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Environmental Risk Factors and Parkinson's Disease: A Metaanalysis

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The study aim was to examine the association between Parkinson's disease (PD) and exposure to environmental factors such as living in a rural area, well water use, farming, exposure to farm animals, or living on a farm, and pesticides. A series of metaanalyses of peer-reviewed studies were performed, using 16 studies for living in rural area, 18 studies for well water drinking, 11 studies for farming, and 14 studies for pesticides. Prior to the metaanalyses, all studies were reviewed and evaluated for heterogeneity and publication bias. Significant heterogeneity among studies was detected and combined odds ratio (OR) was calculated using the random and the fixed-effect models. The majority of the studies reported consistent elevation in the risk of PD with exposure to environmental factors such as rural living and farming. The combined OR for rural residence was 1.56 [95% confidence interval (95% CI) 1.18–2.07] for all the studies, and 2.17(95% CI 1.54–3.06) for studies performed in United States. The combined OR for well water use was 1.26 (95% CI 0.97–1.64) for all the studies, and 1.44(95% CI 0.92–2.24) for studies done in United States. The combined OR for farming, exposure to farm animals, or living on a farm was 1.42 (95% CI 1.05–1.91) for all studies, and 1.72(95% CI 1.20–2.46) for studies done in United States. The combined OR for pesticides exposure was 1.85(95% CI 1.31–2.60) for all studies, and 2.16(95% CI 1.95–2.39) for studies done in United States. Dose-response relationships could not be established due to the imprecise nature of the reported data. Our findings suggest that living in a rural area, drinking well water, farming, and exposure to pesticides may be a risk factor for developing PD. © 2001 Academic Press

Key Words: **Parkinson's disease; rural; well water; farming; pesticides; metaanalysis.**

INTRODUCTION

Parkinson's disease (PD) is a common idiopathic, neurodegenerative disorder that produces slow bodily movements, muscular rigidity, frequent tremor of resting limbs, and loss of postural balance (Zhang and Roman, 1993). The etiology of PD is largely unknown, although there is growing body of evidence implicating environmental risk factors including rural living, consumption of well water, and pesticide exposure. (Tanner and Langston, 1990; Tanner and Goldman, 1996).

In this study, we evaluate the studies published in peer-reviewed literature on the subject. A series of metaanalyses was performed and evaluated in the context of exposure to environmental factors and PD.

MATERIALS AND METHODS

The articles were searched by using the medical database Medline and PubMed as of January 2000. The articles retrieved were about the exposure to environmental factors such as living in rural area, drinking well water, farming as an occupation, living on a farm or exposure to farm animals, pesticide exposure, and the risk of getting PD. Articles were excluded from the analyses for any one of the following reasons: (1) they were in a language other than English, (2) they did not include rural living, well water use, exposure to farming, and pesticides exposure as a risk factor, (3) there was duplication of the studies with same cohort, (4) there was insufficient published data for determining an estimator of relative risk or a confidence interval, or (5) the disease studied was not specifically designated as PD.

The articles were carefully examined. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated for the studies which either mentioned relative risk or a χ^2 value or did not provide 95% CI (Koller *et al.*, 1990; Jimenez *et al.*, 1992;

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Golbe *et al.*, 1990; Wong *et al.*, 1991; Butterfield *et al.*, 1993; Morano *et al.*, 1994).

The remaining articles were then examined and estimators of the relative risks (RR) were extracted independently by the authors (Table 1). All studies followed a case-control design and therefore the estimators of RR were OR for all these studies. Once the studies had been selected, a series of metaanalyses were conducted and the results were evaluated in the context of the published literature. The homogeneity of the estimators of relative risk was tested using Cochran's Q statistics (Cochran, 1954). This is a χ^2 test with degrees of freedom equal to the number of studies minus one, and tests the null hypothesis that the within-study estimates of relative risk are homogeneous across studies. Significant heterogeneity was detected within the groups of studies; therefore, the random-effect model (DerSimonian and Laird, 1987) was used to obtain the combined OR and its standard error (SE).

The first metaanalysis examined all studies that met the criteria for inclusion. A second metaanalysis was conducted by place of study.

An adjusted rank correlation test (Begg and Mazumdar, 1994) was used to test for potential bias due to study size. The absence of significant correlation suggests that the studies have been selected in an unbiased manner.

