The relation between type of farming and prevalence of Parkinson's disease among agricultural workers in five french districts.

Frédéric Moisan, Johan Spinosi, Jean-Luc Dupupet, Laurène Delabre, Jean-Louis Mazurie, Marcel Goldberg, Ellen Imbernon, Christophe Tzourio, Alexis Elbaz

RESEARCH ARTICLE

The Relation Between Type of Farming and Prevalence of Parkinson's Disease Among Agricultural Workers in Five French Districts

Frédéric Moisan, MSc,[1,2]* Johan Spinosi, MSc,[3,4] Jean-Luc Dupupet, MD,[5] Laurène Delabre, BSc,[3] Jean-Louis Mazurie, MD,[6] Marcel Goldberg, MD, PhD,[3,7,8,9] Ellen Imbernon, MD,[3] Christophe Tzourio, MD, PhD,[1,2] and Alexis Elbaz, MD, PhD[1,2,3]

[1]*INSERM, Paris, France*
[2]*UPMC Univ Paris, Neuroepidemiology, Paris, France*
[3]*Département santé travail, Institut de veille sanitaire, Saint-Maurice, France*
[4]*Umrestte (Unité mixte de recherche épidémiologique et de surveillance transport, travail, environnement) InVS/UCBL/Inrets, Lyon, France*
[5]*Caisse centrale de la Mutualité sociale agricole, Bagnolet, France*
[6]*Caisse départementale de la Gironde, Mutualité sociale agricole, Bordeaux, France*
[7]*INSERM, U1018, Epidemiology of occupational and social determinants of health, Centre for research in Epidemiology and Population Health, Villejuif, France*
[8]*University of Versailles St-Quentin, Paris, France*
[9]*Univ Paris, Villejuif, France*

ABSTRACT: Retrospective assessment of pesticide exposure is complex; however, patterns of pesticide use strongly depend on farming type, which is easier to assess than pesticide exposure. Our aim was to estimate Parkinson's disease (PD) prevalence in five French districts in 2007 among affiliates of *Mutualité Sociale Agricole* (MSA) and to investigate the relation between PD prevalence and farming type. We identified PD cases from administrative files as persons who used levodopa and/or benefited from free health care for PD. Densities of 16 farming types were defined at the canton of residence level (1988 French agricultural census). We used logistic regression to study the relation between PD prevalence and density of farming types and a semi-Bayes approach to deal with correlated exposures. We identified 1,659 PD cases, yielding an age- and sex-standardized PD prevalence of 3.01/1,000. Prevalence increased with age and was higher in men than women. We found a higher PD prevalence among affiliates living in cantons characterized by a higher density of farms specialized in fruits and permanent crops (multivariable semi-Bayes model: $OR_{4+5 \text{ vs } 1+2+3 \text{ quintiles}} = 1.21$, 95% CI = 1.08–1.36; test for trend, $P = 0.035$). In France, farms specialized in fruits and permanent crops rank first in terms of insecticide use per hectare. Our findings are consistent with studies reporting an association between PD and insecticide use and show that workers in farms specialized in fruits or permanent crops may be an occupational group at higher PD risk.

Key Words: agriculture; environmental exposure; Parkinson disease; prevalence; pesticides

The cause of Parkinson's disease (PD) is multifactorial and involves environmental risk factors and susceptibility genes.[1] Among environmental exposures, an epidemiological association between pesticides and PD has been shown;[2,3] these findings are supported by laboratory data.[4]

Retrospective assessment of pesticide exposure is complex: workers use a large variety of products; pesticides have considerably evolved through time; several factors determine exposure level (e.g., equipment, spraying frequency/duration, quantity). These complexities may lead to measurement error, multiple correlated exposures, and missing values. Because pesticide use patterns (including products and

---

Additional Supporting information may be found in the online version of this article.

***Correspondence to:** Frédéric Moisan, INSERM Unité 708, Neuroépidémiologie, Hôpital de la Salpêtrière, 47 Bvd de l'Hôpital, 75651 Paris Cedex 13, France; frederic.moisan@upmc.fr

Relevant conflict of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

This work was supported by *Institut national de la santé et de la recherche médicale* (Inserm), *Agence nationale de la recherche*, *Agence française de sécurité sanitaire de l'environnement et du travail* (Afsset) and *France Parkinson*. Frédéric Moisan was supported by a scholarship from the *Ministère de l'enseignement supérieur et de la recherche*.

Received: 22 May 2010; **Revised:** 24 June 2010; **Accepted:** 5 July 2010

Published online 13 December 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23370

characteristics outlined above) strongly depend on farming type, which is considerably easier to assess than pesticide use, we hypothesized that investigating the relation between PD and farming type may help characterize the type of exposure associated with PD and identify occupational groups at higher risk.

Our objective was to investigate the relation between PD prevalence and farming type in five French districts in 2007 among affiliates to the health insurance for farmers and workers in agriculture [*Mutualité Sociale Agricole* (MSA)] using data from the French agricultural census.

