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

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**ABSTRACT**

**Background:** 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.

**Methods:** 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.

**Results:** 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).

**Conclusion:** 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.

**KEYWORDS**: 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 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; 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*, *Mayenne*) that 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-containing medication in 2007; (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 levodopa delivery in the six 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 (Supplemental Figure 1). All subjects with at least one delivery of levodopa, 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 legs syndrome (RLS); treatment was discontinued after ≤1 month; there was a clear history of drug-induced parkinsonism) in order to confirm PD using standardized criteria.[5] Those using APDs rarely prescribed for PD (piribedil, amantadine, 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 levodopa and/or had FHC/PD (sensitivity=91%); of 794 persons without PD: 122 used levodopa 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] km²; median number of affiliates=904 [1 094]).

The following information was available at the individual level: birth year, sex, 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.

We first built separate models for each farming type, while adjusting for covariates (age, sex, district, income); we adjusted for district in order 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, 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 (≥3 deliveries between 1/1/2007-6/1/2007) 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, Inc., Cary, North Carolina) and Stata 10 (StataCorp LP, College Station, Texas). *S*ignificance level was considered at the two-sided 0.05 level.

## RESULTS

Among 239 576 MSA affiliates ≥18 years in five districts, we identified 1 659 PD cases (Table 1). Cases were older (median age=80.6 [9.8]) than unaffected subjects (53.5 [36.1]; 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.

Supplemental 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 (Supplemental Table 2).

### PD prevalence

PD prevalence among affiliates ≥18 years old 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 ≥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 to the French population (Supplemental Table 1). Prevalence ≥65 years was 19.64/1,000, and 16.86/1,000 after standardization (reference: 2007 French population ≥65 years).

Prevalence increased with age and was higher in men than women (Table 1; Supplemental Figure 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 (interaction, *P*=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; mixed cropping) but without significant trends.

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 $OR_{4+5\ vs\ 1+2+3\ quintiles}$=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 (Supplemental Figure 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).

Orchards (apples, pears, cherries, apricots, plums, 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, 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, while 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. There are therefore 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 to 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 macro-environmental factors (e.g., type of soil, climate, agronomic history) 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 towards 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 over estimated exposure to some farming types in persons who worked <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 towards 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 nowadays, 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 towards 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 non-differential 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.

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**TABLES AND FIGURES LEGENDS**

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

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

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

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

| Characteristics | | Affected subjects (No.=1 659) | | Unaffected subjects (No.=237 917) | | Multivariable logistic model | |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | OR[a] | 95% CI[a] |
| Sex | Women | 824 | 49.7 | 115 466 | 48.5 | Ref. | |
| | Men | 835 | 50.3 | 122 451 | 51.5 | 1.52 | 1.38-1.68 |
| Age | 18 to 49 years | 4 | 0.2 | 106 828 | 44.9 | 14.29[b] | 9.99-20.44 |
| | 50 to 59 years | 26 | 1.6 | 34 445 | 14.5 | 0.93[c] | 0.92-0.94 |
| | 60 to 69 years | 119 | 7.2 | 27 167 | 11.4 | | |
| | 70 to 79 years | 623 | 37.5 | 38 414 | 16.2 | | |
| | 80 to 89 years | 741 | 44.7 | 26 514 | 11.1 | | |
| | ≥ 90 years | 146 | 8.8 | 4 549 | 1.9 | | |
| District | Gironde | 441 | 26.6 | 89 011 | 37.4 | Ref. | |
| | 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 | Ref. | |
| | Low | 447 | 26.9 | 46 499 | 19.5 | 1.16 | 1.04-1.31 |
| Identification of cases | Free heathcare for PD only | 235 | 14.2 | -- | -- | | |
| | Levodopa users only | 704 | 42.4 | -- | -- | | |
| | Free heath care for PD and levodopa users | 720 | 43.4 | -- | -- | | |

PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; Ref., reference category.

[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 years in age (linear term).

[c] OR for an increase of 5 years 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.

**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 (/ 100 km²) | No. cases | No. unaffected | OR[a] | 95% CI[a] | P-trend |
|---|---|---|---|---|---|---|---|
| Cattle-dairying, rearing and fattening combined | 1 | 0-0 | 400 | 69 525 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 |

**Table 2 follows**

| Farming types | Quintiles | Range (/100 km²) | No. cases | No. unaffected | OR[a] | 95% CI[a] | P-trend |
|---|---|---|---|---|---|---|---|
| Specialist cereals, oilseed and protein crops | 1 | 0-1 | 369 | 46 798 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 2 | 0-1 | 278 | 43 030 | 1.01 | 0.86-1.18 | |
| | 3 | 1-1 | 287 | 43 064 | 0.98 | 0.84-1.14 | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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 | Ref. | | |
| | 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; Ref., reference category.

**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*

| Farming type | Univariate models[a] | | Fixed-effects multivariable model[b] | | Semi-Bayes multivariable model[c] | |
|---|---|---|---|---|---|---|
| | OR (95% CI)[d] 4+5 vs 1+2+3 quintiles | P-trend[e] | OR (95% CI)[d] 4+5 vs 1+2+3 quintiles | P-trend[e] | OR (95% CI)[d] 4+5 vs 1+2+3 quintiles | P-trend[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, 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.