

## REGULAR ARTICLE

# County-level pesticide use and risk of shortened gestation and preterm birth

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## Keywords

Gestation, Pesticide, Pregnancy, Preterm birth

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## Received

18 June 2015; revised 18 November 2015; accepted 23 November 2015.

DOI:10.1111/apa.13288

## ABSTRACT

**Aim:** This study assesses the association between pesticide exposure in pregnancy, preterm birth (PTB) and shortened gestation.

**Methods:** Pregnancy information was abstracted from the Centers for Disease Control (CDC) Non-Public Use Natality Datasets 1990–2005. Pesticide use in maternal county of residence was calculated using California Pesticide Use Reporting (PUR) data 1990–2005. Counties were ranked by pesticide use, and birth months were sorted by *peak* (May–June) or *nonpeak* (other months) pesticide use. Multivariate logistical regression models were used.

**Results:** Counties with higher pesticide use were associated with higher PTB (*low*  $8.59 \pm 0.11\%$ , *moderate*  $9.25 \pm 0.07\%$ , *high*  $10.0 \pm 0.06\%$ ,  $p$ 's  $< 0.001$ ) and shorter gestations (*low*  $39.197 \pm 0.014$  weeks, *moderate*  $39.126 \pm 0.011$  weeks, *high*  $39.049 \pm 0.011$  weeks,  $p$ 's  $< 0.001$ ). Peak pesticide months were associated with higher PTB ( $10.01 \pm 0.05\%$  vs.  $9.36 \pm 0.05\%$ ,  $p < 0.001$ ) and shorter gestations ( $39.069 \pm 0.007$  weeks vs.  $39.122 \pm 0.007$  weeks,  $p < 0.001$ ). The pesticide effect on shortened gestation and higher PTB was found in all racial groups. Pesticide use was highest for fungicides > insecticides > fumigants > herbicides > others. Each pesticide type was found to be associated with higher PTB and shorter gestation.

**Conclusion:** PTB and shortened gestation were significantly associated with pesticide use in maternal county of residence regardless of race, gestation at birth, and in most risk categories.

## INTRODUCTION

Infants born preterm (<37 weeks of gestation) are the greatest contributors to infant mortality and morbidity in the United States (U.S.) (1). Shorter gestations, even among healthy 'term' babies (gestations less than 39 weeks), have been associated with lower cognitive ability (2). In the United States, preterm births (PTB) increased 30% over the past two decades and the length of gestation has declined (3,4). Environmental pesticides may contribute to PTB and shortened gestation.

Associations between pesticides and birth weight were reported, but the relationship between pesticides, PTB and shortened gestation remains controversial (5–7). *In utero* organophosphate pesticide exposure was found to be associated with higher PTB and shortened gestation in Latina women living in the Salinas Valley, California (6). However, the relevance of their findings at the population

level was questioned (6). Our aim was to examine whether pesticide exposure significantly impacted the risk of PTB and shortened gestation at the population level.

## Methods

California county-level pesticide use between 1990 and 2005 was obtained from the California PUR database (8). Total pounds applied and pounds per acre for all pesticides in each county were abstracted by month and year. Pesticides were classified by type: fungicide, insecticide, fumigant, herbicide or other based on primary use type as indicated in the PAN Pesticides Database.

## Key notes

- Higher pesticide-use counties are associated with higher preterm birth (PTB) rates and shorter gestations.
- Months of peak pesticide use (May–June) are also associated with higher PTB and shorter gestations.
- Pesticide adverse effects are found in all racial groups and are correlated with each pesticide type (fungicide, insecticide, fumigant or herbicide).

## Abbreviations

CDC, Centers for Disease Control; PTB, Preterm birth(s); PUR, Pesticide use reporting; U.S., United States.

The study population included California singleton live births between 24 and 42 weeks of gestation from 1990 to 2005. An institutional data-use agreement was approved to obtain the CDC Non-Public Use Natality Datasets with all counties identified. An IRB for Human Subjects Research was not required for this study.

Maternal age, race, hypertension, diabetes, tobacco or alcohol use, and birth defects were abstracted. Gestational age was derived from the methods outlined in the CDC Natality Data User and Technical Guidelines (9). Mean PTB and gestational lengths were calculated for each maternal county of residence and each birth month. Gestation <37 weeks was defined as preterm, and gestation ≥37 weeks was defined as term. PTB and gestational lengths were calculated for Hispanic, White, Black and other maternal race.

In a separate analysis, counties were stratified by population size and categorised as large metro, medium metro or small metro (derived from the 2006 NCHS Urban-Rural Classification Scheme for Counties). These are meant to reflect relatively urban versus relatively rural counties. Within each metro category, counties were ranked by pesticide use. PTB and gestation were then calculated for these subcategories of counties within rural/urban populations.

For the dichotomous outcome variable of preterm birth, multivariate logistical regression models were used. In the *geographic* analysis, pesticide use in maternal county of residence (low vs. moderate vs. high pesticide use) was tested for interactions with each controlling covariate (maternal age, race/ethnicity, maternal tobacco use, hypertension, diabetes and birth defects). To account for clustering correlation within each county, a random effect was

used (PROC GLIMMIX). Using the logistical model framework, PTB was estimated for each pesticide-use level and compared between counties at varying pesticide-use levels. Further, such comparisons were performed between pesticide-use levels within subpopulations stratified by the controlling covariates. In the *temporal* analysis, peak month (a binary variable of months, May–June vs. other months) was used in the multivariate regression model controlling for the same covariates adjusting for county clustering. The same covariates were used for the continuous outcome variable gestational age. Based on these models, means were estimated and compared *geographically* between pesticide-use levels and *temporally* between peak vs. non-peak pesticide-use months for both the total population and subpopulations. All statistical analyses were performed using SAS 9.4 software (SAS, Cary, NC, USA) package. P-values <0.05 were considered statistically significant.

