ORIGINAL ARTICLE

Parkinson's Disease and Pesticides Exposure: New Findings From a Comprehensive Study in Nebraska, USA

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Abstract

Background: The association between exposure to agricultural pesticides and Parkinson's Disease (PD) has long been a topic of study in the field of environmental health. This research takes advantage of the unique Nebraska PD registry and state-level crop classification data to investigate the PD-pesticides exposure relationship.

Methods: First, Geographic Information System and satellite remote sensing data were adopted to calculate exposure to different pesticides for Nebraska residents. An integrated spatial exploratory framework was then adopted to explore the association between PD incidence and exposure to specific pesticide ingredients at the county level.

Results: Our results reveal similarities in geographic patterns of pesticide exposure and PD incidence. The regression analyses indicate that, for most Nebraska counties, PD incidence was significantly associated with exposure to certain pesticide ingredients such as alachlor and broxomy. However, the results also suggest that factors other than pesticide exposure may help further explain the risk of PD at the county level.

Conclusions: We found significant associations between PD incidence and exposure to different pesticide ingredients. These results have useful implications for PD prevention in Nebraska and other agricultural states in the United States.

Key words exposure modeling, GIS, Parkinson's disease, pesticides exposure, spatial analysis.

Parkinson's disease (PD) is a common neurodegenerative disease, second worldwide only to Alzheimer's disease. In the United States, PD affects up to 1 million individuals and accounts for more than 60,000 new cases each year.[1] Although the etiology of PD has not been fully understood, it is believed to be related to both genetic susceptibility and environmental factors.[2-4] Environmental risks of PD have been attributed primarily to exposure to toxins, especially agricultural pesticides that are harmful to the human neurological system.[4-6] Animal experiments indicate that certain pesticides could cause Parkinsonism and other neurodegenerative symptoms.[6-9] When applied to the ground or released in the air, pesticide ingredients may drift for up to 1,000 meters from a treatment site to nearby locations, causing unexpected exposures for local residents.[10,11] Human pesticide exposure can be classified into 2 categories: occupational exposure and nonoccupational exposure.[12] Occupational exposure occurs among individuals (eg, farmers, pesticide applicators) whose occupation exposes them and their immediate family members to pesticides. Nonoccupational exposure occurs among individuals who live close to farmlands and pesticide application sites. Although occupational exposure generally involves higher doses, nonoccupational exposure covers larger populations and geographical areas. This study will focus on nonoccupational exposure of pesticides.

Research findings over the last 2 decades support the relationship between PD incidence and pesticide exposure.[2,4,13,14] However, findings from these studies

are inconsistent in terms of relative risks and statistical significance.[4,15,16] These inconsistencies are believed to be related to factors of small study areas and limited sizes of patient cohorts.[3,17] Since it is hard to obtain a full range of PD incidence data for a large area, researchers have turned to other patient resources such as clinics,[18,19] hospital registries and health system databases.[13,20-22] Although these findings are valid in their own contexts, they may not be applicable to a general population. For example, results derived from urban PD registries may not be applicable to rural residents, who are more likely to be exposed to pesticides. Hospital registries may suffer from selection bias if subject enrollment is influenced by factors such as PD severity, geographic location, and socioeconomic status (SES).[5,23] The lack of large population-based evidence has limited the understanding of the basic epidemiological characteristics of PD as well as environmental contributors to PD.[5,24]

In addition, traditional case-control studies generally rely on subject interviewing or a questionnaire to obtain exposure information. A major advantage of these methods is that they are easy to implement and could retrieve long-term exposure information of individuals, regardless of their moving history during earlier stages of life. However, they could be influenced by subjectivity and recall bias.[5,25-27] For example, a subject may not know how many crops are planted within a radius of his/her residence, what kind of pesticide is applied, or how much pesticide is applied within a radius. The standard and definition of "exposure" also differs among individuals, which may lead to inconsistency in criterion of exposure.

In recent years, Geographic Information Systems (GIS) and satellite remote sensing data have emerged as new methods of pesticide exposure modeling.[12,28,29] Generally, these studies first use remote sensing satellite images to estimate high-resolution land use and crop information, which can then be integrated within a GIS to assess the extent of exposure for individuals. Compared to traditional measures (ie, survey, questionnaire), GIS-based methods require less interaction with subjects to derive accurate and objective information about exposure to crop fields and pesticides.[12] Using this method, researchers can also focus on specific pesticide ingredients that have various levels of toxicity. This ability is especially important for finding the source of exposure risks. In addition, the existence of historical remote sensing images makes it possible to recover long-term exposure information for large areas, which is critical for research on chronic diseases such as PD. However, these methods are limited by their dependence on historical pesticides usage data for specific areas during a specific period, which is not always available.

