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Original Contribution

Pesticide Exposure and Self-reported Parkinson's Disease in the Agricultural Health Study

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Previous studies based on limited exposure assessment have suggested that Parkinson's disease (PD) is associated with pesticide exposure. The authors used data obtained from licensed private pesticide applicators and spouses participating in the Agricultural Health Study to evaluate the relation of self-reported PD to pesticide exposure. Cohort members, who were enrolled in 1993–1997, provided detailed information on lifetime pesticide use. At follow-up in 1999–2003, 68% of the cohort was interviewed. Cases were defined as participants who reported physician-diagnosed PD at enrollment (prevalent cases, $n = 83$) or follow-up (incident cases, $n = 78$). Cases were compared with cohort members who did not report PD ($n = 79{,}557$ at enrollment and $n = 55{,}931$ at follow-up). Incident PD was associated with cumulative days of pesticide use at enrollment (for highest quartile vs. lowest, odds ratio (OR) = 2.3, 95% confidence interval: 1.2, 4.5; p-trend = 0.009), with personally applying pesticides more than half the time (OR = 1.9, 95% confidence interval: 0.7, 4.7), and with some specific pesticides (ORs $\geq$ 1.4). Prevalent PD was not associated with overall pesticide use. This study suggests that exposure to certain pesticides may increase PD risk. Findings for specific chemicals may provide fruitful leads for further investigation.

case-control studies; herbicides; insecticides; Parkinson disease; pesticides

Abbreviations: AHS, Agricultural Health Study; OR, odds ratio; PD, Parkinson's disease.

Parkinson's disease (PD) is a common neurodegenerative disease, affecting up to a million people in the United States (1). Its etiology is uncertain but probably involves both genetic and environmental components (1). Numerous studies have established the role of specific genes in familial forms of PD (2). Mutations in these genes are rare in the more common sporadic form of PD, however, and twin studies have suggested a strong environmental component to sporadic PD (3, 4).

A consistent finding of epidemiologic studies is an association of PD with rural living or farming as an occupation (1, 5). Although this association may reflect several exposures, many studies have focused on pesticides. Overall evidence suggests that PD is associated with pesticide exposure (6–10), although it may not yet support a causal inference (9, 10). Variable results may be due to differences in study design, particularly in methods used for exposure assessment (8–10). Most studies have evaluated exposure to any pesticide or to broad functional classes such as insecticides or herbicides, and little information is available for specific chemicals or factors that may affect exposure, such as use of personal protective equipment. Few investigators

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have assessed exposure prospectively or been able to separate prevalent and incident cases.

The Agricultural Health Study (AHS) is a large cohort study of licensed pesticide applicators and their spouses (11). Cohort members provided detailed information on lifetime pesticide use at enrollment. They reported physician-diagnosed PD either at enrollment or during a follow-up interview conducted 5 years later. We used data from these self-reports to evaluate the association of PD with pesticide exposure.

MATERIALS AND METHODS

Population and questionnaires

The AHS cohort was established in 1993–1997. Persons applying for certification to use restricted-use pesticides in Iowa or North Carolina were enrolled (11). Figure 1 summarizes the process of data collection. At enrollment, 52,393 private applicators (84 percent of those eligible), mostly farmers, completed a self-administered Enrollment Questionnaire. All enrolled applicators were requested to complete a supplemental self-administered Applicator Questionnaire, and 22,915 (44 percent) complied. Applicators completed the two questionnaires a median of 1 month apart. Based on data from the Enrollment Questionnaire, persons who completed the Applicator Questionnaire were similar in most respects to those who did not, including pesticide exposure (12). Most (43,692; 83 percent) of the enrolled private applicators were married, and 32,345 (74 percent) of their spouses enrolled in the study by completing a Spouse Questionnaire, either self-administered (80 percent) or by telephone (20 percent). The Enrollment and Spouse questionnaires elicited information on pesticide use, demographic factors, lifestyle, and medical history, including physician-diagnosed PD. The Applicator Questionnaire collected additional information on pesticide exposure and medical history, including physician-diagnosed PD and neurologic symptoms.

Five years after enrollment, we conducted follow-up telephone interviews with 57,251 cohort members (68 percent). Thirteen percent of the cohort could not be contacted, 12 percent declined the interview, 3 percent were excluded for various other reasons, 2.5 percent were deceased, and the remainder were not interviewed because of illness (<1 percent), language difficulties (<1 percent), or other reasons (1 percent). Cohort members who were interviewed, compared with those who were not, were slightly younger (16 percent vs. 18 percent were more than 60 years old) and were more likely to be spouses (42 percent vs. 31 percent), to be from Iowa (66 percent vs. 57 percent), to have more than a high school education (48 percent vs. 41 percent), and to have never smoked (62 percent vs. 56 percent). The proportions who had ever personally mixed or applied pesticides were similar (82 percent vs. 83 percent). Information from the follow-up interviews used for the present analysis was self-reported physician-diagnosed PD, age at diagnosis, age at interview, and smoking status.

The institutional review boards of the National Institutes of Health (Bethesda, Maryland), Westat, Inc. (Rockville, Maryland; Coordinating Center), the University of Iowa (Iowa City, Iowa; Iowa Field Station), and Battelle (Durham, North Carolina; North Carolina Field Station) approved the AHS. At enrollment, the study was explained to potential participants, who indicated consent by returning questionnaires; consent for follow-up interviews was indicated by participation. Questionnaires are available at the AHS website (www.aghealth.org/questionnaires.html).

