NeuroToxicology

NeuroToxicology 26 (2005) 99–105

Occupations and Parkinson's Disease: A Multi-Center Case-Control Study in South Korea

Jungsun Park[1], Cheol-In Yoo[2], Chang Sun Sim[2], Hyo Kyung Kim[2], Jae Woo Kim[3], Beom S. Jeon[4], Ki-Rak Kim[5], Oh-Young Bang[6], Won-Yong Lee[7], Yunjeong Yi[8], Kap-Yeol Jung[3], Soo-Eun Chung[8], Yangho Kim[2,*]

[1]*Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency, Incheon, South Korea*

[2]*Department of Occupational and Environmental Medicine, Ulsan University Hospital, #290-3 Cheonha-Dong, Dong-Ku, Ulsan 682-060, South Korea*

[3]*Department of Neurology, Dong-A Unversity Hospital, Busan, South Korea*

[4]*Department of Neurology, Seoul National University Hospital, Seoul, South Korea*

[5]*Health Promotion Center, Asan Medical Center, Seoul, South Korea*

[6]*Department of Neurology, Ajou University Medical Center, Suwon, South Korea*

[7]*Department of Neurology, Samsung Medical Center, Seoul, South Korea*

[8]*Department of Environmental Health, School of Public Health, Seoul National University, Seoul, South Korea*

Received 14 April 2004; accepted 1 July 2004
Available online 19 August 2004

Abstract

Objective: We performed a hospital based case-control study in South Korea (1) to clarify the role of occupational exposure, and especially manganese (Mn) exposure in the etiology of Parkinson's disease (PD) and (2) to discover the association between any occupations and PD. *Methods:* We selected two groups, PD patient group (N_1) and controls (N_2). Three hundred sixty-seven consecutive outpatients with PD (177 men, 190 women) and 309 controls were interviewed about life style, past history, family history, education level, and occupational history etc. We employed a range of industrial categories as defined by section (the most broad category) and division (sub-category) of the Korea Standard Industry Code (KSIC) Manual. Along with KSIC, we also used the Korea Standard Classification of Occupations (KSCO) as proxies of occupational exposure. The odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for age, sex, smoking status, and education level are presented. *Results:* As regarding the exposure to hazardous materials, especially Mn, more subjects in the control group than the PD patient group 'have worked in the occupations with potential exposure to Mn ($P < 0.001$). Ever having worked in 'agriculture, hunting, and forestry' section of industry was positively associated with PD (OR 1.88), and 'agriculture production crops (OR 1.96)' division of industry was positively associated with PD. On the other hand, ever having worked in the 'manufacturing (OR 0.56)', 'transportation (OR 0.28)' section of industry, and 'transporting (OR 0.20)' division of industry were negatively associated with PD. 'Drivers (OR 0.13)' division of occupation also was negatively associated with PD. *Conclusions:* To our knowledge, this is the first case-control studies to find an inverse relationship between 'transporting' or 'technicians like machinery engineers' as his/her longest job and PD risk. Because of this unexpected finding, our work should be replicated in various populations.

Keywords: **Occupation; Industry; Parkinson's disease; Case-control study; Manganese**

* Corresponding author. Tel.: +82 52 250 7281; fax: +82 52 250 7289.
E-mail address: yanghokm@nuri.net (Y. Kim).

