

Occupation and Risk of Parkinsonism

A Multicenter Case-Control Study

Caroline M. Tanner, MD, PhD; G. Webster Ross, MD; Sarah A. Jewell, MD, MPH; Robert A. Hauser, MD; Joseph Jankovic, MD; Stewart A. Factor, DO; Susan Bressman, MD; Amanda Deligtisch, MD; Connie Marras, MD, PhD, FRCPC; Kelly E. Lyons, PhD; Grace S. Bhudhikanok, PhD; Diana F. Roucoux, MPH; Cheryl Meng, MS; Robert D. Abbott, PhD; J. William Langston, MD

Background: We examined risk of parkinsonism in occupations (agriculture, education, health care, welding, and mining) and toxicant exposures (solvents and pesticides) putatively associated with parkinsonism.

Objective: To investigate occupations, specific job tasks, or exposures and risk of parkinsonism and clinical subtypes.

Design: Case-control.

Setting: Eight movement disorders centers in North America.

Participants: Inclusion criteria were parkinsonism (≥ 2 cardinal signs), diagnosis within 8 years of recruitment (to minimize survival bias), and ability to participate in detailed telephone interviews. Control subjects were primarily nonblood relatives or acquaintances of patients.

Main Outcome Measures: This multicenter case-control study compared lifelong occupational and job task histories to determine associations with parkinsonism and certain clinical subtypes (postural instability and gait difficulty and age at diagnosis ≤ 50 years).

Results: Findings in 519 cases and 511 controls were analyzed. Work in agriculture, education, health care, or welding was not associated with increased risk of parkinsonism. Unexpected increased risks associated with legal, construction and extraction, or religious occupations were not maintained after adjustment for duration. Risk of parkinsonism increased with pesticide use (odds ratio, 1.90; 95% confidence interval, 1.12-3.21), use of any of 8 pesticides mechanistically associated with experimental parkinsonism (2.20; 1.02-4.75), and use of 2,4-dichlorophenoxyacetic acid (2.59; 1.03-6.48). None of the specific occupations, job tasks, or task-related exposures were associated with younger age at diagnosis (≤ 50 years). Ever working in business and finance, legal occupations, construction and extraction, or transportation and material moving was associated with postural instability and gait difficulty subtype of parkinsonism. Tobacco use was inversely associated with parkinsonism risk.

Conclusion: The association of disease risk with pesticides support a toxicant-induced cause of parkinsonism.

Arch Neurol. 2009;66(9):1106-1113

Author Affiliations are listed at the end of this article.

PARALYSIS AGITANS WAS DESCRIBED at the height of the industrial revolution,¹ yet it was not until the late 20th century that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-associated parkinsonism prompted investigations of occupational chemical exposures and disease.² Since then, occupations such as farming, teaching, and welding have been proposed to increase risk of Parkinson disease (PD), but associations have been inconsistent.³⁻⁷ Few investigations have evaluated a direct relationship between occupational chemical exposures and PD. Toxicant-induced parkinsonism may have atypical features,^{8,9}

but this factor has not been investigated systematically.

To address these concerns, we examined risk of parkinsonism in occupations (agriculture, education, health care, welding, and mining) and toxicant exposures (solvents and pesticides) putatively associated with PD. To minimize exposure misclassification, we used lifelong job task-specific occupational histories. To avoid overly restrictive diagnostic criteria that might exclude toxicant-induced cases, we enrolled subjects with typical or atypical parkinsonism. Detailed clinical characterization of cases was performed by movement disorders specialists (C.M.T., G.W.R., R.A.H., J.J., S.A.F., S.B., A.D.,

Table 1. Study Enrollment by Site

Study Site	Cases			Controls		
	No. (%) (n=519)	Men, %	Mean Age, y	No. (%) (n=511)	Men, %	Mean Age, y
The Parkinson's Institute	134 (25.8)	56.0	66.8	144 (28.2)	57.6	66.5
University of South Florida	92 (17.7)	58.7	65.0	107 (20.9)	51.4	66.1
Emory University School of Medicine	90 (17.3)	65.5	63.7	42 (8.2)	54.7	65.2
Baylor College of Medicine	80 (15.4)	60.0	61.2	93 (18.2)	47.3	61.8
Beth Israel Medical Center	73 (14.1)	49.3	63.0	47 (9.2)	53.1	62.9
Toronto Western Hospital	26 (5.0)	73.0	62.2	14 (2.7)	85.7	63.4
University of Kansas Medical Center	16 (3.1)	43.8	67.0	9 (1.8)	55.5	70.2
Veterans Affairs Pacific Islands Health Care System	8 (1.5)	100	70.5	6 (1.2)	100	67.7
Telephone recruitment	NA	NA	NA	49 (9.6)	100	64.2

Abbreviation: NA, not applicable.

