

Parkinson's Disease and Exposure to Rural Environmental Factors: A Population Based Case-Control Study

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ABSTRACT: To determine whether a history of exposure to rural environmental factors leads to an increased likelihood of developing idiopathic Parkinson's disease, we conducted a case-control study of 130 cases and 260 randomly selected community controls (matched with the cases by sex and age ± 2.5 years at a ratio of 2 controls: 1 case) in the city of Calgary. The data were collected by personal interviews and were analyzed using conditional logistic regression for matched sets. The ages of the cases ranged from 36.5 to 90.7 years (mean = 68.5 ± 11.3 years). The mean age at diagnosis was 61.1 ± 12.4 years. The mean duration of disease was 7.8 ± 0.6 years. Eleven (9.1%) cases were diagnosed before age 40. In this sample from the Province of Alberta, Canada, no significant increase in risk for Parkinson's disease was associated with a history of rural living, farm living, or well water drinking in early childhood or at any time during the first 45 years of life.

RÉSUMÉ: Maladie de Parkinson et exposition à des facteurs environnementaux ruraux: une étude de population cas-témoin. Nous avons procédé à une étude cas-témoin sur 130 cas et 260 contrôles sélectionnés de façon aléatoire dans la communauté (appariés aux cas pour le sexe et l'âge ± 2.5 ans dans la proportion de 2 contrôles pour 1 cas) dans la ville de Calgary, afin de déterminer si une histoire d'exposition à des facteurs environnementaux ruraux entraîne une probabilité augmentée de développer une maladie de Parkinson idiopathique. Les données ont été recueillies lors d'entrevues personnelles et ont été analysées au moyen de la régression logistique conditionnelle pour des groupes appariés. L'âge des cas variait de 36.5 à 90.7 ans (moyenne = 68.5 ± 11.3 ans). L'âge moyen au diagnostic était de 61.1 ± 12.4 ans. La durée moyenne de la maladie était de 7.8 ± 0.6 ans. Onze cas (9.1%) avaient été diagnostiqués avant l'âge de 40 ans. Dans cet échantillon résidant dans la province d'Alberta, Canada, aucune augmentation significative du risque de développer la maladie de Parkinson n'était associée à une histoire de résidence rurale, de résidence sur une ferme, ou d'absorption d'eau de puits dans la petite enfance ou à tout autre moment pendant les 45 premières années de vie.

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Parkinson's disease (PD) is one of the most common adult neurological disorders.^{1,2} Despite major advances in the understanding of its pathogenesis and in its treatment, and despite intensive research over the past two decades, the etiology of PD is still unknown. It has been postulated, but in no case confirmed, that Parkinson's disease is: inherited;³⁻¹⁵ linked to known viruses;^{6,16-22} associated with other diseases and conditions including: arteriosclerosis,²³⁻²⁵ diabetes,²³⁻²⁵ cancer,²³⁻²⁵ coronary heart disease,²³⁻²⁶ hypotension,^{6,22,25,27,28} peptic ulcer,^{23,24} pulmonary tuberculosis,²⁵ stroke,^{6,23,24} thyroid disease,^{23,24} and other diseases and conditions;^{6,23-25,28,29} a neurofilament disorder;³⁰⁻³³ the result of defective DNA repair mechanisms;³⁴ associated with: certain personality traits,^{10,35,36}

dietary factors,³⁷ familial essential tremor,^{4,6,9,38-42} ionizing radiation,²² and toxic and/or environmental factors.^{10,23,29,43-61} More recently, a multifactorial etiology has been hypothesized, that is PD is the result of a combined effect of genetic and environmental factors acting on a background of aging.^{22,44,49,52,53,62-64} There has been a recent focus on urban-rural differences, on well water drinking in childhood, and on pesticide use.^{49,50,52,53,60,61,65-72}

To date, there have been no cohort studies of PD, and no environmental factors have been consistently identified in case-control studies. Previous case-control studies have attempted to investigate the relationships between the risk for developing PD, rural living and well water drinking,⁶⁷⁻⁷¹ but they have yielded

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inconsistent results (Table 1). On review, the results reported in this paper conflict with the results of the previous case-control studies. However, unlike this study, none of the previous case-control studies were population based.