Subjects and Methods

Participants

MSA is responsible for the reimbursement of health-related expenses to agricultural populations (farmers; farm workers: workers in silos, agricultural cooperatives, seed shops; professional gardeners; and employees of MSA, an insurance company, and a bank). Workers (and spouses, if unemployed) benefit from health insurance while employed and retired. In 2007, MSA covered ~4 millions of persons. This study is based on MSA affiliates ≥18 years who lived in 2007 in five French districts (départements; Charente-Maritime, Côte-d'Or, Gironde, Haute-Vienne, and Mayenne), which cover 6.5% of France. There are marked differences in farming types, both between and within districts. The study protocol was approved by the Ethical Committee of the *Pitié-Salpêtrière* University hospital.

Cases

Cases were identified through two computerized MSA databases: (i) drug claims: in France, antiparkinsonian drugs (APD) cannot be obtained without medical prescription, their delivery is registered in a drug delivery database; we identified MSA affiliates who bought any levodopa (L-dopa)-containing medication in 2007; and (ii) PD belongs to a list of 30 diseases for which free health care (FHC) is granted, usually after a neurologist confirmed the diagnosis; MSA affiliates with FHC/PD were identified.

The prevalence date was June 1, 2007. PD cases were subjects with: (i) at least one L-dopa delivery in the 6 months preceding and following the prevalence date and/or (ii) FHC/PD at the prevalence date. We performed a validation study of our case definition among all persons who bought any APD in 2007 and verified the following criteria: age ≤80 years; disease duration ≤15 years; no FHC for dementia or psychiatric disease (Supporting Information Fig. 1). All subjects with at least one delivery of L-dopa, entacapone, tolcapone, ropinirole, pramipexole, apomorphine, bromocriptine, or selegiline or with FHC/PD (using any APD) were invited to be examined by a neurologist (unless they used small doses of dopamine agonists for restless leg syndrome (RLS); treatment was discontinued after ≤1 month; there was a clear history of drug-induced parkinsonism) to confirm PD using standardized criteria.[5] Those using APDs rarely prescribed for PD (piribedil, amantadine, and anticholinergics) were first contacted by mail; they were asked why APDs were prescribed and those who answered PD/parkinsonism or did not know were invited to be examined by a neurologist if they verified the inclusion criteria. We excluded women ≤50 years who used small doses of bromocriptine for a short time (lactation suppression) and subjects who received anticholinergics with neuroleptics (drug-induced parkinsonism). Of 1,114 persons identified in 2007 for whom we could obtain clinical information, 320 had PD: 290 used L-dopa and/or had FHC/PD (sensitivity = 91%); of 794 persons without PD: 122 used L-dopa and/or had FHC/PD (specificity = 85%); the *c*-statistic was 0.88. To compute prevalence, we obtained a list of all affiliates ≥18 years alive at the prevalence date in the participating districts.

Characteristics of the Participants

Participants' characteristics were defined at the individual and canton (small administrative subdivision of districts) level. There were 208 cantons [median (interquartile range) area = 17,009 [12,811] km^2; median number of affiliates = 904 (1,094)].

The following information was available at the individual level: birth year, sex, and district/canton of residence. For participants with FHC/PD, age at request was available; it was strongly correlated with age at onset in the validation study (Pearson correlation coefficient = 0.94).

Farming type was defined at the canton level based on the 1988 French agricultural census.[6] Our analyses are based on the density of 16 farming types, a common definition used by European administrations[7]; it is defined based on the relative importance of the different farm's activities and reflects the ratio of each activity's standard gross margin (SGM) to the farm's total SGM. SGM characterizes economic importance and is defined as the output value from one hectare or animal minus the input costs required to produce it. Farming type density was computed by dividing the number of farms with a given type by cantons' area.

There is evidence of socioeconomic variations in PD prevalence.[8] We used the cantons' 2007 median household income as a surrogate for socioeconomic level.[9]

Statistical Methods

We computed prevalence, overall and by sex and 10-year age groups. We estimated sex- and age-standardized prevalence (direct standardization) based on the age/sex distribution of the 2007 French population.[9] To assess the impact of diagnostic misclassification, we computed a corrected number of PD cases by applying sensitivity/specificity estimates of our case definition to all persons using any APD at the prevalence date[10]; we divided this number by the number of MSA affiliates (corrected prevalence).

We used logistic regression to model prevalence.[11] The relation between prevalence and farming type was first investigated using a mixed-effects model with a random intercept per canton. After adjustment for age, sex, district, and income, the residual intraclass correlation was not different from zero ($P = 0.49$); we, therefore, used fixed-effects models.

First, we built separate models for each farming type while adjusting for covariates (age, sex, district, and income); we adjusted for district to take into account differences in unmeasured confounders that may vary across districts. Densities of farming types were categorized into quintiles of their distribution among unaffected subjects; for dose-effect analyses, we used the median of categories.[12] Age was included as linear and quadratic terms. We categorized median household income into quintiles; because there was no difference in PD prevalence in the four highest quintiles, we used a dichotomous coding, comparing cantons in the lowest quintile to those in the remaining four. Interactions were tested by including multiplicative terms.

