality's groundwater protection list, as well as application of certain odiferous compounds.[47] Arizona's PUR, managed by the Arizona Department of Agriculture, reports information on active ingredient, acres, pounds applied, concentration, Public Land Survey Section (ie, location), and application method. The Public Land Survey Section grid corresponds to approximately a resolution of 1 square mile. To enhance this resolution, we linked reported pesticide applications to fields by linking the reported crop target on the PUR with crops from the US Department of Agriculture (USDA) CropScape rasters, a satellite-based rendering of crop identification, following methods previously used for the California PUR.[48-50] We matched targeted crops for the relevant chemical on the pesticide use report to the satellite-identified crop fields on the CropScape rasters, by year from 2006 to 2020. Because the USDA rasters are not available before 2008 in Arizona, we used the 2008 USDA crop rasters for 2006 and 2007 instead.

For this study, we examined the most commonly used insecticide classes over the past decades—OPs, pyrethroids, and carbamates—as well as all the specific pesticides that belonged to those classes. We limited pesticides to those ingredients that exposed at least 50 participants at the 500-m buffer during the entire study period. This buffer provides an optimal tradeoff for sensitivity and specificity of exposure.[49] Mothers were defined as exposed if their residential address on the birth certificate was within 500 m of a given pesticide application during a specified trimester (preconception, trimester 0, or trimester 1). We limited to these trimesters because, in our data, the risk for stillbirth is highest in the second trimester (by definition, stillbirths in these data occur after 20 weeks of gestation). We evaluated 2 preconception periods that were 90 days long, to be consistent with the length of other trimesters, to allow for possible long-term effects of pesticide exposure and to account for possible errors around gestational dates. These periods included the window from 180 days to 91 days prior to conception (trimester 0, first window, which we indicate as T0.1), and the window from 90 days prior to conception, to conception (trimester 0, second window [T0.2]).

We considered a binary measure of exposure by trimester (eg, any exposure to a given pesticide during a specified trimester), as well as pounds of active ingredient and acres applied to in the 500 m buffer during the specified trimester. For acres and pounds, we replaced values of 0 with 0.1×10^{-15} divided by the square root of 2, which was approximately equal to the lowest detectable value divided by the square of 2, and logged the values. We also summed pounds and acres applied across the 90-day preconception window and the ~90 days of the first trimester, and we evaluated this total pounds and acres variable for this approximate 180–day exposure period, using the 180 days after the estimated due date as the NCE period for these models.

Statistical analysis and covariates

We describe demographics and key exposure characteristics by stillbirth status. We also describe correlations of pesticides across the first trimester and the preconception period, and correlations across included pesticides.

To evaluate the associations of individual pesticides with stillbirth, we used complete case analyses and log binomial regression.

Because there may be residual confounding due to spatial correlations of events and exposures, we adopted an NCE framework[33,34] using exposure in the 90 days after the estimated due date as the negative exposure. For each model's NCE, we used the same ingredient for the specific pesticide or class as the exposure of interest, for the period after the due date. For example, when examining permethrin exposure in the preconception period, we controlled for permethrin exposure in the period after the due date. We additionally controlled for a priori selected covariates after a review of the literature, including maternal age, education, maternal race/ethnicity, child sex, season of conception, and year of conception.

We report both crude (unadjusted) and adjusted risk ratios (RRs). Because behaviors in the 90 days after the due date may be quite different from behaviors during the exposure window, we additionally evaluated the period from 90 days to 180 days after the estimated due date as an additional NCE window. We compared estimates from the 2 NCE models against a traditional model without the NCE variable. Additionally, because living in an agricultural region or in close proximity to crops may act as a confounder or modifier, due to higher probability of co-exposure to pesticides, or lifestyle variables with positive or negative effects on the outcome (eg, lower stress, more greenspace, rural living with less access to quality health care), we performed a sensitivity analysis restricting to births in agricultural regions only, and defined agricultural-region mothers as those who had been exposed during any trimester or preconception to any pesticide. We also performed sensitivity analyses evaluating modification of pesticide exposures by Medicaid status and by sex, and we set our α for interaction at .05. For these analyses, we evaluated interactions for the binary pesticide exposures during the first trimester and the 90-day window immediately preceding conception.

Results

Our study sample included 1 235 460 births, of which 2290 were stillborn. Overall, mothers were predominantly between ages 20 and 35 year, most had higher than a high school education, and most were non-Hispanic White or Hispanic (Table 1). Several characteristics differed by stillbirth; both older (>40 years) and younger (<20 years) mothers were more likely to experience stillbirth, and women with higher education were less likely to have a stillborn baby. Black women and Native American women were also at higher risk of stillbirth than non-Hispanic White or Hispanic women (Table 1).

During preconception, we observed several associations for pesticide exposures during the second preconception window (the 90 days immediately preceding conception) and the first trimester, but only 1 significant association for the first preconception window (the window from 180 days to 90 days prior to conception). For the binary metric of any applications in 500 m during the first preconception window, we report associations for the OP tribufos (RR = 2.66; 95% CI, 1.00-7.13), although this was based on only 4 exposed cases. During the second preconception window, we observed associations for the specific pyrethroids cyfluthrin (RR = 1.97; 95% CI, 1.17-3.32), zeta-cypermethrin (RR = 1.81; 95% CI, 1.20-2.74), bifenthrin (RR = 1.56; 95% CI, 0.97-2.49), and pyrethroids as a class (RR = 1.27; 95% CI, 0.95-1.71), although bifenthrin and pyrethroids as a class did not meet statistical significance (Table 2). We also observed elevated but nonsignificant associations for cypermethrin and fenpropathrin, which both had very few exposed cases (Table 2).