This paper presents the results of a population based case-control study of PD which was conducted in the city of Calgary to investigate whether or not exposure to environmental factors associated with rural living leads to an increased likelihood of developing idiopathic PD. This study is the largest environmental case-control study of PD, reported to date, and it is the first one which was population based. The study tested the following hypotheses: a) individuals with a history of rural living, particularly in areas specializing in agriculture, have an increased risk of developing Parkinson's disease; b) well water drinking, especially in early childhood, is associated with an increased risk of developing Parkinson's disease.

METHODS

Prior to starting this study, a case register of 232 Calgary residents with neurologist-confirmed idiopathic PD was developed as follows. With the assistance of the Medical Records Department at each of the five general hospitals, a computer listing was made of all patients with a primary or additional diagnosis of PD who were discharged from hospital between January 1, 1984 and December 31, 1987. With the aid of the computerized Longterm Care Information System for Calgary, which maintains a current listing of all Calgary longterm care facility residents, along with their diagnoses, and with the cooperation of auxiliary hospitals, which allowed the study personnel to review their residents' charts, a computer listing was made of current longterm care facility residents with a diagnosis of PD. The Movement Disorder Clinic (The University of Calgary Medical Clinic) and the 16 neurologists practicing in Calgary assisted the study personnel in compiling a list of their patients with PD. The Parkinson's Society of Southern Alberta provided a roster of its current Calgary membership.

The data from all of these sources were merged into one master file. For every patient identified from these sources, a review of the medical chart was done in order to locate documentation by a qualified consulting neurologist confirming the diagnosis of idiopathic PD. For each name gathered through the Parkinson's Society, the attending neurologist was contacted in order to confirm the diagnosis. Thus, for each case, the

diagnosis of idiopathic PD was made by a qualified consultant neurologist. In general, this diagnosis was made in the presence of two or more of the four cardinal signs of PD: resting tremor, muscle rigidity, bradykinesia, and disturbances of posture and equilibrium. We excluded from the register those cases whose parkinsonian symptoms were drug-induced or could be attributed to: essential tremor, a Parkinson syndrome (i.e., progressive supranuclear palsy, normal pressure hydrocephalus, multi-infarct dementia, olivopontocerebellar degeneration, and Shy-Drager syndrome), encephalitis, Alzheimer's disease, head trauma, tumor, or to chemical intoxication. The names of all non-Calgary residents and of all individuals in whom the diagnosis of PD was not confirmed by a neurologist were removed from the master file, leaving a case register of Calgary residents in whom the diagnosis of idiopathic PD had been confirmed by a qualified neurologist.

For each case included in the case register, the attending neurologist was contacted in order to determine the case's eligibility for the study. Eighty-five ineligible cases (37 deceased, 27 demented, 13 non-resident, and 5 in whom the diagnosis of PD was not confirmed by their current attending neurologists) were excluded from the study. Surrogates of deceased and demented cases were not used due to the questionable accuracy of information obtained from surrogates about factors such as well water consumption during early childhood. The initial contact with each eligible case about the study was made through the case's attending physician.

For each case, two community controls, who were individually matched with the index case by sex and age ± 2.5 years, were randomly selected from the Calgary general population using random-digit-dialing (RDD) sampling procedures.⁷³⁻⁷⁶ The sampling frame for the community controls included all Calgary residential telephone numbers including those unlisted and unpublished. Approximately 95 percent of all Calgary households have a telephone.⁽¹⁾ The RDD procedures were as follows. Using a list of operating telephone exchanges in Calgary, and the Minitab⁷⁷ statistical software program, a random sample of Calgary telephone numbers was generated. Each generated number was called up to 10 times (at different times of the day and week) in order to determine if the number was a

(1) Estimate provided by the City of Calgary Corporate Resources Department.

