




Associations between residential proximity to agricultural land use as pesticides exposure and birth outcomes

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Received: 8 August 2022 / Accepted: 30 November 2022 / Published online: 7 December 2022
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Abstract

Pesticides are widely used globally. Due to their widespread use, exposure to pesticides is of concern. In addition to occupational exposure, residential exposure during pesticide application is a concern for those living in or near agricultural areas. The objective of this study was to analyze the association between residential proximity to agricultural pesticide use and birth outcomes. The association between residential proximity to agricultural land use as pesticide exposure and birth outcomes was explored in a birth cohort including 283 pregnant women from a medical center in Hualien during 2013–2016. In the third trimester, we collected demographic information and the residential addresses of pregnant women via structured questionnaires. After delivery, newborn birth weight, gestational age, and head circumference were collected from medical records. Maternal residential address during pregnancy was collected for geospatial mapping. The percentages of farmland area within circular buffers of different sizes were applied to estimate pesticide exposure. Associations between residential proximity to agricultural land use as pesticide exposure and birth outcomes were analyzed by multiple linear regression analyses. A significantly smaller head circumference was associated with agricultural farmland located within 400 m ($\beta = -0.51$ [95% CI, $-0.99, -0.03$], $P = 0.037$) and 500 m ($\beta = -0.67$ [95% CI, $-1.14, -0.19$], $P = 0.006$) radii of residences in the tertile 2 group. A significantly smaller head circumference was also associated with dry farming area within 400 m ($\beta = -0.70$ [95% CI, $-1.17, -0.24$], $P = 0.003$) and 500 m ($\beta = -0.81$ [95% CI, $-1.27, -0.34$], $P = 0.001$) radii of residences in the tertile 2 group. The multivariate linear regression analyses did not show any significant association between residential farmland area and birth weight or gestational age. In conclusion, residential proximity to agricultural land use as pesticide exposure was associated with negative infant birth outcomes, especially a small head circumference. In the future, agricultural land use information could be combined with biological samples to more accurately assess exposure in pregnant women.

Keywords Residential proximity · Pesticides · Prenatal · Pregnant woman · Birth outcome · Geographic information system

Introduction

Pesticides are widely used globally; it has been estimated that approximately two million tonnes of pesticides are applied annually (EPA 2021; Mathiesen et al. 2020). Based

Responsible Editor: Lotfi Aleya

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on data from the Food and Agriculture Organization in 2018, the most commonly used pesticides are herbicides, which account for 52.5%, followed by fungicides (23.6%), insecticides (19.6%), and other pesticides (4.3%) (FAO 2018). Due to their widespread usage, ubiquitous exposure to pesticides is of continuous concern. In addition to occupational exposure when working on farmland, residential exposure during pesticide application is a concern for those living in or near agricultural areas. Fetal exposure to pesticides is a global concern because of the sensitivity of fetuses to particular chemical toxicants (Abu-Qare et al. 2000; Mathiesen et al. 2020). Pesticide exposure during the gestational period, which is a critical phase for the developing fetus, may increase the risk of adverse health outcomes. Evidence has shown that chemicals can cross the placental barrier (Barr et al. 2007). Moreover, the exposure pattern in the growing fetus is substantially different from that in adults. Therefore, it is crucial to explore the potential health effects of pesticide exposure during pregnancy.

In recent decades, epidemiological studies applying spatial data are becoming popular due to rapid development of Geographic Information System (GIS) (Chang et al. 2014; Jerrett et al. 2010). The associations between residential proximity to agricultural areas and pesticide concentrations in environmental samples have been reported (Cordoba Gamboa et al. 2020; Gunier et al. 2011; Ward et al. 2006). Gamboa et al. found that pesticide concentrations tend to be higher in air samples from proximal schools to banana plantation than in those from non-proximal schools (Cordoba Gamboa et al. 2020). Moreover, residences that reported use of agricultural pesticides nearby showed higher pesticide concentrations in carpet dust than those without neighboring agricultural areas (Gunier et al. 2011). One meta-analysis concluded that the concentrations of dust pesticides quantifiably increased with increasing house proximity to treated agricultural fields (Deziel et al. 2017). Previous studies in Taiwan also found that residential proximity to an agricultural area was associated with the pesticide concentrations on outdoor dust particles around urban-like houses (Hung et al. 2018) and indoor dust particles in rural houses (Simarremare et al. 2021). Moreover, similar results were also revealed in human biomonitoring studies. Chevrier et al. found that residential proximity to corn crops was related to higher urinary concentrations of herbicide metabolites (Chevrier et al. 2014). Urinary metabolite levels of organophosphorus pesticides in children living in the agricultural area were also higher than those in the non-agricultural area (Fenske et al. 2000).