The primary purpose of this study was to use GIS and spatial methods to explore the association between PD incidence and exposure to agricultural pesticides. Taking advantage of the unique Nebraska PD registry and the statewide, high-resolution land-use classification data for Nebraska, we aimed to answer 2 questions: (1) What are the spatial patterns of PD incidence and exposure to specific pesticide ingredients in Nebraska? and (2) How is PD incidence related to exposure to specific pesticide ingredients? The results will provide new perspectives on PD-pesticide associations and new insights on PD prevention.

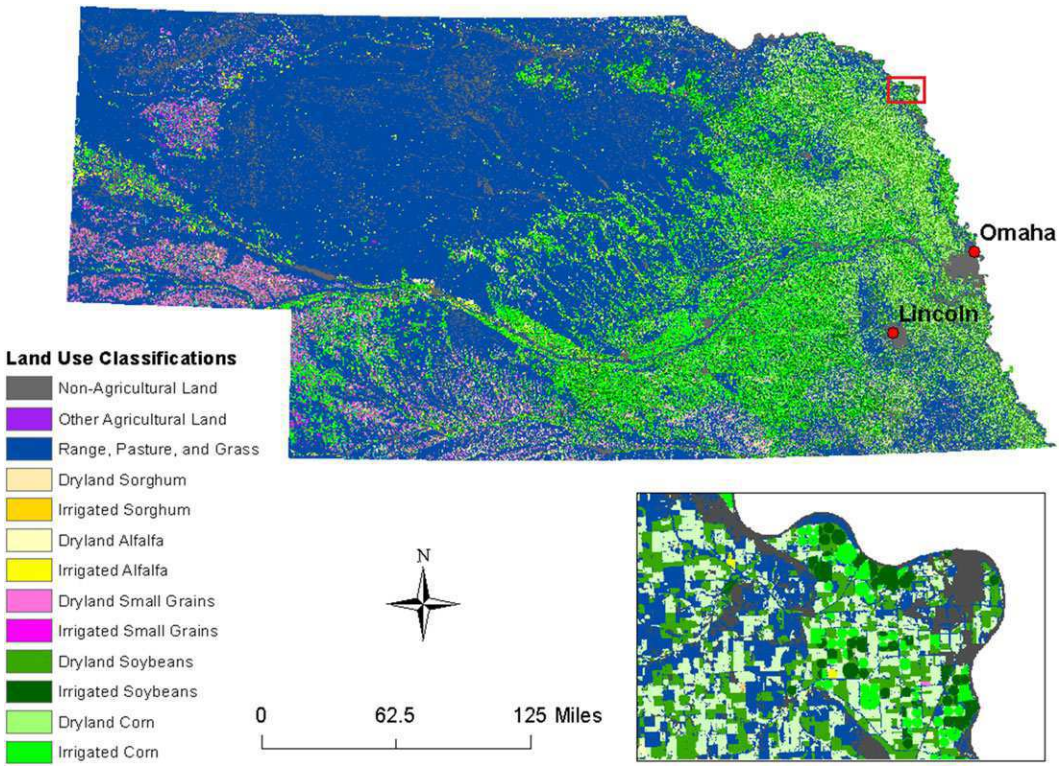
Materials and Methods

Study Area and Data

This study focuses on Nebraska, one of the top agricultural states in the United States. About 93% of Nebraska lands are used as farms and ranches. Rural areas of Nebraska hold 40% (ie, 750,000 out of 1.8 million) of the state population,[30] and rural populations are especially more likely to experience pesticide exposure. The major crops of Nebraska are corn, soybeans, sorghum, and alfalfa, all of which require extensive application of pesticides before harvest. An estimated 15 million kg of pesticides were applied in Nebraska in 2005, among which the most commonly used were glyphosate; atrazine; acetochlor; 2,4-D; and metolachlor.[31]

Three major categories of data were used in this study: PD incidence data, land-use data, and pesticide usage data. County-level PD incidence data for Nebraska from 1997 through 2008 were derived from the Nebraska PD Registry. As a result of 1996 legislation, Nebraska became the first and only state to create a statewide, population-based PD registry. The Nebraska Department of Health and Human Services utilizes various sources to identify PD incidence cases in the state. Physicians are required to report information about patients who are newly diagnosed with PD within 60 days of diagnosis. Pharmacies are also required to report information semiannually about patients who received 1 or more anti-PD medications. Cases identified through pharmacies were traced back to physicians to confirm that the patient had PD and to infer/determine the date and address of diagnosis as accurately as possible. A total of 6,557 PD incidence cases were identified from 1997 through 2008. We obtained statewide land-use data for Nebraska from the Center for Advanced Land Management Information Technologies at the University of Nebraska-Lincoln. Specifically, they used standard methods to determine pixel-level land-use categories based on 37 Landsat 5 Thematic Mapper satellite images that were taken from May to September 2005.[32] The entire strategy derived 19 categories of crop

Figure 1 Land-Use Classifications of Nebraska in 2005.



fields with an overall accuracy of 83.9%. The classified agricultural land use includes all types of major crops that are further distinguished as irrigated or dryland (Figure 1). The crop types in this study were restricted to corn, soybeans, small grains, alfalfa, and sorghum because, according to the classification results, together they account for about 98% of crop planting in Nebraska.

