Descriptive Epidemiology of Parkinson's Disease through Proxy Measures

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ABSTRACT: ***Background and Objective:*** In preparation for analytic study we undertook to describe areas of *relative* excess and deficit of Parkinson's Disease (PD) in Nebraska and tested two methodologic tools for inexpensive assessment of descriptive epidemiology of PD. ***Methods:*** In lieu of large-scale population screening and diagnosis, we obtained sales information of anti-PD drugs in the state in 1988 - 1990 as well as listings of all people dying from 1984 to 1993 who had Parkinson's Disease mentioned anywhere on their death certificate. The anti-PD drug sales data are intended as a proxy for prevalence, while the death certificate data are intended as a proxy for incidence. ***Results:*** Sales divided by population over age 54 indicates where anti-PD drug sales differ from expected. We found high correlation of drug sales rates with several farming exposures. Age-adjusted death rates, however, showed a low degree of association with sales or farming variables. This may be attributable to differences in death certificate completion or in underlying incidence versus prevalence. ***Conclusions:*** These techniques provide a useful tool for delineating possible differences in incidence and prevalence. While not as accurate as full community survey with expert diagnosis, they are not as expensive, and can be followed by local cluster investigations and individual-level etiologic studies to test hypotheses resulting from the initial study.

RÉSUMÉ: Épidémiologie descriptive de la maladie de Parkinson au moyen de variables substitutives. ***Introduction et Objectif:*** En vue d'une étude analytique, nous avons entrepris de décrire des régions à prévalence relative élevée et basse de la maladie de Parkinson (MP) au Nébraska et nous avons étudié deux outils méthodologiques pour une évaluation peu coûteuse de l'épidémiologie descriptive de la maladie de Parkinson. ***Méthodes:*** Au lieu de procéder à un dépistage à grande échelle de la population, nous avons obtenu l'information sur les ventes de médicaments antiparkinsoniens dans cet état de 1988 à 1990 ainsi que la liste des personnes décédées entre 1984 et 1993 dont le certificat de décès mentionnait la maladie de Parkinson. Les données sur les ventes de médicaments antiparkinsoniens sont utilisées comme substitut pour la prévalence, alors que les données provenant des certificats de décès servent de substitut pour l'incidence. ***Résultats:*** Les ventes divisées par la population âgée de plus de 54 ans indiquent où la vente de médicaments antiparkinsoniens diverge de ce qui est prédit. Nous avons constaté une corrélation élevée entre les ventes de médicaments et plusieurs expositions à l'agriculture. Les taux de décès ajustés pour l'âge ont cependant montré un faible degré d'association avec les ventes ou les variables associées à l'agriculture. Ceci peut être attribuable à des différences dans la façon de remplir le certificat de décès ou dans l'incidence sous-jacente par rapport à la prévalence. ***Conclusions:*** Ces techniques fournissent un outil utile pour détecter des différences dans l'incidence et la prévalence. Bien qu'elles ne soient pas aussi fiables qu'une enquête exhaustive dans la population, associée à une expertise diagnostique, elles ne sont pas aussi coûteuses et elles peuvent être suivies d'une investigation des foyers locaux et d'études étiologiques à l'échelle individuelle pour évaluer des hypothèses résultant de l'étude initiale.

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Estimation of the impact of a disease upon a population is essential to study of that disease. Inital attempts to estimate prevalence of Parkinson's Disease (PD) used physician contacts and medical or clinic records. Later studies improved upon this by utilizing record systems that cover most of a defined population. For example, a rural community of 80,000 in British Columbia, Canada was surveyed for prevalence by medical record review.[1] All 142 physicians in the community cooperated and referred 78 PD patients to the investigators.

Concern over reporting biases and undiagnosed patients led to a number of studies of entire communities, with all testing positive to an initial screen subjected to confirmatory neurologic exam. One of the earliest of these was the Copiah County[2] study. Those with positive results on a screen (3,193 people)

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were examined by neurologists who diagnosed 31 cases of PD, including 13 new cases.

