

Pesticide Exposure and Risk for Parkinson's Disease

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Objective: Chronic, low-dose exposure to pesticides is suspected to increase the risk for Parkinson's disease (PD), but data are inconclusive.

Methods: We prospectively examined whether individuals exposed to pesticides have higher risk for PD than those not exposed. The study population comprised participants in the Cancer Prevention Study II Nutrition Cohort, a longitudinal investigation of US men and women initiated in 1992 by the American Cancer Society. Follow-up surveys were conducted in 1997, 1999, and 2001. The 143,325 individuals who returned the 2001 survey and did not have a diagnosis or symptoms of PD at baseline (1992) were included in the analyses.

Results: Exposure to pesticides was reported by 7,864 participants (5.7%), including 1,956 farmers, ranchers, or fishermen. Individuals exposed to pesticides had a 70% higher incidence of PD than those not exposed (adjusted relative risk, 1.7; 95% confidence interval, 1.2–2.3; $p = 0.002$). The relative risk for pesticide exposure was similar in farmers and nonfarmers. No relation was found between risk for PD and exposure to asbestos, chemical/acids/solvents, coal or stone dust, or eight other occupational exposures.

Interpretation: These data support the hypothesis that exposure to pesticides may increase risk for PD. Future studies should seek to identify the specific chemicals responsible for this association.

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The results of twin studies suggest that factors other than inherited genes have a prominent role in the cause of Parkinson's disease (PD).^{1,2} The recognition that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a chemical with structural similarity to the herbicide paraquat, can cause degeneration of dopaminergic neurons and parkinsonism³ raised the question of whether chronic low-dose exposure to pesticides could be a risk factor for PD. Accumulating data support this hypothesis.⁴ Exposure to pesticides is associated with increased risk for PD in several ecological^{5,6} and case-control studies,^{7–9} and the selective dopaminergic toxicity of rotenone and other pesticides has been demonstrated in experimental studies.^{10–12} Nevertheless, the overall evidence, albeit suggestive, remains inconclusive, in part because the results of case-control studies could be systematically affected by recall or selection bias. These limitations could be overcome by using a prospective study design. Two investigations have examined prospectively the relation between pesticide exposure and

PD risk. In one investigation, the risk for PD was increased among individuals exposed to pesticides, but the association did not reach statistical significance¹³; in the other investigation, a small study among elderly subjects, pesticide exposure predicted the risk for PD among men, but not among women.¹⁴ We therefore examined whether individuals exposed to pesticides have an increased risk for PD in a large cohort of US men and women, comprising more than 140,000 participants and 413 incident cases of PD.

Subjects and Methods

Study Population

The study was conducted among participants in the Cancer Prevention Study (CPS) II Nutrition Cohort, a prospective investigation of 184,190 individuals (86,404 men and 97,786 women) initiated in 1992 by the American Cancer Society to investigate the roles of diet and other lifestyle factors in cancer incidence.¹⁵ At enrollment, participants completed a questionnaire on smoking, physical activity, and

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other aspects of lifestyle. Follow-up surveys were conducted in 1997, 1999, and 2001, the last including for the first time a question on lifetime occurrence of PD. The 143,325 individuals who returned the 2001 survey (89% of all living cohort members) and did not have a diagnosis or symptoms of PD at baseline (1992) were included in this study. Participants in the study were mostly white (97.5%), and mean age at enrollment was 63.7 years for men (median, 63; range, 41–90 years) and 62.0 years for women (median, 62; range, 40–85 years).

The study was approved by the Human Subject Committee at Harvard School of Public Health and the Institutional Review Board at Emory University.

Assessment of Exposure

Participants in the CPS II Nutrition Cohort were drawn from a cohort of 1.2 million US men and women recruited by American Cancer Society volunteers in 1982 for a study of cancer mortality (CPS II).¹⁶ In 1982, as part of the original CPS II mortality study, participants completed a four-page survey that included questions on occupation and exposure to selected chemicals or dusts. Specifically, participants were asked whether they were currently exposed or had been regularly exposed in the past to asbestos, chemicals/acids/solvents, coal or stone dust, coal tar/pitch/asphalt, diesel engine exhaust, dyes, formaldehyde, gasoline exhaust, pesticides/herbicides, textile fibers/dust, wood dust, or x-ray/radioactive material. If exposed, participants were asked to report the duration of exposure in years. Information on chemical exposures was not updated in subsequent surveys. Participants were also asked to report their current job and the job kept for the longest period of time. The reported jobs were categorized according to the 1980 Bureau of the Census occupational titles.¹⁷ Individuals were considered as farmers if any of the jobs reported were coded with the Census category “farmers, ranchers or fishermen”; farming was the longest held occupation in 76% of these individuals.