We obtained pesticide usage data from multiple sources. First, information about county-level usage of active pesticide ingredients in Nebraska in 2005 was derived from the estimated annual agricultural pesticide use database at the US Geological Survey.[31] This data set was estimated by integrating the pesticide usage survey data of proprietary Crop Reporting Districts (CRDs) and county-level harvested-crop acreage information. The data set provides 2 indicators of estimated pesticide usage (EPest): EPest-low and EPest-high, among which EPest-low assigns zero value to CRDs that were surveyed but did not provide any feedback on pesticide usage information, and EPest-high estimated values for those CRDs based on the value of their neighbors. This study used EPest-high because it covers more counties than EPest-low.

Since the county-level pesticide usage data do not differentiate pesticide usage by crop type and irrigation status, we derived such information from historical data sets, including the surveys of farmers' pesticide use (for 1982 and 1987) by the University of Nebraska-Lincoln, and the pesticide use database (for 1992 and 1997) from the National Center for Food and Agricultural Policy.[33] From these data, we derived the 4-year average and calculated the relative usage of specific pesticide ingredients for each major crop listed in Table 1. The entire calculation follows the protocol of a previous study.[12] Since there were inconsistencies in terms of covered pesticide ingredients between the county-level pesticide

Table 1 Crop Land Use Information in Nebraska, 2005

Class Name	Irrigation Status	Pixel Count	Percent of Plant Area among All Crops (%)
Corn	Irrigated	23,629,578	29.2
Corn	Dryland	17,976,113	22.2
Soybeans	Irrigated	10,304,420	12.7
Soybeans	Dryland	11,619,691	14.4
Small grains	Irrigated	844,859	1.0
Small grains	Dryland	6,868,539	8.5
Alfalfa	Irrigated	3,009,977	3.7
Alfalfa	Dryland	3,781,465	4.7
Sorghum	Irrigated	184,233	0.2
Sorghum	Dryland	778,567	1.0

Table 2 Information of Selected Pesticide Ingredients Applied in Nebraska in 2005

Ingredient Name	Type	Applied Crops	Amount Applied (in kg)
2,4D	Herbicide	Corn, soybean, small grains, sorghum	491,177
Acetochlor	Herbicide	Corn	1,689,164
Alachlor	Herbicide	Corn, soybean, sorghum	259,320
Atrazine	Herbicide	Corn, sorghum	3,318,525
Bentazone	Herbicide	Corn, soybean	33,949
Bromoxynil	Herbicide	Corn, small grains, sorghum	25,887
Butylate	Herbicide	Corn	95,110
Dicamba	Herbicide	Corn, small grains, sorghum	87,006
EPTC	Herbicide	Corn, alfalfa	145,605
Ethalfluralin	Herbicide	Soybean	20,330
Glyphosate	Herbicide	Corn, soybean, alfalfa, sorghum	4,511,183
Metolachlor	Herbicide	Corn, soybean, sorghum	240,304
Metribuzin	Herbicide	Corn, soybean	52,557
Paraquat	Herbicide	Corn, soybean, sorhgum	80,212
Pendimethalin	Herbicide	Corn, soybean	287,211
Carbaryl	Insecticide	Corn, soybean, alfalfa, sorghum	26,192
Carbofuran	Insecticide	Corn, alfalfa, sorghum	32,443
Chlorpyrifos	Insecticide	Corn, soybean, alfalfa, sorghum	70,025
Phorate	Insecticide	Corn, sorghum	55,109
Terbufos	Insecticide	Corn, sorghum	20,116

usage data and crop-irrigation-status data, we included only ingredients for which the data were available from both data sets. We also excluded ingredients with less than 10,000 kg of usage in 2005. In this way, 20 pesticide ingredients, including 15 herbicides and 5 insecticides, were selected for subsequent analyses (Table 2).

Study Design

Analyses in this study consisted of 2 major parts: GIS-based modeling of pesticide exposure and spatial analysis of PD-exposure associations. The first part used a proven GIS method to calculate population exposure to various pesticide ingredients in Nebraska. The second part adopted hot spot analysis to analyze the spatial pattern of PD incidence, and Ordinary Least Square (OLS) linear regression to evaluate the PD-exposure associations.