We then built a multivariable model that included all farming types and other covariates (age, sex, district, and income). Exposure variables were dichotomized by grouping the two highest quintiles versus the three lowest; trend tests were also performed. Because, this approach may be problematic for multiple correlated exposures, alternative approaches have been suggested.[13] Semi-Bayes models offer several advantages over traditional methods, including dealing with correlated exposures and multiple testing.[13–15] We implemented an intercept-only model in which all farming types are considered exchangeable, with a second-level residual variance of 0.345.[16]

We conducted sex-stratified analyses because PD prevalence is higher in men than women, and men are occupationally exposed to pesticides more frequently than women. Because neuroleptics can induce parkinsonism, we excluded patients who regularly used typical neuroleptics ($\geq$3 deliveries between January 1, 2007, and June 1, 2007) in sensitivity analyses. Cigarette smoking is inversely associated with PD.[17] Because we did not have smoking data, we used external adjustment using data from a case-control study nested within our validation study.[18]

Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC) and Stata 10 (StataCorp LP, College Station, TX). Significance level was considered at the two-sided 0.05 level.

Results

Among 239,576 MSA affiliates $\geq$18 years in five districts, we identified 1,659 PD cases (Table 1). Cases were older [median age = 80.6 (9.8) years] than unaffected subjects [53.5 (36.1) years; Wilcoxon rank-sum test, $P < 0.001$]. Among 955 cases with FHC/PD, median age at request was 73.4 (12.6) years, with a median disease duration at prevalence date of 5.4 (7.1) years.

Supporting Information Table 1 shows the age and sex distribution of MSA affiliates by district; Mayenne and Haute-Vienne affiliates were the oldest. Densities of 16 farming types varied significantly across districts (Supporting Information Table 2).

PD Prevalence

PD prevalence among affiliates $\geq$18 years was 6.92/1,000. The corrected prevalence using sensitivity/specificity of our case definition was 6.80/1,000. Sex- and age-standardized prevalence (reference: French population $\geq$18 years) was 3.87/1,000; assuming that there were no cases <18 years, the overall standardized prevalence (reference: total 2007 French population) was 3.01/1,000. The marked prevalence decrease results from the older age of MSA affiliates compared with the French population (Supporting Information Table 1). Prevalence $\geq$65 years was 19.64/1,000 and 16.86/1,000 after standardization (reference: 2007 French population $\geq$65 years).

Prevalence increased with age and was higher in men than women (Table 1; Supporting Information Fig. 2). The highest prevalence was observed in Mayenne and Haute-Vienne. Prevalence was higher in cantons with the lowest income.

PD Prevalence and Farming Type

Table 2 shows analyses of the relation between PD and densities of farming type. After adjustment for age, sex, district, and income, prevalence increased with the density of farms specialized in fruits and permanent crops (FSFPC); this association was confirmed in a mixed-effects model [$OR_{5th\ vs\ 1st\ quintile} = 1.21$ (1.02–1.43); P-trend = 0.008]. The relation between PD prevalence and FSFPC density was similar across districts (P-interaction = 0.410). PD prevalence remained higher in Mayenne and Haute-Vienne after adjustment for FSFPC density (data not shown), thus suggesting that other factors explain prevalence differences across districts. PD prevalence was increased in some quintiles of other farming types (various crops and livestock combined; specialist dairying; and mixed cropping) but without significant trends.

TABLE 1. Characteristics of Parkinson's disease cases and unaffected subjects from five French districts in 2007

	Affected subjects (N = 1,659)		Unaffected subjects (N = 237,917)		Multivariable logistic model	
Characteristics	N	%	N	%	OR[a]	95% CI[a]
Sex						
Women	824	49.7	115,466	48.5	Reference	
Men	835	50.3	122,451	51.5	1.52	1.38–1.68
Age (yr)						
18–49	4	0.2	106,828	44.9	14.29[b]	9.99–20.44
50–59	26	1.6	34,445	14.5	0.93[c]	0.92–0.94
60–69	119	7.2	27,167	11.4		
70–79	623	37.5	38,414	16.2		
80–89	741	44.7	26,514	11.1		
≥90	146	8.8	4,549	1.9		
District						
Gironde	441	26.6	89,011	37.4	Reference	
Charente-Maritime	415	25.0	57,288	24.1	1.11	0.96–1.27
Côte-d'Or	175	10.5	27,385	11.5	1.00	0.84–1.19
Haute-Vienne	265	16.0	25,772	10.8	1.18	1.01–1.39
Mayenne	363	21.9	38,461	16.2	1.20	1.05–1.39
Median household income of the canton of residence[d]						
High	1,212	73.1	191,418	80.5	Reference	
Low	447	26.9	46,499	19.5	1.16	1.04–1.31
Identification of cases						
Free healthcare for PD only	235	14.2	–	–		
Levodopa users only	704	42.4	–	–		
Free healthcare for PD and levodopa users	720	43.4	–	–		

[a]OR (95% CI) from a multivariable model including sex, age (linear and quadratic terms), district and median household income.
[b]OR for an increase of 5 yr in age (linear term).
[c]OR for an increase of 5 yr in age squared (quadratic term).
[d]High median household income was defined by grouping the four highest quintiles; low median household income was defined by the lowest quintile.
PD, Parkinson's disease; OR, odds ratio; CI, confidence interval.