## RESULTS

### Pesticide use

Pesticide use ranged from 53 646 lbs (Alpine county) to 540 057 105 lbs (Fresno County). Total pesticide use was categorised by terciles for *low* (19 counties; 53 646–4 935 034 lbs applied), *moderate* (20 counties; 5 302 968–40 096 097 lbs applied) and *high* (19 counties; 51 188 816–540 057 105 lbs applied). Total pesticide-use mean ± SE was higher in *peak* months (528 070 ±

**Table 1** Demographic and preterm risk factors

Risk factor	Category	Total N	Preterm births	
			Cases	Incidence (95% CI)
All	All	7 940 794	754 375	9.5 (9.4, 9.6)
Race/ethnicity	Hispanic	3 695 641	362 173	9.8 (9.7, 9.9)
	White	2 771 158	238 320	8.6 (8.5, 8.7)
	Black	532 456	77 206	14.5 (14.3, 14.7)
	Other	941 539	85 680	9.1 (9.0, 9.2)
Age (years)	<20	867 299	89 332	10.3 (9.7, 11.0)
	20–35	6 151 861	485 997	7.9 (7.6, 8.2)
	>35	858 075	79 801	9.3 (8.7, 10.0)
Hypertension	Yes	178 722	43 787	24.5 (24.0, 25.0)
	No	7 698 513	700 565	9.1 (9.1, 9.2)
Diabetes	Yes	161 759	21 837	13.5 (13.2, 13.7)
	No	7 779 035	731 229	9.4 (9.3, 9.5)
Tobacco	Yes	1201	259	21.6 (19.1, 24.2)
	No	7 939 593	754 261	9.5 (9.4, 9.6)
Alcohol	Yes	407	103	25.4 (20.7, 30.2)
	No	7 940 387	754 337	9.5 (9.4, 9.6)
Birth defect	Yes	51 168	9978	19.5 (17.9, 21.2)
	No	7 889 626	646 949	8.2 (7.9, 8.5)

**Table 2** Preterm birth and gestational length by county fumigant, fungicide, herbicide and insecticide use

Pesticide-use type	Statistics	Pesticide-use rank	Incidence	
			preterm birth (%)	Mean gestation (weeks)
Fumigant	Mean ± SE	Low	8.71 ± 0.10	39.181 ± 0.014
		Mod	9.43 ± 0.07	39.132 ± 0.011
		High	9.81 ± 0.06	39.052 ± 0.011
	p-Value	Low vs. Mod	<0.001	0.005
		Low vs. High	<0.001	<0.001
Fungicide	Mean ± SE	Low	8.66 ± 0.10	39.192 ± 0.014
		Mod	9.50 ± 0.07	39.089 ± 0.011
		High	9.81 ± 0.07	39.084 ± 0.011
	p-Value	Low vs. Mod	<0.001	<0.001
		Low vs. High	<0.001	<0.001
Herbicide	Mean ± SE	Low	8.74 ± 0.10	39.159 ± 0.014
		Mod	9.18 ± 0.06	39.145 ± 0.011
		High	10.12 ± 0.06	39.048 ± 0.011
	p-Value	Low vs. Mod	<0.001	0.404
		Low vs. High	<0.001	<0.001
Insecticide	Mean ± SE	Low	8.64 ± 0.10	39.205 ± 0.014
		Mod	8.99 ± 0.06	39.137 ± 0.010
		High	10.25 ± 0.06	39.033 ± 0.010
	p-Value	Low vs. Mod	0.003	<0.001
		Low vs. High	<0.001	<0.001
		Med vs. High	<0.001	<0.001

20 549 lbs) than *nonpeak* months (249 960 ± 18 779 lbs) (data not shown). Total pesticide use over the 16-year study period was 3 077 170 355 lbs (fungicides 38.56% > insecticides 23.48% > fumigants 19.07% > herbicides

9.43% > all other 9.39%). Ranking counties by total lbs or by lbs/acre did not change the results; therefore, this study presents all measures as total lbs pesticides used per county. Only county-level birth outcomes were available from the