GIS-Based Exposure Modeling

The exposure modeling followed a proven method.[12] Specifically, for each pesticide ingredient listed in Table 2, the county-level usage data were first downgraded to crop pixel level based on crop-irrigation-specific information. Based on that information, population grid data were then used to model exposure to the ingredient at a fine spatial resolution. Finally, the fine resolution exposure information was upgraded back to the county level to match the scale of PD incidence data. The details of each step may be found in Appendix A (online only).

Analyzing Basic Characteristics of PD Incidence in Nebraska

Summary statistics were generated to describe basic characteristics of PD incidence in Nebraska. Patients were categorized into 3 age groups (ie, 40-64, 65-74, and ≥75 years). Poverty rate was used to represent the SES of counties. Based on poverty rate, counties were categorized into quartiles to represent different SES groups. The rural/urban status of a county was determined according to the 2003 Rural Urban Commuting Area codes, which categorized Nebraska counties into Metropolitan (n = 9), Micropolitan (n = 33), Small Town Rural (n = 3), and More Isolated Rural (n = 48). PD incidence rate was compared by age, poverty rate, and rurality. We did not differentiate subjects by race/ethnicity because Nebraska has a predominantly white population.

Analyzing the Spatial Pattern of PD Incidence in Nebraska

The spatial pattern of PD incidence was obtained using the Gettis-Ord Gi* statistic,[34] which is given as

$$G_i^* = \frac{\sum_{j=1}^{n} w_{i,j}x_j - \bar{X}\sum_{j=1}^{n} w_{i,j}}{S\sqrt{\frac{\left[n\sum_{j=1}^{n} w_{i,j}^2 - \left(\sum_{j=1}^{n} w_{i,j}\right)^2\right]}{n-1}}}$$

where x_j corresponds to the PD incidence rate for county j, $w_{i,j}$ is the spatial weight between county i and j, n is the

total number of counties, $\bar{X}$ is the mean incidence rate of all counties, and

$$S = \sqrt{\frac{\sum_{j=1}^{n} x_j^2}{n} - (\bar{X})^2}.$$

For each county, the Gi* statistic returned a z-score (ie, GiZScore) that denotes the clustering of high PD incidence (hot spot) or low PD incidence (cold spot). Generally, a high z-score denotes high risk of PD, and vice versa. The statistical significance of GiZScore is evaluated by the *P* value. Therefore, counties with a high z-score and a low *P* value denote areas with significantly high risks, or hot spots, and those with a low z-score and low *P* value denote areas with significantly low risks, or cold spots. To avoid the small number problem, an indirect age adjustment was used to calculate the PD incidence rate.

Analyzing the Associations Between PD Incidence and Pesticide Exposure

The regression analyses of this study relied primarily on OLS. OLS is a linear regression model that minimizes the sum of squared difference between observed and predicted values. As a standard function in ArcGIS, OLS regression also provides a Koenker Statistic to assess the stationarity of the model coefficient. In case of a significant Koenker Statistic, Geographic Weighted Regression (GWR) could be used to adjust for stationarity.[35]

In this study, the regression analysis was composed of 2 steps: we first examined the associations between PD incidence and pesticide exposure across the entire state. Then, in order to distinguish the influence of factors other than pesticide exposure, we grouped counties according to the inconsistency of spatial patterns between PD incidence and pesticide exposure. Another round of regressions was then conducted for the regrouped counties. For both steps, OLS was first adopted to investigate the global associations.

For all regression analyses, the dependent variable was set to be county-level age-adjusted observed/expected ratio of PD incidence, the same variable that was used in the hot spot analyses. For each pesticide ingredient, the dependent variables were 4 dummy variables indicating whether the county had low (Q1), medium-low (Q2), medium-high (Q3), or high (Q4) levels of exposure. In addition to pesticide exposure, we also included poverty rate, crop density, and percent of farmers to examine whether these factors helped to explain variances of PD incidence among counties. For each county, crop density was calculated by dividing the total crop area by the county area; percent of farmers was calculated by dividing the number of individuals with farming, fishing, and forestry occupations by the county population. Crop density was introduced to see if crop proximity alone was associated with PD. We used percent of farmers to approximate the extent of occupational exposure to agricultural pesticides within the county population. The SES and percent of farmers were derived from the Census 2000 data sets. Following the protocols for pesticide exposure, counties were also classified into quartiles based on the 2 variables, with Q1 being the most advantaged quartile and Q4 being the most disadvantaged quartile. In order to avoid multicollinearity, for all variables only Q2, Q3, and Q4 were included in the regression.