C.M., K.E.L., and J.W.L.). Multicenter case and control ascertainment was used to avoid geographic bias.

METHODS

RECRUITMENT

Cases

Enrolling investigators (C.M.T., G.W.R., R.A.H., J.J., S.A.F., S.B., C.M., and K.E.L.) at 8 North American movement disorders centers recruited consecutively eligible subjects between July 1, 2004, and May 31, 2007 (**Table 1**); they evaluated diagnostic features for parkinsonism,^{10,11} age at diagnosis, cognitive status, response to therapy, and Unified Parkinson Disease Rating Scale scores. At 2 centers, staff shortages limited strictly consecutive enrollment. Inclusion criteria were the following: (1) parkinsonism of no known cause, defined as 2 or more signs (resting tremor, bradykinesia, rigidity, and postural reflex impairment), 1 of which must be resting tremor or bradykinesia; (2) diagnosis within 8 years to minimize the risk of survival bias; and (3) absence of dementia.¹²

Control Subjects

Controls were frequency matched to cases by age, sex, and location. Persons with neurodegenerative disorders were excluded. To minimize bias related to demographic or socioeconomic differences, controls were primarily identified from (1) nonblood relatives (excluding spouses) or acquaintances of cases enrolled in the study or (2) nonblood relatives or acquaintances of other patients with parkinsonism in the movement disorders clinics. To minimize overmatching, workmates were ineligible as controls. Additional controls were recruited by the use of a commercial list of telephone numbers (A. Caldwell List Company, Inc, Norcross, Georgia) for men aged 50 to 65 years with zip codes matching those of enrolled cases.

Subjects were informed that the study objective was to investigate putative environmental risk factors for parkinsonism, without indicating specific hypotheses. Subjects were screened using the Telephone Interview for Cognitive Status.¹³

HUMAN SUBJECTS/RISK FACTOR INTERVIEWS

Human subject committees at each site approved the protocol. All subjects provided written informed consent. Interview-

ers at The Parkinson's Institute, Sunnyvale, California, used standardized computer-assisted telephone interviews to collect lifelong histories of tobacco, caffeine, and alcohol use and history of head injury and occupational histories (all jobs held for ≥ 3 months). For each job, information about the industry, location, processes, materials, and job tasks was collected.¹⁴ To determine toxicant exposure, detailed information was collected for the following job tasks: cleaning and degreasing, gluing, machining, painting, using pesticides, soldering, stripping paint, welding, and woodworking. Specific occupations (agriculture, education, health care, mining, and welding) and toxicant exposures (solvents and pesticides) were identified a priori as putative risk factors for parkinsonism based on mechanistic theories or information from prior publications.^{3-5,8,9,15-18}

DEFINITION OF EXPOSURE VARIABLES

Analysis was limited to exposures before the reference age (age at diagnosis for cases and median age at diagnosis for cases in the appropriate sex and birth year-specific stratum for controls). Exposure variables were defined categorically and cumulatively. Tobacco, caffeine, and alcohol use for at least 6 months was defined as regular use. Cumulative exposure was defined as quantity over time using pack-years for cigarettes (1 pack of cigarettes per day for 1 year), milligram-years for caffeine (1 mg/d for 1 year), and drink-years for alcohol (1 alcoholic drink/d for 1 year). Head injury was defined as injury with loss of consciousness or as a physician-diagnosed concussion. Each occupation held before the reference date was classified by the use of the 2000 Standard Occupational Classification (SOC) Manual.¹⁹ Coders were unaware of case status. The SOC codes, specific job tasks, and occupational exposures were classified categorically and for duration of time worked before the reference date. The a priori hypotheses were represented by SOC 25-0000 (education), 29-0000 and 31-0000 (health care), and 45-0000 (farming), any welding or mining task and occupational exposure to solvents or pesticides.

DEFINITION OF CLINICAL FEATURES

Diagnosis and type of parkinsonism, Unified Parkinson Disease Rating Scale score, and clinical features were determined by the enrolling investigator. The postural instability and gait difficulty (PIGD) subtype was defined by the use of an established method.²⁰

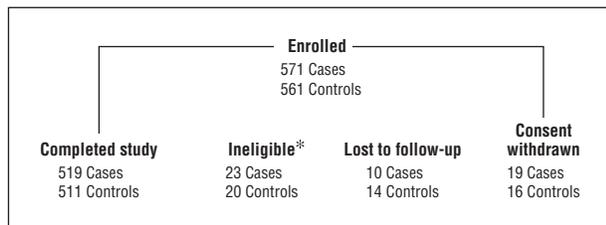


Figure. Study enrollment. * Indicates that reasons for ineligibility of cases and controls included severe hearing impairment, non-English speaking, and dementia.