**Table 3** Preterm birth by county pesticide use

Gestation	Population/subpopulation	Category	Preterm birth per 10 000 live births					
			Mean ± SE	Mean ± SE	Mean ± SE	p-Value	p-Value	p-Value
			Low (L)	Moderate (M)	High (H)	L vs. M	L vs. H	M vs. H
≤36 weeks	All		8.59 ± 0.11	9.25 ± 0.07	10.00 ± 0.06	<0.001	<0.001	<0.001
	No risk factors*		8.12 ± 0.11	8.83 ± 0.07	9.68 ± 0.06	<0.001	<0.001	<0.001
	Maternal age	<20	10.07 ± 0.22	11.28 ± 0.10	11.95 ± 0.08	<0.001	<0.001	<0.001
		20–35	8.21 ± 0.11	8.84 ± 0.07	9.54 ± 0.06	<0.001	<0.001	<0.001
		>35	10.23 ± 0.21	11.28 ± 0.11	12.24 ± 0.11	<0.001	<0.001	<0.001
	Race/ethnicity	Hispanic	9.15 ± 0.18	9.43 ± 0.08	10.26 ± 0.06	0.149	<0.001	<0.001
		White	8.20 ± 0.10	8.39 ± 0.07	8.90 ± 0.07	0.123	<0.001	<0.001
		Black	13.93 ± 0.50	14.23 ± 0.14	14.90 ± 0.14	0.563	0.062	0.001
	Hypertension	Yes	21.71 ± 0.63	24.87 ± 0.37	25.02 ± 0.35	<0.001	<0.001	0.768
		No	8.22 ± 0.11	8.90 ± 0.07	9.73 ± 0.06	<0.001	<0.001	<0.001
	Diabetes	Yes	13.03 ± 0.45	13.51 ± 0.18	13.48 ± 0.18	0.328	0.347	0.933
		No	8.50 ± 0.11	9.16 ± 0.07	9.94 ± 0.06	<0.001	<0.001	<0.001
	Tobacco	Yes	25.84 ± 2.47	22.44 ± 2.07	17.29 ± 2.10	0.291	0.009	0.082
		No	8.56 ± 0.11	9.25 ± 0.07	10.00 ± 0.06	<0.001	<0.001	<0.001
	Alcohol	Yes	15.63 ± 5.78	25.21 ± 3.85	29.85 ± 3.75	0.170	0.040	0.389
	No	8.59 ± 0.11	9.25 ± 0.07	10.00 ± 0.06	<0.001	<0.001	<0.001	
≤33 weeks	All		2.12 ± 0.04	2.42 ± 0.02	2.67 ± 0.02	<0.001	<0.001	<0.001
	No risk factors*		1.94 ± 0.05	2.26 ± 0.03	2.55 ± 0.02	<0.001	<0.001	<0.001
	Maternal age	<20	2.72 ± 0.12	3.32 ± 0.04	3.52 ± 0.04	<0.001	<0.001	<0.001
		20–35	1.98 ± 0.05	2.25 ± 0.02	2.48 ± 0.02	<0.001	<0.001	<0.001
		>35	2.63 ± 0.10	3.05 ± 0.05	3.38 ± 0.05	<0.001	<0.001	<0.001
	Race/ethnicity	Hispanic	2.22 ± 0.08	2.45 ± 0.03	2.73 ± 0.02	0.006	<0.001	<0.001
		White	1.99 ± 0.04	2.10 ± 0.02	2.26 ± 0.02	0.031	<0.001	<0.001
		Black	4.31 ± 0.28	4.79 ± 0.07	5.06 ± 0.07	0.100	0.010	0.009
	Hypertension	Yes	6.99 ± 0.36	8.52 ± 0.20	8.42 ± 0.19	<0.001	<0.001	0.717
		No	1.98 ± 0.04	2.28 ± 0.03	2.56 ± 0.02	<0.001	<0.001	<0.001
	Diabetes	Yes	3.37 ± 0.24	3.44 ± 0.09	3.30 ± 0.09	0.772	0.776	0.245
		No	2.09 ± 0.04	2.40 ± 0.02	2.66 ± 0.02	<0.001	<0.001	<0.001
	Tobacco	Yes	12.21 ± 1.93	9.79 ± 1.71	8.67 ± 1.73	0.348	0.172	0.646
		No	2.10 ± 0.04	2.42 ± 0.02	2.67 ± 0.02	<0.001	<0.001	<0.001
	Alcohol	Yes	6.86 ± 4.65	14.10 ± 3.19	16.24 ± 3.12	0.201	0.096	0.632
	No	2.12 ± 0.04	2.42 ± 0.02	2.67 ± 0.02	<0.001	<0.001	<0.001	
≤27 weeks	All		0.27 ± 0.01	0.33 ± 0.01	0.36 ± 0.00	<0.001	<0.001	<0.001
	No risk factors*		0.26 ± 0.01	0.32 ± 0.01	0.35 ± 0.00	<0.001	<0.001	<0.001
	Maternal age	<20	0.37 ± 0.04	0.48 ± 0.01	0.46 ± 0.01	0.011	0.021	0.413
		20–35	0.24 ± 0.01	0.31 ± 0.01	0.34 ± 0.01	<0.001	<0.001	<0.001
		>35	0.37 ± 0.03	0.40 ± 0.01	0.49 ± 0.01	0.428	0.001	<0.001
	Race/ethnicity	Hispanic	0.27 ± 0.02	0.32 ± 0.01	0.35 ± 0.01	0.054	0.001	<0.001
		White	0.25 ± 0.01	0.27 ± 0.01	0.31 ± 0.01	0.240	0.001	<0.001
		Black	0.80 ± 0.11	0.90 ± 0.02	0.94 ± 0.02	0.401	0.250	0.244
	Hypertension	Yes	0.72 ± 0.10	0.93 ± 0.04	1.01 ± 0.04	0.063	0.010	0.198
		No	0.26 ± 0.01	0.32 ± 0.01	0.35 ± 0.00	<0.001	<0.001	<0.001
	Diabetes	Yes	0.28 ± 0.07	0.29 ± 0.03	0.34 ± 0.02	0.868	0.441	0.200
		No	0.27 ± 0.01	0.33 ± 0.01	0.36 ± 0.00	<0.001	<0.001	<0.001
	Tobacco	Yes	0.65 ± 0.74	2.43 ± 0.61	1.58 ± 0.62	0.065	0.337	0.326
		No	0.27 ± 0.01	0.33 ± 0.01	0.36 ± 0.00	<0.001	<0.001	<0.001
	Alcohol	Yes	0.00 ± 1.45	1.84 ± 0.90	1.62 ± 0.84	0.282	0.334	0.860
	No	0.27 ± 0.01	0.33 ± 0.01	0.36 ± 0.00	<0.001	<0.001	<0.001	

\*Excludes risk factors: hypertension, alcohol, tobacco and diabetes.

CDC Natality Datasets; thus, only county-level pesticide data were used.