0161-813X/$ – see front matter
doi:10.1016/j.neuro.2004.07.001

INTRODUCTION

Parkinson's disease (PD) could be caused by environmental exposure to exogenous neurotoxins on a patient's genetic background (Barbeau, 1984; Calne et al., 1994; Michele et al., 1996; Gorell et al., 2004). Studies on the relation between environmental factors and PD have also focused on agents that could cause nigrostriatal damage and, therefore contribute to PD. Several studies have examined a possible relationship between PD and a premorbid exposure to various occupational factors, such as farming, rural living or well water (Semchuk et al., 1992; Rocca et al., 1996; Gorell et al., 1997, 1998), heavy metal industries (Tanner et al., 1997; Gorell et al., 1997, 1998, 2004). Yet the overall epidemiological evidence in support of this relation between metal exposure and PD remains inconclusive. Data on the role of manganese (Mn) as a risk factor for PD is also contradictory. Gorell et al. (1997, 1999, 2004) and Zayed et al. (1990) reported an association between PD and Mn exposure. However, Semchuk et al. (1993), Seidler et al. (1996), and Vieregge et al. (1995) failed to demonstrate any association between PD and Mn exposure. In our previous report on PD patients with Mn exposure, we discussed our concerns about the role of Mn as a risk factor for PD (Kim et al., 1999, 2002). However, in our recent animal experimental study, our data suggested that Mn does not potentiate the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Baek et al., 2003). Using this background, we performed a multi-center case-control study around the two metropolitan cities of South Korea (1) to clarify the role of occupational exposure, and especially Mn exposure in the etiology of PD; and (2) to discover the association between any occupation and PD.

METHODS

The PD patients were recruited in five neurological clinics at the university hospitals around Seoul and Busan, two metropolitan cities of South Korea. These clinics were selected because the involved neurologists had a great expertise in PD. All the incident cases diagnosed newly in 2001 or later were identified. All the patients seventy years of age or more were excluded in order to select a series of cases with the same time experience. All the PD patients in the clinics were diagnosed according to the diagnostic criteria of United Kingdom Parkinson's Disease Society Brain Bank (Gibb and Lees, 1988). The exclusion criteria were: (1) Parkinsonism plus; (2) secondary Parkinsonism (psychiatric drug medication, CO intoxication, aftereffect of encephalitis, manganism etc.) and (3) essential tremor.

Of the PD patients identified, 367 patients (N_1) (177 men, 190 women; mean onset age ± S.D. = 59.93 ± 7.18 year) agreed to participate. We selected control group for the PD patient group, 309 controls (N_2) (198 men, 111 women; mean onset age ± S.D. = 58.24 ± 7.06 year) from the same clinic of the same hospital. The controls were composed of cerebrovascular disease patients without PD. They were also applied the above exclusion criteria. An informed consent was obtained from all the participants, after an explanation was given about the present study.

A structured questionnaire on risk factors was given to the study subjects, and trained research interviewers questioned the subjects in a face-to-face interview. The questionnaire elicited detailed occupational histories of the subjects' jobs that they had held for 6 months or longer before PD onset. This history included information such as job title, company of employment, duration of employment, task performed, equipment and protective measures used, exposure to Mn as well as life style, past history and family history, education level etc.

The job histories of the subjects ran throughout adult life, and this material was classified using both the Korea Standard Industry Code (KSIC) (Korea National Statistical Office, 2000a) and the Korea Standard Classification of Occupations (KSCO) (Korea National Statistical Office, 2000b) for all case and control subjects. We employed a range of industrial categories as defined by section (the most broad category) and division (sub-category) of the KSIC. Along with the KSIC, we also used the KSCO as proxies of occupational exposure. The KSIC is a system for classifying business establishments into 20 industrial "sections" and it sub-categorizes industries by a five-digit code. The first two digits designate the "division" of the Industry. The KSCO codes group different jobs into occupational classes based on their similarities and it defines them using a five-digit occupational code, with the first two digits identifying a particular occupational group as a "division". All occupations were clustered into one of nine broad "sections". These occupational histories were coded by trained staff members who were familiar with both coding schemes.

The χ^2 statistics were computed to test the differences in the general characteristics of the study subjects and the distribution of PD risk factors between the case and control group. A p-value less than 0.01 was considered statistically significant. Logistic regression was used to test our hypotheses concerning potential associations between the subjects having ever worked in specified occupational groups, as defined by the broad categories of the KSCO and the related PD risk. When the broad section sample sizes were sufficient, more specific sub-categorical divisions were then evaluated. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated after adjusting for confounders such as age, sex, smoking, and education level. Similarly, any associations between an industry and the PD risk were analyzed.

RESULTS

Table 1 shows the general characteristics of the case and control groups. The two groups had significantly different distribution regarding sex ($P < 0.001$), education level ($P = 0.001$), and smoking habit ($P < 0.001$).