In sex-stratified analyses, PD prevalence increased with FSFPC density in men (P-trend = 0.020), with a similar but weaker pattern among women (P-trend = 0.147); this association was not modified by sex (P-interaction = 0.256). No differences were noted between men and women for other farming types. The relation between PD prevalence and FSFPC density was not modified by age (P-interaction = 0.332). Among cases with FHC/PD (n = 995), disease duration was not associated with FSFPC density (P = 0.312).

In univariate analyses including farming types as dichotomous variables, FSFPC were the only ones associated with PD (Table 3). When all farming types were included in a multivariable fixed-effects model, FSFPC remained associated with PD. The semi-Bayes model yielded similar findings: PD prevalence was associated with FSFPC density and ORs increased with density (P-trend = 0.035). For farms specialized in market garden vegetables, prevalence decreased with increasing density (P-trend = 0.041), but the OR for the two top quintiles was not significantly <1.

Ninety-five (5.7%) cases used typical neuroleptics regularly. After excluding them, PD prevalence remained associated with FSFPC density [semi-Bayes $OR_{4+5 \text{ vs } 1+2+3 \text{ quintiles}}$ = 1.20 (1.06–1.35); P-trend = 0.046]. As part of a case-control study that included PD cases identified in the validation study (Supporting Information Fig. 1) and two controls per case matched on sex, age (±2 years), and district (randomly selected among all MSA affiliates; participation rate = 77%), PD was inversely associated with cigarette smoking (OR = 0.60); controls who lived in cantons with high FSFPC density were less often smokers than other controls (OR = 0.87). Based on these estimates, the OR for PD associated with FSFPC unadjusted for cigarette smoking was 1.02 times higher than an externally adjusted OR.

Discussion

Crude PD prevalence among MSA affiliates ≥18 years was 6.92/1,000. Using direct standardization (reference: total 2007 French population), the overall sex- and age-standardized prevalence was 3.01/1,000. Prevalence was higher in men than women and increased with age and FSFPC density (20% increased prevalence for persons living in cantons with high FSFPC density).

TABLE 2. Relation between the prevalence of Parkinson's disease in 2007 and the density of farming types in five French districts

Farming types	Quintiles	Range (per 100 km^2)	No. cases	No. unaffected	OR[a]	95%CI[a]	*P*
Cattle—dairying-rearing, and fattening combined	1	0–0	400	69,525	Reference		
	2	0–1	241	41,610	1.02	0.87–1.21	
	3	1–2	286	42,056	1.00	0.85–1.17	
	4	2–9	352	41,470	1.04	0.88–1.22	
	5	9–58	380	43,256	0.77	0.57–1.02	0.096
Field crops—grazing livestock combined	1	0–2	214	46,979	Reference		
	2	2–4	305	47,714	1.09	0.91–1.31	
	3	4–8	396	46,266	1.10	0.91–1.33	
	4	8–16	378	49,178	1.08	0.89–1.31	
	5	16–53	366	47,780	1.04	0.85–1.27	0.656
General field cropping	1	0–0	253	47,393	Reference		
	2	0–2	367	47,213	1.03	0.87–1.21	
	3	2–8	322	47,992	0.89	0.74–1.07	
	4	9–26	342	46,803	1.02	0.84–1.24	
	5	26–106	375	48,516	1.04	0.83–1.30	0.416
Mixed cropping	1	0–1	364	47,197	Reference		
	2	1–5	377	47,485	1.02	0.88–1.19	
	3	5–18	270	47,195	1.21	1.01–1.45	
	4	19–39	291	47,941	1.18	0.95–1.47	
	5	42–133	357	48,099	1.30	1.03–1.63	0.088
Mixed livestock, mainly granivores	1	0–0	627	101,356	Reference		
	2	0–1	225	33,757	0.98	0.84–1.15	
	3	1–1	216	34,027	0.98	0.84–1.15	
	4	1–4	273	34,616	0.97	0.82–1.14	
	5	4–27	318	34,161	0.96	0.70–1.32	0.813
Mixed livestock, mainly grazing livestock	1	0–3	252	47,093	Reference		
	2	3–5	288	47,524	1.14	0.95–1.36	
	3	5–9	301	47,050	0.96	0.80–1.15	
	4	10–15	389	47,689	1.08	0.90–1.29	
	5	15–61	429	48,561	1.05	0.88–1.26	0.808
Sheep, goats, and other grazing livestock	1	0–4	259	46,944	Reference		
	2	4–8	320	47,543	1.07	0.90–1.28	
	3	8–14	264	48,172	0.95	0.79–1.14	
	4	14–34	325	45,422	1.03	0.85–1.23	
	5	34–210	491	49,836	1.09	0.86–1.39	0.545
Specialist cattle—rearing and fattening	1	0–1	315	47,446	Reference		
	2	1–4	270	47,446	0.92	0.78–1.09	
	3	4–7	261	47,573	0.87	0.74–1.04	
	4	8–39	318	44,621	0.91	0.76–1.09	
	5	40–129	495	50,831	0.92	0.73–1.16	0.796
Specialist cereals, oilseed, and protein crops	1	0–1	369	46,798	Reference		
	2	2–4	300	48,067	0.94	0.80–1.11	
	3	4–8	285	45,636	1.10	0.91–1.33	
	4	8–14	347	48,814	1.13	0.94–1.35	
	5	14–81	358	48,602	1.07	0.88–1.29	0.389
Specialist dairying	1	0–1	246	46,638	Reference		
	2	1–3	317	45,886	1.19	1.00–1.41	
	3	3–6	281	49,449	1.00	0.84–1.20	
	4	6–19	393	47,214	1.17	0.98–1.39	
	5	19–331	422	48,730	0.95	0.74–1.21	0.251
Specialist fruits and permanent crops	1	0–0	315	47,232	Reference		
	2	0–1	314	47,625	1.05	0.90–1.24	
	3	1–2	377	47,398	0.99	0.85–1.16	
	4	2–4	343	47,437	1.19	1.01–1.39	
	5	4–31	310	48,225	1.21	1.02–1.43	0.008
Specialist granivores	1	0–0	392	65,577	Reference		
	2	0–1	278	43,030	1.01	0.86–1.18	
	3	1–1	287	43,064	0.98	0.84–1.14	