### Preterm birth

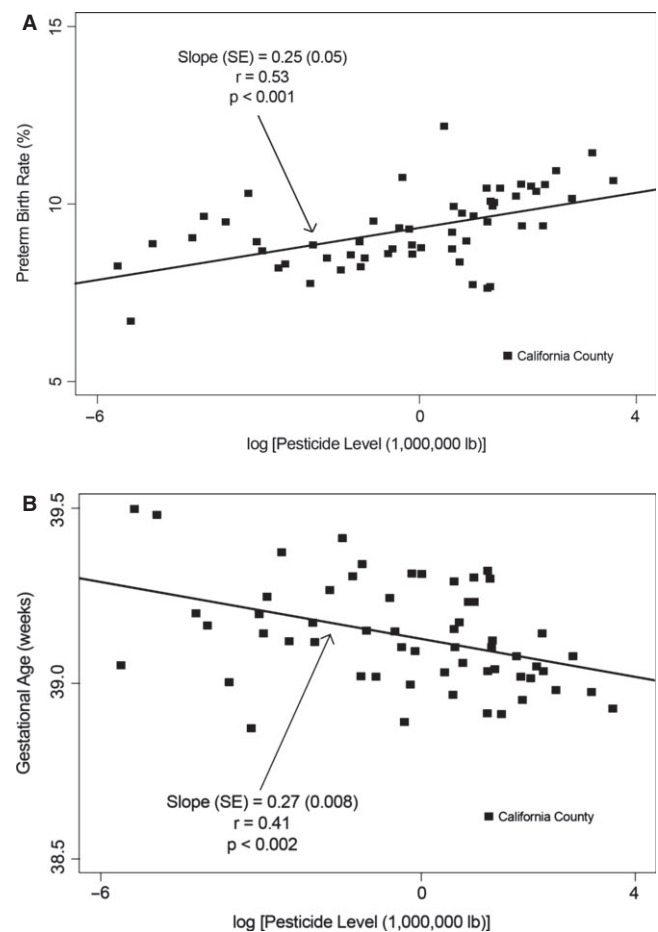
A total of 7 940 794 singleton live births from 58 California counties from 1990 to 2005 were analysed for PTB and gestational length. The mean (95% CI) PTB was 9.5% (9.4%, 9.6%) (Table 1). PTB varied significantly by maternal race (Black > Hispanic > other > White) and maternal age [ $<20$  years) > ( $>35$  years) > (20–35 years)]. PTB was significantly increased in pregnancies complicated by hypertension, diabetes, tobacco or alcohol use, and birth defects (Table 1). PTB increased for each race over the study period (data not shown). PTB was significantly increased with increasing total pesticide use and for increasing pesticide-use type (Table 2).

PTB rates were lower in *low* ( $8.59 \pm 0.11\%$ ) than in *moderate* ( $9.25 \pm 0.07\%$ ) and *high* pesticide-use counties ( $10.0 \pm 0.06\%$ )  $p$ 's < 0.001 (Table 3). Births in counties with *low vs. high* and *moderate vs. high* pesticide use were significantly more likely to be preterm in Hispanics and Whites, but similar trends did not reach significance for Blacks (Table 3). Trends for increasing PTB with increasing pesticide use remained significant after hypertension, and diabetes, tobacco or alcohol use was excluded. Three levels of preterm birth ( $\leq 36$ ,  $\leq 33$ ,  $\leq 27$  weeks) were separately analysed for counties of *low*, *moderate* and *high* pesticide use (Table 3). This was performed to establish whether pesticide use influences differing degrees of prematurity, where extreme prematurity ( $\leq 27$  weeks) would have the greatest clinical impact. Associations remained significant for  $<33$  and  $<27$ -week preterm births. All comparisons between *low vs. high* and *moderate vs. high* pesticide-use counties were significant for all preterm birth levels for Whites and Hispanics. Blacks in *high* pesticide-use counties were more likely to be  $\leq 33$  weeks premature than in *low* and *moderate* pesticide-use counties (Table 3). Pesticides were significantly associated with PTB: slope (SE) = 0.25(0.05),  $r = 0.53$ ,  $p < 0.001$  (Fig. 1A).

PTB ( $\leq 36$  weeks) was significantly higher ( $p < 0.001$ ) in the months of *peak* pesticide use ( $10.01 \pm 0.05\%$ ) vs. *nonpeak* months ( $9.36 \pm 0.05\%$ ) (Table 4). PTB was likewise higher for  $\leq 33$  and  $\leq 27$  weeks for all races in *peak vs. nonpeak* months. Mothers with or without hypertension and diabetes were more likely to have preterm births in *peak vs. nonpeak* months. Pregnancies without reported tobacco or alcohol use were more likely to have preterm births in *peak vs. nonpeak* months ( $p < 0.001$ ), but tobacco- or alcohol-use pregnancies did not show significant differences in *peak vs. nonpeak* months in  $<36$  and  $<33$ -week PTB. Pregnancies with alcohol or tobacco use were more likely to have PTB at  $<27$  weeks in *peak vs. nonpeak* pesticide months (Table 4).