Table 2 shows the distribution of risk factors for PD in the case group and control groups.

All two groups usually had piped water or clean water to drink, and the statistical difference between the groups was not significant.

Concerning the taking of nutrients such as mineral tablets, most of the subjects in the two groups 'didn't take any nutrients' and the differences found were not significant.

As regarding the exposure to hazardous materials, especially Mn, more subjects in the control group than the case group have worked in the occupations with potential exposure to Mn such as welder, smelter, welding rod manufacturer, manganese miner, workers in the iron and steel industries, dry cell batteries manufacturers, etc. ($P < 0.001$).

Table 1
General characteristics of study subjects

Category	Case (N = 367)	Control (N = 309)	P-Value
Age at onset			
40s	45 (12.3)	39 (12.6)	$P = 0.049$
50s	100 (27.2)	110 (35.6)	
60s	222 (60.5)	160 (51.8)	
Sex			
Male	177 (48.2)	198 (64.1)	$P < 0.001$
Female	190 (51.8)	111 (35.9)	
Education level			
Middle school	171 (46.7)	179 (58.0)	$P = 0.001$
High school	98 (26.7)	82 (26.5)	
College	95 (25.9)	43 (13.9)	
No response	3 (0.8)	5 (1.6)	
Smoking			
Non-smoker	260 (70.8)	127 (41.1)	$P < 0.001$
Ex-smoker	80 (21.8)	120 (38.8)	
Smoker	26 (7.1)	62 (20.1)	
No response	1 (0.3)	0 (0.0)	

Table 2
Distribution of PD risk factors

Category	Case (367)	Control (309)	P-Value
Drinking water			
Piped/clean water	285 (77.7)	265 (85.8)	$P = 0.021$
Well water etc.	81 (22.1)	44 (14.2)	
No answer	1 (0.3)	0 (0.0)	
Taking nutrients			
No	306 (83.4)	280 (90.6)	$P = 0.019$
Yes	57 (15.5)	28 (9.1)	
No answer	4 (1.1)	1 (0.3)	
Exposure to hazardous materials			
No	349 (95.1)	271 (87.7)	$P < 0.001$
Yes	15 (4.1)	38 (12.3)	
No answer	3 (0.8)	0 (0.0)	

'Yes' means have ever worked in the occupations with potential exposure to various hazards including Mn, for instance welder, smelter, welding rod manufacturer, manganese miner, workers in the iron and steel industries, dry cell batteries manufacturers, etc. 'No' means have never worked in the occupations with potential exposure to various hazards.

Table 3 shows the association of the longest held occupation, that is, the section of industry and occupation with PD. ORs and 95% CIs that are adjusted for age, sex, smoking status, and education level are presented.

Ever having worked in 'agriculture, hunting, and forestry' section of industry classification was positively associated with PD (OR 1.88, 95% CI 1.12–3.15). On the other hand, OR suggest that there is a decreased risk for PD with ever having worked in the 'manufacturing (OR 0.56, 95% CI 0.34–0.92)', 'transportation (OR 0.28, 95% CI 0.09–0.87)' of section of industry, or with ever having worked as 'service workers (OR 0.42, 95% CI 0.21–0.86)', 'technicians (OR 0.46, 95% CI 0.24–0.87)' of section of occupation.

Table 4 shows the association of the longest held occupation, as defined by the division of industry and occupation, with PD.

Ever having worked in the 'transporting (OR 0.20, 95% CI 0.06–0.71)' division of industry were negatively associated with PD. Ever having worked in 'metal, machinery and related engineers (OR 0.30, 95% CI 0.12–0.74)' and 'drivers (OR 0.13, 95% CI 0.03–0.57)' division of occupation also were negatively associated with PD. On the other hand, 'agriculture production crops (OR 1.96, 95% CI 1.16–3.30)' division of industry was positively associated with PD.