The Washington Heights-Inwood section of New York City was the site for a population-based case-ascertainment survey of PD.[3] Crude prevalence overall was 99.4 per 100,000, ranging from 2.3 per 100,000 in those under 50 to 1144.9 per 100,000 for those 80 and above. The survey included neurologist review of records or direct exam and consensus diagnosis after exam and review.

A third less resource intensive method is use of pre-existing records, especially death certificates or medical records in areas where a central health system uniformly serves the population.

Sethi et al.,[4] using death certificates where PD was reported as the underlying cause of death, calculated age-adjusted death rates of 1.73 per 100,000 in the USA, based upon either first or underlying cause of death. De Pedro-Cuesta, in a review of European surveys and studies of PD[5,6] concluded that while methodology in this area is weak, mortality rates generally represent prevalence. Their age-adjusted estimates of prevalence calculated from previous studies range from roughly 100 to 300 per 100,000.

In New Zealand a similar prevalence (110.4/100,000) was observed through review of the national health service records.[7] This was compared to 99.6/100,000 in 1962 for Wellington, NZ, and to 102.7/100,000 in Aberdeen, Scotland. Review of data from the Alberta Health Care Insurance Plan in Canada[8] yielded figures of 248.9 and 239.8 per 100,000 for males and females respectively.

Rural Living Environment Associated With Parkinson's Disease

Delineation of etiologic factors of a disease typically proceed from anecdotal observations to ecologic or correlational studies to specific hypothesis testing studies comparing population-based cases and controls.

Concern about agricultural exposures arose from incidents with the designer drug breakdown product MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which is chemically related to the herbicide Paraquat and a number of other compounds that may be present in an agricultural or industrial environment.[9,10] MPTP is destructive to the substantia nigra, resulting in rapid onset of acute Parkinsonism, and causes neuromuscular symptoms in animal models resulting from that destruction.[10] Those incidents have driven the search for a chemical cause for PD since.[10,11]

Barbeau[11,12] determined prevalence of PD in Quebec, Canada, by four methods[12] including reports to physicians, sales data for anti-PD medications, examination of death certificates, and contact of major movement disorder clinics and neurologists. The areas of highest relative prevalence were those with the most land in intensive high-irrigation and chemical use agriculture.

Zayed et al.[13] followed Barbeau's work in Quebec, finding rural residence and residence near industry or mining to be protective. However, there was a significant tendency for both risks to increase with increasing exposure (i.e., longer residence in those areas).

Rajput and colleagues[14,15] focused on early-onset PD in the province of Saskatchewan. Comparisons with the later-onset PD patients showed no differences, but the authors found an association of early-onset PD with rural living and wellwater use in childhood.

In a case-control study in Kansas,[16] cases had significantly greater number of years of rural residence and well-water drinking.

Stern et al.[17] compared young-onset versus old-onset PD patients in a case-control design, and found no differences except for an elevated risk of head injury in young-onset cases and less likelihood of ever smoking in all subjects.

The first population-based case-control study of PD was done in Calgary, Alberta, Canada by Semchuk and colleagues, who first examined the previously studied risk factors,[18] including rural living, farm living, and well-water exposure. They found no differences on these three variables, with a large proportion of both groups responding positively to all three questions. Univariate analysis[19] showed increased PD risk for agricultural work, herbicide use, and pesticide use. After multivariate analysis to control for interaction and confounding,[20] family history of PD, head trauma, and herbicide use remained elevated.

Butterfield et al.[21] studying young-onset PD, found crude odds ratios of 3.22 for herbicide exposure and 5.75 for insecticide exposure. Multivariate analysis showed differences for insecticide exposure, nut or seed eating, rural residence and residence in a house that was fumigated.

The Kansas group[22] reexamined the hypotheses of rural living, well-water consumption, and pesticide exposure using two sets of cases and controls: one set urban-based and the other drawn from a rural community in western Kansas. They found that pesticide exposure and family history of neurologic disease were significantly associated with PD.