Because of the large number of subjects in a birth cohort study and a wide distribution of their residential address, collection of environmental samples is highly resource demanding (Cornelis et al. 2009; Hoek et al. 2008). Therefore, GIS-based methods, which are more convenient and

less time consuming, are commonly used in exposure assessment nowadays (Chang et al. 2014; Hoek et al. 2008, Ryan and LeMasters 2007). Although using human biomonitoring data to access the exposure status was one of the most used methods in epidemiology studies, one potential limitation is that the short half-lives of some biomarkers cannot represent long-term exposure. In contrast, the barely changed agricultural land use is suitable to evaluate long-term exposure to pesticides during pregnancy. Studies examining the association between residential proximity to pesticide application and fetal growth have been conducted (Almberg et al. 2014; Cecchi et al. 2021; Gemmill et al. 2013; Petit et al. 2010; Xiang et al. 2000). These studies used different residential proximity indicators, including rural and urban classifications (Cecchi et al. 2021), densities of particular crops (Almberg et al. 2014; Petit et al. 2010; Xiang et al. 2000) and estimated amounts of applied pesticides (Gemmill et al. 2013), to analyze associations with fetal outcomes. In general, most studies found adverse effects on birth outcomes, including birth weight (Gemmill et al. 2013; Xiang et al. 2000), birth length, head circumference (Cecchi et al. 2021; Gemmill et al. 2013; Petit et al. 2010), gestational age (Cecchi et al. 2021), low birth weight (Almberg et al. 2014), and preterm birth (Almberg et al. 2014). However, some studies showed no effects on birth weight (Cecchi et al. 2021; Petit et al. 2010), and increase gestational age (Gemmill et al. 2013). In addition, few studies have distinguished between occupational and residential pesticide exposure. Moreover, one review indicated a methodological limitation of using only the distance from the home (Shirangi et al. 2011). A review indicated that using the farmland area or amount of pesticides applied may improve accuracy (Dereumeaux et al. 2020). Accordingly, to exclude possible effects of occupational exposure and evaluate the effect of farmland area near the home, we conducted a prospective cohort study to examine whether agricultural land use near the home was associated with adverse birth outcomes.

Materials and methods

Study population and design

A birth cohort study was designed and conducted in Hualien County, Taiwan, from 2013 to 2016. Hualien County, which is located in the eastern part of Taiwan, contains approximately 10% agricultural land (according to the data provided by the Council of Agriculture, Executive Yuan, R.O.C., <https://agrstat.coa.gov.tw/sdweb/public/official/OfficialInformation.aspx>). Eligible participants, i.e., women over the age of 20 who underwent a prenatal examination in the selected hospital, were invited to enroll in the study. Overall, 401 mother-infant pairs were invited. Informed consent was

obtained from all the participants. Of the 401 participants included in the cohort, a total of 118 were excluded, and 283 (70.5%) were enrolled in the study. Twenty-six subjects were excluded due to a missing maternal residential address, 20 subjects due to missing birth outcome information, 15 subjects due to maternal smoking or alcohol consumption during pregnancy, 8 subjects due to twin birth or the presence of birth defects, 16 subjects due to maternal gestational diabetes mellitus or hypertension, and 33 subjects due to incomplete confounding factor information (Fig. S1). The study protocol was reviewed and approved by the Ethical Committee of Tzu Chi General Hospital (Number: IRB102-71). To collect the information about the study population and potential confounding factors, a face-to-face interview with each pregnant woman was conducted by trained research staff during the 3rd trimester using a structured questionnaire. The structured questionnaire collected demographic, medical history, residential history, lifestyle, occupational history, and home environment data.

Occupational pesticide exposure

To explore the possible effects of occupational pesticide exposure on infant birth outcomes, parental occupational information, such as employment as a farmer or selling or contacting pesticides during pregnancy, was gathered during the face-to-face interview.

Maternal residential proximity to farmland during pregnancy

Maternal residential addresses during pregnancy were collected for geospatial mapping. Land cover and land use information was obtained from the National Land Surveying and Mapping Center, Ministry of the Interior, Taiwan (<https://www.nlsc.gov.tw/cl.aspx?n=13705>). Land use information was mainly classified by remote sensing technology combined with geographic information systems data and field surveys. Predictor variables, i.e., the percentages of farmland area within circular buffers of different sizes, were applied to estimate pesticide exposure. The considered buffer radii were 100, 200, 300, 400, and 500 m around each subject's house. The definition of maternal residential proximity to farmland is shown in Fig. 1. The type of crop farming, including dry farming (i.e., vegetables, edible mushrooms, miscellaneous crops), fruit farming, and rice farming, was considered, and the area percentages within the buffers were treated as individual predictors. All the predictor variables were extracted using ArcGIS software (version 10.3, Esri, Redlands, CA, USA) with the Taiwan Datum 1997 (TWD97) coordinate system.

Birth outcomes

Fetal growth indicators, including birth weight [continuous; in grams (g)], head circumference [continuous; in centimeters (cm)], and gestational age (continuous; in weeks) of the infant at birth, were measured by experienced obstetric nurses and extracted from infants' medical records by pediatric clinical nurses.

Covariates

Risk factors that could potentially interfere with the causal relationship between pesticide exposure and infant birth outcomes were controlled as described in previous studies. In brief, maternal age (continuous; in years), education (categorical; \leq senior high school, college/university, or \geq master's degree/PhD), family income (< 0.5 million, 0.5 – 1 million, and > 1 million), parity (categorical; nulliparous or parous), and infant sex (categorical; male or female) were controlled for in the basic model (Model 1) in all the data analyses. Prepregnancy body mass index (BMI, continuous), exposure to secondhand smoke during pregnancy (categorical; yes or no), and season of early pregnancy (categorical; February to April, May to July, August to October, November to January) were additionally adjusted for in Model 2. Model 3 was adjusted for all the covariates in Model 2 plus gestational age (continuous; in weeks).