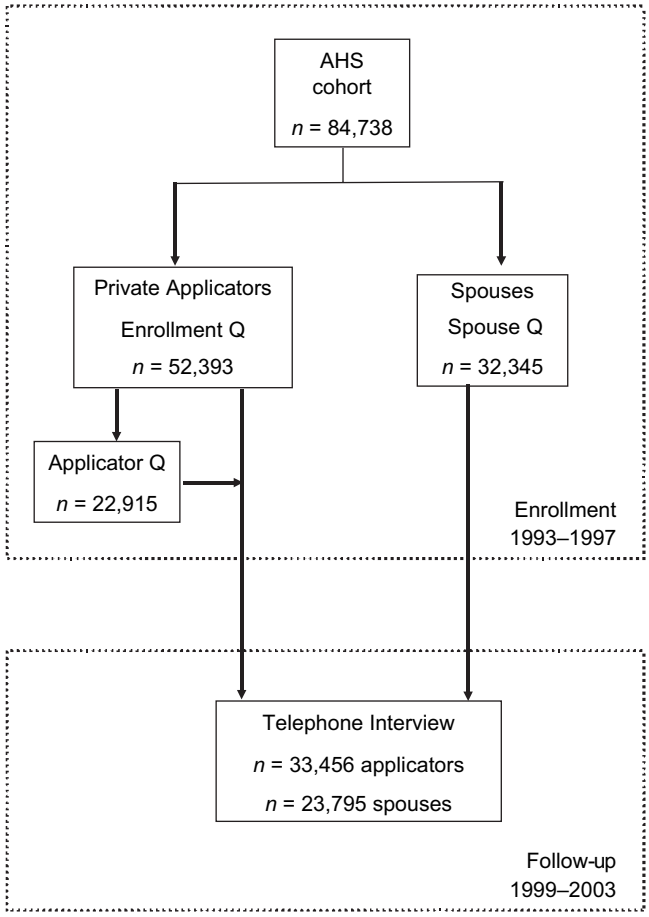

FIGURE 1. Data collection in the Agricultural Health Study (AHS). At enrollment (1993–1997), licensed private pesticide applicators in Iowa and North Carolina completed a self-administered Enrollment Questionnaire. A subset (44%) also completed a self-administered supplemental Applicator Questionnaire. Their spouses completed a Spouse Questionnaire, either self-administered (80%) or by telephone (20%). At follow-up (1999–2003), cohort members were interviewed by telephone. Q, Questionnaire.

Case definition

At enrollment, cohort members were asked, ''Has a doctor ever told you that you had been diagnosed with Parkinson's disease?'' This question was included in the Enrollment, Applicator, and Spouse questionnaires, so applicators who completed both the Enrollment Questionnaire and the Applicator Questionnaire had two opportunities to respond. At

follow-up, cohort members were asked, ''Has a doctor or other health professional ever told you that you had Parkinson's disease?'' We excluded from the analysis any applicator who provided conflicting information on PD on the Enrollment and Applicator questionnaires (i.e., responded ''yes'' on one and ''no'' on the other; $n = 12$). Applicators who had missing information on one questionnaire but responded to the other were included. We also excluded applicators and spouses who responded ''yes'' to the question on PD at enrollment and ''no'' in the follow-up interview ($n = 13$).

We defined prevalent PD on the basis of self-report at enrollment. We first excluded persons with missing information on PD at enrollment ($n = 5{,}073$). We then defined prevalent cases as applicators who reported PD on either the Enrollment Questionnaire or the Applicator Questionnaire (or both) or spouses who reported PD on the Spouse Questionnaire. Controls were participants who responded negatively to the PD question. There were 83 prevalent cases (60 applicators and 23 spouses) and 79,557 controls.

We defined incident PD on the basis of self-report at follow-up. We first excluded prevalent cases ($n = 83$) and persons with missing information on PD, either because they were not interviewed or because they did not respond to the PD question ($n = 28{,}621$). We then defined incident cases as applicators and spouses who reported PD in the telephone interview; controls were those who did not. There were 78 incident cases (56 applicators and 22 spouses) and 55,931 controls. This definition included eight cases and 2,675 controls whose PD status at enrollment was unknown because of missing data but who provided information at follow-up. Excluding these participants from the analyses did not change results.

Pesticide exposure

More than 99 percent of applicators and 56 percent of spouses had personally mixed or applied pesticides. Both applicators and spouses reported duration (years) and frequency (days per year) of use of any pesticide, as well as ever use of 50 commonly used pesticides. Cumulative days of use of any pesticide was the product of duration and frequency, categorized in quartiles.

For applicators, information on pesticide-related medical attention was collected using the question, ''As a result of using pesticides, how often have you seen a doctor or been hospitalized?'' Responses were dichotomized as ever/never. Information on events involving high personal pesticide exposure was collected using the question, ''Have you ever had an incident or experience while using any type of pesticide which caused you unusually high personal exposure?'' Persons who gave positive responses were asked about the time interval between the incident and washing with soap and water. Responses were categorized as ''no event,'' ''washed within 1 hour,'' or ''washed after 1 hour.''

Applicators provided information on use of six types of personal protective equipment: fabric or leather gloves, chemical-resistant gloves, face shield or goggles, cartridge respirator or gas mask, disposable outer clothing, and other. We constructed a personal protective equipment score according to the method of Dosemeci et al. (13), by assigning points for use of each type or combination of equipment based on its potential to decrease exposure. Scores ranged from 0.1 to 1.0; a lower score indicated greater protection (lower exposure). For example, the score for use of chemical-resistant gloves was 0.4. Scores were used in two ways: as an independent variable after categorization into tertiles or to weight cumulative days of pesticide use.