Table 3 Selected Characteristics of PD in Nebraska, 1997-2008

Variable	Case/Population	Rate (per Million)
Age		
Group 1 (40-64)	857/501,101	1,710
Group 2 (65-74)	1,494/115,699	12,912
Group 3 (≥75)	4,206/116,496	36,104
Poverty rate		
Q1 (low)	3,836/1,111,956	3,450
Q2	1,414/370,492	3,817
Q3	438/87,984	4,978
Q4 (high)	869/140,831	6,171
Rurality		
Metropolitan	2,827/942,503	3,047
Micropolitan	2,561/576,660	4,441
Small town rural	66/19,450	3,393
More isolated rural	1,058/172,650	6,128

Results

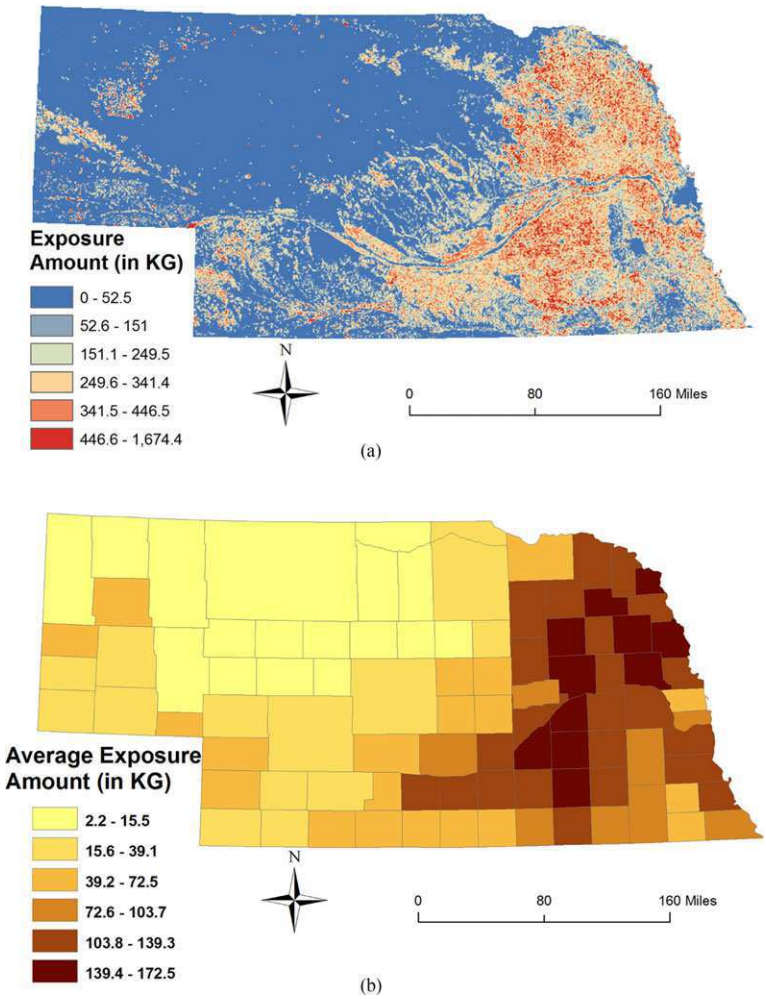
Summary Statistics of PD

Table 3 shows the basic characteristics of PD incidence in Nebraska. As reflected in the table, individuals older than 75 years, those live in low SES areas, and those live in More Isolated Rural areas had the highest rate of PD incidence compared to their counterparts. For example, the incidence rate was almost 3 times higher for the 75+ age group than for the 65-74 age group. Higher poverty rate also corresponded to higher rate of PD incidence. For isolated rural residents, the rate of PD was almost twice as high as that of metropolitan and small town residents.

Pattern of Pesticides Exposure

Figure 2 shows exposure to the 20 pesticides combined in Nebraska at both the population grid level and the county level. As can be seen from the figure, pesticide exposure was high in the eastern part of the state except for the Omaha and Lincoln metropolitan areas. Low-risk areas were primarily concentrated in the northwestern part of

Figure 2 Exposure to Pesticides Combined in Nebraska, 2005 (a) exposure amount at the population grid level, (b) county-level average exposure amount.
Note that the pesticide ingredients involved in these 2 maps were restricted to the 20 ingredients listed in Table 2.



Nebraska. The county-level pattern of exposure to all pesticides combined was similar to that at the population grid level. Generally, higher exposures were observed in eastern and southern parts of Nebraska, and low-risk areas were concentrated in the northwestern part. Since there were many pesticide ingredients involved in this study, we show only the combined exposure in Figure 2. The spatial distributions of specific ingredients (not shown here but available upon request) follow a similar pattern as shown in Figure 2.