The British Columbia group[23] improved their techniques for examination of exposures related to orchard work, which they had found to be associated with PD in their initial study,[1] and found significantly elevated risk for occupational exposure to pesticides in males.

The current study is intended to introduce techniques to describe areas of *relative* excess and deficit of Parkinson's Disease, not absolute prevalence and incidence. While a study similar to the Copiah County study[2] involving examination of an entire community or random sample thereof is the most accurate way to estimate prevalence, the cost is intimidating. As a less ambitious but still useful alternative, we followed Barbeau's[11,12] methods and obtained anti-PD drug sales data, and all death certificates that mentioned Parkinson's Disease. Again following Barbeau,[12] Zayed,[13] and Rajput's[15] leads, we obtained from the U.S. Bureau of Census, Census of Agriculture[24] data on agricultural production and associated activities. These we compared on a county level with both per capita drug sales and age-adjusted mortality, to assess the degree of correlation of relative excess of PD with farming activities.

Methods

The measures we used to describe PD prevalence were the total sales of drugs used to treat PD, by county, for the years 1988 through 1990. While the sales of these agents are far from a perfect proxy for actual prevalence of PD, it is likely that in comparing counties in Nebraska, the principal factor affecting differences in sales once age differences are controlled for will

be differences in prevalence of diagnosed PD. One principal difference between this and actual prevalence therefore will be regional differences in ability to be diagnosed and treated. Some other conditions these agents are used for are dystonia and drug-induced PD, restless legs syndrome, treatment of viral illneses (rarely), treatment of pituitary adenoma and occasional other uses.

Sales data are collected and reported to pharmaceutical manufacturers by survey firms. Sales are described by zip code of point of retail sale. If a customer uses mail order, then the customer's zip becomes the point of sale. Sales data were aggregated into counties, and population figures from the 1990 census[25] were used as the denominator for the sales data. Since PD is a degenerative disease with symptoms usually arising later in life, we decided upon population over age 54 as the denominator. It should be noted that some regions of the state are very sparsely populated, therefore lack of sales in those regions is to be expected, and a number of those counties have no pharmacy.

Death certificates for the state of Nebraska for the years 1984 to 1993 having the diagnosis of Parkinson's Disease (PD) listed anywhere on the certificate were obtained and analyzed, a total of 1693 deaths. Up to 15 causes of death could be coded. Rates were age-adjusted by the direct method using the total population of the state of Nebraska in 1990 as the reference standard.

Agricultural data by county were available from the U.S. Bureau of Census,[24] from the Census of Agriculture which is done every 5 years (years ending with 2 and 7). We used data from the 1987 census, since that was closest in time to our drug sales data. These included fertilizer use by acreage, irrigation, use of pesticides and herbicides, and acres harvested with a great variety of crops. Principal crops in this area are corn, hay, soy, and sorghum, with some wheat as well. We also had available well-water test data[26] that included nitrate levels, presence or absence of major pesticides, coliform count, and gross alpha level (some areas of the state have natural radioactivity in the water table). Of these we used nitrate levels and proportion of wells in a county with positive test for atrazine, the most commonly used pesticide in Nebraska during the study period.

This descriptive study differs from the more usual analytic study in that *a priori* hypotheses are not formulated, but neither are *post hoc* comparisons of interest. The tools therefore differ correspondingly.

Since our interest is, for purposes of future studies, in locating areas of either high or low prevalence, we chose mapping as our principal tool. Mapping allows visual comparisons of intercounty prevalence rates as well as facilitating rough comparisons of agricultural factors that have been found to be associated with PD in previous work.

In comparing drug sales with agricultural activities, if comparison of maps revealed the possibility of association, regression models were fitted to the variables of interest concurrent with examination of scatterplots to check assumptions of the linear model.

Results

Figure 1 compares findings from sales data and death certificates. Rates for each agree in elevations of PD along the Platte River in the south central portion of the state, and in a region of lowered prevalence in the northeast sector. There appears to be less concordance along the south border to the east. There is discordance in the north and northwest areas. Since drug sales are to the existing population of PD patients (prevalent patients) and mortality if perfectly determined would equal incidence, since PD is not curable, these two measures can function as imperfect estimates of incidence and prevalence.