Data analysis

We used logistic regression to evaluate the relation of either prevalent PD or incident PD to general pesticide variables. We constructed models with applicators and spouses combined and for the two groups separately. Models included adjustment for 1) age at enrollment, using a four-level categorical variable with persons aged 51–60 years designated the referent group; 2) state (Iowa or North Carolina); and 3) type of participant (applicator or spouse), in models including both. Most applicators were men (>99 percent) and most spouses were women (96 percent), so no further adjustment was made for gender. Neither race nor education confounded the relation of PD with pesticide exposure (<10 percent change in estimate), so these factors were not included in the final models. Additional models were created after stratification by state or adjustment for cigarette smoking. Neither strategy had a substantive effect on risk estimates; selected results from these models are presented.

We used two-stage hierarchical logistic regression to increase precision when evaluating multiple specific pesticides (14). The first-stage model contained covariates and indicators for specific pesticides with at least four exposed cases. The second-stage model included variables for functional pesticide groups (insecticides, herbicides, fungicides, fumigants) and several chemical groups (organophosphates, organochlorines, carbamates, phenoxyacetates, triazines/triazones); all groups included at least three pesticides. We assumed that the odds ratio for each pesticide would fall within a 10-fold range around its prior mean, with 95 percent certainty, by defining the prior residual variance as 0.35.

Odds ratios and 95 percent confidence intervals are reported. Two-sided p-trend values for cumulative days of pesticide use were calculated using a continuous variable defined by the midpoints of the levels in the categorical variable. We used enrollment data from the September 2002 AHS data prerelease and follow-up data from the AHS data release P2REL0312.01 (unpublished data). Analyses were performed using version 8.2 of SAS (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Demographic and lifestyle characteristics

Both prevalent PD and incident PD were associated with older age at enrollment; the relation was stronger for prevalent PD (table 1). Incident PD was also associated with greater age at follow-up (for age ≥71 years, odds ratio (OR) = 4.4, 95 percent confidence interval: 2.4, 8.1). For both

TABLE 1. Demographic and lifestyle characteristics of self-reported Parkinson's disease (PD) cases and controls identified in the Agricultural Health Study at enrollment in 1993–1997 (prevalent PD) or at follow-up in 1999–2003 (incident PD)*

Characteristic	Prevalent PD						Incident PD					
	Cases		Controls		OR†,‡	95% CI†	Cases		Controls		OR‡	95% CI
	No.	%	No.	%			No.	%	No.	%		
Age (years) at enrollment												
12–50	7	8	49,600	62	0.1	0.1, 0.3	7	9	34,050	61	0.1	0.0, 0.2
51–60	22	27	17,261	22	1.0	Referent	31	40	12,878	23	1.0	Referent
61–70	33	40	10,126	13	2.6	1.5, 4.4	32	41	7,406	13	1.8	1.1, 3.0
71–92	21	25	2,570	3	6.8	3.8, 12.5	8	10	1,597	3	2.2	1.0, 4.7
State												
Iowa	57	69	52,294	66	1.0	Referent	54	69	37,573	67	1.0	Referent
North Carolina	26	31	27,263	34	0.6	0.4, 0.9	24	31	18,358	33	0.6	0.4, 1.0
Type of participant												
Applicator	60	72	48,878	61	1.0	Referent	56	72	33,020	59	1.0	Referent
Spouse	23	28	30,679	39	0.7	0.4, 1.1	22	28	22,911	41	0.6	0.4, 1.0
Race/ethnicity												
White, not Hispanic	78	95	76,448	97	1.0	Referent	70	93	53,181	97	1.0	Referent
Other	4	5	2,354	3	1.7	0.6, 4.9	5	7	1,508	3	2.5	1.0, 6.5
Missing data§	1		755				3		1,242			
Education												
Less than high school	14	18	5,736	8	0.9	0.5, 1.7	11	15	3,763	7	1.2	0.6, 2.5
High school	48	62	33,855	45	1.0	Referent	35	48	22,821	44	1.0	Referent
More than high school	16	21	35,043	47	0.5	0.3, 0.9	27	37	25,118	49	1.2	0.7, 2.0
Missing data	5		4,923				5		4,229			
Smoking status at enrollment												
Never smoker	58	71	47,460	61	1.0	Referent	41	55	33,603	62	1.0	Referent
Former smoker	20	24	19,715	25	0.5	0.3, 0.9	29	39	13,683	25	1.1	0.7, 1.8
Current smoker	4	5	10,651	14	0.4	0.2, 1.2	4	5	6,602	12	0.6	0.2, 1.7
Missing data	1		1,731				4		2,043			
Smoking (pack-years) at enrollment												
Nonsmoker	58	72	47,460	62	1.0	Referent	41	56	33,603	63	1.0	Referent
1–5	9	11	10,373	14	0.7	0.4, 1.5	8	11	7,043	13	0.9	0.4, 1.8
6–15	7	9	8,395	11	0.6	0.3, 1.3	8	11	5,500	10	0.9	0.4, 2.0
16–30	4	5	5,746	8	0.4	0.1, 1.1	9	12	3,831	7	1.3	0.6, 2.7
>30	3	4	4,446	6	0.3	0.1, 0.9	7	10	3,034	6	1.0	0.4, 2.3
Missing data	2		3,137				5		2,920			
Ever use of alcohol in the year preceding enrollment¶												
Nondrinker	43	56	29,613	38	1.0	Referent	31	44	20,389	39	1.0	Referent
Drinker	34	44	47,787	62	0.9	0.6, 1.5	40	56	32,556	61	1.1	0.7, 1.8
Missing data	6		2,157				7		2,986			
No. of alcoholic drinks per month during the year preceding enrollment¶												
Nondrinker	43	56	29,613	38	1.0	Referent	31	44	20,389	39	1.0	Referent
1–10	28	36	32,747	42	1.1	0.6, 1.8	29	41	23,084	44	1.1	0.7, 2.0
11–30	4	5	8,360	11	0.6	0.2, 1.8	5	7	5,451	10	0.8	0.3, 2.2
≥31	2	3	6,680	9	0.4	0.1, 1.9	6	8	4,021	8	1.3	0.5, 3.3
Missing data	6		2,157				7		2,986			

* Participants were licensed pesticide applicators and their spouses.