Case Ascertainment

The case ascertainment procedures were similar to those that we used in our previous studies of PD.¹⁸ In brief, we wrote to all participants who reported a diagnosis of PD on the 2001 questionnaire and asked for permission to contact their treating neurologists and obtain copy of the medical records. We then asked their treating neurologists (or internists if the neurologists did not respond) to complete a diagnostic questionnaire or to send a copy of the medical record. The questionnaire included questions about cardinal signs of PD (rest tremor, rigidity, bradykinesia, and postural instability), response to L-dopa treatment, and the presence of signs and symptoms or other features that may corroborate a diagnosis of PD or suggest an alternative diagnosis. Confirmed cases were those for whom the PD diagnosis was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of PD made by a neurologist or evidence at a neurological examination of at least two of the four cardinal signs (with one being rest tremor or bradykinesia), a progressive course, and the absence of unresponsiveness to L-dopa or other features suggesting an alternative diagnosis. The review of medical

records was conducted by our movement disorder specialist (M.A.S.), who was blinded to the exposure status.

A total of 840 participants reported a diagnosis of PD at any time in the past, and 677 (81%) of these participants provided informed consent for contacting the treating neurologists. We obtained a completed diagnostic questionnaire or medical record for 648 (96%) of the 677 participants who provided consent, and then confirmed the diagnosis in 588 (91%). Of these, 175 had onset before 1992 and were excluded from the analyses. Among the 413 PD incident cases included in this report, 67.6% of the diagnoses were confirmed by the treating neurologists (55.0%) or movement disorder specialists (12.6%), 21.1% by review of the medical records, and 11.4% by the treating internists or family physicians. The proportion of cases confirmed by different methods did not vary significantly by occupation (farmers vs nonfarmers) or exposure to pesticides.

Statistical Analyses

Although data on pesticide exposure were collected in 1982, we used the date of return of the 1992 questionnaire as the date when follow-up began for PD. Follow-up ended on the date of the first symptoms of PD for PD cases or September 30, 2001, for participants without PD. For each environmental exposure, we defined participants as exposed if they responded “yes” to the question about regular current or past exposure or nonexposed if they responded “no.” Participants who left blank the answer to one or more questions on chemical exposures were initially considered as a separate group, with missing exposure. Because the risk for PD (adjusted for age, sex, and smoking) among the latter group was virtually identical to that in the corresponding unexposed group, in final analyses, these individuals were considered as not exposed. Exposed individuals were further categorized according to self-reported duration of exposure.

Primary analyses were conducted using Cox proportional hazard models, adjusted for age, sex, and smoking (never, past, or current: 1–14 cigarettes/day, 15–24 cigarettes/day, 25+ cigarettes/day). Further analyses were adjusted for potential risk factors for PD, including coffee consumption (none, 3–6 cups/week, 1 cup/day, 2–3 cups/day, 4–5 cups/day, 6+ cups/day, missing); education (five categories, from some high school to college graduate or higher); use of ibuprofen, aspirin, or other NSAIDs (<2 tablets/week, 2–6.9 tablets/week, and ≥ 1 tablet/day)¹⁹; and physical activity (metabolic equivalents, in quintiles). These variables were derived from the 1992 survey, except for coffee consumption and education, which were derived from the 1982 questionnaire, because they were not included in the 1992 survey. Stratified analyses were conducted according to occupation (farmers and nonfarmers), attained age (<65 and ≥ 65 years), and smoking status (never smokers and ever smokers). Because there were no apparent differences in the association between pesticide exposure and PD risk by sex, we presented the results for men and women combined unless otherwise specified. Additional sensitivity analyses were conducted by censoring the follow-up at age 75 years for all participants, excluding PD cases not confirmed by a neurologist, and by including participants who confirmed the diagnosis of PD but did not provide consent for review of their medical records. All *p* values are two-tailed and consid-

ered significant if less than 0.05. Because the primary hypothesis of the study was that exposure to pesticides/herbicides, but not other chemical exposures, would be associated with increased risk for PD, we did not adjust the statistical tests for multiple comparisons.