For the OPs, we observed associations with any exposure to OPs as a class (RR = 1.60; 95% CI, 1.16-2.19) and malathion (RR = 2.02; 95% CI, 1.26-3.24), along with elevated but nonsignificant associations for dimethoate (RR = 1.56; 995% CI, 0.86-2.84). The carbamates carbaryl (RR = 6.39; 95% CI, 2.07-19.74) and propamocarb hydrochloride (RR = 7.72; 95% CI, 1.10-54.20) were also associated during this window. During the first trimester, the pyrethroids fenpropathrin (RR = 4.36; 95% CI, 1.09-17.50) and permethrin (RR = 1.57; 95% CI, 1.02-2.42), OPs as a class (RR = 1.50; 95% CI, 1.11, 2.01), and the specific OPs acephate (RR = 2.31; 95% CI, 1.22-4.40) and dimethoate (RR 1.63; 95% CI, 0.94-2.84), and the carbamate formetanate hydrochloride (RR = 7.22; 95% CI, 1.03-50.58) were associated with stillbirth, although the finding for dimethoate was not statistically significant.

Interpretations were similar when evaluating associations with log acres and log pounds (Figure 1). Summing the exposures across the entire early pregnancy period (ie, the 90 days preconception and the first trimester) did not strengthen effects but appeared to be an average of the window-specific associations. In general, acres appeared to be slightly more sensitive than pounds for cyfluthrin, fenpropathrin, and tribufos, although the differences were mostly negligible.

Pesticides were not highly correlated across classes or active ingredients, with low to moderate correlations (Figure 2). Exposure to different pyrethroid active ingredients were moderately correlated; for instance, zeta-cypermethrin and cyfluthrin were correlated at 0.44 for the first trimester, and permethrin and zeta cypermethrin were correlated at 0.55 for the preconception period. However, correlations among specific OPs were very low. The class of OPs, as a whole, was moderately correlated with the class of pyrethroids as a whole, at 0.62 and 0.61, respectively, for the first trimester and the preconception period.

Associations were generally not affected by the use of the NCE framework or the selection of the NCE window (Figure 3), although variability did affect significance for exposures with confidence limits that were close to the null.

Effect estimates were similar when restricting to agricultural regions only, although SEs and *P* values were greater, likely because of the decrease in sample size (Tabel S1).

In sensitivity analyses, we generally did not observe any interactions with sex or Medicaid status at birth, with 2 exceptions. There was an interaction between malathion in the second preconception window (90 days prior to conception) with Medicaid status. Malathion was positively associated with stillbirth among women who were not enrolled in Medicaid (RR = 2.99 [95% CI, 1.76-5.10]; *P* = 0.046 for interaction), and null for women who were enrolled in Medicaid (RR = 0.94; 95% CI, 0.35-2.55). First-trimester acephate effect estimates were stronger among female fetuses (RR = 4.03; 95% CI, 1.39-8.22) than male fetuses (RR = 0.85 [95% CI, 0.21-3.45]; *P* = 0.049 for interaction).

Discussion

In this study, we linked 15 years of data from a PUR enhanced with satellite-based crop linkage in Arizona with more than 1 million births registered on Arizona birth certificates, to examine associations of exposure to specific pesticides during early pregnancy and the preconception period with stillbirth. We report signals for exposure during the 90 days prior to conception or the first trimester for multiple pyrethroid pesticides (namely, cyfluthrin, fenpropathrin, permethrin, and zeta-cypermethrin), multiple OPs (ie, any OP, acephate, malathion, and dimethoate), and the carbamates carbaryl, propamocarb hydrochloride, and formetanate