Table 3
Association of the longest held section of industry and occupation with PD: adjusted by sex, age, smoking, and education level

Classification	N_1	N_2	OR (95% CI)
Industry			
Agriculture, hunting and forestry	50	36	1.88 (1.12–3.15)
Fishing	4	5	0.68 (0.17–2.77)
Manufacturing	33	54	0.56 (0.34–0.92)
Construction	28	27	1.29 (0.71–2.37)
Wholesale, retail trade	51	46	0.90 (0.57–1.42)
Housing and refectory	9	10	0.80 (0.30–2.12)
Transportation	4	23	0.28 (0.09–0.87)
Finance, insurance	10	3	2.44 (0.62–9.62)
Services	29	14	1.37 (0.68–2.79)
Public administration	18	8	1.71 (0.66–4.43)
Educational service	36	9	2.25 (0.99–5.08)
Health and welfare	4	2	0.90 (0.15–5.51)
Miscellaneous repair services	14	20	0.55 (0.26–1.17)
Private households	71	42	1.03 (0.63–1.70)
Occupation			
Legislators, senior officials and managers	13	12	0.84 (0.36–1.96)
Professional	51	18	1.56 (0.82–2.97)
Technicians and associate professionals	8	3	2.78 (0.66–11.67)
Clerk	54	25	1.57 (0.90–2.73)
Service	14	27	0.42 (0.21–0.86)
Sales	37	38	0.77 (0.47–1.29)
Agriculture, fishery and forestry	46	38	1.54 (0.92–2.59)
Technicians	16	41	0.46 (0.24–0.87)
Machine operators and assemblers	19	36	0.68 (0.36–1.28)
Laborers in mining, construction, manufacturing and transport	97	68	1.06 (0.69–1.61)
Army	5	1	–

DISCUSSION

Our study had several strengths and strong points.

A fundamental step in the avoidance of selection bias is to ensure that the cases and controls are drawn from the same study base (the population/time experience) (Shapiro and Rosenberg, 2000). Workers who were of the active age in 1970s, the beginning era of the rapid and high economic development in South Korea, are mostly people under age 70 years. Thus limiting the study subjects under age 70 years may homogenize the prevalence of exposure in the control and the case group.

Selecting of controls among cerebrovascular disease patients in the same department of the same hospital has some advantages. First, the cerebrovascular disease patients are of similar age distribution as PD. Second, cerebrovascular disease patients are rather common in the neurology clinic. However, there may be some concerns in the interaction or co-morbidity of cerebrovascular disease and PD. Data on the relationship between PD and stroke are conflicting. Korten et al. (2001) speculate that dopamine deficiency may protect against ischemic brain damage, perhaps by reducing the effects of excitotoxicity on PD prevalence figures from a Dutch population-based. However, Mastaglia et al. (2002) reported that their findings did not indicate either a protective effect against stroke, or a greater susceptibility to death from stroke, in the postmortem population studied. Moreover, we examined the occupational history prior to the new development of PD cases, thus some concerns in the interaction of cerebrovascular disease and PD would not matter in our study. We also confirmed if the controls had the coexistence of PD in order to avoid a form of selection bias.

We controlled age and the confounders such as sex, smoking, and education level which were significantly different in the case and control groups.

We utilized quite a detailed method of coding occupational histories of PD patients and (neurologic disease) controls. Because the KSCO classification scheme is comprehensive and the job categories are well defined, this probably leads to minimal misclassification of occupations and an increased validity, and this added to the strength of our study. Moreover, in order to minimize the possibility of observation bias, the coded occupational histories were reviewed by an industrial hygienist that worked with our team, and this

Table 4
Association of the longest held division of industry and occupation with PD: adjusted by sex, age, smoking and education level