Statistical analysis

Statistical analysis

For continuous variables in the descriptive analysis, means and standard deviations (SDs) obtained from independent sample *t* tests were used for comparisons between two groups. Numbers (frequencies) with corresponding percentages obtained with chi-square tests were used for comparisons of categorical variables. We divided farmland area into three groups according to the area percentages within the buffers of different radii for further analysis: tertile 1 (≤ 33.3 rd percentile), tertile 2 (33.3rd – 66.7th percentile), and tertile 3 (> 66.7 th percentile). The categorization failed when more than 33.3% of subjects had no exposure information, i.e., there was no farmland within the buffer of certain radius. The farmland area within a specific buffer size that could not be classified was not included in the subsequent linear regression analysis. We examined associations between the percentage of farmland and birth outcomes (birth weight, head circumference, and gestational age) with uni- and multivariate linear regression analyses and 95% confidence intervals (CIs). Trend tests were conducted to explore the dose–response relationship between residential proximity to agricultural land use for pesticide exposure and

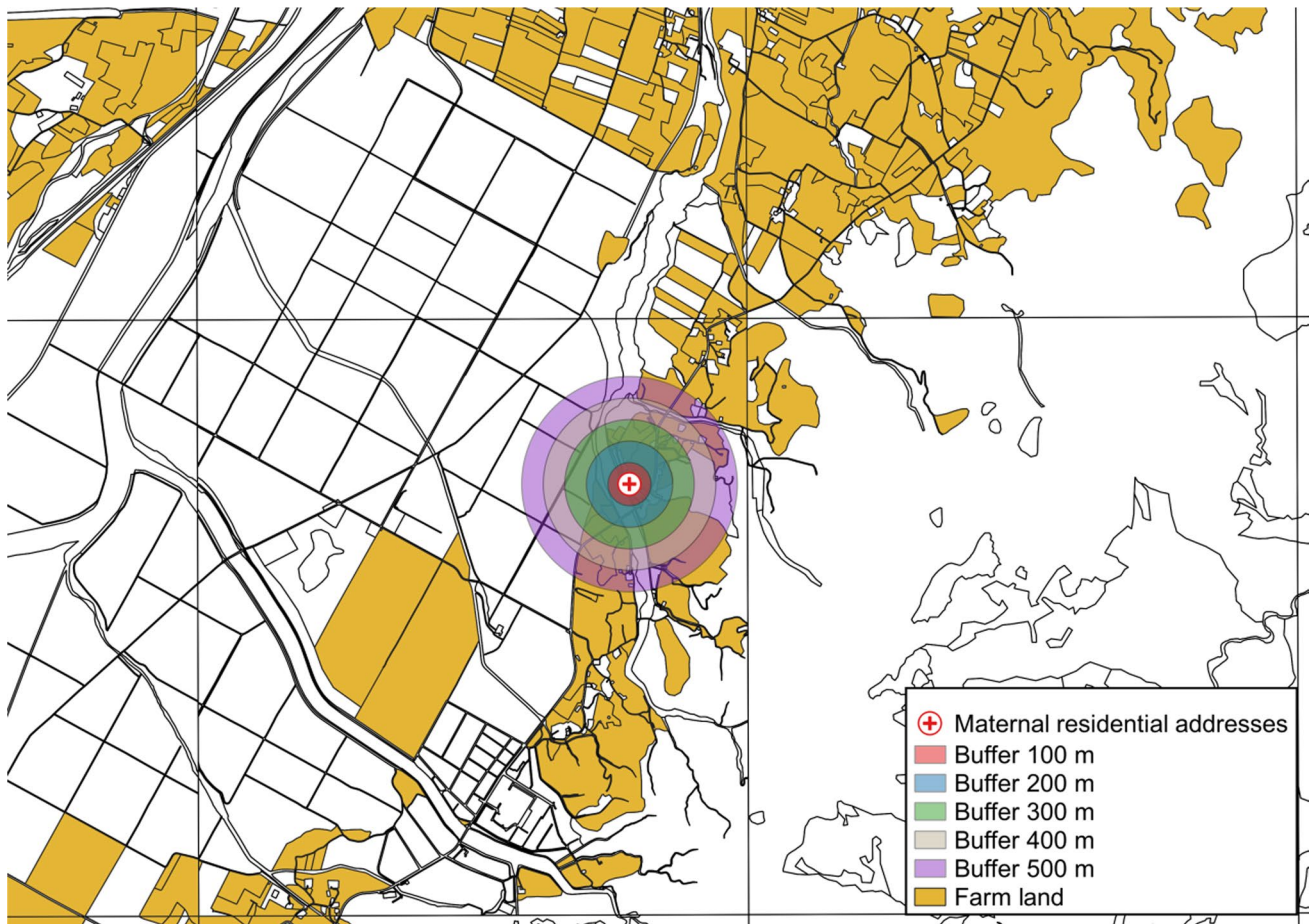


Fig. 1 Definition of maternal residential proximity to farmland

birth outcomes. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS Statistics version 28.0 (IBM, Armonk, NY, USA). All tests were two tailed, and statistical significance was considered at $P < 0.05$.