† OR, odds ratio; CI, confidence interval.

‡ Odds ratios were calculated by logistic regression with adjustment for age at enrollment, state, and type of participant (applicator or spouse). Most applicators were men (>99%) and most spouses were women (96%), so no further adjustment was made for gender.

§ In this table and subsequent tables, column percentages were calculated after exclusion of participants with missing data.

¶ Models for alcohol use were additionally adjusted for smoking status.

TABLE 2. Symptoms reported at enrollment by self-reported Parkinson's disease (PD) cases and controls identified in the Agricultural Health Study at enrollment in 1993–1997 (prevalent PD) or at follow-up in 1999–2003 (incident PD)*

Symptom†	Prevalent PD						Incident PD					
	Cases		Controls		OR‡,§	95% CI‡	Cases		Controls		OR§	95% CI
	No.	%	No.	%			No.	%	No.	%		
Shaking or trembling of hands	34	92	2,457	11	109	34, 358	7	24	1,783	11	3.4	1.4, 7.9
Difficulty with balance	22	61	2,715	12	9.7	5.0, 19	5	17	1,993	12	1.4	0.5, 3.8
Dizziness	13	33	2,112	10	4.1	2.1, 8.0	3	10	1,543	10	1.0	0.3, 3.3
Difficulty speaking	14	38	1,015	5	17	8.5, 33	1	3	743	5	1.1	0.2, 8.1
Changes in sense of smell or taste	12	33	1,456	7	7.8	3.9, 16	4	14	1,096	7	2.5	0.9, 7.3

* Participants were licensed pesticide applicators who completed the supplemental Applicator Questionnaire. Symptom information was collected at the time diagnosis was reported for prevalent PD cases and approximately 5 years before diagnosis for incident PD cases.

† Symptoms were reported on the questionnaire as frequencies ranging from never to more than once per week, and were then dichotomized so that 5–15% of controls were in the "positive" group.

‡ OR, odds ratio; CI, confidence interval.

§ Odds ratios were calculated by logistic regression with adjustment for age at enrollment and state. For each symptom, the referent group was participants without the symptom.

prevalent PD and incident PD, risk was lower in North Carolina than in Iowa, lower for spouses (96 percent women) than for applicators (99 percent men), and higher for non-Whites than for Whites (table 1). Risk was also lower in North Carolina in models including cigarette smoking or pesticide use (not shown). Five of the nine non-White cases (prevalent and incident) and approximately 50 percent of non-White controls were African-American. Using enrollment data, prevalent PD was inversely associated with both former and current cigarette smoking, and a gradient was observed for pack-years of smoking, but incident PD was inversely associated only with current smoking, not with former smoking (table 1). Incident PD was also inversely associated with current but not former smoking using follow-up data on smoking status (not shown). Prevalent, but not incident, PD was inversely associated with alcohol consumption at enrollment after adjustment for smoking (table 1). Similar results for demographic and lifestyle characteristics were observed in both applicators and spouses when these groups were considered separately (not shown).

Parkinsonian symptoms

Applicators who completed the supplemental Applicator Questionnaire provided information on several parkinsonian symptoms at enrollment—that is, at the same time prevalent cases reported PD and approximately 5 years before incident cases reported PD. Prevalent PD was associated with hand tremor, difficulty with balance, dizziness, difficulty speaking, and changes in sense of smell or taste (table 2). Increases in hand tremor and changes in smell or taste were also apparent at enrollment in persons who later reported PD at follow-up (incident PD cases) (table 2).

Exposure to any pesticide

There was a weak inverse association of prevalent PD with ever use of any pesticide and with personally mixing or applying pesticides (table 3). This relation was apparent only after adjustment for type of participant (applicator or spouse) but was seen in both groups (for ever use, OR = 0.4 for applicators and OR = 0.6 for spouses). In contrast, there was a positive association of incident PD with ever use of pesticides and with personally mixing pesticides, and there was a stronger association for those who personally applied pesticides more than half the time (table 3). Cumulative lifetime days of use was associated with a dose-related increase in incident PD but not prevalent PD (table 3).

Similar results for cumulative lifetime days of pesticide use were seen when applicators and spouses were considered separately. For prevalent PD, odds ratios for the highest quartile were 0.8 for applicators and 0.6 for spouses; for incident PD, odds ratios were 2.2 and 2.8. Results for applicators were unchanged after exclusion of persons who never used pesticides (<1 percent); odds ratios for the highest quartile of use were 0.8 for prevalent PD and 2.1 for incident PD. Adjustment for smoking did not change results: In models including smoking status, odds ratios for the highest quartile of use were 0.8 for prevalent PD and 2.3 for incident PD. Results were similar in both states: For the highest quartile of use, odds ratios for prevalent PD were 0.9 in North Carolina and 0.7 in Iowa; odds ratios for incident PD were 2.7 in North Carolina and 2.0 in Iowa. Similar results were obtained when lifetime years of use (duration) rather than cumulative days of use (the product of frequency and duration) was used as a measure of exposure: Odds ratios for the highest quartile of years of use were 0.9 for prevalent PD and 2.5 for incident PD.