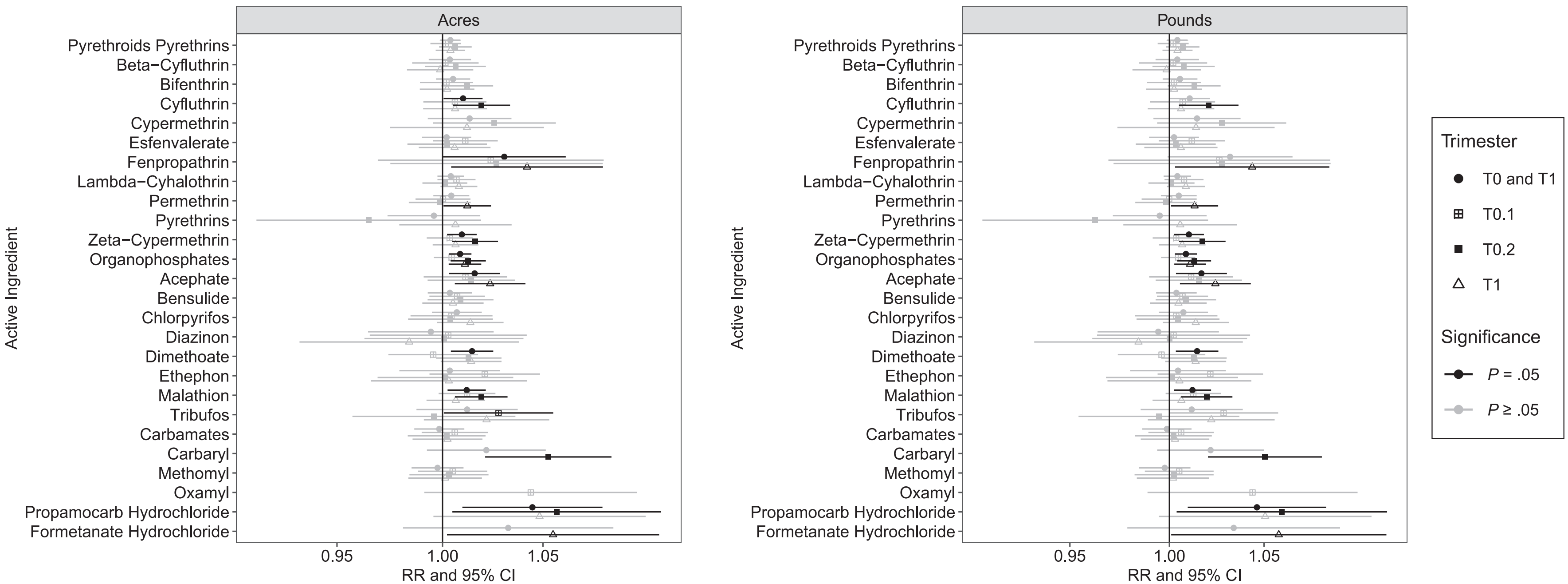

Figure 1. Adjusted risk ratios (RRs) of exposure to continuous measures of pesticides during preconception and first trimester with stillbirth in the Arizona Pregnant Women's Environment and Reproduction Study ($n = 1\,237\,750$). Associations estimated with log binomial regression models in 1 237 750 births from 2006 to 2020 in Arizona, adjusted for maternal race/ethnicity, child sex, maternal education, maternal age, conception year, conception season, and exposure in the 90 days after the estimated due date (for the negative control exposure). Acres and pounds were logged. T0.1, the exposure window beginning 180 days before preconception and ending 91 days preconception; T0.2, the 90-day preconception window beginning 90 days preconception and ending the day before conception; T1, first trimester. RRs and CIs for some time windows and pesticides are missing because not all associations were estimable, due to zero exposed deaths.

Table 1. Characteristics of Arizona Pregnant Women's Environment and Reproductive Health Study (n = 1 237 750) by stillbirth status, 2006-2020.

Characteristic[a]	No stillbirth (n = 1 235 460), No. (%)	Stillbirth (n = 2,290), No. (%)
Maternal age, years		
<20	85 822 (6.95)	215 (9.39)
20-35	999 672 (80.91)	1780 (77.73)
36-40	124 846 (10.11)	234 (10.22)
>40	25 120 (2.03)	61 (2.66)
Maternal education		
Less than high school	717 358 (58.06)	1375 (60.04)
High school graduate	209 250 (16.94)	485 (21.18)
Some college	160 292 (12.97)	261 (11.40)
College or higher	148 560 (12.02)	169 (7.38)
Maternal race/ethnicity		
Non-Hispanic White	548 750 (44.42)	808 (35.28)
Hispanic	532 219 (43.08)	1065 (46.51)
Black	66 599 (5.39)	247 (10.79)
Native American	57 598 (4.66)	110 (4.80)
Asian/Pacific Islander	27 692 (2.24)	57 (2.49)
Other/Unknown	2602 (0.21)	3 (0.13)
Pyrethroid exposure across pregnancy		
None	1 163 452 (94.17)	2144 (93.62)
Any	72 007 (5.83)	146 (6.38)
Organophosphate exposure across pregnancy		
None	1 182 958 (95.75)	2179 (95.15)
Any	52 501 (4.25)	111 (4.85)
Carbamate exposure across pregnancy		
None	1 220 289 (98.77)	2261 (98.73)
Any	15 170 (1.23)	29 (1.27)

[a]Maternal age, education, and race/ethnicity are variables derived from birth certificate data from the Arizona Department of Health Services. Pyrethroids, organophosphate, and carbamate exposure are defined by whether or not mothers lived within 500 m of an agricultural application of pyrethroid, organophosphate, or carbamate pesticides during pregnancy or the 90-day preconception period, at the address recorded on the birth certificate.

hydrochloride. A few other pesticides had elevated effect estimates, but these were not statistically significant, including for bifenthrin, cypermethrin, chlorpyrifos, and dimethoate. We generally did not observe associations for exposures during an earlier preconception window (3-6 months prior to conception), except for tribufos.

The literature on associations of these insecticides with stillbirth is sparse.[51] In occupational studies of women and their partners who work in agriculture, pesticide exposures are associated with increased risk of stillbirth.[52-54] Other studies of specific pesticides or pesticide classes in humans report associations of pyrethroids with decreased fertility and suggestive associations for OPs and carbamates as a class,[55] although another smaller study during the same period reported null associations.[56] In a California study of fetal deaths in 1984, exposure to carbamates during the third month of gestation was associated with fetal death,[26] which is consistent with our observations during early pregnancy for carbaryl, formetanate hydrochloride, and propamocarb hydrochloride, although these findings were only based on fewer than 3 exposed cases for each pesticide. In the same 1984 study, associations for pyrethroids and OPs as a class were null, although this period was prior to when pyrethroids were a commonly used class. A study of malathion in 1982 in California for mosquito control found no association between malathion and fetal anomalies.[57] A more recent study in Brazil found that exposure to pesticides in general was associated with increased odds of stillbirth,[27] although the researchers did not report on specific active ingredients. In a toxicology study, the pyrethroid cyfluthrin altered placental development,[58] and disrupted placental development is hypothesized to be an important cause of stillbirths and miscarriages.[59] Chlorpyrifos in mice has been associated with postimplantation loss and early neonatal death in mice and rats,[60-62] but not specifically stillbirth. We generally did not observe strong signals for chlorpyrifos, other than an elevated but not significant association in mothers who were exposed during the first trimester.