SAMPLE SIZE

Lifetime frequencies of the a priori-specified occupations and tasks of interest were estimated to range from 1% to 33% based on published studies^{4,21,22} and on our unpublished control data from 2003 (C.M.T. et al). With an odds ratio (OR) of 3.5 and an exposure frequency of 1% or with an OR of 1.5 and an exposure frequency of 20%, 500 cases and 500 controls would be needed to have an 80% power to identify an association between the exposure and parkinsonism at a 2-sided 5% level of significance.

STATISTICAL ANALYSIS

Our primary occupational analysis determined risk of parkinsonism associated with categorical and cumulative work in the a priori-specified occupations, job tasks, or exposures. Secondary analyses included association of other major and minor occupational codes and parkinsonism. Additional analyses determined risk in subgroups (PD, atypical parkinsonism, the PIGD clinical subtype, or early age [≤ 50 years] at diagnosis) compared with controls. The Wilcoxon rank sum test was used for continuous variables and the Fisher exact test for categorical variables. Crude and adjusted ORs were calculated by the use of logistic regression models. Multiple logistic regression analysis was also used to obtain ORs adjusting for age (continuous), sex, race/ethnicity (white vs nonwhite), smoking (cigarette pack-years), caffeine use (milligram-years), alcohol use (drink-years), head injury (ever vs never), and duration of job or task (4 groups [never and tertiles of duration]). Site was modeled as a random effect, as was its interaction with an occupation, a job task, or an exposure. All analyses were performed by the use of commercially available software (SAS version 9.1.3 [SAS Institute, Cary, North Carolina]²³ and SPSS version 12.01 [SPSS Inc, Chicago, Illinois]²⁴).

RESULTS

Ninety-one percent of enrolled cases (519 of 571) and controls (511 of 561) were included in the primary analysis (**Figure**). Cases not analyzed were similar to those included, but controls not analyzed had a slightly lower educational level (<12 years of education in 36.0% not analyzed vs in 18.0% analyzed). About 90% of cases and 85% of controls were recruited from 5 sites (Table 1). The cases and controls were similar overall and among individual sites, except that controls recruited by telephone were mostly men aged 50 to 65 years. Subjects were primarily white males (**Table 2**); 96.9% had PD.

NONOCCUPATIONAL RISK FACTORS

Ever smoking cigarettes and number of pack-years smoked were inversely associated with risk of parkinsonism

(**Table 3**). Ever drinking coffee and cumulative caffeine intake showed an inverse association of borderline statistical significance. Head injury was directly associated with PD risk, but the confidence intervals (CIs) were broad.

STANDARDIZED OCCUPATIONAL CODES

All 23 major occupational codes, 92 of 99 minor codes, and 838 of 1600 unique 6-digit SOC codes were assigned at least once to cases and controls (mean, 9.5 codes for cases and 9.9 codes for controls) (**Table 4**). None of the a priori-identified occupational categories were associated with parkinsonism. Among the remaining major SOC categories, ever working in a legal or construction/extraction occupation was directly associated with parkinsonism. Among 92 minor SOC categories, ever working as a lawyer or judge (OR, 3.15; 95% CI, 1.3-7.6; $P = .01$ for SOC 23-1000) or as a religious worker (2.4; 1.04-5.52; $P = .04$ for SOC 21-2000) was associated with greater risk of parkinsonism, while lower risk was noted for personal care and service workers (0.58; 0.35-0.95; $P = .03$ for SOC 39-9000), food preparation workers (0.54; 0.36-0.82; $P = .003$ for SOC 35-2000), and military tactical weapons specialists (0.43; 0.28-0.65; $P < .001$ for SOC 55-3000). When these SOC code comparisons were adjusted for duration of work, associations were not maintained, and analyses repeated among PD cases did not change findings significantly.

SPECIFIC JOB TASKS AND EXPOSURES

Neither welding (any specific type) nor use of solvents (including carbon tetrachloride and trichloroethylene) increased risk of parkinsonism (Table 4 and **Table 5**). Ever painting, soldering, machining, using glue or adhesives, woodworking, and stripping wood or paint also did not differ between cases and controls. No individual type of glue or paint was associated with parkinsonism. No subjects had worked as miners. Of 144 subjects who did farm work, only 48 (33.3%) endorsed pesticide use. Among those farmers who did not use pesticides, 54.0% had stopped farming before age 20 years. Of 71 pesticide users, 51 (71.8%) were farmers, 18 (25.4%) worked in building and grounds maintenance, and 2 (2.8%) were soldiers. Cases were more likely to have ever used pesticides. Cases were also more likely to have ever used any of the 8 pesticides selected a priori as being of particular interest and to have ever used 2,4-dichlorophenoxyacetic acid. Paraquat and permethrin were rarely used, but association with greater risk of parkinsonism was suggested. Duration of any of the job tasks or exposures did not differ between cases and controls.