The high per capita sales areas lie along the Platte River and Interstate 80, in the highly irrigated and fertilized grain farming regions. Lower per capita sales areas tend to be more arid, cattle ranching regions. Table 1 lists agricultural items compared with anti-PD drug sales.

Since any of the associations we observed may be the result of outliers or other distribution aberrations, we examined maps of the agricultural variables that showed statistical association, one example of which is Figure 2. We noticed that three counties were particularly high in anti-PD drug sales, but in the mid-range or lower on agricultural variables. Regression diagnostics revealed that those points had some effect on the degree of correlation and statistical significance, but almost no effect on the regression slope. A scatterplot of the most highly correlated agricultural variable, acres fertilizer used, is displayed in Figure 3, with estimates of the regression equation parameters included.

Average annual rate of PD reported on death certificates was 1.07 per 10,000 per year for the entire state, representing the minimum rate for annual PD incidence. This is based upon 1,693 deaths over 10 years, with an average population of 1.5 million. PD was reported in 7.8% of the cases as the principal cause (130 deaths), in 25.3% of the cases as the underlying cause (554 deaths), in 11.9% of the cases as the second cause, in 24.8% of the cases as the third cause, and in 17.0% of the cases as the fourth cause. Over 97% had PD listed on the death certificate by the sixth cause. There was no association seen of the number of PD death certificates as a proportion of all deaths (at county level) to number of physicians and to number of neurologists. The most commonly listed cause of death was cardiovascular disease, followed by respiratory disease (principally pneumonia). Time

Table 1. Agricultural Activities and Correlation with anti-PD Drug Sales.

Acres fertilizer used	0.45 *
Acres weeds sprayed	0.45 *
Acres hay insect sprayed	0.37 *
Acres corn harvested	0.34
Acres irrigated	0.32
% wells positive for atrazine	0.31
Acres sorghum harvested	0.29
Acres nematodes sprayed	0.25
Hogs, inventory	0.24
Sheep, inventory	0.21
Milk cows, inventory	0.19
Acres soybeans harvested	0.18
Acres disease sprayed	0.13
Acres wheat harvested	0.11
Acres defoliant sprayed	0.11
Chickens, inventory	0.02
Acres alfalfa harvested	–0.05

Correlation is Pearson's. Asterisks denote associations that were statistically significant ($p < 0.001$).