Results

Overall, exposure to pesticides was reported by 5,203 men (8.2%) and 2,661 women (3.3%). Individuals who reported exposure to pesticides were 14 times more likely to report their occupation as “farmer, rancher or fisherman” and twice more likely to be blue collar workers than those not exposed (Table 1). Furthermore, the educational level was slightly lower among the exposed, whereas smoking behavior, coffee consumption, and other aspects of lifestyle were similar between the two groups (see Table 1).

The mean age at PD onset was 70 years and was unrelated to pesticide exposure (70.9 years in exposed and 70.3 years in nonexposed participants). Age-specific incidence rates of PD per 100,000 person-years were: in men: 31.8 (age range, 50–59 years), 53.2 (60–69 years), 86.8 (70–79 years), and 102 (80–89 years); and in women: 10.1 (50–59 years), 28.0 (60–69 years), 48.3 (70–79 years), and 29.1 (80–89 years), but the latter rate is based on small numbers and is thus unstable. In analyses adjusted for age, sex, and smoking, the risk for PD was 70% higher among individuals exposed to pesticides than among those not exposed (relative risk [RR], 1.7; 95% confidence interval [CI], 1.2–2.3; $p = 0.002$); this association was slightly stronger in analyses adjusted for other potential confounders (RR, 1.8; 95% CI, 1.3–2.5; $p = 0.0003$). In contrast, none of the other exposures was significantly associated with risk for PD (Fig). The association between pesticide exposure and PD did not differ appreciably in analyses restricted to cases confirmed by a neurologist or movement disorder specialist, or within strata defined by occupation (farmers or non-farmers), sex, age, or smoking status (Table 2). Only 2,308 (28%) of the individuals who reported exposure to pesticides indicated the duration of exposure. The risk for PD was not significantly different among individuals who reported exposure for 10 or more years (multivariate RR, 2.3; 95% CI, 1.1–4.9) compared with those with shorter (RR, 2.1; 95% CI, 0.7–6.5) or missing (RR, 1.7; 95% CI, 1.2–2.5) duration.

Finally, we were concerned about the possibility of bias due to the exclusion of those subjects with PD who did not provide permission to review their medical records. Prevalence of exposure to pesticides among these cases was higher than among cases who consented to medical record review (6.9 vs 4.6%), and their exclusion may thus have attenuated the association between exposure and PD. Because the diagnosis of PD in this group is not confirmed and the date of onset of

Table 1. Age- and Sex-Adjusted Population Characteristics in 1992 According to Exposure to Pesticides/Herbicides

Characteristics	Exposed to Pesticides in 1982	Not exposed to Pesticides in 1982
N	7,864	135,461
Mean age, yr	63.3	62.7
Male, %	66.2	42.9
Race, %		
White	97.4	97.5
Black	1.1	1.3
Other	1.5	1.2
Body mass index, kg/m ²	26.4	25.9
Current smokers, %	7.9	7.6
Past smokers, %	42.5	45.7
Coffee drinkers, %		
None	12.8	12.0
≤1 cup/day	15.8	14.9
2-3 cups/day	27.3	29.0
4+ cups/day	21.2	20.8
Missing	23.0	23.3
Ibuprofen use, %		
No use	72.4	74.7
<2 tablets/week	6.1	6.4
2-6.9 tablets/week	5.2	5.0
≥1 tablet/day	7.0	6.1
Missing	9.4	7.9
Alcohol intake, %		
None	43.7	38.3
<1 drink/day	37.2	39.4
1+ drinks/day	15.4	18.5
Missing	3.8	3.9
Supplement use (% current users)		
Vitamin E	22.6	19.7
Vitamin C	28.2	25.9
Multivitamin	37.3	37.5
Occupation, %		
White collar	43.8	55.9
Blue collar	24.0	12.4
Housewife	18.3	17.2
Unknown occupation	13.9	14.4
Physical activity in leisure time, %		
None or low	76.6	80.0
Moderate	19.3	15.9
High	2.6	2.6
Missing	1.6	1.4
Total mets/week	29.9	25.8
Education, %		
Some high school or less	7.8	5.4
High school graduate	27.2	25.1
Vocational	5.8	5.6
Some college	23.7	22.9
College graduate or higher	35.3	40.2
Farmer, rancher, or farm hand (% main occupation)	15.0	1.1