ASSOCIATION WITH CLINICAL FEATURES

None of the occupations, job tasks, or task-associated exposures were associated with atypical parkinsonism or with younger age at diagnosis (≤ 50 years). Ever working in business and finance, legal occupations, construction and extraction, or transportation and material moving was associated with PIGD subtype but not after adjustment for duration.

Table 2. Demographic and Clinical Characteristics of Study Subjects^a

Characteristic	Cases (n=519)	Controls (n=511)
Men	309 (59.5)	302 (59.1)
Age, median (range), y	65 (30-88)	65 (33-95)
White race/ethnicity ^b	451 (86.9)	466 (91.2)
Education, median (range), y	16 (8-17)	16 (7-17)
Employed at enrollment	210 (40.5)	224 (43.8)
Adjusted Telephone Interview for Cognitive Status score at enrollment, median (range) ^b	33 (17-48)	35 (20-46)
Parkinson disease	503 (96.9)	NA
Multiple system atrophy	12 (2.3)	NA
Progressive supranuclear palsy	4 (0.8)	NA
Age at diagnosis, mean (range), y	62 (30-88)	NA
Disease duration, mean (range) time between diagnosis and study enrollment, y	2.8 (0-8)	NA
Enrolled within 4 y of diagnosis	424 (81.7)	NA
Age at diagnosis ≤50 y	73 (14.1)	NA
Postural instability and gait difficulty subtype ²³	110 (21.2)	NA
Unified Parkinson Disease Rating Scale score, mean (SD) [range]		
Activities of daily living	9.8 (5.7) [0-35]	NA
Motor	19.2 (11.2) [0-73]	NA
Resting tremor	390 (75.1)	NA
Rigidity	477 (91.9)	NA
Bradykinesia	489 (94.2)	NA
Postural reflex impairment	141 (27.2)	NA
Asymmetric onset	435 (83.8)	NA
Sustained response to dopaminergic therapy ^c	320 (87.2)	NA

Abbreviation: NA, not applicable.

^aUnless otherwise indicated, values are given as number (percentage).

^b $P < .05$.

^cIn a total of 367 cases, patients took levodopa.

Table 3. Nonoccupational Risk Factors^a

Risk Factor	Cases	Controls	Odds Ratio (95% Confidence Interval)
Tobacco use ever (n=977) ^b	227 (46.0)	264 (54.5)	0.711 (0.553-0.915)
Cigarette pack-years, median (range) (n=435) ^{b,c}	10.4 (0.1-188.0)	15.8 (0.1-116.0)	NA
Cigarette smoker ever (n=979) ^b	205 (41.5)	241 (49.7)	0.718 (0.558-0.924)
Coffee consumption ever (n=980)	481 (97.4)	481 (99.0)	0.385 (0.136-1.087)
Caffeine intake, milligram-years, median (range) (n=955) ^c	6114.8 (2.9-87 069.4)	7037.9 (5.1-80 311.4)	NA
Alcohol use ever (n=975)	462 (94.3)	458 (94.4)	0.973 (0.564-1.676)
Head injury ever (n=1030)	119 (24.4)	99 (20.6)	1.248 (0.922-1.689)

Abbreviation: NA, not applicable.

^aUnless otherwise indicated, values are given as number (percentage).

^b $P < .05$.

^cPack-years and caffeine milligram-years were computed among smokers and coffee drinkers only.

COMMENT

Occupational use of pesticides was associated with an almost 80% greater risk of parkinsonism. Growing evidence suggests a causal association between pesticide use and parkinsonism.^{15,17,21,25-28} However, the term "pesticide" is broad and includes chemicals with varied mechanisms. Because few investigations have identified specific pesticides, we studied 8 pesticides with high neurotoxic plausibility based on laboratory findings.²⁹ Use of these pesticides was associated with higher risk of parkinsonism, more than double that in those not exposed.