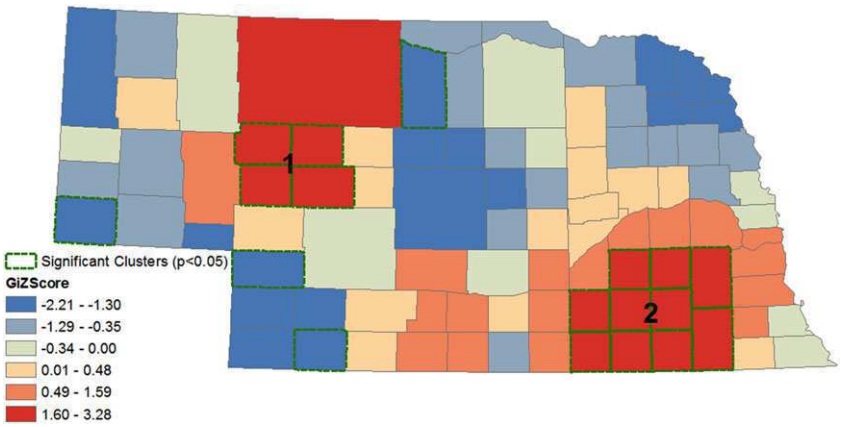
Spatial Pattern of PD Incidence

The spatial pattern of PD incidence in Nebraska from 1997 to 2008 is shown in Figure 3. We found 2 hot spots with significantly higher risk of PD incidence ($P < .05$), 1 located in the central-northern part of the state (area 1 in Figure 3) and the other located in the southeastern part of the state (area 2 in Figure 3). Both areas had at least a 1.6 SD higher risk of PD incidence than the state mean. Cold spots were primarily located in the central part, the eastern part, and some border counties of Nebraska. Medium-risk counties (eg, those with GiZScore values between -0.34 and 0.48) were also randomly distributed within the state.

Regression Results

The first round of OLS regression did not identify significant associations between PD and any of the independent variables. Comparing the spatial distributions of PD incidence (Figure 3) and pesticide exposure (Figure 2), we found that the 2 followed a similar pattern except for the first PD hot spot (area 1 in Figure 3), for which

Figure 3 Spatial Pattern of PD Incidence in Nebraska, 1997-2008.



Note: GiZsore denotes z-score; for example, a z-score of 1.6 means that the risk of PD incidence is 1.6 SD higher than the state mean, a z-score of -1.3 means that the risk of PD incidence is 1.3 SD lower than the state mean.

Table 4 Individual-Factor OLS Linear Regression Results for PD Incidence

Factor	Coefficient for Q2	Coefficient for Q3	Coefficient for Q4	Adjusted R^2
SES	−0.148	−0.287*	−0.269*	0.227
Crop density	0.105*	0.193*	0.196*	0.161
Percent of farmers	−0.183	−0.102	−0.357	0.258
2,4D	0.235*	0.151	0.168	0.167
Atrazine	0.159	0.211*	0.310*	0.210
Acetochlor	0.104	0.380*	0.20*	0.272
Broxomy	0.113	0.288*	0.387*	0.300
Alachlor	0.186	0.235*	0.414*	0.288
Bentazone	−0.101	0.084	0.467	0.153
Terbufos	0.083	0.062	0.283	0.209
Carbaryl	0.052	0.320	0.130	0.236
Carbofuran	0.230	0.267	0.199	0.191
Chlorpyrifos	0.020	0.098	0.287	0.224
Phorate	0.026	−0.143	−0.082	0.150
Metolachlor	−0.003	0.197	0.133	0.174
Metribuzin	0.063	0.231*	0.288*	0.227
Paraquat	0.343	0.255*	0.231*	0.233
Pendimethalin	0.124	0.091	0.114	0.128
Dicamba	0.320	0.07	0.132	0.229
EPTC	−0.107	−0.236	−0.047	0.180
Ethalfuralin	0.166	0.009	0.002	0.155
Glyphosate	0.118	0.279*	0.313*	0.240
Butylate	0.190	0.316	0.208	0.211

*$P < .05$.