### Gestational length

The overall mean  $\pm$  SE gestation was  $39.0 \pm 0.002$  weeks among all births in all counties. Counties with *low* pesticide



**Figure 1** (A) County preterm birth rates versus county pesticide use in California. (B) County gestational lengths versus county pesticide use in California.

use had significantly longer gestations than *moderate* or *high* pesticide use ( $p < 0.001$ ); mean  $\pm$  SE was  $39.197 \pm 0.014$ ;  $39.126 \pm 0.011$ ; and  $39.049 \pm 0.011$  weeks, respectively (Table 5). For all races, county pesticide-use comparisons of *low vs. high* and *moderate vs. high* were significant. *Low vs. moderate* pesticide-use comparisons by race was not significant except for Blacks. Generally, no significant trends were found when gestations were compared with county pesticide use in pregnancies complicated by diabetes, tobacco and alcohol use. However, in pregnancies with hypertension, *low vs. high* and *low vs. moderate* comparisons were significant. In mothers without diabetes, tobacco or alcohol use, newborns had longer gestations in lower vs. higher pesticide-use counties, (*low*  $39.248 \pm 0.014$  weeks; *moderate*  $39.170 \pm 0.011$  weeks; and *high*  $39.086 \pm 0.010$  weeks) (Table 5). When only term babies ( $\geq 37$  weeks) were analysed, gestational length was significantly shorter in *low vs. high* and *moderate vs. high* infants. The effect was only significant in White mothers and pregnancies without hypertension, diabetes, tobacco and alcohol.

**Table 4** Preterm birth by peak and nonpeak pesticide use

Gestation	Population/subpopulation	Category	Preterm birth per 10 000 live births		p-Value (I) vs. (II)	
			(I) Mean ± SE May and June	(II) Mean ± SE Other months		
≤36 weeks	All		10.01 ± 0.05	9.36 ± 0.05	<0.001	
	No risk factors*		9.61 ± 0.06	8.97 ± 0.05	<0.001	
	Maternal age	<20		11.34 ± 0.07	1.60 ± 0.02	<0.001
		20–35		12.48 ± 0.10	1.80 ± 0.04	<0.001
		>35		8.95 ± 0.05	1.15 ± 0.01	<0.001
	Race/ethnicity	Hispanic		10.62 ± 0.06	9.68 ± 0.05	<0.001
		White		8.84 ± 0.06	8.52 ± 0.05	<0.001
		Black		15.50 ± 0.15	14.32 ± 0.10	<0.001
	Hypertension	Yes		25.07 ± 0.34	24.37 ± 0.24	0.015
		No		9.68 ± 0.06	9.04 ± 0.05	<0.001
	Diabetes	Yes		14.16 ± 0.24	13.33 ± 0.13	0.001
		No		9.93 ± 0.05	9.28 ± 0.05	<0.001
	Tobacco	Yes		22.07 ± 3.06	21.52 ± 1.41	0.868
		No		10.00 ± 0.05	9.35 ± 0.05	<0.001
Alcohol	Yes		25.81 ± 5.34	25.37 ± 2.60	0.939	
	No		10.01 ± 0.05	9.36 ± 0.05	<0.001	
≤33 weeks	All		2.74 ± 0.02	2.45 ± 0.02	<0.001	
	No risk factors*		2.59 ± 0.02	2.30 ± 0.02	<0.001	
	Maternal age	<20		0.96 ± 0.01	2.55 ± 0.02	<0.001
		20–35		1.17 ± 0.02	3.10 ± 0.04	<0.001
		>35		1.26 ± 0.03	3.37 ± 0.06	<0.001
	Race/ethnicity	Hispanic		2.95 ± 0.03	2.52 ± 0.02	<0.001
		White		2.25 ± 0.03	2.14 ± 0.02	<0.001
		Black		5.30 ± 0.09	4.81 ± 0.05	<0.001
	Hypertension	Yes		8.79 ± 0.20	8.18 ± 0.13	0.001
		No		2.60 ± 0.02	2.32 ± 0.02	<0.001
	Diabetes	Yes		3.66 ± 0.13	3.31 ± 0.06	0.007
		No		2.72 ± 0.02	2.43 ± 0.02	<0.001
	Tobacco	Yes		13.20 ± 2.20	9.46 ± 1.09	0.107
		No		2.74 ± 0.02	2.44 ± 0.02	<0.001
Alcohol	Yes		18.12 ± 4.21	12.73 ± 2.15	0.226	
	No		2.74 ± 0.02	2.45 ± 0.02	<0.001	
≤27 weeks	All		0.38 ± 0.01	0.33 ± 0.00	<0.001	
	No risk factors*		0.36 ± 0.01	0.32 ± 0.00	<0.001	
	Maternal age	<20		9.57 ± 0.05	1.26 ± 0.01	<0.001
		20–35		11.50 ± 0.08	1.53 ± 0.02	<0.001
		>35		11.95 ± 0.12	1.66 ± 0.04	<0.001
	Race/ethnicity	Hispanic		0.37 ± 0.01	0.33 ± 0.00	<0.001
		White		0.30 ± 0.01	0.28 ± 0.00	0.037
		Black		1.03 ± 0.03	0.89 ± 0.02	<0.001
	Hypertension	Yes		1.00 ± 0.06	0.93 ± 0.03	0.244
		No		0.36 ± 0.01	0.32 ± 0.00	<0.001
	Diabetes	Yes		0.38 ± 0.04	0.30 ± 0.02	0.062
		No		0.38 ± 0.01	0.33 ± 0.00	<0.001
	Tobacco	Yes		3.63 ± 0.93	1.29 ± 0.41	0.022
		No		0.37 ± 0.01	0.33 ± 0.00	<0.001
Alcohol	Yes		4.34 ± 1.35	0.87 ± 0.62	0.020	
	No		0.37 ± 0.01	0.33 ± 0.00	<0.001	

\*Excludes risk factors: hypertension, alcohol, tobacco and diabetes.