Table 1: Case-Control Studies of Parkinson's Disease and Rural Environmental Factors

Study	Location	Sample Size		Variable	Odds Ratio	p
		Cases	Controls			
Tanner ⁶⁷	China	100	200	village residence	0.57	<0.5
				well water drinking	0.74	NS
Ho ⁶⁸	Hong Kong	35	105	rural living	4.9	0.006
Koller ⁶⁹	Kansas	150	150	rural living	1.9	0.01
				well water drinking	1.7	0.03
Hertzman ⁷⁰	British Columbia	57	122	well water use	NR*	NS
Zayed ⁷¹	Quebec	42	84	rural living	0.31	<0.05
				well water drinking	1.40	NS

*Not reported

residential number and, if so, to obtain a listing, by age and sex, of all eligible household residents. Residents who were unable to understand and answer the research questions and those with parkinsonism or other neurologic conditions were excluded as potential controls. Only one potential control was selected from each household, using a table of random number when two or more residents were eligible.

To permit analysis of any bias due to institutionalization, for each of 23 cases who resided in longterm care facilities, one additional matched control was selected from the resident censuses of 6 longterm care facilities in which the institutionalized cases resided.

Once identified, all eligible cases and controls were provided with an introductory letter inviting their participation in the study. The letters to the cases were signed by the patients' attending physicians. The letters to the controls were signed by the investigators. Those cases and controls who were willing to participate were interviewed by trained experienced interviewers. To minimize recall bias pains were taken to ensure consistency, between the cases and the controls, in the procedures used to obtain information about exposure. A list of dates of significant historical events was used to assist the respondents in recalling the year of exposure. To assist the respondents in recalling the month, the interviewers were trained to prompt the respondent for the season, first. To minimize interviewer and respondent bias the underlying hypotheses of the study were not revealed to either the interviewers or the respondents. A number of consistency checks were built into the interview to validate responses, for example, by asking the same question in a number of different ways.

Each respondent was asked for a complete residential history, including the location and dates of residence for each place resided, for the first 45 years of life, and for various demographic data: age, sex, date of birth, marital status, educational level, annual family income, ethnic background, and household size. The cases were also asked to recall the age at symptom onset and the age at diagnosis. For each residence named, the respondent was asked about the source of drinking water (i.e., well, central water supply, river, lake, etc.) and whether the residence was located in a city or town, or on a farm or acreage. In the interview the residential history was reviewed and revised until the respondent was satisfied with its accuracy.

Each completed residential history was reviewed by one of the authors (KMS) who hand-coded the respondent's past exposures (i.e., exposed versus not exposed) to rural living, to farm living, and to well water drinking during the first year of life, during each five-year age interval period up to and including the respondent's 45th birthday, and during exposure periods of increasing duration (by 5-year increments) up to and including the entire first 45 years of life. These exposure data were hand-coded, twice, prior to data entry, to minimize coding error. The data were entered into a microcomputer and verified using the SPSS Data Entry II Program for IBM-PC's.⁷⁸ The SPSS^x statistical software package⁷⁹ was used for data cleaning and for the descriptive analysis. Conditional logistic regression analysis for matched sets,⁽²⁾ ⁸⁰ using the EGRET statistical software package for IBM-PC's,⁸¹ was used to estimate the odds ratios for developing PD associated with each exposure variable. Potential gender differences were examined using stratified analysis techniques and by testing for interaction between each exposure

variable and the variable sex. For all statistical tests, parallel comparisons were made between the cases and their matched community controls and between the cases and a mixed control group, comprised of the 23 institutional controls, each of whom was substituted for one of the two original community controls who where individually matched to 23 institutionalized cases, plus the remaining 237 individually matched community controls. Statistical significance was indicated by an alpha level of 0.05 or less. Since none of the results differed depending on which control group was used, only the results for the cases versus the community controls are presented here.