Note: The dependent variable is age-adjusted PD incidence rate; a dummy variable was included in all regression analyses to distinguish counties of hot spot 1 in Figure 3 from other counties; for pesticide exposure, Q2, Q3, and Q4 represent the quartile of counties with medium-low, medium-high, and high level of exposure, respectively.

pesticide exposure was low but PD incidence risk was high. We suspect reasons other than pesticide exposure caused the elevated risk in the first PD hot spot. Therefore, another dummy variable was incorporated into the OLS regressions to distinguish these counties from others. We also included the county (ie, the largest county, which is red in Figure 3) to the north of area 1 in the cluster because it was also characterized by high PD risk (GiZScore >1.6). The results of the second round of regressions are shown in Table 4. For each quartile of pesticide exposure (eg, Q2, Q3, Q4), a positive coefficient means higher risk of PD than the reference quartile (ie, Q1), and vice versa. The larger the coefficient, the higher the risk. Therefore, a group of increased coefficients

Table 5 Results of Joint OLS Linear Regression

Factor	Coefficient for Q2	Coefficient for Q3	Coefficient for Q4
Crop density	−0.06	−0.175	−0.303
Atrazine	−0.264	−0.251	−0.169
Broxomy	0.106	0.267	0.328
Alachlor	0.746*	0.799*	0.908*
Metribuzin	−0.506*	−0.444	−0.557*
Glyphosate	−0.041	0.083	0.135
	Adjusted R^2: 0.32; Koenker statistic: 25.809		

*$P < .05$.

Note: The dependent variable is age-adjusted PD incidence rate; independent variables include all variables that showed significant associations with PD incidence in the individual-factor OLS regression in Table 4; a dummy variable was included in all regression analyses to distinguish counties of hot spot 1 in Figure 3 from other counties; for pesticide exposure, Q2, Q3, and Q4 represent the quartile of counties with medium-low, medium-high, and high level of exposure, respectively.

along Q2, Q3, and Q4 (ie, 0.186, 0.235, and 0.414 for alachlor in Table 4) means that the risk of PD incidence increased with the increase of pesticide exposure. The R^2 explains how much variance of the dependent variable (ie, PD incidence) could be explained by the independent variable(s) (eg, pesticide exposure, SES). As reflected in Table 4, some ingredients, including atrazine, broxomy, alachlor, metribuzin, and glyphosate, exhibited significant association with PD incidence after the inclusion of the dummy variable. Among these ingredients, exposure to broxomy and alachlor explain the most variance in PD incidence (R^2 being 30% and 28.8%, respectively). SES was negatively associated with PD incidence, but crop density was significantly associated with PD. There was no significant association between percent of farmers and PD incidence, suggesting that occupational exposure to agricultural pesticides might be less related to the risk of PD than nonoccupational exposure in Nebraska. None of these OLS models revealed a significant Koenker statistic, suggesting no necessity of implementing GWR.

To explore the joint influence of multiple pesticides on PD, we implemented another OLS regression, which included all 6 significant factors (ie, crop density and exposure to atrazine, broxomy, alachlor, metribuzin, and glyphosate) as independent variables. The joint regression erased the significance of all other factors except for exposure to alachlor, for which the adjusted R^2 rose to 32% (Table 5).

Discussion

To the best of our knowledge, this research is the first to examine the association between PD incidence and exposure to agricultural pesticides at the state level. We found similarities as well as differences in spatial patterns of pesticide exposure and PD incidence across the entire state of Nebraska. The regression analyses suggest that, for a majority of counties in Nebraska, PD incidence was significantly related to exposure to pesticide ingredients such as atrazine, broxomy, alachlor, metribuzin, and glyphosate, among which alachlor and broxomy exposure explains most of the variance of PD incidence at the county level. The major advantage of this study lies in the large study area and the unique, statewide PD incidence data for Nebraska, which provide a unique background for examining PD and pesticide exposure. In addition, GIS and high-accuracy land-use classification data also ensure objective estimation of exposure to various pesticide ingredients at finer scales.

This study revealed different types of associations between PD incidence and pesticide exposure from previous studies that focused on specific pesticides. For example, studies have found increased risk of PD with exposure to chorpyrifos and paraquat.[18,20,27,36,37] However, such associations were not confirmed in this investigation. In addition, this study found elevated risk of PD in counties with higher levels of exposure to atrazine, broxomy, alachlor, metribuzin, and glyphosate, which have seldom been reported by previous studies. The differences between our study and previous findings may lie in the study area (ie, state vs local areas), the analysis scale (county-level aggregated data vs individual-level data), the study design (cohort study vs case-control study), and the exposure measure (ie, GIS-based measure vs survey or questionnaire). Inconsistencies in these aspects have been suggested to be partly responsible for inconsistent findings regarding PD epidemiology.[4,16] In order to better understand the inherent association between pesticide exposure and PD, individual-level PD incidence data should be used in the future.