TABLE 1
Description of the Studies on Exposure to Environmental Factors and PD[a]

Reference	Country	Number of cases	Number of control
Jimenez *et al.* (1992)	Spain	128	256
Koller *et al.* (1990)	United States	150	150
Semchuk *et al.* (1991)	Canada	130	260
Tanner *et al.* (1989)	China	100	200
Ho *et al.* (1989)	Hong Kong	35	105
Butterfield *et al.* (1993)	United States	63	68
Golbe *et al.* (1990)	United States	106	106
Stern *et al.* (1991)	United States	149	149
Wong *et al.* (1991)	United States	38	38
McCann *et al.* (1998)	Australia	224	310
Martyn and Osmond (1995)	United States	172	343
Chan *et al.* (1998)	Hong Kong	215	313
Morano *et al.* (1994)	Spain	74	148
Wang *et al.* (1993)	China	93	186
Liou *et al.* (1997)	Taiwan	120	240
Gorell *et al.* (1998)	United States	144	464
De Michele *et al.* (1996)	Italy	100	200
Marder *et al.* (1998)	United States	89	188
Hertzman *et al.* (1994)	Canada	127	245
Smargiassi *et al.* (1998)	Italy	86	86
Wechsler *et al.* (1991)	United States	34	25
Rocca *et al.* (1996)	Italy	62	124

[a]Relative risk.

RESULTS

Rural Living

Sixteen case-control studies examining the association between exposure to rural living and PD were identified (Table 2). The number of females was similar to the number of males for both cases and controls for majority of the studies. The mean age of the cases ranged from less than 50 years to 70.3 years. Three studies (Semchuk *et al.*, 1991; Tanner *et al.*, 1989; Wang *et al.*, 1993) reported negative association, and two studies (Jimenez *et al.*, 1992; Chan *et al.*, 1998) reported no association. The remaining 11 studies reported positive association. Only one of the negative studies was significant (Tanner *et al.*, 1989). Eight studies (Koller *et al.*, 1990; Ho *et al.*, 1989; Butterfield *et al.*, 1993; Golbe *et al.*, 1990; Wong *et al.*, 1991; McCann *et al.*, 1998; Morano *et al.*, 1994; Liou *et al.*, 1997) had estimated OR that were statistically significant.

Significant heterogeneity was detected among the studies ($P = 0.01$). The random-effect model including all studies yielded a combined OR of 1.56 (95% CI 1.17–2.07). The combined estimate for the studies conducted in United States was 2.17 (95%CI, 1.54–3.06).

Six studies provided data on duration of rural living and the risk of PD (Table 3). The highest risk was 4.9 (95% CI, 1.4–18.2) and reported for exposure in living in rural area for more than 40 years.

Well Water Drinking

Nineteen case-control studies examining the association between exposure to well water and PD were identified (Table 2). One study (DeMichele *et al.*, 1996) was excluded from the analysis as the data was included in another study by the same researcher (DeMichele *et al.*, 1996). The number of cases ranged from 34 (Wechsler *et al.*, 1991) to 224 (McCann *et al.*, 1998) and the number of controls ranged from 25 (Wechsler *et al.*,1991) to 464 (Gorell *et al.*, 1998). The number of females was similar to the number of males for both cases and controls for majority of the studies. The mean age of the cases ranged from less than 50 years to 70.3 years.

Five studies (Tanner *et al.*, 1989; Hertzman *et al.*, 1994; Stern *et al.*, 1991; McCann *et al.*, 1998; Wang *et al.*, 1993) reported negative association. One study showed no association (Gorell *et al.*, 1998). The

TABLE 2
Description of the Studies Reporting Risks on Exposure to Environmental Factors and PD