Our findings suggest that the preconception period, and to some degree the first trimester, may be important windows for exposure to some insecticides. This may be due to biological effects on the female reproductive organs,[63] changes in hormonal activity,[64] or other unknown biological factors. Metabolites of permethrin and cypermethrin (which are shared with zeta-cypermethrin) act as endocrine disruptors and interact with cellular estrogen receptors.[63] Such hormonal influences can affect women's reproductive cycles and cycle lengths, and the overall quality of the uterine environment during pre-implantation.[65,66] Although pyrethroids are rapidly excreted, with half-lives on the order of hours to days,[67-70] exposure can result in apoptotic and senescent cells,[71] and environmentally induced senescent cells may persist in the human body for months, with long-term expression of senescent markers,[72,73] even after the environmental exposure has ended.

Uterine and reproductive tract cells form the architecture for a successful pregnancy, and past exposure may thus continue to exert influence on pregnancy and placental health. Alternatively, associations during this exposure window may be due to possible confounding by effects on father's sperm, which we were unable to account for. Because we assigned exposure by residence, exposure is likely shared with fathers who live in the same residence. A study of malathion and male reproductive

Table 2. Crude and adjusted associations[a] of a binary measure of insecticides with fetal death, by exposure window in Arizona Pregnant Women's Environment and Reproductive Outcomes Study, $n = 1\,237\,750$.