(*Continued*)

TABLE 2.,(*Continued*)

Farming types	Quintiles	Range (per 100 km^2)	No. cases	No. unaffected	OR[a]	95%CI[a]	*P*
	4	1–2	330	43,059	1.09	0.93–1.27	
	5	2–12	372	43,187	1.10	0.92–1.31	0.245
Specialist horticulture	1	0–0	371	46,397	Reference		
	2	0–1	348	47,854	1.00	0.86–1.16	
	3	1–2	366	48,341	1.06	0.90–1.24	
	4	2–3	283	47,047	1.06	0.89–1.25	
	5	3–47	291	48,278	1.08	0.92–1.27	0.391
Specialist market garden vegetables	1	0–0	541	68,420	Reference		
	2	0–1	315	42,175	0.98	0.85–1.13	
	3	1–2	307	42,204	1.11	0.94–1.31	
	4	2–6	254	42,145	1.03	0.86–1.23	
	5	6–349	242	42,973	0.97	0.83–1.15	0.506
Specialist vineyards	1	0–0	763	87,431	Reference		
	2	0–24	201	36,136	0.90	0.71–1.16	
	3	24–76	261	37,892	1.22	0.94–1.58	
	4	78–203	246	36,809	1.17	0.92–1.48	
	5	213–565	188	39,649	1.06	0.82–1.36	0.570
Various crops and livestock combined	1	0–3	362	46,839	Reference		
	2	3–5	366	47,118	1.01	0.86–1.19	
	3	5–10	301	48,398	1.20	1.01–1.43	
	4	10–16	311	47,078	1.11	0.91–1.34	
	5	16–44	319	48,484	1.17	0.97–1.41	0.203

[a]OR (95% CI) adjusted for sex, age (linear and quadratic terms), district, and median household income.
OR, odds ratio; CI, confidence interval.

Orchards (apples, pears, cherries, apricots, plums, and peaches), citrus, kiwi, shell and berry trees, and nurseries represent the main FSFPC activities. In 1989, FSFPC were the second farming type in terms of crop protection costs per hectare, after farms specialized in horticulture/vegetables.[7] In 1992, FSFPC (excluding nurseries and berry trees) used herbicides three times, fungicides five times, and insecticides nine times more than other farms (per hectare); they ranked first in terms of insecticide and herbicide use.[19] In 1998, although FSFPC (excluding nurseries) accounted for 1% of total French agricultural area, they represented 21% of the overall insecticide market. In addition, FSFPC are characterized in France by a specific technique of insecticide/fungicide application (air-assisted spraying),[20] which involves a higher loss of pesticides in the environment during application than non–air-assisted spraying. Besides, product loss takes place in a confined environment caused by the trees, and operator cabs for tractors are difficult to use. Therefore, there are important differences in type and amount of pesticides used for different farming types; pesticide applicators in FSFPC are potentially more exposed to pesticides, particularly to insecticides, than persons applying pesticides to other crops. For instance, farms specialized in market garden vegetables used five times less insecticides (per hectare) than FSFPC in 1992; vineyards ranked second in terms of insecticide use (per hectare), but they used half the amount of insecticides compared with FSFPC. Because the relation between farms specialized in market garden vegetables and PD became only apparent in the semi-Bayes multivariable model with borderline significance, we do not believe that too much emphasis should be placed on this finding.

Our finding of a higher PD prevalence in cantons with high FSFPC density is consistent with a study that reported an increased PD risk for orchards' workers[21] and with studies reporting an association between PD and insecticides[3,22–25] or increased levels of organochlorine insecticides in the brain[26] or serum[27] of PD patients. In addition, laboratory studies show that some insecticides are neurotoxic and may be involved in PD pathophysiology. Injection of the rotenone insecticide in rats reproduces several PD features.[28] In mice, dieldrin increases alpha-synuclein expression, alters dopamine metabolism, and increases markers of oxidative stress.[29] *In vitro* studies show that organochlorines, rotenone, and pyrethrenoids inhibit complex I of the mitochondrial respiratory chain.[30,31] Thus, insecticides may lead to oxidative stress,[32] proteasome dysfunction, alpha-synuclein aggregation, and cell death.[33]