Three individual compounds, the organochlorine 2,4-dichlorophenoxyacetic acid, the herbicide paraquat, and the insecticide and acaricide permethrin, were associated

with more than a 3-fold increased risk of disease, although precision was poor for paraquat and permethrin. Combined exposure was observed in 44.8% of subjects (Table 5). To our knowledge, this is the first documented association of 2,4-dichlorophenoxyacetic acid with PD risk. Other organochlorines have been associated with increased risk of PD, and excessive amounts of organochlorines have been found in PD brains.^{22,25,30,31} Paraquat has also been associated with increased risk of PD.^{15,21,27,28} Paraquat³² and certain organochlorines³³ are used to create experimental models of parkinsonism, which adds biologic plausibility to the hypothesis that pesticide exposure may be causal. Permethrin has not previously been associated with PD, to our knowledge. In mice, permethrin affects dopamine transport and may increase sus-

Table 4. Odds Ratios for Parkinsonism and Association With Major Occupational Code Groups From the Standard Occupational Classification (SOC) Manual¹⁹ and Selected Job Tasks

Major Occupational Code Group ^a	SOC	No. (%)		Adjusted Model Odds Ratio (95% Confidence Interval) ^b
		Cases (n=519)	Controls (n=511)	
11-0000	Management occupations	224 (43.2)	209 (40.9)	1.13 (0.86-1.47)
13-0000	Business and financial operations	126 (24.3)	116 (22.7)	1.06 (0.78-1.45)
15-0000	Computer and mathematical	35 (6.7)	38 (7.4)	1.01 (0.61-1.66)
17-0000	Architecture and engineering	57 (11.0)	67 (13.1)	0.75 (0.50-1.12)
19-0000	Life, physical, and social science	45 (8.7)	60 (11.7)	0.69 (0.45-1.07)
21-0000	Community and social service	50 (9.6)	39 (7.6)	1.32 (0.83-2.10)
23-0000	Legal occupations	30 (5.8)	10 (2.0)	2.95 (1.34-6.48) ^d
25-0000	Education, training, and library ^c	152 (29.3)	167 (32.7)	0.82 (0.62-1.09)
27-0000	Arts, design, entertainment, sports, and media	106 (20.4)	88 (17.2)	1.18 (0.85-1.63)
29-0000	Health care practitioner and technical ^c	55 (10.6)	63 (12.3)	0.81 (0.54-1.22)
31-0000	Health care support ^c	45 (8.7)	60 (11.7)	0.72 (0.46-1.13)
33-0000	Protective service	36 (6.9)	50 (9.8)	0.71 (0.44-1.15)
35-0000	Food preparation and serving related	125 (24.1)	152 (29.7)	0.79 (0.59-1.05)
37-0000	Building and grounds cleaning	143 (27.6)	165 (32.3)	0.79 (0.60-1.06)
39-0000	Personal care and service workers	68 (13.1)	85 (16.6)	0.72 (0.50-1.04)
41-0000	Sales and related occupations	246 (47.4)	257 (50.3)	0.95 (0.74-1.24)
43-0000	Office and administrative support	357 (68.8)	366 (71.6)	0.87 (0.65-1.16)
45-0000	Farming, fishing, and forestry ^c	87 (16.8)	83 (16.2)	1.10 (0.78-1.57)
47-0000	Construction and extraction	135 (26.0)	102 (20.0)	1.45 (1.04-2.03) ^d
49-0000	Installation, maintenance, and repair	94 (18.1)	104 (20.4)	0.84 (0.59-1.19)
51-0000	Production occupations	196 (37.8)	211 (41.3)	0.88 (0.67-1.16)
53-0000	Transportation and material moving	268 (51.6)	278 (54.4)	0.91 (0.68-1.20)
55-0000	Military-specific occupations	145 (27.9)	165 (32.3)	0.71 (0.50-1.01)
Pesticide use	Pesticide use ^c	44 (8.5)	27 (5.3)	1.90 (1.12-3.21) ^d
Woodworking	Woodworking	63 (12.1)	49 (9.6)	1.49 (0.97-2.29)
Gluing	Glue or adhesive use	57 (11.0)	49 (9.6)	1.31 (0.85-2.02)
Welding	Welding ^c	41 (7.9)	38 (7.4)	1.01 (0.61-1.66)
Soldering	Soldering	57 (11.0)	60 (11.7)	1.05 (0.69-1.59)
Cleaning	Cleaning with solvents ^c	136 (26.2)	144 (28.2)	1.01 (0.74-1.38)
Stripping	Stripping wood or paint	15 (2.9)	13 (2.5)	1.30 (0.59-2.85)
Machining	Machining	26 (5.0)	25 (4.9)	0.93 (0.51-1.69)
Household painting	Household painting, varnishing, or staining	28 (5.4)	26 (5.1)	1.11 (0.61-2.00)
Industrial painting	Industrial painting, varnishing, or staining	74 (14.3)	68 (13.3)	1.18 (0.80-1.74)

^aAll major (2-digit) SOC codes are shown, as are all job tasks investigated in detailed interviews.

^bEver vs never exposure to a specific occupation or task before the reference date, adjusted for sex, age (continuous), white race/ethnicity, smoking (cigarette pack-years), caffeine use (milligram-years), alcohol use (drink-years), and ever head injury.