Active ingredient	Exposure status	No. alive at T0.1	Case T0.1, No.	No. alive at T0.2	Case T0.2, No.	No. alive at T1	Case T1, No.	Model	T0.1 RR (95% CI)	T0.2 RR (95% CI)	T1 RR (95% CI)
Pyrethroids and pyrethrins											
Pyrethroids and pyrethrins as a class	Unexposed	1 207 124	2226	1 206 448	2216	1 204 549	2218	Crude	1.22 (0.96-1.57)	1.39 (1.10-1.75)	1.26 (1.00-1.60)
	Exposed	28 335	64	29 011	74	30 910	72	Adjusted	1.08 (0.81-1.42)	1.27 (0.95-1.71)	1.15 (0.88-1.50)
Beta-cyfluthrin	Unexposed	1 230 145	2279	1 230 043	2276	1 229 500	2279	Crude	1.12 (0.62-2.02)	1.40 (0.83-2.36)	1.00 (0.55-1.80)
	Exposed	5 315	11	5 417	14	5 960	11	Adjusted	1.08 (0.60-1.96)	1.30 (0.75-2.24)	0.96 (0.53-1.76)
Bifenthrin	Unexposed	1 226 698	2269	1 226 654	2263	1 226 452	2269	Crude	1.30 (0.84-1.99)	1.66 (1.14-2.42)	1.26 (0.82-1.93)
	Exposed	8762	21	8806	27	9008	21	Adjusted	1.07 (0.66-1.74)	1.56 (0.97-2.49)	1.07 (0.65-1.76)
Cyfluthrin	Unexposed	1 230 448	2277	1 230 182	2271	1 229 960	2277	Crude	1.40 (0.81-2.41)	1.95 (1.24-3.06)	1.28 (0.74-2.20)
	Exposed	5012	13	5278	19	5500	13	Adjusted	1.28 (0.73-2.27)	1.97 (1.17-3.32)	1.22 (0.68-2.20)
Cypermethrin	Unexposed	1 234 740	2290	1 234 689	2287	1 234 695	2288	Crude	NE	2.10 (0.68-6.49)	1.41 (0.35-5.63)
	Exposed	720	0	771	3	765	2	Adjusted	NE	2.47 (0.80-7.65)	1.58 (0.39-6.30)
Esfenvalerate	Unexposed	1 231 949	2278	1 231 856	2280	1 231 822	2280	Crude	1.85 (1.05-3.25)	1.50 (0.81-2.79)	1.48 (0.80-2.76)
	Exposed	3511	12	3604	10	3638	10	Adjusted	1.49 (0.82-2.72)	1.13 (0.55-2.32)	1.24 (0.64-2.40)
Fenpropathrin	Unexposed	1 235 247	2289	1 235 244	2289	1 235 210	2288	Crude	2.53 (0.36-17.86)	2.49 (0.35-17.62)	4.29 (1.08-17.08)
	Exposed	213	1	216	1	250	2	Adjusted	2.52 (0.35-17.83)	2.45 (0.34-17.84)	4.36 (1.09-17.50)
Gamma-cyhalothrin	Unexposed	1 235 451	2290	1 235 446	2290	1 235 455	2290	Crude	NE	NE	NE
	Exposed	9	0	14	0	5	0	Adjusted	NE	NE	NE
Lambda-cyhalothrin	Unexposed	1 221 451	2253	1 220 906	2258	1 220 189	2250	Crude	1.43 (1.03-1.98)	1.19 (0.84-1.68)	1.42 (1.04-1.94)
	Exposed	14 009	37	14 554	32	15 271	40	Adjusted	1.30 (0.92-1.84)	1.03 (0.69-1.55)	1.33 (0.95-1.85)
Permethrin	Unexposed	1 227 013	2271	1 226 499	2270	1 226 321	2262	Crude	1.21 (0.77-1.91)	1.21 (0.78-1.87)	1.66 (1.14-2.41)
	Exposed	8447	19	8961	20	9139	28	Adjusted	0.99 (0.60-1.64)	0.95 (0.54-1.67)	1.57 (1.02-2.42)
Pyrethrins	Unexposed	1 233 861	2290	1 233 806	2289	1 233 725	2286	Crude	NE	0.33 (0.05-2.30)	1.24 (0.47-3.31)
	Exposed	1599	0	1654	1	1735	4	Adjusted	NE	0.26 (0.03-2.02)	1.24 (0.44-3.48)
Zeta-cypermethrin	Unexposed	1 224 234	2263	1 223 901	2253	1 223 444	2260	Crude	1.30 (0.89-1.90)	1.74 (1.26-2.40)	1.35 (0.94-1.94)
	Exposed	11 226	27	11 559	37	12 016	30	Adjusted	1.14 (0.75-1.73)	1.81 (1.20-2.74)	1.25 (0.82-1.90)
Organophosphates											
Organophosphates as a class	Unexposed	1 217 496	2249	1 217 247	2239	1 216 248	2238	Crude	1.24 (0.91-1.68)	1.52 (1.15-2.01)	1.47 (1.12-1.93)
	Exposed	17 963	41	18 212	51	19 211	52	Adjusted	1.19 (0.86-1.64)	1.60 (1.16-2.19)	1.50 (1.11-2.01)
Acephate	Unexposed	1 233 028	2283	1 233 142	2283	1 233 059	2280	Crude	1.55 (0.74-3.26)	1.63 (0.78-3.42)	2.25 (1.21-4.18)