PD symptoms is unknown, these participants could not be included in the primary analyses. To examine the robustness of the results, we repeated the analyses assuming that all individuals who denied consent for

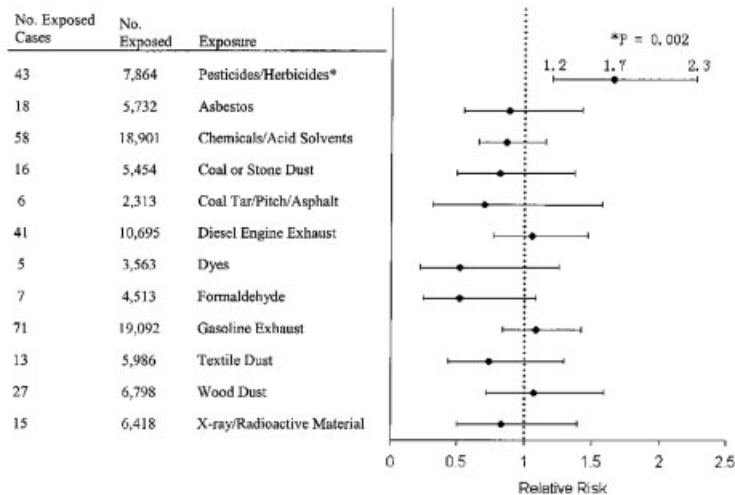


Fig. Relative risks and 95% confidence intervals of Parkinson's disease according to environmental exposures reported in 1982 in the Cancer Prevention Study II Nutrition Cohort (1992–2001).

Table 2. Relative Risk for Parkinson's Disease according to Exposure to Pesticides in Stratified Analyses

Characteristics	Cases, N	Person-Time	RR (95% CI)
All			
Not exposed to pesticide	370	1,167,603	Reference
Exposed to pesticide	43	67,901	1.8 (1.3–2.5)
Only cases confirmed by neurologist ^a			
Not exposed to pesticide	329	1,167,773	Reference
Exposed to pesticide	37	67,935	1.8 (1.3–2.5)
Occupation			
Not a farmer			
Not exposed to pesticide	362	1,148,865	Reference
Exposed to pesticide	30	50,938	1.7 (1.2–2.5)
Farmer			
Not exposed to pesticide	8	18,738	0.9 (0.5–1.9)
Exposed to pesticide	13	16,964	1.6 (0.9–2.7)
Sex			
Men			
Not exposed to pesticide	232	504,816	Reference
Exposed to pesticide	34	45,210	1.8 (1.2–2.6)
Women			
Not exposed to pesticide	138	662,787	Reference
Exposed to pesticide	9	22,691	1.9 (1.0–3.8)
Age			
<65 yr			
Not exposed to pesticide	171	719,681	Reference
Exposed to pesticide	19	40,072	1.7 (1.1–2.8)
≥65 yr			
Not exposed to pesticide	199	447,922	Reference
Exposed to pesticide	24	27,829	1.9 (1.2–2.9)
Smoking			
Never smoker			
Not exposed to pesticide	179	532,365	Reference
Exposed to pesticide	22	29,762	2.1 (1.3–3.3)
Ever smoker			
Not exposed to pesticide	183	620,815	Reference
Exposed to pesticide	21	37,229	1.7 (1.1–2.7)

^aCases were confirmed by treating neurologist, movement disorder specialist, or neurologist review of medical records.

RR = relative risk; CI = confidence interval.

review of the medical records were confirmed incident cases of PD (with date of onset arbitrarily set at middle of follow-up). In these analyses, as expected, we found a slightly stronger association between exposure to pesticides and risk for PD (RR, 1.8; 95% CI, 1.4–2.4; $p < 0.0001$).