Reference	Odds ratio (95% CI)			
	Rural living	Well water drinking	Farming	Pesticides
Jimenez *et al*. (1992)	1.1 (0.7–1.63)	1.22 (0.77–1.94)	—	1.34 (0.85–2.12)
Koller *et al*. (1990)	1.9 (1.61–2.22)	1.7 (1.45–2.0)	1.3 (1.1–1.53)	1.1 (0.94–1.3)
Semchuk *et al*. (1991)	0.78 (0.51–1.21)	1.07 (0.57–2.02)	0.90 (0.58–1.37)	—
Tanner *et al*. (1989)	0.57 (0.33–0.98)	0.74 (0.41–1.32)	—	—
De Michele *et al*. (1996)	—	2.35 (1.32–4.18)	—	—
Marder *et al*. (1998)	—	15.3* (1.0–224.8)	—	—
Golbe *et al*. (1990)	2.0 (1.7–2.4)	1.1 (0.91–1.33)	1.3 (1.1–1.6)	7.0 (5.8–8.5)
Hertzman *et al*. (1994)	—	0.89 (0.48–1.66)	1.16 (0.62–2.18)	1.75 (0.95–3.23)
Stern *et al*. (1991)	1.7 (0.9–3.1)	0.8 (0.4–1.6)	—	0.79 (0.53–1.18)
Wong *et al*. (1991)	4.3 (3.13–5.91)	2.8 (2.04–3.85)	2.7 (1.96–3.7)	1.0 (0.73–1.4)
Smargiassi *et al*. (1998)	—	2.78 (1.46–5.28)	1.25 (0.65–2.43)	1.15 (0.56–2.36)
McCann *et al*. (1998)	1.7 (1.17–2.57)	0.6 (0.38–0.92)	—	1.2 (0.8–1.5)
Chan *et al*. (1998)	1.0 (0.995–1.01)	1.04 (0.70–1.54)	0.92 (0.59–1.43)	1.80 (0.90–3.58)
Morano *et al*. (1994)	2.5 (1.41–4.42)	2.77 (1.51–5.08)	—	1.73 (0.98–3.02)
Wang *et al*. (1993)	0.76 (0.49–1.18)	0.59 (0.36–0.95)	—	—
Liou *et al*. (1997)	2.04 (1.23–3.38)	1.07 (0.19–5.98)	1.81 (1.25–2.64)	3.32 (1.59–6.94)
Gorell *et al*. (1998)	1.19 (0.73–1.93)	0.97 (0.65–1.40)	1.30 (0.88–1.93)	4.10 (1.37–12.24)
Wechsler *et al*. (1991)	—	1.27 (0.44–3.63)	3.1 (0.3–35.2)	—
Ho *et al*. (1989)	4.9 (1.4–18.2)	—	5.2 (1.6–17.7)	3.6 (1.0–12.9)
Butterfield *et al*. (1993)	2.72 (2.12–3.48)	—	—	3.22 (2.51–4.12)
Martyn and Osmond (1995)	1.4[a] (0.82–2.49)	—	—	
Rocca *et al*. (1996)	—	—	0.6 (0.3–1.3)	

[a]Reported only for African-Americans.

remaining 11 studies reported positive association. Two of these studies were significant (McCann *et al*., 1998; Wang *et al*., 1993). Five of these studies (Koller *et al*., 1990; De Michele *et al.*, 1996; Smargiassi *et al*., 1998; Wong *et al*., 1991; Morano *et al*., 1994) had estimated OR that were statistically significant.

Significant heterogeneity was detected among the studies ($P = 0.01$). The random-effect model including all studies yielded a combined OR of 1.26 (95% CI 0.96–1.64). The combined estimate for the studies conducted in United States was 1.44 (95%CI, 0.92–2.24). Five studies identified duration of exposure to well water and risk of getting PD. (Table 3). The highest risk was 3.28 (95% CI, 0.93–11.51) and reported for exposure to well water for at least 1 year.

Farming

Twelve studies examining the association between exposure to farming, living on a farm, or exposure to farm animals, and PD were identified (Table 2).

The number of cases ranged from 34 (Wechsler *et al*., 1991) to 215 (Chan *et al*., 1998) and the number of controls ranged from 25 (Wechsler *et al.*, 1991) to 464 (Gorell *et al*., 1998). The number of females was similar to the number of males for both cases and controls for majority of the studies. One study (Rocca *et al.*, 1996) reported negative association. Two studies show no association (Chan *et al*., 1998; Semchuck *et al*., 1991). The remaining 9 studies reported positive association between PD and exposure to farming. The OR for the negative study was not significant (confidence interval included 1). Five of these studies (Koller *et al.*, 1990; Ho *et al.*, 1989; Golbe *et al.*, 1990; Wong *et al*., 1991; Liou *et al.*, 1997) had estimated OR that were statistically significant.

Significant heterogeneity was detected among the studies ($P = 0.01$). The random-effect model including all studies yielded a combined OR of 1.42 (95% CI 1.05–1.91). The combined estimate for the studies conducted in United States was 1.72 (95%CI, 1.20–2.46).

Four studies identified duration of exposure to farming and risk of getting PD (Table 3). The highest risk was 5.2 (95% CI, 1.6–17.7) and reported for exposure to farming for more than 20 years.