Classification	N_1	N_2	OR (95% CI)
Industry			
Agriculture production crops	50	35	1.96 (1.16–3.30)
Fishing	3	5	0.48 (0.10–2.20)
Manufacturing for apparel and other finished products made from fabrics and similar materials	6	4	1.30 (0.34–4.99)
Manufacturing for industrial and commercial machinery and computer equipment	17	30	0.65 (0.33–1.27)
Manufacturing for transportation equipment	3	3	0.77 (0.14–4.22)
General construction	25	26	1.04 (0.56–1.94)
Construction special trade contractors	4	3	2.89 (0.60–13.93)
Automotive dealers and gasoline service stations	6	2	3.66 (0.66–20.35)
Wholesale and brokerage business	12	6	1.33 (0.47–3.77)
Retails	29	35	0.70 (0.40–1.21)
Housing and refectory	9	12	0.64 (0.25–1.63)
Transporting	3	23	0.20 (0.06–0.71)
Finance and insurance	7	2	2.21 (0.43–11.47)
Computation and information services	3	2	1.11 (0.17–7.42)
Research and developmental services	3	1	2.32 (0.23–23.61)
Business services	25	12	1.32 (0.61–2.83)
Public administration	17	7	1.77 (0.65–4.85)
Educational service	36	10	1.94 (0.88–4.27)
Health service	4	1	2.06 (0.22–19.71)
Membership organization	4	1	2.02 (0.20–20.71)
Other services	6	12	0.39 (0.14–1.11)
Private households	71	42	1.03 (0.63–1.70)
Occupation			
Directors and chief executives	6	3	1.98 (0.48–8.21)
General managers	8	7	0.84 (0.29–2.47)
Architects, engineers and related professionals	3	4	0.49 (0.10–2.43)
Health professionals	4	1	2.06 (0.22–19.71)
Teaching professionals	37	10	1.97 (0.90–4.34)
Legal, social service and religious professions	5	1	2.87 (0.30–27.14)
Engineering science technicians	5	2	2.83 (0.48–16.61)
General office workers	49	25	1.36 (0.77–2.39)
Customer services	8	15	0.43 (0.17–1.10)
Restaurant service workers	3	8	0.38 (0.09–1.58)
Personal and protective service workers	3	1	1.81 (0.17–19.21)
Whole/retails sales	38	35	0.82 (0.49–1.38)
Farmers	43	34	1.64 (0.96–2.81)
Fishery workers	3	4	0.74 (0.15–3.63)
Metal, machinery and related engineers	7	28	0.30 (0.12–0.74)
Industrial machinery mechanics and fitters	4	2	1.74 (0.29–10.43)
Machinery/system operators	13	5	2.68 (0.89–8.07)
Automated-assembly-line operators	6	4	1.50 (0.40–5.66)
Drivers	2	24	0.13 (0.03–0.57)
Laborers in general services	73	48	0.97 (0.60–1.56)
Manufacturing laborers	2	5	0.27 (0.05–1.44)
Laborers in mining, construction	21	18	1.36 (0.67–2.75)
Army	5	1	–

person was "blinded" to the subjects' case-control status. We employed well-trained interviewers to ascertain the lifetime occupational histories. The presence of an interviewer ensured accuracy and completeness of the data collected, and this decreased the number of invalid responses and unanswered questions.

The data on the role of Mn as a risk factor for PD is contradictory. Gorell et al. (1997, 1999, 2004) and Zayed et al. (1990) reported an association between PD and Mn exposure. However, Semchuk et al. (1993), Seidler et al. (1996), and Vieregge et al. (1995) failed to demonstrate any association between PD and Mn exposure. In our previous report of PD patients with Mn exposure, we discussed our concerns about the role of Mn as a risk factor of PD (Kim et al., 1999, 2002), and our recent animal experimental study suggested that Mn does not potentiate the neurotoxicity of MPTP (Baek et al., 2003). As regarding the exposure to hazardous materials, especially Mn, more subjects in the control group than the PD patient group have worked in the occupations with potential exposure to Mn such as welder, smelter, welding rod manufacturer, Mn miner, workers in the iron and steel industries and dry cell battery manufacturers. Furthermore, according to logistic regression in the present study, above occupations with a high potential exposure to Mn showed consistently negative association with PD after adjusting the confounders such as age, sex, smoking and education level (OR: 0.42, 95% CI 0.22–0.81). However, further epideimiological study on Mn-related occupation should be needed.

Some occupations showed significant associations with the PD risk. The 'agriculture, hunting, and forestry' (OR 1.88, 95% CI 1.12–3.15) section of industry showed a positive association. And its sub-category, 'agriculture production crops (OR 1.96, 95% CI 1.16–3.30)' consistently showed a positive association. On the other hand, the 'transportation' section of industry, its sub-category 'transporting', and 'drivers' division of occupation showed a negative association consistently. The 'technicians' section of occupation and its sub-category 'metal, machinery and related engineers' also showed a negative association consistently.