We found that coexposure to multiple pesticides explained more variance of PD incidence than exposure to an individual pesticide. As shown in Table 5, the incorporation of all 5 pesticides into the regression model enhanced the adjusted R^2 to 0.32 from an average of 0.24 among the individual-factor models. The coefficients for alachlor increased sharply from the single factor model (eg, from [0.186, 0.235, 0.414] to [0.746, 0.799, 0.908]). These findings corroborate previous studies that examined the effects of multiple pesticides. For example, Costello et al[19] found that exposure to both maneb and paraquat showed a stronger influence on PD than either factor alone. Wang et al[27] reported that individuals with combined exposure to ziram, paraquat, and maneb had the highest PD risk. Animal studies have demonstrated that the toxicity of a pesticide could be enhanced when coadministered with other pesticides.[38-40] These facts suggest the necessity of identifying individuals and areas with high-level exposure to multiple pesticide ingredients.

Several factors might help explain the elevated risk of PD in the 5 central-northern counties (area 1 in Figure 3). First, although these counties are not major producers of traditional crops such as corn and soybeans, they are noted for hay and livestock production. For example, Cherry County (the largest of the 5 counties) leads the nation in wild hay production, with an output of 221,377 tons in 2002.[30] Cherry County also ranks first in cattle inventory in the state of Nebraska, attaining 291,536 head in 2002.[30] Hay harvesting processes, hay stocking, and cattle ranching may introduce environmental hazards to workers and local residents, which could increase the risk of PD incidence. In another US study, higher risk of PD mortality was observed among livestock farmers compared to crop farmers, and organic solvents were suspected as a factor for this difference.[41] Second, well water consumption has long been suspected to increase the risk of PD incidence.[23,42] Although there are no direct data to show well water consumption in rural Nebraska, we suspect this may be a factor for high PD risk in this area.

The multifaceted factors for PD incidence indicate that a simple regression or examination may not reveal the true underlying factors for PD risk. Instead, hybrid analysis strategies may reveal the multiple contributors to PD. Our spatial exploratory method, including spatial pattern examination and selective regression, explored the potential causes of PD incidence better than using regression methods or cluster detection methods alone. This strategy could also be extended to examine other health consequences (eg, cancer, reproductive problems) of pesticide exposure in the future.

Our findings have the following 3 policy implications: (1) The significant association between pesticide exposure and PD could serve as the overall guideline for designing policies to alleviate adverse health effects of pesticides on population health. (2) The small R^2 (although statistically significant) of the regressions indicates that pesticide exposure is not the sole contributor to PD. Other environmental and life-style factors may also contribute to the prevalence of PD in Nebraska. The development of PD is a complex process that involves genetic, environmental, and personal aspects.[16,23] This complexity suggests the necessity of a more comprehensive examination of potential factors in the future. (3) The 2 hot spots of PD incidence could serve as potential sites for immediate PD prevention strategies of Nebraska. Hot spot 1 in Figure 3 would also be a good study area for investigating nonpesticide factors of PD.

This study has the following limitations. First, we used the 2005 land-use data to approximate pesticides exposure for PD patients diagnosed between 1997 and 2008, and this land-use data may be subject to temporal changes of crop lands. The 2005 data were used because 2005 was the only year with state-level land-use classifications. We did not truncate the PD data to between 2005 (or a later year) and 2008 because that would lead to the small number problem, a problem caused by unstable rates due to a small or zero number of cases.[43] Actually, during 1992 and 2007, the total size of cropland in Nebraska changed only slightly (ie, 4% decrease from 1992 to 2007 according to the US Agriculture Census), suggesting that patterns of land use and pesticides exposure might be relatively stable across time. In the future, we will incorporate more recent years' PD data to adjust for this temporal change problem. Second, in the land-use classification, summer fallow was classified as other agricultural land instead of a specific crop. Although summer fallow represents only 6% of the crop area, the classification we used may slightly influence the exposure calculation. Third, county level might be too coarse a geographic scale for the regression analysis, which may suffer from the so-called "ecology fallacy." The fourth limitation is that our exposure model used uniform parameters for different pesticides, which may not be the case. Different pesticides may have different transmission radii which vary by the spraying method (eg, hand spray vs airplane spray) and the system of dispersion (eg, by air, by soil, by water). The exposure indicators would be more meaningful if all these factors were considered. In addition, we did not adjust for confounding effects among different pesticide ingredients in the regressions, which could potentially influence the multiple regression results of the study. For example, metribuzin exhibited a facilitating effect on PD in the individual-factor regression (Table 4) but a protective effect in the joint regression (Table 5). This contradicting effect might be due to confounding effects.

Despite the limitations, this study represents the first state-level comprehensive examination of the association between PD incidence and various pesticide ingredients. The application of GIS and remote sensing land-use data significantly enhances the accuracy of pesticide exposure compared to traditional measures. We found significant associations between PD incidence and exposure to multiple pesticide ingredients. Our findings will benefit PD prevention efforts not only in Nebraska but in all other Midwestern states that have an elevated risk of PD.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site.

Appendix A: GIS-Based Exposure Modeling.