We used a semi-individual design and assumed that same canton residents have the same exposure. Assuming that the agricultural census is comprehensive, this approach leads to Berkson exposure measurement error.[34] Exposure estimates were based on a large number of farms per canton [median = 317 (386)]. In addition, cantons are small spatial units and farming type depends on macroenvironmental factors (e.g., type of soil, climate, and agronomic history)

TABLE 3. Relation between the prevalence of Parkinson's disease in 2007 and the density of farming types in five French districts: univariate and multivariable models

	Univariate models[a]		Fixed-effectsmultivariable model[b]		Semi-Bayes multivariable model[c]	
Farming type	OR (95% CI)[d], 4+5 *vs* 1+2+3 quintiles	P^e	OR (95% CI)[d], 4+5 *vs* 1+2+3 quintiles	P^e	OR (95% CI)[d], 4+5 *vs* 1+2+3 quintiles	P^e
Cattle-dairying, rearing, and fattening combined	0.99 (0.86–1.13)	0.096	0.98 (0.82–1.17)	0.221	0.98 (0.84–1.14)	0.170
Field crops-grazing livestock combined	0.98 (0.88–1.10)	0.656	0.92 (0.80–1.06)	0.765	0.92 (0.82–1.05)	0.740
General field cropping	1.09 (0.95–1.24)	0.416	1.06 (0.89–1.28)	0.337	1.06 (0.90–1.25)	0.282
Mixed cropping	1.08 (0.92–1.27)	0.088	1.05 (0.85–1.29)	0.556	1.05 (0.87–1.26)	0.508
Mixed livestock— mainly granivores	0.97 (0.84–1.14)	0.813	0.91 (0.77–1.07)	0.839	0.91 (0.79–1.05)	0.818
Mixed livestock— mainly grazing livestock	1.04 (0.93–1.17)	0.808	1.03 (0.88–1.21)	0.998	1.03 (0.90–1.19)	0.998
Sheep-goats and other grazing livestock	1.03 (0.89–1.20)	0.545	1.02 (0.83–1.26)	0.414	1.02 (0.85–1.23)	0.359
Specialist cattle-rearing and fattening	0.97 (0.84–1.14)	0.796	0.99 (0.80–1.21)	0.927	0.99 (0.82–1.18)	0.919
Specialist cereals—oilseed and protein crops	1.08 (0.96–1.22)	0.389	0.99 (0.84–1.16)	0.457	0.99 (0.86–1.14)	0.407
Specialist dairying	1.06 (0.93–1.20)	0.251	1.09 (0.92–1.30)	0.913	1.09 (0.93–1.27)	0.895
Specialist fruits and permanent crops	1.18 (1.06–1.32)	0.008	1.22 (1.07–1.39)	0.062	1.21 (1.08–1.36)	0.035
Specialist granivores	1.09 (0.97–1.23)	0.245	1.09 (0.95–1.24)	0.296	1.09 (0.97–1.22)	0.239
Specialist horticulture	1.04 (0.94–1.16)	0.391	1.08 (0.94–1.23)	0.171	1.08 (0.96–1.21)	0.124
Specialist market garden vegetables	0.96 (0.86–1.08)	0.506	0.89 (0.77–1.03)	0.069	0.89 (0.78–1.02)	0.041
Specialist vineyards	1.09 (0.94–1.25)	0.570	0.94 (0.78–1.12)	0.718	0.94 (0.80–1.10)	0.686
Various crops and livestock combined	1.04 (0.91–1.18)	0.203	0.93 (0.80–1.09)	0.562	0.93 (0.81–1.07)	0.512

[a]Logistic regression model built for each farming type separately; adjusted for sex, age (linear and quadratic terms), district, and median household income.
[b]Logistic regression model including all farming types in the same model; adjusted for sex, age (linear and quadratic terms), district, and median household income.
[c]Semi-Bayes logistic regression model adjusted for sex, age (linear and quadratic terms), district, and median household income, with all farming types in the same model and assumed to be exchangeable with a prior variance of 0.345.
[d]OR for the effect of the two highest quintiles of the density of farming types compared to the three lowest quintiles.
[e]Test for trend across the five quintiles. OR, odds ratio; CI, confidence interval.

defined at a larger scale; therefore, between-worker variance of true exposure is not likely to be large. In logistic regression, Berkson error biases exposure-effect estimates toward the null, and under these conditions (large number of measures, small variance), it has a small impact on effect estimates.[35] The semi-individual design does not allow controlling for within-area confounding by unmeasured factors. The number of 208 cantons reduces the importance of this issue because it is unlikely that unmeasured factors covary with exposure across the entire range of areas.[36] An important feature of this design, however, is that because it uses individual information for the outcome and confounders, it is closer to individual-level than to ecological studies in terms of etiologic inference.[37]

We defined agricultural exposures using the 1988 census. We may have under- or overestimated exposure to some farming types in persons who worked before 1988. Because all analyses are age adjusted, error measurement applies similarly to cases and unaffected subjects in a given age group and leads to bias ORs toward the null. In addition, there was a strong correlation in farming types, including FSFPC, over time at the canton level. The surface of land devoted to FSFPC in the five districts has remained stable between the 1960s and today, and the association between PD and FSFPC was not modified by age, thus suggesting that the impact of age-dependent measurement error was not important.