	Exposed	2432	7	2318	7	2401	10	Adjusted	1.49 (0.70-3.19)	1.65 (0.75-3.65)	2.31 (1.22-4.40)
Bensulide	Unexposed	1 229 141	2273	1 228 874	2273	1 229 084	2275	Crude	1.45 (0.90-2.34)	1.39 (0.87-2.25)	1.27 (0.77-2.11)
	Exposed	6319	17	6586	17	6376	15	Adjusted	1.30 (0.79-2.16)	1.38 (0.76-2.50)	1.20 (0.69-2.10)
Chlorpyrifos	Unexposed	1 232 123	2283	1 232 103	2283	1 231 735	2279	Crude	1.13 (0.54-2.38)	1.13 (0.54-2.36)	1.59 (0.88-2.88)
	Exposed	3337	7	3357	7	3725	11	Adjusted	1.16 (0.55-2.44)	1.16 (0.54-2.49)	1.65 (0.90-3.01)
Diazinon	Unexposed	1 234 592	2288	1 234 499	2288	1 234 523	2289	Crude	1.24 (0.31-4.96)	1.12 (0.28-4.49)	0.58 (0.08-4.09)
	Exposed	868	2	961	2	937	1	Adjusted	1.13 (0.28-4.58)	0.98 (0.23-4.22)	0.55 (0.08-3.97)
Dimethoate	Unexposed	1 231 933	2284	1 231 852	2278	1 231 457	2277	Crude	0.92 (0.41-2.04)	1.80 (1.02-3.16)	1.75 (1.02-3.02)
	Exposed	3527	6	3608	12	4003	13	Adjusted	0.86 (0.38-1.92)	1.56 (0.86-2.84)	1.63 (0.94-2.84)
Ethephon	Unexposed	1 234 578	2286	1 234 589	2287	1 234 641	2288	Crude	2.44 (0.92-6.50)	1.86 (0.60-5.75)	1.32 (0.33-5.26)
	Exposed	882	4	871	3	819	2	Adjusted	2.14 (0.80-5.71)	1.06 (0.31-3.63)	1.13 (0.28-4.54)
Malathion	Unexposed	1 230 011	2275	1 229 856	2272	1 229 034	2276	Crude	1.49 (0.90-2.47)	1.74 (1.09-2.76)	1.18 (0.70-1.99)
	Exposed	5449	15	5604	18	6426	14	Adjusted	1.58 (0.95-2.62)	2.02 (1.26-3.24)	1.27 (0.75-2.14)
Oxydemeton-methyl	Unexposed	1 235 454	2290	1 235 456	2290	1 235 454	2290	Crude	NE	NE	NE
	Exposed	6	0	4	0	6	0	Adjusted	NE	NE	NE
Phorate	Unexposed	1 235 264	2290	1 235 215	2290	1 235 164	2290	Crude	NE	NE	NE
	Exposed	196	0	245	0	296	0	Adjusted	NE	NE	NE
Tribufos	Unexposed	1 234 797	2286	1 234 824	2288	1 234 813	2287	Crude	3.25 (1.22-8.63)	1.69 (0.42-6.77)	2.50 (0.81-7.73)
	Exposed	663	4	636	2	647	3	Adjusted	2.66 (1.00-7.13)	0.84 (0.19-3.65)	2.16 (0.69-6.71)
Carbamates											
Carbamates as a class	Unexposed	1 229 987	2278	1 229 600	2280	1 229 299	2279	Crude	1.18 (0.67-2.09)	0.92 (0.49-1.71)	0.96 (0.53-1.74)
	Exposed	5472	12	5859	10	6160	11	Adjusted	1.26 (0.69-2.29)	1.04 (0.51-2.11)	1.08 (0.57-2.04)
Carbaryl	Unexposed	1 235 144	2290	1 235 176	2287	1 235 113	2290	Crude	NE	5.66 (1.83-17.45)	NE
	Exposed	316	0	284	3	347	0	Adjusted	NE	6.39 (2.07-19.74)	NE
Carbofuran	Unexposed	1 235 433	2290	1 235 432	2290	1 235 437	2290	Crude	NE	NE	NE
	Exposed	27	0	28	0	23	0	Adjusted	NE	NE	NE
Methomyl	Unexposed	1 230 387	2279	1 229 961	2280	1 229 751	2280	Crude	1.17 (0.65-2.11)	0.98 (0.53-1.82)	0.94 (0.51-1.76)
	Exposed	5073	11	5499	10	5709	10	Adjusted	1.21 (0.65-2.27)	1.09 (0.53-2.23)	1.03 (0.53-2.02)
Oxamyl	Unexposed	1 235 340	2289	1 235 354	2290	1 235 340	2290	Crude	4.47 (0.63-31.48)	NE	NE
	Exposed	120	1	106	0	120	0	Adjusted	4.87 (0.69-34.31)	NE	NE
Propamocarb hydrochloride	Unexposed	1 235 380	2290	1 235 390	2289	1 235 362	2289	Crude	NE	7.62 (1.09-53.34)	5.46 (0.78-38.41)
	Exposed	80	0	70	1	98	1	Adjusted	NE	7.72 (1.10-54.20)	5.80 (0.82-40.89)
Formetanate hydrochloride	Unexposed	1 235 407	2290	1 235 400	2290	1 235 394	2289	Crude	NE	NE	8.07 (1.15-56.48)
	Exposed	53	0	60	0	66	1	Adjusted	NE	NE	7.22 (1.03-50.58)