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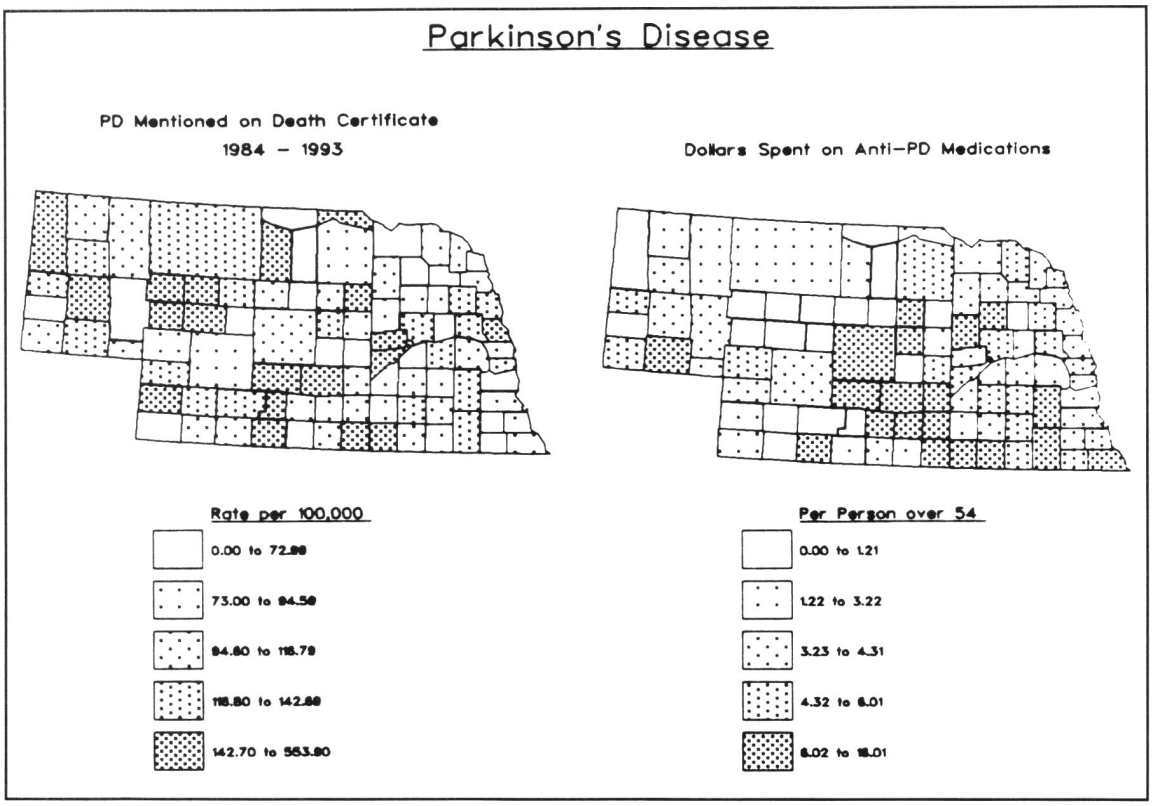

Figure 1: *State of Nebraska, by County; (left) Age-adjusted mortality rates for persons with Parkinson's Disease mentioned on the death certificate, years 1984-1993; (right) Dollars spent per person age 50 and over, for anti-Parkinson's Disease medication.*

trends were examined using proportional mortality ratios (PMR), since reliable annual population counts are not available. Briefly put, this examines PD as a proportion of total deaths each year. The PMR did not vary significantly, even when stratified by gender. We tested PD rates for association with the agricultural variables, but did not find any.

Discussion

We have two principal objectives in this study: the delineation of the descriptive epidemiology of Parkinson's Disease in Nebraska, and the demonstration of methods for doing such description without mounting a study on the scale of the Copiah County Study.[2] Our interest in description of PD in Nebraska when it has already been described elsewhere is based on our plan to do etiologic investigations in a population-based case-control design. Therefore we need to know a minimal number for the available patient pool and any regions where there might be more or less than expected based on just population. Work of other investigators would not be of direct help in this situation. Further, the association of PD and farming exposures is not uniform across settings.[13,27,28] Our second objective is to demonstrate the most efficient use of already existing databases to quickly and cheaply assemble a description. Again, while some of these techniques have been applied in other settings, they have not always been applied well, nor do they necessarily translate well into Nebraska. Canadian investigators, for example, have the enormous advantage of centralized medical records systems. We suggest that our techniques would help workers in the U.S., both neuroepidemiologists and public health officials, who desire to better understand the epidemiology of PD in their region at a reasonable expenditure of time and expense.

A typical initial approach is to examine vital records for deaths over time and by location for the disease in question. PD, however, is of long enough duration that its victims have ample opportunity to expire from other often unrelated causes. Therefore those recorded as dying of PD as first cause would be a very select subgroup of PD patients. Although the state of Nebraska allows up to fifteen contributing or co-existing conditions to be listed on death certificates, often only the immediate cause of death is entered, and there is likely considerable bias as to whether PD is included. Our examination of death certificates showed areas of overlap and concordance with the anti-PD drug sales, suggesting that those are areas of true excess or deficit. An area of likely elevation of PD is along the Platte River in the south central portion of the state, and a region of lowered prevalence is in the northeast sector. There appears to be some concordance along the southern border, where there is a high proportion of elderly in the population. There is strong discordance in the north and northwest areas, where sparse population makes the stability of the calculated rates questionable. It may be that the low drug sales and high death certification of PD reflect lack of access to medical services, and hence to diagnosis and treatment for PD. This may be especially true in the four counties clustered under the large north-central county and of the county in the northwest corner. None of those counties has a pharmacy, and all are very sparsely populated, but the death certificate study indicates an elevation in PD death rates. These

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rate differences may also reflect underlying differences in incidence and prevalence. One explanation might be that PD patients become disabled enough by their disease to stop farming or ranching and move into towns or nursing homes.