Pesticides

Fourteen studies examining the association between exposure to pesticides and risk of getting PD were identified (Table 2).

TABLE 3
Description of the Studies According to Duration of Exposure to Environmental Factors and PD

Reference	Duration of exposure (years)	Rural living OR (95% CI)	Well water drinking OR (95% CI)	Farming OR (95% CI)	Pesticides OR (95% CI)
Ho *et al*. (1989)	>40	4.9 (1.4–18.2)	—	—	—
	21–40	2.1 (0.7–6.7)	—	—	—
	1–20	1.3 (0.4–4.4)	—	—	—
	≥ 20	—	—	5.2 (1.6–17.7)	—
Liou *et al*. (1997)	1–19	1.23 (0.51–2.98)	0.58 (0.26–1.32)	1.54 (0.73–3.23)	—
	≥ 20	1.68 (0.81–3.47)	0.71 (0.40–1.28)	0.85 (0.43–1.69)	—
Semchuk *et al*. (1991)	1	1.09 (0.69–1.72)	0.94 (0.57–1.55)	1.11 (0.70–1.75)	—
	5	1.05 (0.66–1.66)	0.89 (0.54–1.46)	1.05 (0.66–1.66)	—
	10	1.30 (0.81–2.08)	1.24 (0.77–2.00)	1.23 (0.76–1.97)	—
	15	1.40 (0.86–2.26)	1.22 (0.75–1.98)	1.37 (0.85–2.21)	—
	20	1.58 (0.95–2.62)	1.25 (0.76–2.04)	1.55 (0.93–2.60)	—
	25	1.31 (0.73–2.35)	0.95 (0.54–1.66)	1.33 (0.73–2.44)	—
	30	1.08 (0.55–2.11)	0.55 (0.28–1.11)	1.29 (0.65–2.60)	—
	35	0.81 (0.36–1.80)	0.55 (0.25–1.22)	1.00 (0.44–2.30)	—
	40	0.76 (0.31–1.89)	0.58 (0.21–1.56)	1.00 (0.39–2.60)	—
	45	0.71 (0.22–2.32)	0.95 (0.31–2.88)	0.79 (0.24–2.61)	—
	16–25	—	—	—	1.41 (0.73–2.73)
	16–35	—	—	—	1.38 (0.53–3.57)
	16–45	—	—	—	0.88 (0.26–2.99)
Stern *et al*. (1991)	1–10	2.5 (1.2–5.3)	1.0 (0.5–2.4)	—	—
	10 +	1.3 (0.7–2.4)	0.9 (0.5–1.7)	—	—
Morano *et al*. (1994)	At least 1	—	3.28 (0.93–11.51)	—	1.73 (0.98–3.02)
	>40	—	2.77 (1.51–5.04)	—	—
	>50	2.5 (1.41–4.42)	—	—	—
Jimenez *et al*. (1992)	1 year or longer	—	1.22 (0.77–1.94)	—	—
Smargiassi *et al*. (1998)	At least 10 years	—	—	1.25 (0.65–2.43)	1.15 (0.56–2.36)
Chan *et al*. (1998)		—	—	—	1.05 (1.01–1.09)
Gorell *et al*. (1998)	<10	—	—	—	2.39 (0.89–6.40)
	≥ 10	—	—	—	5.81 (1.99–16.97)
	>20	—	—	—	3.02 (0.59–15.37)

The number of cases ranged from 38 (Wong *et al*., 1991) to 224 (McCann *et al*., 1998) and the number of controls ranged from 38 (Wong *et al*., 1991) to 464 (Gorell *et al*., 1998). The number of females was similar to the number of males for both cases and controls for majority of the studies. One study (Stern *et al*., 1991) reported negative association. Two studies show no association (Koller *et al*., 1990; Wong *et al*., 1991). The remaining 11 studies reported positive association between PD and exposure to farming. The OR for the negative study was not significant (95% CI included 1). Four of these studies (Gorell *et al*., 1998; Butterfield *et al*., 1993; Golbe *et al*., 1990; Wong *et al*., 1991; Liou *et al*., 1997) had estimated OR that were statistically significant.

Significant heterogeneity was detected among the studies ($P = 0.01$). The random-effect model including all studies yielded a combined OR of 1.85 (95% CI 1.31–2.60). The combined estimate for the studies conducted in United States was 2.16 (95%CI, 1.95–2.39) by using the fixed-effect model.