Gestations were significantly shorter ( $p < 0.001$ ) for babies born in the *peak* pesticide months ( $39.069 \pm 0.007$ ) compared with *nonpeak* months ( $39.122 \pm 0.007$ ) (Table 6). Shortened gestations in *peak* months were

significant for all races, and in pregnancies with maternal hypertension and maternal diabetes. Mothers with reported use of alcohol or tobacco had no difference in gestations in *peak* vs. *nonpeak* months (Table 6). When

**Table 5** Gestational length by county pesticide use

Gestation	Population/subpopulation	Category	Gestational length			p-Value L vs. M	p-Value L vs. H	p-Value M vs. H	
			Mean ± SE Low (L)	Mean ± SE Moderate (M)	Mean ± SE High (H)				
All gestations	All		39.197 ± 0.014	39.126 ± 0.011	39.049 ± 0.011	0.000	0.000	<0.001	
	No risk factors*		39.248 ± 0.014	39.170 ± 0.011	39.086 ± 0.010	0.000	0.000	<0.001	
	Maternal age	<20		39.287 ± 0.023	39.105 ± 0.013	39.018 ± 0.011	0.000	0.000	<0.001
		20–35		39.227 ± 0.014	39.166 ± 0.011	39.093 ± 0.010	0.001	0.000	<0.001
		>35		38.880 ± 0.022	38.760 ± 0.014	38.683 ± 0.013	0.000	0.000	<0.001
	Race/ethnicity	Hispanic		39.095 ± 0.020	39.120 ± 0.011	39.046 ± 0.009	0.280	0.025	<0.001
		White		39.235 ± 0.015	39.214 ± 0.012	39.141 ± 0.012	0.288	0.000	<0.001
		Black		38.707 ± 0.045	38.603 ± 0.014	38.533 ± 0.014	0.028	0.000	<0.001
	Hypertension	Yes		38.125 ± 0.049	37.869 ± 0.031	37.853 ± 0.029	0.000	0.000	0.716
		No		39.233 ± 0.014	39.159 ± 0.011	39.079 ± 0.010	0.000	0.000	<0.001
	Diabetes	Yes		38.567 ± 0.036	38.553 ± 0.017	38.575 ± 0.016	0.715	0.840	0.330
		No		39.209 ± 0.014	39.137 ± 0.011	39.059 ± 0.011	0.000	0.000	<0.001
	Tobacco	Yes		37.998 ± 0.230	38.211 ± 0.198	38.322 ± 0.201	0.485	0.290	0.693
		No		39.202 ± 0.014	39.126 ± 0.011	39.050 ± 0.011	0.000	0.000	<0.001
Alcohol	Yes		38.779 ± 0.493	37.888 ± 0.320	37.485 ± 0.308	0.132	0.027	0.365	
	No		39.198 ± 0.014	39.126 ± 0.011	39.049 ± 0.011	0.000	0.000	<0.001	
≥37 weeks	All		39.691 ± 0.012	39.667 ± 0.010	39.636 ± 0.010	0.125	0.000	0.025	
	No risk factors*		39.713 ± 0.012	39.684 ± 0.010	39.650 ± 0.010	0.075	0.000	0.014	
	Maternal age	<20		39.906 ± 0.019	39.811 ± 0.012	39.753 ± 0.011	0.000	0.000	<0.001
		20–35		39.692 ± 0.012	39.674 ± 0.010	39.643 ± 0.009	0.250	0.001	0.020
		>35		39.446 ± 0.016	39.391 ± 0.010	39.366 ± 0.009	0.003	0.000	0.075
	Race/ethnicity	Hispanic		39.617 ± 0.016	39.668 ± 0.009	39.646 ± 0.009	0.007	0.119	0.078
		White		39.710 ± 0.013	39.701 ± 0.011	39.658 ± 0.011	0.609	0.003	0.006
		Black		39.571 ± 0.032	39.527 ± 0.012	39.508 ± 0.011	0.188	0.060	0.248
	Hypertension	Yes		39.249 ± 0.027	39.218 ± 0.016	39.251 ± 0.015	0.316	0.943	0.125
		No		39.705 ± 0.012	39.678 ± 0.010	39.644 ± 0.010	0.087	0.000	0.015
	Diabetes	Yes		39.229 ± 0.026	39.253 ± 0.012	39.272 ± 0.011	0.410	0.125	0.237
		No		39.700 ± 0.012	39.675 ± 0.010	39.643 ± 0.010	0.108	0.000	0.023
	Tobacco	Yes		39.789 ± 0.131	39.872 ± 0.105	39.621 ± 0.103	0.619	0.316	0.089
		No		39.691 ± 0.012	39.667 ± 0.010	39.636 ± 0.010	0.124	0.000	0.025
Alcohol	Yes		40.062 ± 0.262	39.529 ± 0.174	39.636 ± 0.168	0.093	0.174	0.659	
	No		39.691 ± 0.012	39.667 ± 0.010	39.636 ± 0.010	0.129	0.000	0.025	

\*Excludes risk factors: hypertension, alcohol, tobacco and diabetes.

term infants were analysed, gestations remained significantly shorter for *peak* vs. *nonpeak* months except in high-risk groups (>35 years of age, hypertension, diabetes, alcohol and tobacco use) (Table 6). Pesticides were significantly associated with shortened gestation: slope (SE) = 0.027(0.008),  $r + 0.41$ ,  $p = 0.002$  (Fig. 1B).

### Pesticide type

Counties were ranked by pesticide type: fungicides, insecticides, fumigants, herbicides, and others. PTB and gestational length were compared between low, moderate and high pesticide-use counties. Each individual pesticide type was found to be significantly correlated with PTB and gestational length. All *low* vs. *high* comparisons were significant ( $p < 0.001$ ), and all *moderate* vs. *high* comparisons were significant except for fungicides. Thus, whether ranked by total pesticides or by individual pesticide type, pesticide use in maternal county of residence predicted

higher PTB rate and shorter gestational length in higher pesticide-use counties (Table 2).