We investigated the possibility that death certificate reporting of PD is dependent upon the number of causes listed on the death certificate, which may be affected by considerations such as the number of death certificates the physician fills out annually. We were unable to detect any such association. The death certificate analysis yielded an age adjusted rate 10.7 per 100,000 per year for the entire state, and while this is likely inflated by misdiagnoses such as essential tremor, it represents a good estimate of the minimum incidence of PD in the state. Sethi's[4] calculation of age-adjusted death rates of 1.73 per 100,000 in the U.S.A. is considerably lower, and we feel is an underestimate because of being based upon either first or underlying cause of death. We found age-adjusted mortality rates based upon PD as first cause of death to be 0.82 per 100,000 per year, based upon underlying cause of death to be 3.5 per 100,000 per year, and 4.3 per 100,000 per year for both combined, less than half our overall estimate but more than triple Sethi's. Another factor that likely biases Sethi's estimates compared to those of Nebraska is the low population density of Nebraska. Most Nebraska physicians and county medical examiners know their patients personally, and are able from that knowledge to complete the death certificate better than would probably be possible in many of the big U.S. cities, where death certification among the elderly is often cursory. Finally, Nebraska has a higher proportion of elderly than many states, and those elderly tend not to move elsewhere at retirement or when they become incapacitated.

Since there are very few drugs used for PD, which are used very little for other diseases, and since the great majority of patients are treated with these drugs, examining patterns of use of these drugs may give a comparative estimate of the prevalence of PD. De Pedro-Cuesta et al.[29] outline a method for calculating prevalence from levodopa use and several other indicators. Their methods, while interesting, are problematic in the U.S.A. because differences in health care delivery systems means the indicators they used are not available. For example, we have access to sales data only, not prescription or use of l-dopa.

In examining these sales across the state of Nebraska, distinct regional variations are revealed. These have some statistical association with several important agricultural variables, suggesting that irrigated, fertilized crop farming occurs in the same areas where more anti-PD drugs are sold.

There are several factors that could contribute to differences in anti-PD drug sales besides prevalence of PD. During the survey period, there were six locations with neurology practices: Omaha, Lincoln, Norfolk, Grand Island, Kearney and Scottsbluff, as well as Sioux City, Iowa and Yankton, South Dakota. Greater sales of anti-PD agents would be expected in the vicinity of those practices. In some areas of the state, notably the sparsely populated Sandhills region in the north-center area, there are few pharmacies or physicians. Thus there may be people there with PD who have been neither diagnosed nor treated – or, if treated, they may be purchasing their drugs in another area. Some of the counties have small populations, so estimates of anti-PD drug sales are less stable than in larger counties. This is true of Garfield County (in the northeast), where the highest sales per population over age 54 is reported. The problem of differing drug dosages from patient to patient presents another difficulty in estimating disease prevalence from sales data.

Bearing these cautions in mind, it is nevertheless possible to delineate areas of both high and low sales. It would seem worthwhile and interesting to mount community-level prevalence surveys in both types of areas. This could be preceded by examination of provider services in those areas, access to care and to pharmacies, and a survey of physicians to ascertain number of PD patients under treatment.