One hundred and thirty (75 males and 55 females) of the 147 eligible cases were interviewed, 9 refused to participate, access was denied to 3 cases by the attending physician and to 1 case by the spouse, and 4 cases could not be located, resulting in an overall response rate of 88.4% (males: 89.3%; females: 87.3%) for the cases. Five hundred and three (253 males and 250 females) of the 609 potential community controls, identified through RDD, gave their names and addresses in order to receive the information letter about the study. Of those who received the letter, 23 (10 males and 13 females) were excluded because they did not meet the inclusion criteria for the controls, 116 (48 males and 68 females) refused the interview, and 364 (195 males and 169 females) were interviewed, for a response rate of 75.8% (males: 80.2%; females: 71.3%) of those eligible. Of those interviewed, 104 (45 males and 59 females) were eliminated from the analysis because the cases to whom they have been matched were excluded from the study. Hence, data were analyzed for 260 community controls (150 males and 110 females) who were individually matched by age and sex with the 130 interviewed cases. The response rate (57.5%) was somewhat lower for the institutional controls, who comprised a very small proportion (5.9%) of the total sample. The respective case and control respondent and nonrespondent groups did not differ significantly in the mean age, the distribution of males and females, and for the cases, the mean age at diagnosis by a neurologist and the estimated duration of the disease.

RESULTS

One hundred and thirty cases (75 men and 55 women) and 260 community controls (150 men and 110 women) were studied. The mean age of the cases was 68.5 ± 11.5 years⁽³⁾ (range: 36.5 to 90.7 years) compared to 68.3 ± 11.3 years (range: 34.9 to 92.7 years) for the controls. The age of disease onset was estimated by three variables: the reported age at symptom onset (mean: 58.0 ± 12.2 years), the reported age at diagnosis by a neurologist (mean: 60.6 ± 12.4 years) and the documented age at diagnosis by a neurologist (mean: 61.1 ± 12.4 years), which was obtained by medical chart review. The mean duration of disease, based on the documented age at diagnosis, was estimated at 7.8 ± 6.8 years. Eleven (9.1%) cases were diagnosed

(2)The analysis used all of the available data, taking account of the full complement of controls selected for each case. While a missing value for the case or for both controls lead to exclusion of the entire matched set, a missing value for one control meant that the number of controls in that set was reduced by one.⁸¹

(3)Mean age \pm 1 standard deviation.

before age 40. The male and the female cases did not differ significantly in age or in the estimated age at diagnosis. The estimated duration of disease, however, was somewhat longer for the females (9.4 ± 7.9 years compared to 6.7 ± 5.7 years for the males; $t = 2.12$; $df = 119$; $p = 0.036$). The cases and the controls were comparable with respect to: age and sex (which were matched for), educational level, annual family income and ethnic background. However, a larger proportion of the cases were married (70.8% compared to 59.2% of the controls; $X^2_c = 4.47$, $p = 0.034$) and fewer cases (9.2% compared to 30.8% of the controls; $X^2_c = 14.25$, $p < 0.001$) lived alone.

As would be expected for a sample of older adults drawn from this Western Canadian province, more than half of both the cases and the controls gave a history of rural living during the first 45 years of life (Table 2). Rural living, farm living, and well water drinking were, for all practical purposes, equally prevalent amongst the cases and the controls during the first 15 years of life, with a maximum excess of exposure of -1.9% for exposure to rural living among the cases. The differences in the proportions of cases and controls exposed to rural environmental factors during the first 45 years of life were somewhat larger, although not remarkable, with a maximum excess of exposure of -6.1% among the cases for exposure to rural living.

Table 3 shows the risk estimates (odd ratios, yielded by the conditional logistic regression or matched sets, for developing PD associated with a history of exposure to rural living, to farm living, and to well water drinking during the first 15 years of life and during the first 45 years of life. As indicated by the corresponding 95% confidence intervals, all of which include 1, none of the odds ratios associated with any of the exposure variables differ significantly from unity. The risk for developing PD associated with each exposure variable was also estimated for a history of exposure during the first year of life and during each five-year age interval period up to and including the respondent's 45th birthday. No significant increase in risk for PD was associated with a history of exposure to rural living, to farm living, or to well water drinking during any of the ten periods examined, regardless of whether the males and the females were considered separately or together. In addition, there were no significant interactions between the variable sex and any of the exposure variables, for any of the periods examined. Hence, no critical exposure period was identified for exposure to rural environmental factors.