Use of personal protective equipment was inversely related to both prevalent and incident PD (table 3). Weighting

TABLE 3. Pesticide use among self-reported Parkinson's disease (PD) cases and controls identified in the Agricultural Health Study at enrollment in 1993–1997 (prevalent PD) or at follow-up in 1999–2003 (incident PD)*

Exposure	Prevalent PD						Incident PD					
	Cases		Controls		OR†,‡	95% CI†	Cases		Controls		OR‡	95% CI
	No.	%	No.	%			No.	%	No.	%		
Ever use of any pesticide												
No	15	18	13,822	18	1.0	Referent	7	9	9,419	17	1.0	Referent
Yes	67	82	65,116	82	0.5	0.2, 1.1	68	91	45,325	83	1.3	0.5, 3.3
Missing data	1		619				3		1,187			
Personally mixing pesticides												
No	21	28	20,300	28	1.0	Referent	14	20	14,167	28	1.0	Referent
<50% of the time	19	25	15,641	22	0.8	0.4, 1.7	12	17	10,667	21	0.8	0.3, 1.9
≥50% of the time	36	47	36,227	50	0.7	0.3, 1.5	43	62	25,238	50	1.2	0.5, 2.7
Missing data	7		7,389				9		5,859			
Personally applying pesticides												
No	16	21	15,473	21	1.0	Referent	8	12	10,611	21	1.0	Referent
<50% of the time	25	33	15,927	22	1.1	0.5, 2.2	12	17	11,038	22	1.2	0.5, 3.1
≥50% of the time	35	46	40,697	56	0.6	0.3, 1.2	49	71	28,372	57	1.9	0.7, 4.7
Missing data	7		7,460				9		5,910			
Cumulative lifetime days of use												
0–64	35	47	33,608	47	1.0	Referent	19	28	23,364	47	1.0	Referent
65–200	11	15	11,540	16	0.7	0.3, 1.3	10	14	8,091	16	1.2	0.5, 2.6
201–396	13	17	13,208	18	0.7	0.4, 1.5	16	23	9,229	18	1.7	0.8, 3.5
≥397	16	21	13,727	19	0.8	0.4, 1.5	24	35	9,320	19	2.3	1.2, 4.5
Missing data	8		7,474				9		5,927			
p for trend					0.49						0.009	
Use of personal protective equipment§,¶												
Low protection	18	32	10,175	22	1.0	Referent	16	31	6,719	22	1.0	Referent
Moderate protection	32	57	28,216	61	0.7	0.4, 1.3	28	54	19,078	61	0.6	0.3, 1.2
High protection	6	11	7,542	16	0.5	0.2, 1.3	8	15	5,242	17	0.7	0.3, 1.7
Missing data	4		2,945				4		1,981			
Pesticide-related medical care§												
No	50	91	44,793	94	1.0	Referent	49	89	30,063	93	1.0	Referent
Yes	5	9	3,087	6	1.3	0.5, 3.4	6	11	2,096	7	1.6	0.7, 3.7
Missing data	5		998				1		861			
Washing after a high personal exposure event#												
No event	33	87	18,813	86	1.0	Referent	26	84	13,619	85	1.0	Referent
Washed within 1 hour	2	5	1,814	8	1.0	0.2, 4.3	2	6	1,403	9	1.1	0.3, 4.7
Washed after 1 hour	3	8	1,179	5	1.5	0.5, 5.0	3	10	930	6	1.7	0.5, 5.9
Missing data	3		762				1		548			

* Participants were licensed pesticide applicators and their spouses.

† OR, odds ratio; CI, confidence interval.

‡ Odds ratios were calculated by logistic regression. All models included adjustment for age at enrollment and state; those including both applicators and spouses also included adjustment for type of participant (applicator or spouse).

§ Data were available only for applicators.

¶ Low protection: score = 0.8–1.0; moderate protection: score = 0.4–0.7; high protection: score = 0.1–0.3 (scores were calculated as described by Dosemeci et al. (13)).

Data were available only for applicators who completed the Supplemental Questionnaire at enrollment.

TABLE 4. Ever use of specific pesticides by self-reported Parkinson's disease (PD) cases and controls identified in the Agricultural Health Study at enrollment in 1993–1997 (prevalent PD) or at follow-up in 1999–2003 (incident PD)*