The association with certain types of agricultural practice suggests that a case-control study of PD patients examining Nebraska farming practice in detail would be informative. The correlations are high, especially for this type of study (ecological or correlational). Since the data for both outcome measures (drug sales and death certification) and agricultural factors are

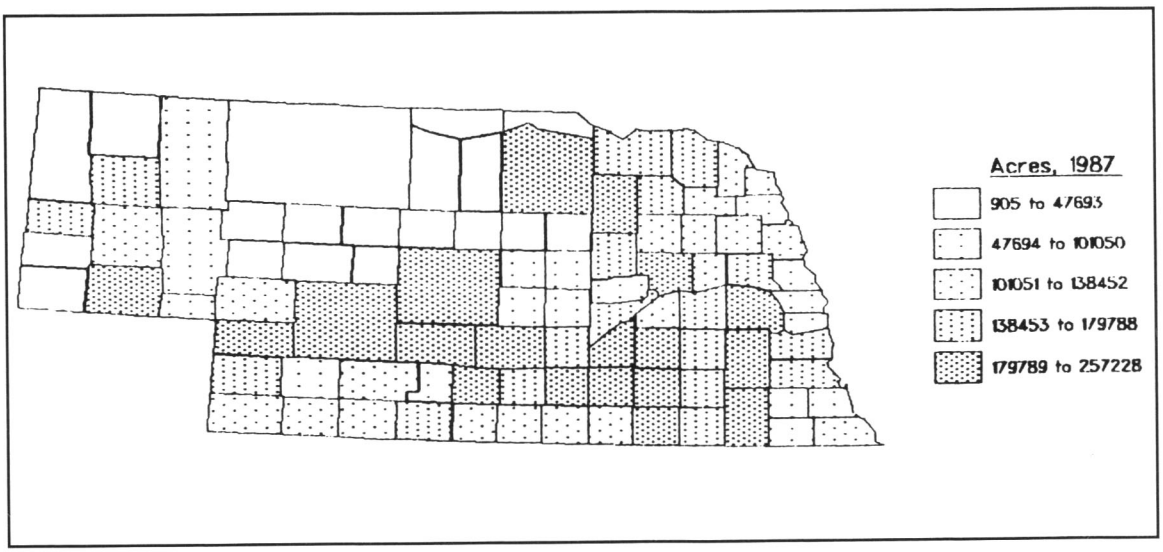

Figure 2: *State of Nebraska, by County; Commercial fertilizer applied, acres from 1987 census of agriculture.*

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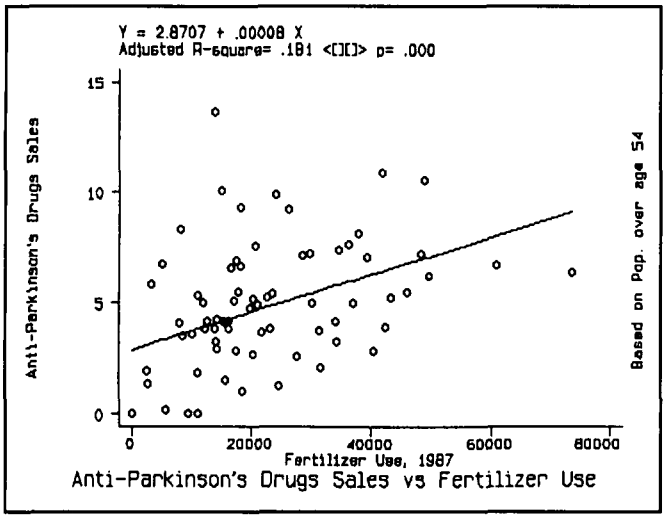

Figure 3: Scatterplot anti-Parkinson's drug sales rates versus fertilizer use with estimate of regression parameters.

on a county level, we are unable to tell whether affected individuals have been exposed to the putative risk factors. A study designed to test that association on individual PD patients, compared with controls drawn from the same population, is the obvious next step. Such case-control studies have been done in other settings, notable in Alberta[18-20] and Kansas.[16,22] Nebraska has a variety of environments, from river valley to arid high plains, and agriculture includes intensive small grain farming and free-range cattle ranching, with some fruit farming in the east along the Missouri River. Semchuk[20] suggests that PD risks from agriculture may differ by location and time, so a number of studies investigating PD etiologies in a variety of farming environments may allow clearer assessment of specific agricultural etiologic factors.

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