If there is a true etiologic association between PD and exposure to rural environmental factors an increase in the duration of exposure to the rural environment would be accompanied by a concomitant increase in the risk for developing PD. That is, there would be evidence of a dose-response relationship. In order to test this hypothesis of a dose-response relationship, for each exposure variable, conditional logistic regression for matched sets was used to estimate the risk for developing PD associated with increasing durations of exposure (by 5-year increments). Hence, the risk for developing PD was estimated for a history of exposure for the entire: first year of life, first 5 years of life, first 10 years of life, etc. As shown in Table 4, for each exposure variable, there appears to be a modest increase in the size of the odds ratio with each 5-year increment in the duration exposed, up to age 20. After age 20, there appears to be a concomitant decrease in risk with each 5-year increment in the duration exposed. However, despite the apparent trends in the odds ratios across the exposure periods none of the risk estimates associated with any of the exposure variables, for any of the exposure periods examined, are statistically significant, as indicated by the corresponding 95% confidence intervals, all of which include 1. Similar results were also found when the males and the females were considered separately. Potential interactions between each exposure variable and the variable sex were assessed for each exposure period and no significant gender effect was found. This analysis failed, therefore, to demonstrate a significant dose-response relationship between the risk for developing PD and a history of exposure to rural environmental factors.

DISCUSSION

Many experts on PD now believe that PD results from interactions of various genetic and environmental factors with age.^{22,44,49,52,53} This multifactorial hypothesis has gained support from: (a) observations that the relative risk of developing PD increased dramatically in those who simultaneously have more risk factors;²² (b) the results of a clinical study⁵² which found significantly more defective hydroxylation mechanisms (which are responsible for detoxifying many potentially toxic environmental substances) among PD patients than among controls; and (c) the identification of the pyridine derivative MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a neurotoxin to which exposure can result in a syndrome closely resembling

Table 2: Cases and Controls exposed During the First 15 Years of Life and During the First 45 Years of Life, by Exposure Variable

Exposure Variable	Cases		Controls		% Excess Exposure Among the Cases
	Exposed/	(%)	Exposed/	(%)	
First 15 Years of Life					
Rural Living	54/130	(41.5)	112/258	(43.4)	-1.9
Farm Living	53/130	(40.8)	109/258	(42.2)	-1.4
Well Water Drinking	74/120	(61.7)	146/237	(61.6)	0.1
First 45 Years of Life					
Rural Living	71/129	(55.0)	157/257	(61.1)	-6.1
Farm Living	60/129	(46.5)	127/257	(49.4)	-2.9
Well Water Drinking	86/104	(82.7)	181/230	(78.7)	4.0

idiopathic PD in man^{45,46,51,56} and in other primates.^{47,48,57} MPTP is similar in chemical structure to many pyridines found in the environment and, in particular, to chemicals commonly used in agriculture.^{53,58}

The results of exploratory epidemiologic investigations^{50,53,59,60,65} suggest that rural environmental exposures might be associated with an increased risk of developing PD. In Saskatchewan, Rajput et al.^{50,60,65} analyzed the childhood environments of 18 patients in whom symptoms of PD had developed by age 40 and noted that all 18 patients relied almost entirely on well water as the source of childhood drinking water. Following a detailed population analysis, these researchers concluded that individuals raised in rural environments were much more liable to develop PD than those who lived in larger communities. The investigators postulated that the PD cases were exposed to some factor(s) that was predominantly operative in

rural communities and that childhood drinking water is a likely vehicle for such an agent. In a subsequent study of 48 midbrain sections from normal brains containing substantia nigra (SN), the research group⁷² found a lower, although not statistically significant, SN neuron count by age 20 in cases with at least 80% life exposure to rural environments in the province of Saskatchewan compared to cases with at least 80% life exposure to urban provincial environments. A more rapid rate of decline in SN neuron counts was noted in urban compared to rural residents between the ages of 20 and 80.