The highest risk was 5.81 (95% CI 1.99–16.97) and reported for exposure to pesticides for more than 10 years.

The adjusted rank correlation test was not significant for studies included in the metaanalysis of rural living, well water, farming, and pesticides exposure. The absence of significant correlation is reassuring that the studies included in the metaanalysis were not affected by publication bias.

DISCUSSION

Our analysis shows that people living in a rural area are at significantly increased risk of getting PD. The association of rural living with PD may be related to exposure to potential neurotoxins present in pesticides, well water, or spring water.

We found an increased risk of getting PD in people who drink well water. However, this risk was not significant. Well water drinking represents a highly variable and heterogeneous exposure. Because private wells are more shallow than those used for larger municipal supplies, the risk of PD is assumed to be due to some form of contamination from pesticides, volatile organic compounds, and other chemicals which have neurotoxic properties (Butterfield *et al*., 1993). Well water could also act as vector for infectious agents and can contain pesticides due to the contamination of the groundwater (Smargiassi *et al*., 1998). Pesticides are leached from the soil into groundwater, where concentrations may build up because there is relatively little turnover of groundwater (Metzler, 1982). Well water drinking might also represent a marker of rural living.

Our analysis shows that farming, exposure to farm animals, or living on a farm can significantly increase the risk of getting PD. The reason could be that pesticides may be used more in farming. Besides being inhaled, pesticides can be absorbed through the skin (Ho *et al*., 1989). Since people engaged in farming are more likely to wear light clothing, and have a longer duration of exposure to high temperature and humidity, they are also at risk of getting dermal exposure. However, they are also likely to use personal protective equipment while engaged in farming.

Rural living, farming, drinking well water, and exposure to pesticides are closely linked and interrelated. Therefore, it is important to consider the composition of soil, water, pesticides, and fertilizers and their means of application to crops, as well as potential lifestyle differences, in future studies on environmental risk factors for PD.

Recent studies indicate that PD is associated with a systemic defect in complex I, an enzyme in the mitochondrial electron transport chain, which is also the site of inhibition of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). This enzyme is reduced in the brain cells and platelets of patients with PD. MPTP is a pyridine similar in structure to a number of agricultural chemicals such as paraquat, which may be environmentally present (Langston, 1989). MPTP causes selective destruction of dopaminergic neurons of the nigrostriatal pathway in humans and other primates. Factors that may predispose to substantial nigral cell loss, including mitochondrial dysfunction and oxidative damage, could be common to a number of separate genetic and environmental etiologies. The observation that the toxin MPTP can cause a syndrome strikingly similar to PD suggests that a similar compound, if environmentally present, might be etiologically related to PD. Recent animal models have suggested a mechanism for the development of PD through chronically exposing laboratory rats to the pesticide rotenone (Friedrich, 1999).

We found a significant heterogeneity among the studies and we performed several metaanalyses by stratifying the analysis by one available source of heterogeneity, the place of study. The combined estimate by place was significant for studies conducted in the United States. Since the rank test revealed no relation between the estimator of relative risk and study size, we feel that publication bias due to preferential publication of large studies with positive findings does not appear to have occurred.

Limitation of this metaanalysis stems from the limitation of epidemiological studies included in the analysis. All studies included in the analysis were case-control studies and these are subjected to a number of limitations on disease and exposure. Limitations on PD cases and controls include methodological difficulties surrounding case definition, completeness of case ascertainment, and selection of appropriate controls (Checkoway *et al.*, 1999). Besides, recall bias represents a common problem in case-control studies. This is especially true in familial PD, because patients have a better knowledge of the disease than unaffected people and may be more likely to recall exposures. Therefore, prospective cohort studies would be a better way to assess the relationship between exposure to environmental factors and PD. However, cohort studies have their own limitations such as cost factor, loss to follow-up, and lack of information on confounders.

In conclusion, our metaanalysis findings suggest a small but significant elevation in the risk of PD in individuals living in a rural area, exposed to farm animals/farming or living on a farm, and exposure to pesticides. Since PD may be occurring at a younger age at onset, perhaps because environmental risk factors are becoming more common (Teravainen *et al*., 1986), there is a need for cohort studies to prospectively evaluate the association of environmental factors and PD. Also needed are studies targeting specific occupational groups with potential for exposures to pesticides such as farmers and chemical workers.

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