We should be cautious in comparing our finding with other study results because of differences in study design and with the methods utilized.

Associations between 'agriculture, fishery, forestry' or 'farmers' occupation and PD are still inconsistent. There is a report that herbal medicine, insecticides and agriculture were related to neurochemical changes such as oxidative stress that's connected with nigral neural death of PD (Olanow and Tatton, 1999). Gorell et al. (1998) reported that 'farming' as an occupation was a risk factor for PD (OR = 2.79, 95% CI, 1.03–7.55). Similarly, Semchuk et al. (1993) found an increased odds ratio for agricultural work (1.94; P = 0.017) and a dose-response relationship between years worked in field crop farming or grain farming occupations and an increasing PD risk. In contrast, results from an Italian case-control study (Rocca et al., 1996) did not suggest that study participants who worked most of their lives as farmers were at an increased risk for PD (OR = 0.6, 95% CI, 0.3–1.3). The present study consistently showed that the farming industry by section and division showed a positive association with PD.

Kirkey et al. (2001) reported for the first time the inverse relationship between ever having worked in a service occupation and PD risk. They obtained complete occupational histories from living study subjects and each job was coded using both the DOT and SIC classification schemes. Additionally, all coding was reviewed by an industrial hygienist. They thought that those people worked in a service occupation may have been more likely to smoke, and it has been consistently shown that smoking provides protection against PD. In contrast with the results of Kirkey et al. (2001), Schulte et al. (1996) observed excess mortality rates from PD for several occupational categories that would potentially be classified as service occupations using the DOT classification scheme. They used the "usual occupation" listed on the death certificate that was collected from the National Occupational Mortality Surveillance System, and the death data were grouped together by an industrial hygienist into different occupational characteristics. In addition, Tsui et al. (1999) examined the association of PD with various occupations. Occupational data of the case subjects were ascertained from medical records, while occupational information for the controls was assessed at the time of the 1991 Canadian Census. When classifying the occupations using the 1980 version of the standard occupational classification, a significantly increased OR for PD was found for the combined category of "other primary" occupations (e.g., forestry, logging, mining, oil/gas field work, etc.), as well as for teaching, social sciences/law/library work, and medicine/health. Significant inverse relationships between management/administration, clerical, construction, and the "not applicable" group and PD risk were found. Because only the current occupation was known, and this was learned by using different methods for the case and control subjects who were less than age 65, their results are a bit difficult to interpret.

In the present study, associations between white-collar occupations such as teaching/education, professional and clerk type occupations and PD almost disappeared after controlling the confounder of the education level additionally. Our results suggest that the differences in the education level between blue and white collar workers may be a source of selection bias.

To our knowledge, this is the first case-control studies to find an inverse relationship between 'transporting' or 'technicians like machinery engineers' as his/her longest job and PD risk. One of some explanations for this might be a form of selection bias. They might have different illness behaviors because of shift-work/nightwork, leading to a kind of selection bias. Because of this unexpected finding, our work should be replicated in various populations.

In summary, as regarding the exposure to hazardous materials, especially Mn, more subjects in the control group than the PD patient group have worked in the occupations with potential exposure to Mn. Furthermore, The 'agriculture, hunting, and forestry' section of industry showed a positive association. And its sub-category, 'agriculture production crops' consistently showed a positive association. On the other hand, the 'transportation' section of industry, its sub-category 'transporting', and 'drivers' division of occupation showed a negative association consistently. The 'technicians' section of occupation and its sub-category 'metal, machinery and related engineers' also showed a negative association consistently.

ACKNOWLEDGEMENT

This work was supported by grant No. (R01-2000-000-00162-0) from the Basic Research Program of the Korea Science & Engineering Foundation.

REFERENCES

Baek SY, Lee M-M, Jung H-S, Kim H-J, Lee C-R, Yoo C, et al. Effect of manganese exposure on MPTP neurotoxicities. Neurotoxicology 2003;24:657–65.