Abbreviations: NE, not estimable, due to zero exposed deaths; T0.1, the exposure window beginning 180 days before preconception and ending 91 days before conception; T0.2, the 90-day preconception window beginning 90 days preconception and ending the day before conception; T1, first trimester.

[a]These models are from binary exposure models (any exposure in preconception periods, any exposure in first trimester exposure). Associations were estimated with log binomial regression models in 1 237 750 births from 2006 to 2020 in Arizona. Adjusted models were adjusted for using negative control exposure models, including maternal race/ethnicity, child sex, maternal education, maternal age, conception year, season of conception, and exposure to the modeled pesticide in the 90 days after the estimated due date. Crude models are unadjusted for covariates. Models with statistically significant adjusted estimates ($P < .05$) are in bold for visualization purposes.

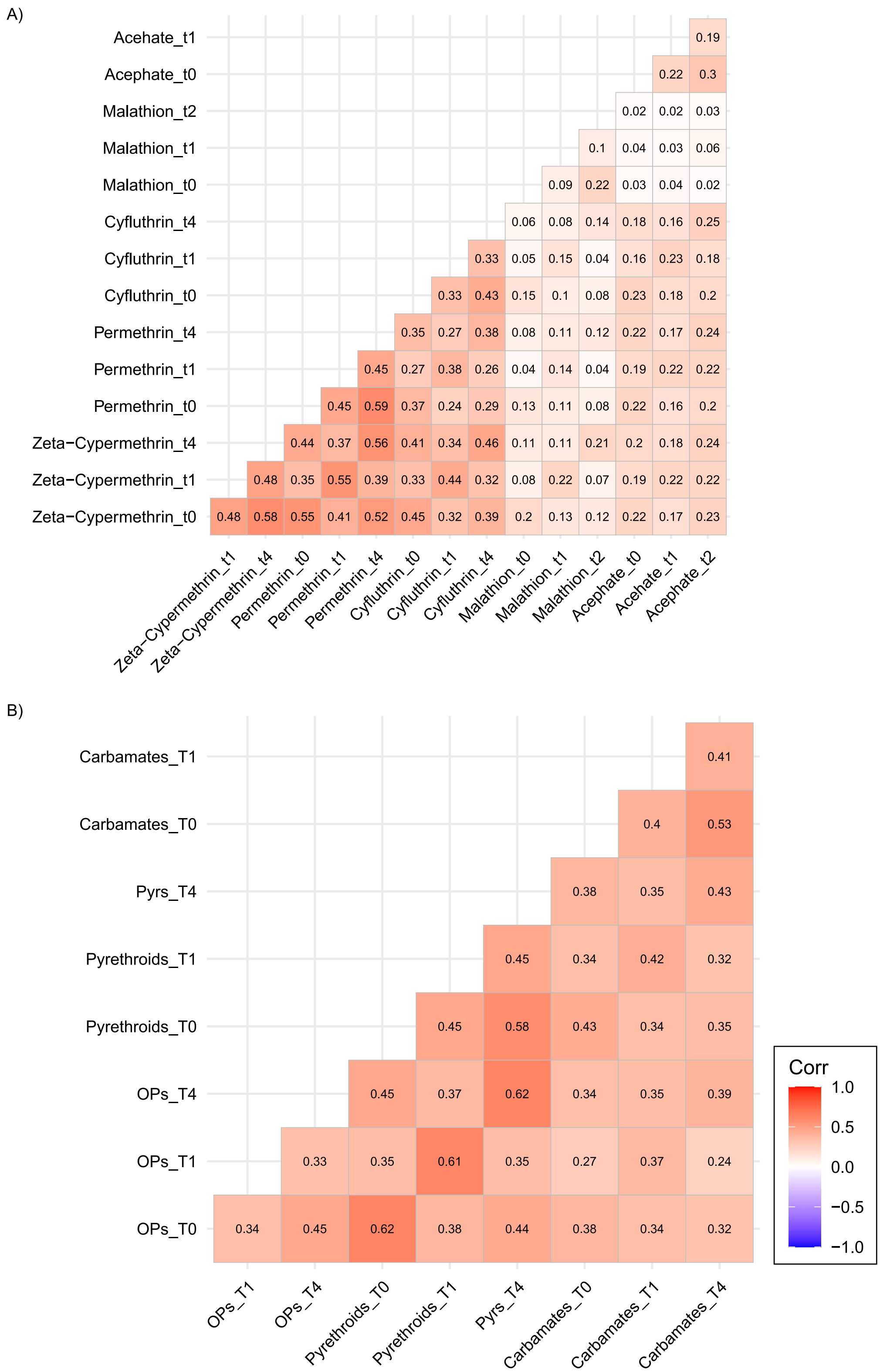

Figure 2. Correlations of pesticides across exposure windows and active ingredients. Left panel shows correlations (Corr) for classes, and the right panel is for select specific insecticides. OP, organophosphate; Pyr, pyrethroid; T0, the preconception period (1-90 days before conception); T1, exposure during the first trimester; T4, the negative control exposure variable (0-89 days after the estimated due date).

parameters in mice showed toxic effects of malathion on sperm count, progressive motility, morphology, and viability; and testosterone.[74] Paternal exposure to pyrethroids causes increased fetal loss among rats.[75]

Differences by exposure window may be due to miscalculation of exposure timing, particularly for fetuses with uncertain gestational ages, and exposure attributed to preconception may actually have happened in the first trimester. Differences

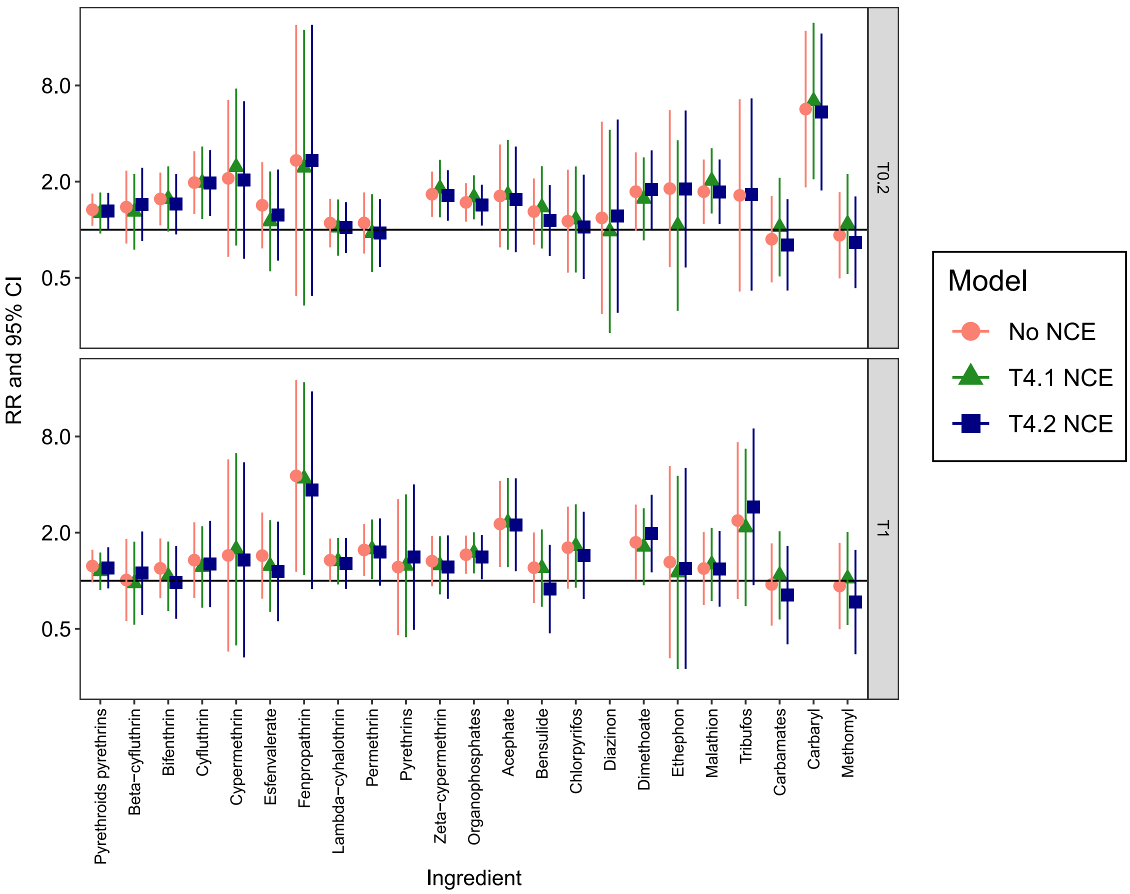

Figure 3. Associations of pesticide exposure by trimester, comparing negative control exposure windows. These models are from binary exposure models (any exposure in the preconception window 90 days before birth (T0.2) and any exposure in first trimester (T1). Associations are estimated with log binomial regression models in 1 237 750 births from 2006 to 2020 in Arizona, adjusted for maternal race/ethnicity, child sex, maternal education, maternal age, conception year, and conception season. "Traditional model" refers to the model with no negative control exposure (NCE). T4.1, time from the due date to 89 days later; T4.2, time beginning 90 days after the due date and ending 180 days after the due date. For visualization purposes, associations with very wide CIs are not shown.

between the 2 preconception windows were somewhat stark, with almost no associations for exposures in the first preconception window (beginning 180 days prior to conception and ending 91 days prior to conception). If causal, exposures closer to conception are driving the elevated risk, which is biologically consistent with the rapid metabolism and clearance of modern pesticides. There may also be some survival bias in our estimates, because we cannot account for early miscarriages. It is possible that pesticide exposures in the preconception period and the first trimester contribute to miscarriage, in addition to stillbirth, and that miscarriage and stillbirth may share biological mechanisms influenced by pesticides. Thus, our estimates are likely an underestimate of the true effect of pesticides on pregnancy loss.