Pesticide classification†	Chemical†	Prevalent PD						Incident PD					
		Cases		Controls		OR‡,§	95% CI‡	Cases		Controls		OR§	95% CI
		No.	%	No.	%			No.	%	No.	%		
Herbicides													
Chloroacetanilide	Alachlor	30	39	25,599	34	0.8	0.5, 1.5	34	49	17,359	34	1.1	0.6, 1.9
	Metolachlor	22	29	22,202	29	0.9	0.5, 1.6	30	45	14,856	29	1.3	0.7, 2.3
Benzoic acid	Dicamba	26	35	23,847	32	0.9	0.5, 1.6	32	47	16,454	32	1.5	0.8, 2.8
Dinotroaniline	Pendimethalin	23	32	21,386	28	1.4	0.8, 2.6	17	25	13,893	27	0.7	0.4, 1.2
	Trifuralin	31	40	25,787	34	0.9	0.5, 1.6	32	48	17,406	34	1.7	1.0, 3.2
Imidazolinone	Imazethapyr	19	25	20,461	27	0.9	0.5, 1.7	22	32	13,747	27	1.2	0.6, 2.1
Mixture	Petroleum oil	22	30	22,295	30	0.5	0.3, 0.9	28	41	15,224	30	1.1	0.6, 1.9
Organophosphorus	Glyphosate	45	55	46,687	60	1.0	0.6, 1.7	49	67	32,686	60	1.1	0.6, 2.0
Phenoxyacetate	2,4-D‡	47	58	40,405	52	0.9	0.5, 1.8	49	68	28,118	52	1.0	0.5. 2.1
	2,4,5-T‡	16	22	9,824	13	0.9	0.5, 1.7	24	35	6,961	14	1.8	1.0, 3.3
	2,4,5-TP‡	4	5	4,229	6	0.8	0.3, 1.9	7	10	2,909	6	0.9	0.4, 1.8
Quaternary ammonium	Paraquat	14	20	11,266	15	1.8	1.0, 3.4	11	16	7,382	14	1.0	0.5, 1.9
Thiocarbamate	EPTC‡	6	8	9,160	12	0.6	0.3, 1.3	14	21	6,409	13	1.1	0.6, 2.1
	Butylate	17	23	14,726	20	0.7	0.3, 1.3	24	35	10,087	20	1.4	0.8, 2.5
Sulfonyl urea	Chlorimuron-ethyl	16	22	17,552	23	0.8	0.4, 1.5	16	24	11,535	23	1.0	0.6, 1.8
Triazine	Atrazine	40	49	35,377	45	1.0	0.5, 1.9	43	59	24,232	45	1.1	0.5, 2.2
	Cyanazine	30	39	19,702	26	2.6	1.4, 4.9	26	38	13,504	26	1.0	0.5, 1.8
Triazinone	Metribuzin	28	38	20,879	28	1.5	0.8, 3.0	19	28	14,251	28	0.5	0.3, 1.0
Insecticides													
Carbamate	Aldicarb	Not calculated						5	7	3,436	7	0.5	0.2, 1.3
	Carbaryl	35	46	35,262	46	1.0	0.6, 1.7	37	51	24,775	47	0.7	0.4, 1.2
	Carbofuran	21	27	12,908	17	1.3	0.7, 2.5	21	31	8,993	18	1.1	0.6, 2.1
Organochlorine	Aldrin	23	31	8,804	12	1.2	0.7, 2.3	22	31	6,136	12	1.1	0.6, 2.0
	Chlordane	15	21	12,731	17	0.1	0.4, 1.4	23	32	9,131	18	0.8	0.4, 1.5
	Dieldrin	9	13	3,128	4	0.9	0.4, 2.0	8	11	2,303	5	0.8	0.4, 1.8
	DDT‡	25	33	12,620	17	1.0	0.6, 1.8	29	40	8,870	17	1.0	0.6, 1.9
	Heptachlor	15	21	7,144	10	1.1	0.6, 2.2	16	23	5,159	10	0.7	0.4, 1.4
	Lindane	14	19	8,883	12	1.0	0.5, 1.9	19	28	6,490	13	1.4	0.8, 2.5
	Toxaphene	5	7	6,719	9	0.3	0.2, 1.0	9	13	4,632	9	0.6	0.3, 1.3

Table continues

cumulative days of pesticide use by the personal protective equipment score did not appreciably change the association of PD with pesticide use: Odds ratios for the highest quartile of weighted cumulative days of use were 0.7 for prevalent PD and 2.2 for incident PD. Weak positive associations of PD with pesticide-related medical care were evident for both prevalent and incident cases (table 3). No case in either group reported a diagnosis of pesticide poisoning. Delaying washing for more than 1 hour after an incident involving high personal pesticide exposure was associated with both prevalent and incident PD (table 3).

For prevalent PD, insufficient data were available to evaluate the temporal relation of pesticide exposure to disease. Among incident PD cases, 64 of 78 (85 percent) reported an age of diagnosis consistent with diagnosis after enrollment; the remaining 14 did not. Twelve of the latter had denied PD at enrollment, while the other two had missing data. Excluding these 14 cases did not substantively change results (for highest quartile of cumulative pesticide use, OR = 2.2, 95 percent confidence interval: 1.0, 4.5).

Information on AHS cohort mortality through June 2005 was available from the National Death Index. Death certificates for 61 persons listed PD as an underlying or contributing cause of death. Nineteen of these PD cases were prevalent cases, six were incident cases, and one case was excluded from both groups because of inconsistent data, leaving 35 potential PD cases identified only by death certificate. Compared with the 78 self-reported incident cases, the 35 death certificate cases were older at enrollment and more likely to have lived in North Carolina; the two groups

TABLE 4. Continued

Pesticide classification†	Chemical†	Prevalent PD						Incident PD					
		Cases		Controls		OR‡,§	95% CI‡	Cases		Controls		OR§	95% CI
		No.	%	No.	%			No.	%	No.	%		
Organophosphate	Dichlorvos	4	5	5,285	7	0.8	0.4, 1.9	8	11	3,959	8	0.7	0.3, 1.4
Organothiophosphate	Chlorpyrifos	25	30	21,380	28	1.2	0.7, 2.1	24	33	14,570	27	0.9	0.5, 1.6
	Coumaphos	4	5	4,185	6	0.8	0.3, 1.9	6	9	3,040	6	0.8	0.4, 1.9
	Diazinon	17	24	17,519	23	1.0	0.5, 1.8	21	30	12,276	24	0.9	0.5, 1.7
	Fonofos	11	14	10,461	14	0.9	0.3, 1.7	12	17	7,121	14	1.0	0.5, 1.8
	Malathion	41	55	38,292	50	1.1	0.6, 2.0	49	67	26,577	51	1.2	0.6, 2.1
	Parathion	11	15	7,338	10	1.3	0.6, 2.7	14	20	4,962	10	1.1	0.6, 2.2
	Phorate	20	28	15,528	21	1.1	0.6, 2.0	26	37	10,402	20	1.4	0.8, 2.5
	Terbufos	22	28	18,805	25	0.9	0.5, 1.7	23	33	12,693	25	1.1	0.6, 2.0
Pyrethroid	Permethrin¶	6	7	12,212	16	0.9	0.4, 2.2	9	12	8,583	16	0.8	0.3, 1.7
Fungicides													
Anilide	Metalaxyl	7	9	11,425	15	0.9	0.4, 2.1	11	16	7,479	15	1.0	0.3, 2.0
Aromatic	Chlorothalonil	Not calculated						6	8	2,759	5	2.0	0.9, 4.4
Carbamate	Benomyl	6	8	5,094	7	0.9	0.4, 2.3	10	14	3,288	6	1.7	0.7, 3.7
Dithiocarbamate	Maneb/mancozeb¶	8	11	4,969	7	1.0	0.4, 2.4	6	9	3,364	7	1.1	0.5, 2.4
Phthalimide	Captan	7	9	5,631	8	1.0	0.5, 2.4	6	9	4,111	8	0.8	0.4, 1.8
Fumigants													
Inorganic	Aluminum phosphide	7	9	2,191	3	1.3	0.5, 3.5	Not calculated					
Inorganic	Carbon disulfide/ carbon tetrachloride	7	9	2,618	3	1.6	0.7, 3.6	5	7	1,890	4	0.7	0.3, 1.9
Inorganic	Ethylene dibromide	5	7	1,723	2	1.4	0.5, 4.0	Not calculated					
Inorganic	Methyl bromide	6	8	7,891	10	0.9	0.4, 2.2	10	13	5,455	10	2.1	0.9, 4.9