^cOccupations and tasks identified a priori.

^dStatistically significant ($P < .05$).

Table 5. Pesticide Use and Risk of Parkinsonism

Exposure	No. (%)		Odds Ratio (95% Confidence Interval) ^a	P Value
	Cases (n=519)	Controls (n=511)		
Pesticides	44 (8.5)	27 (5.3)	1.90 (1.12-3.21)	.02
Any 1 of 8 specific pesticides ^b	21 (4.0)	11 (2.2)	2.20 (1.02-4.75)	.04
2,4-Dichlorophenoxyacetic acid ^c	16 (3.1)	7 (1.4)	2.59 (1.03-6.48)	.04
Paraquat ^c	9 (1.7)	4 (0.8)	2.80 (0.81-9.72)	.10
Permethrin ^c	7 (1.3)	2 (0.4)	3.21 (0.65-15.80)	.15
Dieldrin	3 (0.6)	2 (0.4)	1.30 (0.21-7.94)	.77
Diquat	1 (0.2)	1 (0.2)	1.02 (0.06-16.60)	.99
Maneb	0	0		
Mancozeb	1 (0.2)	1 (0.2)	1.01 (0.06-16.28)	>.99
Rotenone	1 (0.2)	1 (0.2)	0.82 (0.05-13.34)	.89

^aAdjusted for age, sex, race/ethnicity, smoking (pack-years), caffeine use (milligram-years), alcohol use (drink-years), and head injury.

^bEight pesticides of highest interest were 2,4-dichlorophenoxyacetic acid, paraquat, permethrin, dieldrin, mancozeb, rotenone, maneb, and diquat.

^cCombined exposures in 13 of 29 subjects (2,4-dichlorophenoxyacetic acid in 7 subjects, 2,4-dichlorophenoxyacetic acid and paraquat in 1 subject, paraquat and permethrin in 2 subjects, and 2,4-dichlorophenoxyacetic acid, paraquat, and permethrin in 3 subjects).

cep-

tibility of dopamine neurons to toxic insults.^{34,35} Permethrin-treated garments, tents, and netting are commonly used as antimalarial products in the military and in other settings.³⁵ Many subjects may have long-term exposure. Additional assessment of permethrin as a risk factor for parkinsonism is warranted. Because exposure to more than 1 of these pesticides was common, future investigations should also assess the effects of combined exposure.

Longer duration of pesticide exposure has been associated with greater risk of parkinsonism in other populations.¹⁵ In our study, long-term pesticide use was uncommon. We found no association between exposure duration and disease risk. Other investigators have reported greater risk of parkinsonism among agricultural workers,^{3,6,15,17,36-38} but we found no association between the SOC code for agricultural work and parkinsonism, which confirms the suggestion that occupational code is a poor surrogate for pesticide use.³⁹

Neither overall risk of parkinsonism or PD, age at diagnosis, nor PIGD subtype was associated with welding or machining in our study. This finding is in contrast to reports of elevated disease risk among subjects with occupational exposure to metals^{6,22,40} or among welders referred by attorneys⁴¹ and contradicts findings of earlier age at PD onset among welders.⁹ However, our results are in keeping with national databases, industrial populations, and clinic-based case-control studies,^{39,42-47} which do not associate welding with greater risk of PD.

We did not replicate findings of prior studies^{3,4,43} associating education or health care work with greater risk of parkinsonism. Investigation of more specific SOC codes (eg, elementary school teacher) did not change these results. Another large case-control study³⁹ that used occupational codes found no increased risk in these categories, while a smaller study⁴³ found a higher risk among physicians. Methodologic considerations may have contributed to the associations found in other studies. The comparison of specialty clinic cases with census-derived controls may have introduced selection bias in one study.⁴ Another study⁵ reported the usual occupation of subjects from death records, while a third study³ compared tertiary clinic participants with published occupational statistics—which may overrepresent cases with higher educational level or socioeconomic status. Finally, occupational category is a surrogate for a disease-associated exposure; causal exposures may vary across populations.

We also systematically investigated job tasks and specific chemical exposures putatively associated with parkinsonism, with the inclusion of the solvent trichloroethylene.⁴⁸ Apart from pesticides, no type of exposure was associated with disease risk.

Our secondary analyses explored associations of risk of parkinsonism with the major and minor SOC codes not of a priori interest. We found few associations between any SOC code and parkinsonism. The finding of greater parkinsonism risk associated with legal and religious work is not easily explained but is not unique to this study.^{3,5,6} Because religious and legal workers in our control population were not underrepresented,⁴⁹ these findings may not simply reflect selection bias. Only 1 of the SOC codes for which we found an association in these exploratory analyses—construction and extraction

Study Steering Committee

Members

Caroline M. Tanner, MD, PhD; G. Webster Ross, MD; Robert D. Abbott, PhD; and J. William Langston, MD.