We defined exposure based on the address of residence at the prevalence date and assumed that participants lived in the same cantons in 1988 and 2007. As part of a case-control study nested within our validation study, we collected residential history; a similar proportion of cases (78%) and controls (79%, $P = 0.614$) had the same postal code (smaller unit than cantons) in 2007 and 1988. For those who moved, the median distance between centroids of postal codes was small (16 km) and similar for cases and controls ($P = 0.752$). Therefore, exposure misclassification induced by residential mobility would bias association measures toward the null.

Strengths of our study include its population-based design and large size. We were able to use comprehensive and detailed agricultural data covering all farms in five districts, and agricultural characteristics were gathered independently of disease status.

Limitations of our study include case definition, without confirmation by a neurologist. It is, however, unlikely that diagnostic misclassification depends on farming types; therefore, bias is likely to be nondifferential and lead to ORs closer to the null. In the validation study, we found that our case definition had a fair performance; more importantly, its sensitivity/specificity did not depend on FSFPC density ($P = 0.980$). Finally, excluding patients who regularly used typical neuroleptics did not affect our findings.

Studies based on prevalent cases may suffer from prevalence-incidence bias.[38] There is no obvious reason that PD patients working in FSFPC would have a better disease course than other patients, and disease duration was not associated with FSFPC density.

We did not have cigarette smoking data but we adjusted for an indicator of socioeconomic level associated with cigarette smoking.[39] Cigarette smoking would act as a confounder if it was associated with FSFPC density. There was no strong association between these two variables in a case-control study nested within the validation study; therefore, the bias due to failure to adjust for smoking was negligible.

In conclusion, among persons working mainly in agriculture, we found a higher PD prevalence in cantons with high FSFPC density; this finding is consistent with reports of an association between PD and insecticides. We cannot rule out that PD may be associated with other farming types that our study did not identify due to variable power or measurement error for different farming types. Our findings suggest that using farming type as a surrogate for pesticide exposure or agricultural environment is feasible and provides interesting information and that further studies should be conducted among FSFPC workers to study in greater detail this relation and identify ways to reduce pesticide exposure.

Acknowledgments: The authors thank Drs Basile Chaix and Chantal Guihenneuc-Jouyaux for helpful statistical advice, the MSA physicians and personnel at each site (Drs Jacques Aimedieu, Daniel Albert, Catherine Bolut, Christophe Fuzeau, Virginie Gaussères, Maryline Grandjean, Jean Houssinot, Marine Jeantet, Bernard Ladépèche, Didier Menu, Omar Tarsissi; Joël Gourgues, Sandrine Nogues, Emilie Richard, and Pierre Vannier), the study interviewers (Véronique Dumay, Viviane Palleau, Frédérique Pellerin, Estelle Seguin, and Sophie Sinibaldi), the study neurologists (Irina Balaboi, Isabelle Benatru, Julien Dumurgier, Elsa Krim, and Danièle Ranoux), and Aïcha Soumaré for her help in coordinating the study.