Barbeau A. Manganeses and exrapyramidal disorders (a critical review and tribute to Dr. George C. Cotzias). Neurotoxicology 1984;5:12–36.

Calne DB, Chu NS, Huang CC, Lu CS, Olanow W. Manganism and idiopathic Parkinsonism: similarities and differences. Neurology 1994;44:1583–6.

Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatr 1988;51:745–52.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, et al. Occupational exposures to metals as risk factors for Parkinson's disease. Neurology 1997;48:650–8.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 1998;50:1346–50.

Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, et al. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology 1999;20:239–47.

Gorell JM, Peterson EL, Rybicki BA, Johnson CC. Multiple risk factors for Parkinson's disease. J Neurol Sci 2004;217:169–74.

Kim Y, Kim J, Ito K, Lim H-S, Cheong H-K, Kim JY, et al. Idiopathic Parkinsonism with superimposed manganese exposure: utility of positron emission tomography. Neurotoxicology 1999;20:249–52.

Kim Y, Kim JM, Kim J, Yoo C, Lee CR, Lee JH, et al. Dopamine transporter density is decreased in parkinsonian patients with a history of manganese exposure, what does it mean? Mov Disord 2002;17:568–75.

Kirkey KL, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Gorell JM. Occupational categories at risk for Parkinson's disease. Am J Ind Med 2001;39:564–71.

Korea National Statistical Office. Korea Standard Industry Code Manual. 2000a.

Korea National Statistical Office. Korea Standard Classification of Occupations. 2000b.

Korten A, Lodder J, Vreeling F, Boreas A, van Raak L, Kessels F. Stroke and idiopathic Parkinson's disease: does a shortage of dopamine offer protection against stroke? Mov Disord 2001;16:119–23.

Mastaglia FL, Johnsen RD, Kakulas BA. Prevalence of stroke in Parkinson's disease: a postmortem study. Mov Disord 2002;17:772–4.

Michele G, Filla A, Volpe G, Marco V, Gogliettino A, Ambrosio G, et al. Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy. Mov Disord 1996;1:17–23.

Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. Annu Rev Neurosci 1999;22:123–44.

Rocca WA, Anderson DW, Meneghini F, Grigoletto F, Morgante L, Reggio A, et al. Occupation, education, and Parkinson's disease: a case-control study in an Italian population. Mov Disord 1996;11:201–6.

Schulte PA, Burnett CA, Boeniger MF, Jonson J. Neurodegenerative diseases: occupational occurrence and potential risk factors, 1982–1991. Am J Public Health 1996;86:1281–8.

Seidler A, Hellenbrand W, Robra BP, Vieregge P, Nischan P. Possible environmental, occupational and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology 1996;46:1275–84.

Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultureal work and pesticide chemicals. Neurology 1992;42:1328–35.

Semchuk KM, Love EJ, Lee RG. Parkinson's disease: a test of the multifactorial etiologic hypothesis. Neurology 1993;43:1173–80.

Shapiro S, Rosenberg L. Bias in case-control studies. In: Gail MH, Benichou J, editors. Encyclopedia of epidemiologic methods. Chichester: John Wiley & Sons, Ltd, 2000. p. 83–92.

Tanner CM, Hubble CP, Chan P. Epidemiology and genetics of Parkinson's disease. In: Watts RL, Koller WC, editors. Textbook of movement disorders–neurologic principles and practice. New York: McGraw-Hill, 1997. p. 137–52.

Tsui JK, Calne DB, Wang Y, Schulzer M, Marion SA. Occupational risk factors in Parkinson's disease. Can J Public Health 1999;90:334–7.

Vieregge P, Heinzow B, Lorg G, Teichert HM, Schleifenbaum P, Mosinger HU. Long term exposure to manganese in rural well water has no neurological effects. Can J Neurol Sci 1995;22:286–9.

Zayed J, Ducic S, Campanella G, Panisset JC, Andre P, Masson H, et al. Environmental factors in the etiology of Parkinson's disease. Can J Neurol Sci 1990;17:286–91.