Enrolling Institutions, Investigators, and Coordinators (Listed by Number of Subjects Contributed)

The Parkinson's Institute, Sunnyvale, CA: Caroline M. Tanner, MD, PhD; Diana F. Roucoux, MPH; Sauda Yerbati, MPH; and Amanda Smith, MPH. *University of South Florida, Tampa:* Robert A. Hauser, MD; Diana Delaney; Summer Carter Wolfrath, MSPH; Joanne Nemeth; and Terry Mclain. *Baylor College of Medicine, Houston, TX:* Joseph Jankovic, MD; Christine Hunter, RN; Lina Shinawi; and Karen R. Flores. *Emory University School of Medicine, Atlanta, GA:* Stewart A. Factor, DO; and Carol Ingram, RN. *Beth Israel Medical Center, New York, NY:* Susan Bressman, MD; Amanda Deligtisch, MD; Karyn Boyar, RNC, MS, FNP; and Abby Wolff. *Toronto Western Hospital, Toronto, Ontario, Canada:* Connie Marras, MD, PhD, FRCPC; and Manoj Enjati. *University of Kansas Medical Center, Kansas City:* Kelly E. Lyons, PhD; Carey Mack, RN, BSN; April Langhammer; and Tamara Gales, LPN. *Veterans Affairs Pacific Islands Health Care System, Honolulu, HI:* G. Webster Ross, MD; and Frances K. Wakashige.

The Parkinson's Institute Coordination, Interviewer, and Analytic Staff

Meng Lu, MPH; Kathleen Comyns, MPH; Monica Korrell, MPH; Lori Sterling; Rene VanVeghten; Maribel Padua; Jennifer Wright; Brianna Allred; Leah Bushman; Milele Bynum; Cara Cage; Amanda Carroll; Michael Chang; Rachel Cook; Emmet Ferriter; Michael Franco; Kat Gorman; Michelle Kemp; Sarah Knutson; Sarah Lavoie; Erin Mills; Chi Nguyen; Polina Niedle; Jacqueline Pia; Ben Priestley; Valerie Sims; Jane Ann Soetmelk; Brian Song; Bibi Stang; Melanie Staver; and Allison Stover.

work—might carry a risk of chemical exposure. However, others^{4,39,43} found inverse associations between analogous codes and PD, suggesting that this result may be spurious. Several minor occupational codes were inversely associated with parkinsonism risk, including protective service supervisors, food preparation workers, and certain personal care or service workers; these associations were not seen after adjustment for duration of time worked. Only 2 other studies^{3,50} reported decreased PD risk among service occupations. Whether this lower risk is owing to reduced toxicant exposure, the greater physical demands of these occupations (a healthy worker effect), or a spurious finding requires further study.

The PIGD subtype shares clinical features with toxicant-induced parkinsonism,^{18,42,47} yet neither job task nor toxicant exposure increased the risk of the PIGD subtype. However, risk of PIGD subtype was increased in subjects who ever worked in business and finance, construction and extraction, and legal occupations. A biological explanation for these associations remains elusive.

Ever use of tobacco and ever smoking of cigarettes were inversely associated with parkinsonism and PD. Control

smokers consumed more cigarettes than case smokers. Cumulative caffeine intake was greater in controls but not significantly so. Risk of parkinsonism was slightly increased in association with head injury, but precision was poor. Alcohol use was unassociated with disease risk. Like findings have been observed in many studies¹⁶ and indirectly support the similarity of our subjects to other study populations.

This study has several advantages. To our knowledge, it is the only study in which all cases were characterized by movement disorders specialists, which assures confidence in diagnosis and clinical subtype. Subjects were recruited from throughout North America, which provides geographic heterogeneity and a broad range of occupations. We also included subjects with atypical parkinsonism, because toxicant-induced parkinsonism may have atypical features, and studies that use strict diagnostic criteria could exclude toxicant-induced cases. Finally, the detailed interview collected information on key modifying factors (eg, tobacco use) and lifetime occupational and chemical exposure history. While the number of exposures to any individual risk was lower than in a population selected by occupation, potentially reducing the power to investigate an association, key exposures were well within the range of 1% to 33% that we projected (eg, 28.2% of controls worked with solvents, 7.4% welded, and 5.3% used pesticides [Table 4]) and were in keeping with national frequencies. Moreover, pesticide use had a magnitude of association with parkinsonism similar to that of other investigations. Even for our secondary analyses, power to detect moderate ORs was 80% for most exposures.