### Metro areas

Counties were analysed as small, medium or large metropolitan (mostly rural to mostly urban). PTB was significantly higher in *high* pesticide-use counties (*small*  $9.81 \pm 0.10$ , *medium*  $10.78 \pm 0.12$ , *large*  $9.72 \pm 0.10$ ) vs. *low* pesticide-use counties (*small*  $8.95 \pm 0.20$ , *medium*  $8.66 \pm 0.13$ , *large*  $8.86 \pm 0.11$ ) within each metro category ( $p < 0.001$ ). Pesticide use within metro areas had variable effects on gestational length. Only in medium metro counties was gestational length in low pesticide counties significantly longer than in high pesticide counties (*low*  $39.183 \pm 0.021$ , *high*  $38.990 \pm 0.02$ ,  $p < 0.001$ ) (data not shown).

When San Francisco and Los Angeles counties (the two largest metro areas) were excluded, higher PTB (*low*  $8.60 \pm 0.11$ , *mod*  $9.24 \pm 0.07$ , *high*  $9.97 \pm 0.07$ ) and

**Table 6** Gestational length by peak and nonpeak pesticide use

Gestation	Population/subpopulation	Category	Gestational length		p-Value (I) vs. (II)	
			(I) Mean ± SE May and June	(II) Mean ± SE Other months		
All gestation	All		39.069 ± 0.007	39.122 ± 0.007	<0.001	
	No risk factors*		39.022 ± 0.007	39.093 ± 0.007	<0.001	
	Maternal age	<20		39.015 ± 0.011	39.104 ± 0.009	<0.001
		20–35		39.108 ± 0.007	39.159 ± 0.007	<0.001
		>35		38.717 ± 0.011	38.751 ± 0.009	<0.001
	Race/ethnicity	Hispanic		39.112 ± 0.007	39.164 ± 0.007	<0.001
		White		39.167 ± 0.008	39.196 ± 0.008	<0.001
		Black		38.495 ± 0.014	38.593 ± 0.010	<0.001
	Hypertension	Yes		37.856 ± 0.026	37.913 ± 0.020	0.006
		No		39.102 ± 0.007	39.154 ± 0.007	<0.001
	Diabetes	Yes		38.510 ± 0.018	38.575 ± 0.011	<0.001
		No		39.080 ± 0.007	39.132 ± 0.007	<0.001
	Tobacco	Yes		37.818 ± 0.275	38.264 ± 0.129	0.130
		No		39.070 ± 0.007	39.123 ± 0.007	<0.001
Alcohol	Yes		37.701 ± 0.461	37.898 ± 0.215	0.696	
	No		39.069 ± 0.007	39.122 ± 0.007	<0.001	
≥37 weeks	All		39.655 ± 0.006	39.663 ± 0.006	<0.001	
	No risk factors*		39.671 ± 0.006	39.680 ± 0.006	<0.001	
	Maternal age	<20		39.790 ± 0.009	39.803 ± 0.008	0.017
		20–35		39.659 ± 0.006	39.667 ± 0.006	<0.001
		>35		39.388 ± 0.008	39.390 ± 0.006	0.678
	Race/ethnicity	Hispanic		39.646 ± 0.006	39.652 ± 0.006	0.050
		White		39.678 ± 0.007	39.689 ± 0.007	<0.001
		Black		39.508 ± 0.010	39.522 ± 0.008	0.059
	Hypertension	Yes		39.243 ± 0.015	39.236 ± 0.010	0.599
		No		39.665 ± 0.006	39.673 ± 0.006	<0.001
	Diabetes	Yes		39.249 ± 0.013	39.262 ± 0.008	0.282
		No		39.662 ± 0.006	39.670 ± 0.006	<0.001
	Tobacco	Yes		39.616 ± 0.161	39.781 ± 0.070	0.347
		No		39.654 ± 0.006	39.663 ± 0.006	<0.001
Alcohol	Yes		40.023 ± 0.261	39.596 ± 0.120	0.138	
	No		39.654 ± 0.006	39.663 ± 0.006	<0.001	

\*Excludes risk factors: hypertension, alcohol, tobacco and diabetes.

shorter gestations (*low* 39.197 ± 0.014, *mod* 39.134 ± 0.011, *high* 39.058 ± 0.011) in lower to higher pesticide-use counties remained significant ( $p < 0.001$ ) (data not shown).

### Summary

Pesticide use in maternal county of residence was associated with higher PTB rates and shorter gestations (Fig. 2A and B). *Peak* pesticide months were associated with greater PTB and shorter gestations within moderate and high pesticide-use counties (Fig. 2A and B).