Results

Study participant characteristics

A comparison between total study subjects and excluded subjects is shown in Table 1. The excluded subjects were more likely to have worse birth outcomes than the included subjects, including a smaller gestational age, a lower birth weight, a smaller head circumference, and preterm birth. Among the subjects included in the analysis ($n = 283$), the mean age was 31.7 years old, the majority of mothers reported an education level of college or university (79.2%), the mean BMI before pregnancy was 21.7 kg/m², and the season of early pregnancy was mostly February to April (32.9%). A total of 146 (51.6%)

subjects were exposed to environmental tobacco smoke during pregnancy, and 113 (39.9%) were primiparas. In total, 159 (56.2%) newborns were boys. In terms of birth outcomes, mean gestational age, birth weight, and head circumference were 38.5 weeks, 3095.0 g, and 33.8 cm, respectively. The rates of preterm birth and low birth weight were 3.9% and 4.9%, respectively (Table 1). We also present the baseline characteristics of the 283 subjects stratified by parental occupational exposure status. Among them, 253 (89.4%) had no parental occupational exposure, and 30 (10.6%) had parental occupational exposure. Regarding occupational exposure status, head circumference in the parental occupational exposure group was significantly smaller ($P = 0.027$) than that in the non-parental occupational exposure group. There were no differences in the other variables.

Parental occupational exposure during pregnancy and birth outcomes

Table 2 shows the results of the linear regression analyses between parental occupational exposure during pregnancy

Table 1 Characteristics of the study population according to covariates

	Total study subjects (N=283, 100%) Mean ± SD or N (%)	No parental occupational exposure (N=253, 89.4%) Mean ± SD or N (%)	Parental occupational exposure (N=30, 10.6%)	Excluded subjects ^a (N=118) Mean ± SD or N (%)	P value ^b	
Maternal characteristics						
Age at delivery (years)	31.7 ± 4.3	31.7 ± 4.3	31.7 ± 4.1	0.965	31.6 ± 4.8	0.903
Educational level				0.387		0.301
≤ Senior high school	36 (12.7)	30 (11.9)	6 (20.0)		15 (18.1)	
College/University	224 (79.2)	203 (80.2)	21 (70.0)		59 (71.1)	
≥ Master's/PhD	23 (8.1)	20 (7.9)	3 (10.0)		9 (10.8)	
Prepregnancy BMI	21.7 ± 3.5	21.6 ± 3.6	22.5 ± 3.0	0.221	22.9 ± 4.3	0.021
Season of early pregnancy				0.582		0.602
February to April	93 (32.9)	81 (32.0)	12 (40.0)		29 (29.3)	
May to July	74 (26.1)	66 (26.1)	8 (26.7)		25 (25.3)	
August to October	65 (23.0)	61 (24.1)	4 (13.3)		21 (21.2)	
November to January	51 (18.0)	45 (17.8)	6 (20.0)		24 (24.2)	
Secondhand smoke exposure during pregnancy	146 (51.6)	132 (52.2)	14 (46.7)	0.570	35 (29.2)	0.924
Primipara	113 (39.9)	98 (38.7)	15 (50.0)	0.235	31 (33.0)	0.229
Family income, NTD						
< 0.5 million	73 (25.8)	65 (89.0)	8 (11.0)	0.632	16 (23.5)	0.919
0.5–1 million	176 (62.2)	156 (88.6)	20 (11.4)		44 (64.7)	
> 1 million	34 (12.0)	32 (94.1)	2 (5.9)		8 (11.8)	
Child characteristics						
Male sex	159 (56.2)	144 (56.9)	15 (50.0)	0.472	47 (56.0)	0.970
Gestational age (week)	38.5 ± 1.2	38.5 ± 1.2	38.6 ± 1.3	0.872	37.5 ± 2.5	< 0.0001
Birth weight (g)	3095 ± 374.1	3109.3 ± 375	2974.3 ± 347	0.062	2933.7 ± 631.8	0.004
Head circumference (cm)	33.8 ± 1.6	33.9 ± 1.6	33.2 ± 1.4	0.027	33.1 ± 2.19	0.001
Preterm birth	11 (3.9)	9 (3.6)	2 (6.7)	0.407	13 (15.5)	< 0.0001
Low birth weight	14 (4.9)	12 (4.7)	2 (6.7)	0.647	15 (17.6)	< 0.0001

BMI body mass index

^aData were available for maternal age at delivery (n=118), maternal education (n=83), family income (n=68), season of early pregnancy (n=99), prepregnancy BMI (n=67), secondhand smoke exposure during pregnancy (n=67), primipara status (n=94), infant sex (n=84), gestational age (n=84), birth weight (n=80), and head circumference (n=80) for the excluded subjects

^bP value indicates the comparison between the total study subjects and excluded subjects

Table 2 Crude and adjusted estimated differences (95% CIs) for the association between parental occupational exposure during pregnancy and birth outcomes (N=283)

	Parental occupational exposure vs. no parental occupational exposure					
	Birth weight		Head circumference		Gestational age	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Crude	-135.01 (-276.59, 6.57)	0.062	-0.68 (-1.28, -0.08)*	0.028	0.04 (-0.41, 0.49)	0.872
Model 1	-153.75 (-304.80, -2.71)*	0.046	-0.63 (-1.26, 0.002)	0.051	-0.10 (-0.58, 0.38)	0.682
Model 2	-156.15 (-295.57, -16.73)*	0.028	-0.70 (-1.29, -0.11)*	0.021	-0.03 (-0.49, 0.43)	0.894
Model 3	-151.52 (-276.53, -26.50)*	0.018	-0.69 (-1.26, -0.12)*	0.018	-	-