In the United States, Tanner et al.^{59,61} surveyed 512 patients receiving the United Parkinson's Foundation newsletter and found associations between the age of onset of PD and the population density of the place of residence and the source of drinking water. Compared to patients with a later onset of PD, young-onset (onset at age 47 or younger) patients were more likely to

Table 3: Matched Case-Control Sets and Odds Ratio* (OR) by Exposure Variable

Exposure Variable	Matched Sets**										OR	95% CI of OR
	+++/ +++	++	+-	-+/ -++	---	---	+-	-	++	-+		
First 15 Years of Life												
Rural Living	11	24	19	18	30	26	1	1			0.93	0.60-1.43
Farm Living	10	22	20	17	33	27	1				0.95	0.61-1.46
Well Water Drinking	23	28	9	16	16	9	3	1	9	4	0.93	0.58-1.50
First 45 Years of Life												
Rural Living	27	29	15	26	22	10					0.78	0.51-1.21
Farm Living	14	29	17	21	28	20					0.90	0.58-1.37
Well Water Drinking	43	21	4	13	1	2	2		14	2	1.07	0.57-2.02

* Results of conditional logistic regression for matched sets (the cases and the controls were individually matched by sex and age ± 2.5 years).

** The first symbol of each set represents the index case and the next 1 or 2 symbols the matched control(s). A positive exposure is indicated by a "+" while a negative exposure is indicated by a "-".

Table 4: Cumulative Lifetime Exposure to Rural Environmental Factors, Odds Ratio* (OR) by Exposure Variable, Exposure Period, and Duration Exposed

Exposure Period (Birth to Age:)	Estimated duration Exposed (Years)	Exposure Variable					
		Rural Living		Farm Living		Well Water	
		OR	95% CI	OR	95% CI	OR	95% CI
1 Year	1	1.09	0.69-1.72	1.11	0.70-1.75	0.94	0.57-1.55
5 Years	5	1.05	0.66-1.66	1.05	0.66-1.66	0.89	0.54-1.46
10 Years	10	1.30	0.81-2.08	1.23	0.76-1.97	1.24	0.77-2.00
15 Years	15	1.40	0.86-2.26	1.37	0.85-2.21	1.22	0.75-1.98
20 Years	20	1.58	0.95-2.62	1.55	0.93-2.60	1.25	0.76-2.04
25 Years	25	1.31	0.73-2.35	1.33	0.73-2.44	0.95	0.54-1.66
30 Years	30	1.08	0.55-2.11	1.29	0.65-2.60	0.55	0.28-1.11
35 Years	35	0.81	0.36-1.80	1.00	0.44-2.30	0.55	0.25-1.22
40 Years	40	0.76	0.31-1.89	1.00	0.39-2.60	0.58	0.21-1.56
45 Years	45	0.71	0.22-2.32	0.79	0.24-2.61	0.95	0.31-2.88

*Results of conditional logistic regression for matched sets (the cases and the controls were individually matched by sex and age ± 2.5 years).

have lived in an area with a population of less than 1,000 ($p < 0.01$) and to have used well water as a primary source of drinking water for one year or more ($p < 0.01$).

In Quebec, Barbeau et al.⁵³ found an uneven geographic prevalence of PD across nine major hydrographic regions in the province. The highest prevalence rates were found in rural commercial agricultural areas. The investigators gained further support for their hypothesis in another study in which they demonstrated that significantly more PD patients than control subjects had a genetic deficiency in certain detoxifying enzymes of the liver, the P450 monooxygenases.⁵²

Prior to the start of this study, there were no published case-control investigations of the hypothesized relationship between exposure to rural environmental factors and the risk of developing PD. Just prior to completion of this study, however, reports were published of five case-control studies of PD and rural exposures in Chinese,^{67,68} American⁶⁹ and Canadian^{70,71} residents. None of these case-control studies were population based, and their results are conflicting (Table 1).

Hence, this study is the first population based case-control study of the importance of rural environmental exposures in the etiology of PD, and it is the largest case-control study to test this hypothesis, to date. Our results concur with the findings of the two previous Canadian case-control studies^{70,71} and one Chinese study,⁶⁷ which also found no significant increase or decrease in the risk for developing PD associated with a history of well water drinking. These nonsignificant findings conflict, however, with reports of a statistically significant increase in risk for PD associated with over 40 years of rural living in southern China⁶⁸ and with exposure to rural living and to well water drinking in the state of Kansas,⁶⁹ and with reports of a protective effect of rural living in China⁶⁷ and in Quebec.⁷¹ Thus, as indicated by the widely divergent results of these six case-control studies, the role of environment in the etiology of PD is still unclear.