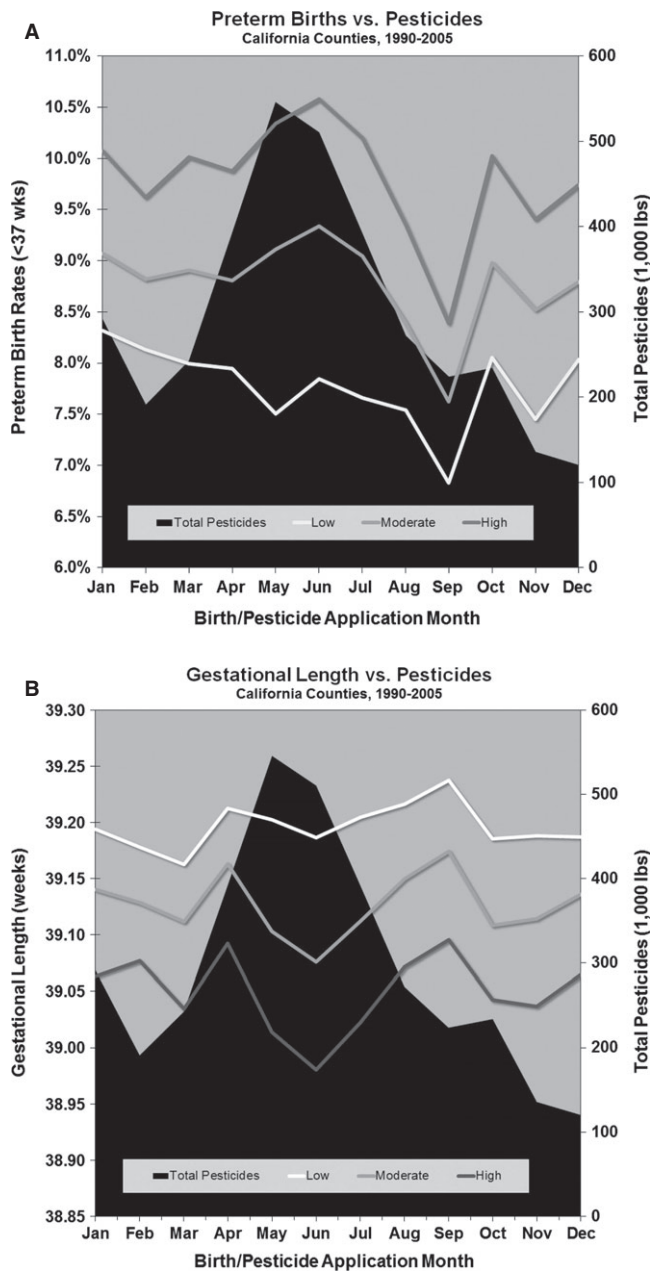
### DISCUSSION

This study found increased PTB and shortened gestation with increasing pesticide use *geographically* in maternal county of residence and *temporally* in *peak* pesticide-use months. Babies born in *peak* pesticide months were more

likely to be preterm and have shorter gestations (Table 5, Fig. 2A and B).

The association between prenatal exposure and foetal growth or gestational duration in humans has been reviewed (6). Organophosphate pesticides, especially at the end of pregnancy, significantly correlated with shortened gestation in a population of Latina women in the Salinas Valley, California (6). As this population had relatively low PTB, the authors concluded that the association between shortened gestation and pesticides 'did not seem to have clinical implications for this (Latina) population.' Women with hypertension, diabetes, twins and prior stillbirths were excluded (6).

In another study, male exposure to combinations of activities with a variety of pesticides [atrazine, glyphosate, organophosphates, 4-(2,4-dichlorophenoxy) butyric acid and insecticides] was associated with odds ratios of two or greater for preterm delivery (10).



**Figure 2** (A) Monthly preterm birth and total pesticide use in low, moderate and high pesticide-use counties. (B) Monthly gestational age and total pesticide use in low, moderate and high pesticide-use counties.

Additional studies have correlated urinary biomarkers of pesticide exposure with PTB and shortened gestation (11–13). Pesticides have been linked to altered cholinesterase enzyme expression and endocrine disruption (6,13,14). Pesticides such as vinclozolin, methoxychlor, permethrin and the insect repellent DEET can alter DNA methylation and cause transgenerational effects in rodents (15–17).

In our study, pesticide exposure was estimated with geospatial and temporal California PUR data. Other studies in California correlated urinary organophosphate pesticide levels with season and location of exposure (18), which suggests that the California PUR data (while not as definitive as biomarker data) will likely correlate with population exposure.

This study has several limitations. Increasing risk with increasing exposure may result from other unmeasured variables. Risk factors such as poverty, air pollution and nitrates might be correlated with pesticide use in California counties.

An approximate increase in PTB by 16% and shorter gestations by 0.135%, though statistically significant, might be interpreted as clinically insignificant. This increased PTB represents 112 000 more infants at risk of hospitalisation, mortality and morbidity in the California population. After controlling for risk factors, county pesticide exposure increased the risk of having a <27-week preterm infant by 35%. These infants have the highest mortality and morbidity of all preterm infants. The average 25- to 26-week preterm will require ~100 days of NICU care (costing between \$350 000 and \$800 000 per baby). Foetal and developmental origins of adult disease research suggested that the life-time risks of preterm birth may be underestimated (19). Prematurity has adverse effects on basic mathematic processing following birth at all gestations <36 weeks and on IQ and mathematic attainment <34 weeks GA (20). Global methylation across multiple organs has been reported in pregnancies with differing gestations (21). Through epigenetic mechanisms, pesticide exposure in pregnancy may alter lifetime risks of diseases. Epidemiological studies have already reported shorter life spans in Americans with birth months in *peak* pesticide months of May and June (22).

Many preterm birth risk factors were confirmed by this study. Maternal race, age, maternal hypertension, diabetes, tobacco or alcohol use, and infants with birth defects are known to be associated with preterm birth. In pregnancies with hypertension and diabetes, PTB were higher in *peak* vs. *nonpeak* pesticide months.

In conclusion, PTB and shortened gestation were found to be significantly related to pesticide use in maternal county of residence and to *peak* pesticide months. These geotemporal data suggest that pesticide exposure shortens the length of gestation and increases preterm birth risk across most demographic groups.

#### DISCLAIMERS

The views expressed in this article are that of the authors and not that of the institution or data providers.

#### SOURCE(S) OF SUPPORT

Unfunded.



**CONFLICT OF INTEREST**

The authors declare no financial conflict of interest.

**ACKNOWLEDGEMENTS**

We would like to thank Indiana University School of Medicine and Franciscan St. Francis Health for their support.

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