Discussion

In this large cohort study of more than 140,000 people, those who reported exposure to pesticides/herbicides before 1982 had a 70% higher incidence of PD 10 to 20 years later than those not exposed to these chemicals. Exposure to many other environmental contaminants was not related to PD risk. Strengths of this study include the large sample size, the prospective collection of information on pesticide exposure, and the availability of information on several potential confounders. The main limitation of the investigation is the lack of detailed information about the duration, frequency, and intensity of the exposure and information on specific pesticides. Furthermore, information on exposure was not updated after 1982, and therefore we cannot exclude the possibility that more recent pesticide exposure contributed to the increased risk for PD. Information on pesticide use, however, was collected 10 or more years before the onset of PD, and the misclassification of exposure is thus most likely nondifferential with respect to PD risk. This misclassification would be expected to attenuate any true association between exposure to pesticides and PD risk, and it is unlikely to result in a spurious positive association. Additional potential sources of bias are differential diagnostic errors or underreporting of PD. Although some diagnostic errors are inevitable, bias from this source is probably modest, because in recent clinicopathological studies, the positive predictive value of clinical diagnoses of PD has been found to be high: 90% for diagnoses made by neurologists²⁰ and 98% for diagnoses made by movement disorder specialists.²¹ Selective underrecognition or underreporting of PD among individuals not exposed to pesticides could also theoretically induce a spurious positive association between pesticide exposure and PD risk, but it would have to be rather extreme to account for the marked increase in risk observed in our study.

Several individual compounds commonly used as pesticides in US agriculture have been found to cause dopaminergic degeneration in the substantia nigra and motor abnormalities when administered at high doses to experimental animals. These include rotenone,^{10,22} paraquat,¹¹ and the combination of paraquat with maneb or other dithiocarbamates.^{12,23–25} A variety of mechanisms have been proposed for the deleterious effects of these pesticides, including oxidative stress, interference with dopamine transporters, mitochondrial dysfunction,²⁶ promotion of α -synuclein fibrillation,²⁷

and inflammation.²⁸ The relevance of these mechanisms in PD remains uncertain.

In postmortem studies, higher levels of organochlorine insecticides have been found in the substantia nigra or striatum of individuals with PD.^{29–31} This finding reflects that organochlorine insecticides, unlike organophosphates and most other pesticides, persist in tissues for many years after cessation of exposure. These measurements indicate that organochlorine pesticides reach the affected tissue, but do not prove that they cause PD and also do not identify which pesticides may be responsible. Ecological and case-control studies support the association of PD with rural residence,^{5,32–39} use of private wells,^{33,34,37,38,40} farming,^{5,35,41,42} as well as exposure to insecticide and herbicide products.^{6,35,36,39,41,43–49} According to a meta-analysis of case-control studies, the risk for PD is about 90% higher among individuals who reported exposure to pesticides than among those not exposed.⁷ Consistent results have been obtained in more recent investigations.^{8,9,50} Finally, in a previous prospective study of more than 8,000 men of Japanese ancestry in Hawaii, a significant positive association was found between duration of work in a plantation and risk for PD.¹³ The RR comparing men who worked in a plantation for 20 or more years with men who never worked in a plantation was 1.9 (95% CI, 1.0–3.5); a positive trend, albeit nonsignificant, was also found between exposure to pesticides and risk for PD.

Exposure to pesticides could be a marker of other unspecified aspects of rural living, rather than the actual cause of disease. A direct effect of pesticides, however, is supported by the finding in this study that farmers not exposed to pesticides were not at increased risk for PD. Consistent with an adverse effect of pesticides is also the finding of stronger associations between use of pesticides and PD among individuals who are poor debrisoquine metabolizers because of genetic variation in the CYP2D6 gene.⁸ The CYP2D6 gene encodes the enzyme debrisoquine hydroxylase, which metabolizes several xenobiotics, including MPTP, the herbicide atrazine, and organophosphate pesticides.⁵¹ Identification of the pesticides directly related to increased PD risk is critical, because generic attempts to reduce overall exposure may be insufficient and impractical. Further investigations should focus on populations exposed to specific chemicals and examine the role of variations in genes affecting xenobiotic metabolism and their functional consequences.

In summary, the findings of this large prospective investigation support the hypothesis that exposure to pesticides is a risk factor for PD. Future studies should seek to identify the specific compounds associated with risk.

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