The inability of this study, and of some previous case-control studies, to find a statistically significant association between the risk for developing PD and a history of exposure to rural environmental factors does not preclude the possibility that rural environmental exposures may be of etiologic importance. In those studies with nonsignificant results, the sample studied may not have been large enough to yield adequate statistical power to detect a true difference in past rural environmental exposures between the cases and the controls. The results of a power analysis, conducted for each exposure variable, indicate that this study had a statistical power of 98.5% or greater to detect a 25% excess (or deficit) in exposure among the cases,⁸² and a power of 92.9% or greater to detect a twofold increase (or decrease) in risk (e.g., an odds ratio of 2.00) for developing PD.⁸³ However, as shown in Table 2, the percent excess of exposure to rural environmental factors amongst the cases was much less than 25%, with a maximum excess of -6.1% for exposure to rural living during the first 45 years of life. The estimated risk (odds ratio) for PD associated with each exposure variable and exposure period was considerably less than 2.00, with a maximum odds ratio of 1.58 for a history of rural living for the entire first 20 years of life (Table 4). This study had a statistical power 24.5% to detect a 6.1% deficit in exposure among the cases and a power of 58.3% to detect a 1.58 increase in risk for developing PD.

Differences in statistical power across studies, however, does not explain the statistically significant, but contradictory, findings of an increased risk for PD associated with rural living in southern China⁶⁸ and in Kansas⁶⁹ and a decreased risk for PD associated with rural living in other areas of China⁶⁷ and in Quebec.⁷¹ While these conflicting significant results could reflect a true geographic variation in the incidence of PD, they also could be artifactual, that is they could reflect differences across studies on one or more of several factors: (a) diagnosis of Parkinson's disease; (b) definition of what constitutes a positive exposure; (c) length and timing of the exposure period of interest; (d) inclusion of demented cases, who may be suffering from a different disease entity or causal mechanism than the non-demented cases;⁶⁴ (e) study design and analytic approach; (f) the effects of bias (i.e., selection, recall, respondent or interviewer); or (g) spurious (chance) positive associations due to the large number of potential risk factors examined within these studies.

Barring the potential effects of the previous seven factors, an alternative explanation for the conflicting findings is that there is geographic variation in the relationship between the risk for developing PD and exposure to rural environmental factors. There is a suggestion in the literature that the incidence of PD⁽⁴⁾ might not be evenly distributed around the world.^{53,59,62,63,65} If this is true, exposure to rural environmental factors in China⁶⁸ and in Kansas⁶⁹ could be associated with an increased risk for developing PD, while exposure to the rural Western Canadian environment is not. This conclusion is consistent with our findings that: (a) the majority (61.1%) of the population controls in our study had some exposure to rural living during the first 45 years of life, (b) any excess in exposure to rural living and to farm living occurred amongst the controls rather than the cases, and (c) all of the risk estimates associated with the various exposure variables and exposure periods are very close to 1.

Thus, the results of this study of Alberta residents do not support the conclusion that a history of exposure to rural environmental factors, that is exposure to rural living, to farm living or to well water drinking, during early childhood, during the first 15 years of life, or at any time during the first 45 years of life, is associated with a significant increase in risk for developing PD. If exposure to rural environmental factors does lead to an increased likelihood of developing PD, for the Alberta population represented in this study, the actual increase in risk is likely less than two-fold. Hence, ruralness, in itself, does not appear to be a strong risk factor for idiopathic PD. If rural exposures do play a role in the etiology of PD, the causative agent(s) must be something particular to the rural environment, and the actual presence and/or virulence of the agent(s) may vary geographically. Results of some recent case-control studies of PD suggest the etiologic importance of occupational factors associated with rural living, that is factors inherent in agricultural work and/or the use of agricultural chemicals,^{67,68,70} although this, too, is an area of great controversy and debate.^{43,60,69,71}

(4)The estimated mean annual incidence of PD is between 7.7 and 18.2, rates per 100,000 population, age-adjusted to the 1960 U.S. population.¹

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