Generally, we did not observe differences in RRs when restricting to agricultural regions, and we found minimal differences between the different NCE models, suggesting minimal residual confounding. We also did not observe substantial modification by sex or by Medicaid status.

Regardless, if causal, this exposure window presents unique problems for prevention and education, particularly because 50% of pregnancies are unplanned. From a policy perspective, buffer zones between fields sprayed with pesticides and residential and educational buildings could be required and/or expanded. Policies that promote integrated pest management may reduce risks from pests and pesticides through integration of biological and chemical controls.[76-78] For example, in Arizona cotton,[79,80] 10-fold reductions in use of OPs, pyrethroids, and carbamates were observed between 1995 and 2006, a period when integrated pest management was implemented and embraced. Behavioral modifications may also reduce exposures to agricultural pesticide use. For instance, changing air filters or increasing vacuuming frequency may reduce pesticide concentrations in household indoor air and dust.[81,82]

Other exposure pathways may be important for nonrural populations. For instance, malathion and some pyrethroids are regularly sprayed via fogging machines in urban and suburban areas in the United States and internationally to control mosquito populations that can carry West Nile virus, although mosquito control can be effectively achieved with better urban planning and landscape design.[83] Permethrin is recommended by the World Health Organization for disinfecting aircraft in countries with endemic malaria and other insect-borne diseases. Permethrin is also the most commonly used ingredient in insecticide-treated clothing, and all US Department of Defense uniforms are required to be treated with permethrin. Soldiers who wear these uniforms have 30 to 50 times higher levels of pyrethroid metabolites than the general population.[84,85] The Department of Defense should continue exploring alternative approaches to reduce vector-borne diseases.

Strengths and limitations

This study has several strengths. The study design allowed us to investigate associations on a population-wide basis without restricting to those actively participating in a research study, thus potentially including people who may be harder to reach in traditional birth cohort studies. The use of a pesticide registry instead of biomarkers allowed us to estimate exposures across multiple windows of exposure for more than 1 million people, as opposed to biomarker-based studies, which typically reflect exposure for a short period (eg, hours to days) and are typically only collected 1-3 times during pregnancy in small cohort studies. Biomarkers may also be specific to a particular pathological pathway, whereas the PUR method is not. We also were able to identify agricultural applications as the source for exposure, which may have implications for agricultural-specific policy (eg, implementation of buffers between fields and housing developments, limiting use of specific pesticides, lowering food tolerances), whereas biomarkers reflect exposure from multiple sources, which may be more difficult to regulate.

The study also had limitations. We were limited to OPs, pyrethroids, and carbamates that we could study with adequate statistical power; thus, we could not estimate some specific OP, pyrethroid, and carbamate effect estimates. We conducted several tests and might have experienced some Type 1 error, although findings should all be replicated in other populations and study designs regardless. We relied on birth certificates that may be less reliable than medical records, generating some outcome misclassification, and possibly exposure misclassification due to misreported addresses or women not staying at the address reported on the birth certificate. However, all stillbirths after 20 weeks' gestation in Arizona are required to be issued a birth certificate and are presumed to be correctly recorded. Additionally, the tradeoff between precision and quantity of data is a commonly encountered issue in large-scale health databases. Because we used PURs, we also do not know if participants were exposed to pesticide drift; because there is likely some misreporting, the field-crop matching is likely inexact, and geological features (eg, hills, large buildings) may affect some people's exposures relative to others at the same buffer. Some people who are defined as unexposed may also be exposed to some small number of grower-applied pesticides that are not in the PUR; that reporting is not required under the state statute. Although some women likely moved during pregnancy, movement is probably nondifferential for case and control participants, and prior studies have suggested that most moves are short distances and exposure estimates are minimally affected.[86-88] Still, we likely experienced residual nondifferential exposure misclassification and thus report effect estimates that are most likely biased toward the null.

It is also unclear why different specific pesticides within the class are associated with stillbirth, and not others. Although these pesticides vary in their chemical properties (eg, log of the *n*-octanol/water partition coefficient, Henry's Law constant, vapor pressure, soil half-life), there is no apparent relationship between these characteristics and the strength of association with stillbirth. We did not account for mixtures, which may be important, and future research will use mixtures modeling techniques. Finally, our exposure measurements do not reflect wind, atmospheric conditions, or resuspension. Efforts are underway to develop atmospheric dispersion models, which will generate continuous measures of air concentrations and deposition, which may have more relevance for monitoring and regulating agricultural applications of pesticides.

Conclusions

Exposure during preconception or early pregnancy to certain OPs, pyrethroid, and carbamate pesticides may be associated with a higher risk of stillbirth.

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Supplementary material

Supplementary material is available at the *American Journal of Epidemiology* online.

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Conflict of interest

P.C.E. has received research grants and contracts from pesticide registrants unrelated to the research reported here. The remaining authors declared no conflicts of interest.

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Data availability

The data used for this study are available upon request to the corresponding author.

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