Model 1 was adjusted for maternal age, education, family income, parity, and infant sex

Model 2 was adjusted for the covariates in Model 1 plus prepregnancy BMI, exposure to secondhand smoke during pregnancy, and season of early pregnancy

Model 3 was adjusted for the covariates in Model 2 plus gestational age

* < 0.05

and birth outcomes. We used different models to confirm the consistency of the results. Model 1 adjusted for maternal age, education, family income, parity, and infant sex. Model 2 was adjusted for the covariates in Model 1 plus prepregnancy BMI, exposure to secondhand smoke during pregnancy, and season of early pregnancy. Model 3 was adjusted for the covariates in Model 2 plus gestational age. Compared with the no parental occupational exposure group, the parental occupational exposure group had a significantly lower birth weight in all the models. In Model 3, the difference in birth weight was significant ($\beta = -151.52$ [95% CI, $-276.53, -26.50$], $P=0.018$). Moreover, the parental occupational exposure group tended to have a smaller head circumference in Model 2 ($\beta = -0.70$ [95% CI, $-1.29, -0.11$], $P=0.021$) and Model 3 ($\beta = -0.69$ [95% CI, $-1.26, -0.12$], $P=0.018$). Gestational age was not significantly different in all the models.

Distribution of residential farmland areas with different crops

Figure S2 shows the percentages of subjects with farmland used for different types of farming, including dry farming (i.e., vegetables, edible mushrooms, miscellaneous crops), fruit farming, and rice farming, within buffer radii of 100, 200, 300, 400, and 500 m of their houses. Regarding total agricultural area, the percentages of subjects with farmland within 100, 200, 300, 400, and 500 m of their house were 61.3%, 85.0%, 92.9%, 95.3%, and 97.2%, respectively. The majority of crops were dry crops, followed by fruit and rice. Regarding dry farming areas, the percentages of subjects with farmland within 100, 200, 300, 400, and 500 m of their house were 52.6%, 81.4%, 90.5%, 95.3%, and 96.4%, respectively. For fruit farming areas, the percentages of subjects with farmland within 100, 200, 300, 400, and 500 m of their house were 31.6%, 58.1%, 79.4%, 90.5%, and 92.5%, respectively. Regarding rice farming areas, the percentages of subjects with farmland within 100, 200, 300, 400, and 500 m of their house were 4.3%, 11.1%, 17.8%, 24.9%, and 30.0%, respectively.

Table 3 shows the areas of residential farmland divided into the three tertiles by crop type. We classified farmland area into tertiles. Only the percentages with farmland exceeding 66.7% within each buffer zone are shown in Table 3. Because the percentages of rice farming with the 100, 200, 300, 400, and 500 m buffer zones were all less than 66.7%, the tertile analysis did not include rice farming areas. The percentages of total farming areas of tertile 1 (33.3rd percentile) within the 200, 300, 400, and 500 m buffer zones were 1.5%, 1.9%, 3.5%, and 5.2%, respectively. The percentages of tertile 2 (33.3rd – 66.7th percentile) within the 200, 300, 400, and 500 m buffer zones were 14.5%, 21.8%, 21.7%, and 23.0%, respectively. The percentages of dry farming areas of tertile 1 (33.3rd percentile) within the 200, 300, 400, and 500 m buffer zones were 0.8%, 1.2%, 1.8%,

Table 3 Percentages of residential farmland areas divided into tertiles by crop type ($N=253$)

Buffer distance (m)	Total farmland area			Dry farming area			Fruit farming area				
	Category of percentage of total farmland area ^a			Category of percentage of dry farming area ^a			Category of percentage of fruit farming area ^a				
	0% (no farmland area)	>0% (with farmland area)	N (%)	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3		
200 m	38 (15.0)	215 (85.0)		1.5%	14.5%	47 (18.6)	206 (81.4)	0.8%	8.5%	106 (41.9)	147 (58.1) ^c
300 m	18 (7.1)	235 (92.9)		1.9%	21.8%	24 (9.5)	229 (90.5)	1.2%	10.7%	52 (20.6)	201 (79.4)
400 m	12 (4.7)	241 (95.3)		3.5%	21.7%	12 (4.7)	241 (95.3)	1.8%	11.2%	24 (9.5)	229 (90.5)
500 m	7(2.8)	246 (97.2)		5.2%	23.0%	9 (3.6)	244 (96.4)	2.8%	13.9%	19 (7.5)	234 (92.5)
				Cutoff point of tertiles ^b			Cutoff point of tertiles ^b			Cutoff point of tertiles ^b	

^aPercentage of residential farmland area (%): proportion of the farmland area among the total area

^bCutoff point of tertile 1 (33.3rd percentile); cutoff point of tertile 2 (66.7th percentile)

^cOnly the percentages with farmland over 66.7% are shown in Table 3

and 2.8%, respectively. The percentages of tertile 2 (> 66.7th percentile) within the 200, 300, 400, and 500 m buffer zones were 8.5%, 10.7%, 11.2%, and 13.9%, respectively. The percentages of fruit farming areas of tertile 1 (33.3rd percentile) within the 300, 400, and 500 m buffer zones were 0.3%, 0.6%, and 0.8%, respectively. The percentages of tertile 2 (33.3rd – 66.7th percentile) within the 300, 400, and 500 m buffer zones were 3.5%, 3.7%, and 3.7%, respectively.