There are several limitations. First, we identified subjects from referral centers. While this approach allowed for improved diagnosis and investigation of clinical subgroups, these results may not apply to populations with different characteristics. Most of our subjects were of non-Hispanic white race/ethnicity. None had dementia, so associations of exposures with parkinsonism dementia could not be tested. However, our population generally resembled other case-control populations in sex, age, and lifestyle characteristics. The established inverse association of tobacco use with parkinsonism was observed in our population. Because cases and controls had similar demographic and socioeconomic characteristics, any potential bias is likely nondifferential. Second, we did not have direct quantitative exposure measurements. Because lifelong environmental or biologic monitoring is unavailable, the use of detailed job task-based interviews to infer exposure profiles is a valid and reliable alternative.^{14,51-53} Recall bias may affect information provided by subjects, particularly for well-known putative risk factors such as welding or pesticide exposure. To minimize this factor during recruitment, specific hypotheses were not mentioned, and interview questionnaires collected a complete life history of jobs and tasks. Third, as in all case-control studies, causal relationships cannot be assumed.⁵⁴ Fourth, we investigated many associations; some findings may be chance associations. Rather than applying stringent corrections for multiple comparisons, we have chosen to report these associations to allow for further investigation.

Occupational pesticide exposure emerges as the most consistent etiologic association with parkinsonism. The

3 specific pesticides identified (2,4-dichlorophenoxyacetic acid, paraquat, and permethrin) all have effects on dopaminergic neurons in experimental settings. This convergence of epidemiologic and laboratory data from experimental models of PD lends credence to a causative role of certain pesticides in the neurodegenerative process. Other pesticide exposures such as hobby gardening, residential exposure, wearing treated garments, or dietary intake were not assessed. Because these exposures may affect many more subjects, future attention is warranted.

Accepted for Publication: April 15, 2009.

Author Affiliations: Department of Clinical Research, The Parkinson's Institute, Sunnyvale, California (Drs Tanner, Jewell, Bhudhikanok, and Langston and Mss Roucoux and Meng); Department of Research and Development, Veterans Affairs Pacific Islands Health Care System, Honolulu, Hawaii (Dr Ross); Department of Neurology, University of South Florida, Tampa, (Dr Hauser); Department of Neurology, Baylor College of Medicine, Houston, Texas (Dr Jankovic); Department of Neurology, Emory University School of Medicine, Atlanta, Georgia (Dr Factor); Department of Neurology, Beth Israel Medical Center, New York, New York (Drs Bressman and Deligtisch); Department of Neurology, Toronto Western Hospital, Toronto, Ontario, Canada (Dr Marras); Department of Neurology, University of Kansas Medical Center, Kansas City (Dr Lyons); and Department of Statistics, University of Virginia School of Medicine, Charlottesville (Dr Abbott).

Correspondence: Caroline M. Tanner, MD, PhD, The Parkinson's Institute, 675 Almanor Ave, Sunnyvale, CA 94085 (CTanner@theipi.org).

Author Contributions: Dr Tanner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Tanner, Ross, Jankovic, and Langston. **Acquisition of data:** Tanner, Ross, Jewell, Hauser, Jankovic, Factor, Bressman, Deligtisch, Marras, Lyons, and Roucoux. **Analysis and interpretation of data:** Tanner, Ross, Jewell, Hauser, Jankovic, Marras, Bhudhikanok, Roucoux, Meng, Abbott, and Langston. **Drafting of the manuscript:** Tanner, Jewell, and Roucoux. **Critical revision of the manuscript for important intellectual content:** Ross, Hauser, Jankovic, Factor, Bressman, Deligtisch, Marras, Lyons, Bhudhikanok, Meng, Abbott, and Langston. **Statistical analysis:** Abbott, Bhudhikanok, and Meng. **Obtained funding:** Tanner and Langston. **Administrative, technical, and material support:** Ross, Jewell, Factor, Bressman, and Roucoux. **Study supervision:** Tanner, Jewell, Bressman, and Roucoux.

Group Information: A list of the Study Steering Committee Members appears on page 1111.

Financial Disclosure: Dr Hauser has received fees for providing expert testimony in cases related to PD in welders. **Funding/Support:** This study was supported by an unrestricted grant from a group of current and former manufacturers of welding consumables awarded to The Parkinson's Institute.

Role of the Sponsor: The study sponsors were not involved in the design, conduct, analysis, or reporting of this

work. All compensation received by investigators for study-related services was paid through contract between The Parkinson's Institute and the investigators' institutions. **Additional Contributions:** Freya Kamel, PhD, MPH, provided helpful comments on the manuscript. We thank the patients who participated in this study, as well as their families.

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