* Participants were licensed pesticide applicators and their spouses. Numbers and percentages are for those reporting ever use of the specific pesticide.

† Pesticides were classified according to Wood's *Compendium of Pesticide Common Names* (51) and are listed in alphabetical order within functional/chemical groups.

‡ OR, odds ratio; CI, confidence interval; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxyproprionic acid; EPTC, *S*-ethyl-dipropylthiocarbamate; DDT, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane.

§ Odds ratios were calculated by hierarchical regression, with adjustment for age, state, and type of participant (applicator or spouse). The second-level model included the variables insecticides, herbicides, fungicides, fumigants, organophospate insecticides, organochlorine insecticides, carbamate insecticides, phenoxyacetate herbicides, and triazine/triazone herbicides. For each pesticide, the referent group was persons who had never used the pesticide. Only pesticides for which there were at least four exposed cases were included in the models.

¶ Two questions on the use of permethrin on crops or animals were combined. Participants were asked about use of maneb and mancozeb in a single question.

were similar in terms of proportion of applicators versus spouses, gender, race, educational level, and smoking status. Associations with pesticide exposure for a combined group ($n = 113$) were similar to those for the self-reported incident cases in table 3 (for highest quartile of pesticide use, OR = 1.8). No association with smoking status was observed in the combined group (for former smokers, OR = 0.9; for current smokers, OR = 0.7).

Exposure to specific chemicals

Considering only chemicals for which there were four or more exposed cases, odds ratios for prevalent PD were elevated ($\geq$1.4) for the herbicides pendimethalin, paraquat, and cyanazine and the fumigants carbon disulfide/carbon tetrachloride and ethylene dibromide (table 4). Odds ratios for incident PD were elevated for the herbicides dicamba, trifuralin, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and butylate, the insecticides lindane and phorate, the fungicides chlorothalonil and benomyl, and the fumigant methyl bromide (table 4). Results were similar when the second-stage model of the hierarchical logistic regression included only variables for functional pesticide groups (not shown).

Applicators who completed the supplemental Applicator Questionnaire provided additional information on some pesticides, including four implicated in PD in previous studies: dieldrin, maneb, paraquat, and rotenone (8–10). When information from the Enrollment and Applicator questionnaires was combined, odds ratios for prevalent PD were 1.3 for dieldrin, 1.5 for maneb/mancozeb, 1.8 for paraquat, and 1.7

for rotenone, and odds ratios for incident PD were 0.9 for dieldrin, 2.1 for maneb/mancozeb, and 1.4 for paraquat; only one incident case had used rotenone. These results were based on 4–10 exposed cases for each pesticide.

DISCUSSION

We found a positive association of self-reported PD with overall pesticide use among incident cases. Increasing cumulative days of use and proportion of time pesticides were personally applied were related to increasing risk for both applicators and their spouses. In contrast, prevalent PD was not associated with overall pesticide use. For both incident and prevalent PD, receiving pesticide-related medical care or experiencing an incident involving high personal pesticide exposure was associated with increased risk, while using personal protective equipment to reduce potential exposure was associated with decreased risk. Increased risk was also associated with several specific pesticides.

Previous studies have suggested that pesticide exposure may increase risk of PD (6–10). Studies published before 1999 were reviewed by Le Couteur et al. (6), who noted that 12 of 20 studies found a positive association, with 1.6- to 7-fold increases in risk. A meta-analysis published in 2000 found a combined odds ratio of 1.9 (7). Investigators in some recent studies have reported positive associations (15–22), although others have not (23–26); in general, studies with positive findings had more detailed exposure assessments. Researchers in three prospective cohort studies reported positive associations of PD with pesticide exposure (27–29). PD risk may depend on an interaction of genetic susceptibility with pesticide exposure: In two studies, persons who were either exposed to pesticides or had polymorphisms in the cytochrome P-450 2D6 (*CYP2D6*) gene that confer a poor-metabolizer phenotype had only a slightly increased risk of PD, but persons with both factors had a greatly increased risk (ORs = 4–8) (30, 31).