Total residential farmland area and birth outcomes

Table 4 shows the associations between total residential farmland area and birth outcomes according to the multiple linear regression analyses. A significantly smaller head circumference was associated with agricultural land within a buffer radius of 500 m ($\beta = -0.64$ [95% CI, -1.13, -0.15], $P = 0.010$) in the tertile 2 group in Model 1. Additionally, adjustment of the

models for gestational age revealed significant associations between a smaller head circumference and agricultural land within buffer radii of 400 ($\beta = -0.51$ [95% CI, -0.99, -0.03], $P = 0.037$) and 500 m ($\beta = -0.67$ [95% CI, -1.14, -0.19], $P = 0.006$) in the tertile 2 group in Model 2. The multivariate linear regression analyses did not show any significant association between total residential farmland area and birth weight or gestational age (Model 1 and Model 2).

Residential farmland area with different crops and birth outcomes

Table 5 shows the associations of dry farming area and birth outcomes. A significantly smaller head circumference was associated with agricultural land within buffer radii of 400 ($\beta = -0.70$ [95% CI, -1.17, -0.24], $P = 0.003$) and 500 m ($\beta = -0.81$ [95% CI, -1.27, -0.34], $P = 0.001$) in the tertile

Table 4 Associations of total residential farmland area with birth outcomes (N=253)

Buffer zone (m)	Birth weight		Head circumference		Gestational age
	Model 1	Model 2	Model 1	Model 2	Model 1
	β (95% CI)		β (95% CI)		β (95% CI)
200 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-27.49 (-141.94, 86.96)	-23.02 (-125.68, 79.63)	-0.05 (-0.54, 0.45)	-0.03 (-0.51, 0.45)	-0.03 (-0.41, 0.34)
Tertile 3	22.67 (-89.95, 135.29)	23.29 (-77.72, 124.29)	0.14 (-0.35, 0.63)	0.14 (-0.33, 0.61)	-0.005 (-0.37, 0.36)
P for trend	0.6836	0.6419	0.5702	0.5441	0.9828
300 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-93.61 (-207.90, 20.67)	-76.58 (-179.14, 25.98)	-0.26 (-0.76, 0.23)	-0.23 (-0.71, 0.25)	-0.12 (-0.50, 0.25)
Tertile 3	-25.01 (-137.81, 87.80)	1.77 (-99.60, 103.14)	-0.03 (-0.53, 0.46)	0.03 (-0.44, 0.51)	-0.20 (-0.57, 0.17)
P for trend	0.6915	0.9396	0.9213	0.8580	0.2970
400 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-15.05 (-130.51, 100.41)	-34.28 (-137.92, 69.35)	-0.45 (-0.95, 0.05)	-0.51 (-0.99, -0.03)*	0.14 (-0.24, 0.52)
Tertile 3	25.21 (-89.23, 139.66)	5.60 (-97.14, 108.34)	-0.11 (-0.60, 0.39)	-0.16 (-0.64, 0.31)	0.14 (-0.23, 0.52)
P for trend	0.6514	0.8929	0.7171	0.5567	0.4575
500 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-66.50 (-180.98, 47.98)	-73.94 (-176.51, 28.63)	-0.64 (-1.13, -0.15)**	-0.67 (-1.14, -0.19)**	0.05 (-0.32, 0.43)
Tertile 3	-9.91 (-124.83, 105.00)	-19.65 (-122.62, 83.32)	-0.23 (-0.72, 0.26)	-0.26 (-0.73, 0.22)	0.07 (-0.30, 0.45)
P for trend	0.8850	0.7297	0.4086	0.3278	0.7111

Tertile 1 (≤ 33.3 rd percentile), tertile 2 (33.3rd–66.7th percentile), and tertile 3 (> 66.7th percentile)

Model 1 was adjusted for maternal age, education, family income, parity, prepregnancy BMI, exposure to secondhand smoke during pregnancy, season of early pregnancy, and infant sex

Model 2 adjusted for the covariates in Model 1 plus gestational age. * <0.05, ** <0.01

2 group in Model 2. A significantly lower birth weight was associated with agricultural land within buffer radii of 500 m ($\beta = -103.03$ [95% CI, $-203.64, -2.43$], $P = 0.045$) in the tertile 2 group in Model 2. There were no significant associations between dry farming area and gestational age. We found no associations between residential fruit farming area and birth outcomes (Table 6).

Discussion

In this prospective birth cohort, we investigated the associations of birth outcomes with occupational pesticide exposure and residential proximity to agricultural land use. We found that there was a significant negative association between

parental occupational exposure during pregnancy and birth outcomes. Moreover, we also found that residential proximity to agricultural land use, especially dry farming areas, as pesticide exposure was associated with a smaller head circumference.