References

1. Warner TT, Schapira AHV. Genetic and environmental factors in the cause of Parkinson's disease. Ann Neurol 2003;53:S16–S23.
2. Dick FD. Parkinson's disease and pesticide exposures. Br Med Bull 2006;79:219–231.
3. Brown TP, Rumsby PC, Capleton AC, Rushton L, Levy LS. Pesticides and Parkinson's disease—is there a link?Environ Health Perspect 2006;114:156–164.
4. Hatcher JM, Pennell KD, Miller GW. Parkinson's disease and pesticides: a toxicological perspective. Trends Pharmacol Sci 2008;29: 322–329.
5. Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. Neurology 1999;52:1214–1220.
6. Ministère de l'agriculture et de l'alimentation. Enquêtes—Recensement agricole—Pourquoi un recensement? 2009. Available at:http:// agreste agriculture gouv fr/enquetes/recensement-agricole/article/ pourquoi-un-recensement. Accessed February 8,2010.
7. FADN (The Farm Accountancy Data Network). 2009. Available at:http://ec.europa.eu/agriculture/rica/index_en.cfm. Accessed February 8, 2010.
8. Lix LM, Hobson DE, Azimaee M, et al. Socioeconomic variations in the prevalence and incidence of Parkinson's disease: a population-based analysis. J Epidemiol Community Health 2010;64: 335–340.
9. NISES (National Institute for Statistics and Economic Studies). 2007. Available at:http://www.insee.fr. Accessed February 8,2010.
10. Couris CM, Colin C, Rabilloud M, Schott AM, Ecochard R. Method of correction to assess the number of hospitalized incident breast cancer cases based on claims databases. J Clin Epidemiol 2002;55:386–391.
11. Zocchetti C, Consonni D, Bertazzi PA. Relationship between prevalence rate ratios and odds ratios in cross- sectional studies. Int J Epidemiol 1997;26:220–223.
12. Greenland S. Avoiding power loss associated with categorization and ordinal scores in dose-response and trend analysis. Epidemiology 1995;6:450–454.
13. Momoli F, Abrahamowicz M, Parent ME, Krewski D, Siemiatycki J. Analysis of multiple exposures: an empirical comparison of results from conventional and semi-Bayes modeling strategies. Epidemiology 2010;21:144–151.
14. Thomas DC. The problem of multiple inference in identifying point-source environmental hazards. Environ Health Perspect 1985;62:407–414.
15. Greenland S. Hierarchical regression for epidemiologic analyses of multiple exposures. Environ Health Perspect 1994;102(suppl 8): 33–39.
16. De Roos AJ, Poole C, Teschke K, Olshan AF. An application of hierarchical regression in the investigation of multiple paternal occupational exposures and neuroblastoma in offspring. Am J Ind Med 2001;39:477–486.
17. Bronstein J, Carvey P, Chen H, et al. Meeting Report: consensus statement—Parkinson's disease and the environment: Collaborative on Health and the Environment and Parkinson's Action Network (CHE PAN) Conference 26–28 June 2007. Environ Health Perspect 2009;117:117–121.
18. Greenland S. Bias analysis, In: Rothman KJ, Greenland S, Lash TL, eds. Modern epidemiology, Third ed. Philadelphia: Lippincott Williams & Wilkins; 2008, p 345–380.
19. ECPA (European Crop Protection Association). Agriculture and Environment: consumption of pesticides. 2009. Available at: http://nui.epp.eurostat.ec.europa.eu/nui/show.do?dataset=env_ag_pest&lang=en. Accessed February 8,2010.
20. French National Institute for Agricultural Research. Pesticides, agriculture et environnement: rapport d'expertise [in French]. 2005. Available at: http://www.inra.fr/l_institut/expertise/expertises_realisees/pesticides_rapport_d_expertise. Accessed February 8, 2010.
21. Hertzman C, Wiens M, Bowering D, Snow B, Calne D. Parkinson's disease: a case-control study of occupational and environmental risk factors. Am J Ind Med 1990;17:349–355.
22. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 1998;50:1346–1350.
23. Kamel F, Tanner C, Umbach D et al. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. Am J Epidemiol 2007;165:364–374.
24. Hancock D, Martin E, Mayhew G, et al. Pesticide exposure and risk of Parkinson's disease: a family-based case-control study. BMC Neurol 2008;8:6.
25. Elbaz A, Clavel J, Rathouz PJ, et al. Professional exposure to pesticides and Parkinson disease. Ann Neurol 2009;66:494–504.
26. Corrigan FM, Wienburg CL, Shore RF, Daniel SE, Mann D. Organochlorine insecticides in substantia nigra in Parkinson's disease. J Toxicol Environ Health A 2000;59:229–234.
27. Waller LA, Gotway CA.Analyzing public heath data. Applied spatial statistics for public health data. New York: Wiley-Interscience; 2004. p 7–37.
28. Sherer TB, Kim JH, Betarbet R, Greenamyre JT. Subcutaneous rotenone exposure causes highly selective dopaminergic degeneration and alpha-synuclein aggregation. Exp Neurol 2003; 179: 9–16.
29. Hatcher JM, Richardson JR, Guillot TS, et al. Dieldrin exposure induces oxidative damage in the mouse nigrostriatal dopamine system. Exp Neurol 2007;204:619–630.
30. Schuh RA, Kristian T, Gupta RK, Flaws JA, Fiskum G. Methoxychlor inhibits brain mitochondrial respiration and increases hydrogen peroxide production and CREB phosphorylation. Toxicol Sci 2005;88:495–504.

31. Gassner B, Wuthrich A, Scholtysik G, Solioz M. The pyrethroids permethrin and cyhalothrin are potent inhibitors of the mitochondrial complex I. J Pharmacol Exp Ther 1997;281: 855–860.

32. Drechsel DA, Patel M. Role of reactive oxygen species in the neurotoxicity of environmental agents implicated in Parkinson's disease. Free Radic Biol Med 2008;44:1873–1886.

33. Kanthasamy AG, Kitazawa M, Kanthasamy A, Anantharam V. Dieldrin-induced neurotoxicity: relevance to Parkinson's disease pathogenesis. Neurotoxicology 2005;26:701–719.

34. Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. Occup Environ Med 1998;55:651–656.

35. Kim HM, Yasui Y, Burstyn I. Attenuation in risk estimates in logistic and Cox proportional-hazards models due to group-based exposure assessment strategy. Ann Occup Hyg 2006;50: 623–635.

36. Navidi W, Thomas D, Stram D, Peters J. Design and analysis of multilevel analytic studies with applications to a study of air pollution. Environ Health Perspect 1994;102:25–32.

37. Kunzli N, Tager IB. The semi-individual study in air pollution epidemiology: a valid design as compared to ecologic studies. Environ Health Perspect 1997;105:1078–1083.

38. Ellenberg JH. Differential postmorbidity mortality in observational studies of risk factors for neurologic disorders. Neuroepidemiology 1994;13:187–194.

39. Diez Roux AV, Merkin SS, Hannan P, Jacobs DR, Kiefe CI. Area characteristics, individual-level socioeconomic indicators, and smoking in young adults: the coronary artery disease risk development in young adults study. Am J Epidemiol 2003;157:315–326.