Information on the relation of PD to specific pesticides or pesticide classes is limited. Several studies found increased risk associated with exposure to either insecticides or herbicides (21, 22, 32, 33), and one study found elevated risks associated with organochlorine, organophosphate, and carbamate insecticides (34). Several studies have implicated the herbicide paraquat (22, 35, 36), which produced selective degeneration of dopaminergic nigral neurons in an animal model (37). Case reports and postmortem studies have described PD in persons exposed to organophosphate insecticides; organochlorine insecticides, including dieldrin; herbicides, including glyphosate, paraquat, and diquat; and fungicides, including maneb and other dithiocarbamates (8). Animal models have implicated rotenone (38) or a combination of paraquat and maneb (39) in the etiology of PD. Finally, certain pesticides promote synuclein fibrillation (40), a mechanism likely to be involved in PD pathogenesis (41). Thus, although some authors suggest that existing data may not yet be sufficient to infer a causal relation (9, 10), the weight of evidence suggests that pesticide exposure is associated with increased risk of PD (6–10).

Our study provides additional evidence to support the hypothesis that PD risk is associated with overall pesticide exposure, as well as new information on the relation of PD to specific pesticides. For prevalent cases, we found elevated risks associated with three herbicides and two fumigants. For incident cases, we found elevated risks associated with nine pesticides from all four functional classes. Four pesticides have previously been implicated in the etiology of PD: dieldrin, maneb, paraquat, and rotenone (8–10). We found associations of all four with prevalent PD and of maneb/mancozeb and paraquat with incident PD in the subset of applicators who completed the supplemental Applicator Questionnaire at enrollment. However, only an association of paraquat with prevalent PD was seen in the complete cohort.

Accounting for exposure to multiple pesticides presents a challenge for analysis. We used hierarchical logistic regression to evaluate exposure to multiple pesticides (14). Definition of meaningful pesticide subgroups is difficult. Our results suggest that categorization by functional group or even chemical structure may be unsatisfactory, because the relation with outcome may be variable within groups. In a recent study, Samanic et al. (42) used factor analysis to identify three groupings of pesticide use and other farm characteristics in the AHS cohort: Iowa agriculture and herbicide use; North Carolina agriculture and use of insecticides, fumigants, and fungicides; and older age and use of chlorinated pesticides. Present knowledge of mechanisms involved in PD is limited but may suggest ways to group chemicals for analysis (41, 43). Conversely, findings that chemicals affecting similar mechanistic pathways increase PD risk would provide strong evidence that these pathways are involved in the etiology of PD.

Differences in results for prevalent and incident cases are striking, but the underlying reasons are unclear. Prevalent cases may be a selected group, representing the more functional cases present in the underlying population when the cohort was enrolled. PD cases with higher pesticide exposure may have been less likely to enroll in the cohort than those with lower exposure, either because the disease course is different in the former or because other effects of pesticide exposure (44, 45) led them to stop farming at an earlier age. Our questionnaires focused on lifetime pesticide use, but prevalent PD cases may have decreased their current use as a result of disability and therefore underreported lifetime use. Sixty-eight percent of the original cohort was interviewed at follow-up. Although there were demographic differences between those interviewed and those not interviewed, pesticide use reported at enrollment was similar in the two groups. Loss of cases at follow-up due to mortality does not appear to account for differences between prevalent cases and incident cases. We lacked precise information on date of diagnosis for prevalent cases, so disease duration was unknown, as was period of pesticide use in relation to time of diagnosis. In contrast, most incident cases reported a disease duration of less than 5 years, and exposure data were collected before diagnosis.

Consistent with previous reports (1, 46), we found an inverse association of cigarette smoking with PD. The association was stronger in prevalent cases than in incident cases. A lower response rate for the follow-up interview among nonsmokers who developed PD after enrollment,

compared with smokers who developed PD, might explain this difference. However, for the cohort as a whole, response at follow-up was greatest in never smokers, intermediate in former smokers, and least in current smokers, based on smoking information collected at enrollment, and smoking behavior was similar in the control groups compared with prevalent or incident cases. Furthermore, when potential PD cases identified by death certificate only were added to the incident case group, the association of PD with current smoking was weakened. Adjustment for smoking did not change associations of PD with pesticide use.

One limitation of this study was its reliance on self-reported diagnosis of PD, but the degree of misclassification may not have been large. Furthermore, misclassification is likely to result in attenuation of associations, making our estimates conservative. Information on neurologic symptoms, available for a subset of applicators, increased confidence in the diagnosis. Prevalent cases were highly likely to report several parkinsonian symptoms in comparison with controls. Interestingly, incident cases also reported high levels of hand tremor and changes in smell or taste at enrollment, 5 years before they reported a diagnosis of PD. A decline in olfaction may be an early symptom of PD (47), although changes may not be evident more than 5 years before diagnosis (48). A further limitation of the study was the use of self-reported exposure data. However, questionnaires are essentially the only way to evaluate chronic exposure to nonpersistent pesticides in nonindustrial populations. Previous studies have found that farmers in general and AHS cohort members in particular report pesticide use reliably (49, 50), although some misclassification undoubtedly occurs.

Strengths of the study included its ability to distinguish between prevalent and incident cases and its base in an agricultural population with many exposed persons. Because farming practices are considerably different in Iowa and North Carolina, the AHS cohort represents a diverse farming population (11). Cohort members provided detailed exposure data, allowing us to evaluate associations not only with overall pesticide use but also with specific chemicals and with factors that may affect exposure, such as use of personal protective equipment. We made internal comparisons of more exposed persons with less exposed persons from the same population, mitigating potential confounding. Future studies will continue to exploit the unique opportunity provided by the AHS to address the association of pesticide exposure with PD using neurologists' diagnoses and extensive exposure information.

In conclusion, the present study provides further support for the hypothesis that pesticide exposure increases PD risk, with detailed data on associations with specific pesticides and several aspects of pesticide use. Findings for specific chemicals may provide fruitful leads for further investigation.

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