In our study, a negative effect of residential proximity to agricultural land use as pesticide exposure on head circumference was observed. This finding was consistent with that of Petit et al.'s study (Petit et al. 2010). Petit et al. analyzed the associations of area of agricultural activity with birth outcomes in a prospective birth cohort. They found that the mean head circumference of children living in areas near pea farms was significantly smaller than that of those living in municipalities without pea farms (-0.2 cm, $P = 0.0002$), similar to our research results. Gemmill et al. conducted a longitudinal cohort

Table 5 Associations of dry farming area with birth outcomes ($N = 253$)

Buffer distance (m)	Birth weight		Head circumference		Gestational age
	Model 1	Model 2	Model 1	Model 2	Model 1
	β (95% CI)		β (95% CI)		β (95% CI)
200 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-9.11 ($-124.09, 105.87$)	-5.23 ($-108.33, 97.87$)	-0.02 ($-0.51, 0.48$)	-0.002 ($-0.48, 0.48$)	-0.03 ($-0.40, 0.35$)
Tertile 3	-16.87 ($-129.88, 96.15$)	20.24 ($-81.54, 122.01$)	0.005 ($-0.48, 0.49$)	0.10 ($-0.37, 0.57$)	-0.27 ($-0.64, 0.10$)
<i>P</i> for trend	0.7686	0.6932	0.9835	0.6679	0.1463
300 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-77.86 ($-195.14, 39.41$)	-102.78 ($-207.53, 1.96$)	-0.28 ($-0.79, 0.22$)	-0.34 ($-0.83, 0.15$)	0.18 ($-0.20, 0.56$)
Tertile 3	-34.25 ($-148.57, 80.07$)	-8.65 ($-110.77, 93.47$)	-0.02 ($-0.52, 0.47$)	0.04 ($-0.43, 0.52$)	-0.18 ($-0.55, 0.19$)
<i>P</i> for trend	0.5782	0.9043	0.9570	0.8186	0.3143
400 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-44.39 ($-157.60, 68.81$)	-75.97 ($-177.51, 25.56$)	-0.61 ($-1.10, -0.12$)*	-0.70 ($-1.17, -0.24$)**	0.23 ($-0.14, 0.59$)
Tertile 3	-38.86 ($-151.93, 74.21$)	-27.78 ($-128.92, 73.36$)	-0.24 ($-0.72, 0.24$)	-0.22 ($-0.68, 0.25$)	-0.08 ($-0.45, 0.29$)
<i>P</i> for trend	0.5017	0.5967	0.3596	0.3967	0.6581
500 m					
Tertile 1	Reference	Reference	Reference	Reference	Reference
Tertile 2	-91.92 ($-204.42, 20.59$)	-103.03 ($-203.64, -2.43$)*	-0.77 ($-1.26, -0.29$)**	-0.81 ($-1.27, -0.34$)**	0.08 ($-0.29, 0.45$)
Tertile 3	-15.98 ($-128.92, 96.96$)	-19.62 ($-120.58, 81.34$)	-0.32 ($-0.80, 0.16$)	-0.33 ($-0.80, 0.13$)	0.03 ($-0.34, 0.40$)
<i>P</i> for trend	0.8017	0.7287	0.2357	0.2004	0.8932

Tertile 1 (≤ 33.3 rd percentile), tertile 2 (33.3rd–66.7th percentile), and tertile 3 (> 66 th percentile)

Model 1 was adjusted for maternal age, education, family income, parity, prepregnancy BMI, exposure to secondhand smoke during pregnancy, season of early pregnancy, and infant sex

Model 2 was adjusted for the covariates in Model 1 plus gestational age. * < 0.05 , ** < 0.01

study to explore associations between residential proximity to methyl bromide use and birth outcomes (Gemmill et al. 2013). They found that living near a location where pesticides were applied was associated with a lower birth weight, smaller head circumference, and shorter body length. The amount of pesticide applied was positively correlated with the number of weeks at birth. Within 5 km of the home, high methyl bromide use was associated with a lower birth weight ($\beta = -113.1$ g), shorter birth length ($\beta = -0.85$ cm), and smaller head circumference ($v = -0.33$ cm). Based on previous studies and our study findings, living near agricultural land is associated with a smaller head circumference. Reiss et al. indicated that the association with head circumference could indicate a neurotoxic effect of pesticide exposure (Reiss et al. 2015), which is consistent with a previous study that showed that pesticides induced neurologic effects (Hernandez et al. 2016). However, we failed to observe a relationship between residential proximity to agricultural land and birth weight or gestational age. This might be due to the possibility that the effects of pesticides are mainly neurotoxic. A previous study indicated that small head circumference was associated with poor cognition and neurodevelopment in adults (Behrman and Rosenzweig 2004). Although similar studies were conducted previously to explore related hypothesis, the

main benefit of our study is the distinguishment between occupational and residential pesticide exposure. Since both exposure scenarios may co-exist for the same study subjects, ruling out the potential bias is crucial for studying the net effect of residential proximity to pesticides use. Moreover, our study use percentage of farmland area instead of distance may improve the accuracy of estimating exposure.

The significant findings in our study were all observed for a buffer radius of 300 m or more. A possible reason may be that only a portion of the study subjects lived in close proximity to agricultural areas, so the proportion of agricultural land within the buffer radii of pregnant women’s houses was relatively small. Taking a buffer radius of 200 m as an example, there were 15.0%, 18.6%, and 41.9% of the subjects with no farmland area with total residential farming, dry farming, or fruit farming, respectively. This suggests that a large percentage of pregnant women with agricultural land within a buffer radius of 300 m were nearly unexposed, and they were less likely to be affected by negative birth outcomes. In addition, a previous study showed a similar effect of buffer distance. Gemmill’s study also found negative associations with residential proximity to methyl bromide use, and the associations with fetal growth were stronger when larger

Table 6 The association of fruit farming area and birth outcomes (N=253)

Buffer distance (m)	Birth weight		Head circumference		Gestational age
	Model 1 β (95% CI)	Model 2	Model 1 β (95% CI)	Model 2	Model 1 β (95% CI)
300 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-80.33 (-312.04, 151.3)	-109.45 (-313.70, 94.80)	-0.52 (-1.28, 0.24)	-0.59 (-1.30, 0.12)	0.21 (-0.58, 1.00)
Tertile 3	8.85 (-113.0, 130.7)	-1.48 (-108.83, 105.8)	-0.03 (-0.43, 0.38)	-0.04 (-0.42, 0.34)	0.07 (-0.34, 0.49)
P for trend	0.8769	0.9926	0.9188	0.8413	0.7315
400 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-27.14 (-143.59, 89.31)	-46.80 (-151.25, 57.66)	-0.26 (-0.77, 0.24)	-0.32 (-0.81, 0.17)	0.14 (-0.24, 0.52)
Tertile 3	-5.06 (-119.63, 109.5)	-24.68 (-127.45, 78.09)	-0.09 (-0.58, 0.41)	-0.15 (-0.62, 0.33)	0.14 (-0.23, 0.52)
P for trend	0.9394	0.6493	0.7503	0.5785	0.4572
500 m					
Tertile 1	Referent	Referent	Referent	Referent	Referent
Tertile 2	-34.76 (-148.43, 78.91)	-32.59 (-134.55, 69.38)	-0.43 (-0.92, 0.06)	-0.43 (-0.90, 0.04)	-0.02 (-0.39, 0.36)
Tertile 3	-4.36 (-119.71, 111.0)	-13.00 (-116.49, 90.50)	-0.15 (-0.65, 0.34)	-0.18 (-0.66, 0.30)	0.06 (-0.31, 0.44)
P for trend	0.9376	0.8016	0.5474	0.4612	0.7417

Tertile 1 (≤ 33.3 rd percentile), tertile 2 (33.3rd–66.7th percentile) and tertile 3 (> 66.7 th percentile)

Model 1 was adjusted for maternal age, education, family income, parity, prepregnancy BMI, exposure to secondhand smoke during pregnancy, season of early pregnancy, and infant sex

Model 2 was adjusted for the covariates in Model 1 plus gestational age

(5 km and 8 km) vs. smaller (1 km and 3 km) buffer zones were used (Gemmill et al. 2013). In our study, the significant findings were generally observed for the tertile 2, but not the tertile 3 (Tables 4 and 5). The possible explanation may include potential confounders and/or sources of exposure that were not considered in our study. However, all the main findings for the tertile 3 exhibited a negative direction, suggesting the potential negative trend of the exposure.

The main strength of this study is that the prospective birth cohort design helped elucidate the temporal relationship between exposure and disease and minimized recall bias in the ascertainment of environmental exposure. However, there are several potential limitations of our study. First, geographic information systems-based agricultural land use was used as an indicator of exposure in our study. We classified agricultural land use into only dry farming, fruit farming, and rice farming. The amounts and types of pesticides used for different crops are different. Although geographic information systems cannot replace the accurate measurement of environmental chemical exposure, the results of this study highlight the potential correlation between agricultural land near a pregnant women's house and negative birth outcomes. Second, although we have adjusted for potential confounding factors in our final models, there may still be some confounders such as maternal nutritional status that were not considered due to lack of information. Therefore, we cannot exclude the possibility of residual confounding. Third, we did not account for factors such as weather, household pesticide use, or dietary pesticide exposure in the analysis. The potential effect of unmeasured factors is possible. However, these limitations would likely lead to a potential underestimation of the impact and bias of our results toward the null hypothesis.

Conclusions

In the present study, we found that maternal residential proximity to farmland during pregnancy was negatively associated with infant birth outcomes, especially head circumference. In contrast to biological monitoring, the non-invasive approach based on geographic information is more socially acceptable and less resource demanding, which is feasible for large-scale screening of environmental pesticide exposure. Additionally, the barely changed agricultural land use is suitable to evaluate long-term exposure to pesticides during pregnancy. To further improve the predictability and accuracy of this approach, small quantities of environmental or biological samples can be used to validate and adjust the models. In the future, agricultural land use information could be combined with biological samples to more accurately assess exposure in pregnant women.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s11356-022-24571-8>.

Author contribution Conceptualization, Y.-H. C, L.-M. Y., and C.-J. H.; Methodology, L.-M. Y., S.-W. L., and C.-J. H.; Software, S.-W. L., K.-C. C., J.-S. X., S.-F. L, S.-W.L., and C.-J. H.; Resources, S.-W.L. and C.-J. H.; Data curation, K.-C. C., J.-S. X., S.-F. L, S.-W.L., and C.-J. H.; Writing—original draft preparation, Y.-H. C, L.-M.Y., and C.-J. H.; Writing—review and editing, C.-J. H.; Supervision, C.-J. H.; funding acquisition, C.-J. H. All authors have read and agreed to the published version of the manuscript.

Funding This research was funded by National Science Council, Taiwan, grant number NSC 102–2314-B-320–004, and the Ministry of Science and Technology, Taiwan, grant number MOST 103–2314-B-320–005-MY2.

Data availability The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the ethical restriction.

Declarations

Ethics approval and consent to participate The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Tzu Chi General Hospital (protocol code IRB102-71 and approved on 26 June 2013).

Informed consent Informed consent was obtained from all subjects involved in the study.

Competing interests The authors declare no competing interests.

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