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Pesticides expenditures by farming type and incidence of Parkinson disease in farmers: a French nationwide study

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ABSTRACT

Background: Professional pesticides exposure is associated with PD risk, but it remains unclear whether specific products, which strongly depend on farming type, are specifically involved. We performed a nationwide ecological study to examine the association of pesticides expenditures for the main farming types with PD incidence in French farmers

Methods: We used the French National Health Insurance database to identify incident PD cases in farmers (2010-2015). We combined data on pesticides expenditures with the agricultural census to compute pesticides expenditures for nine farming types in 2000 in 3,571 French cantons. The association between pesticides expenditures and PD age/sex standardized incidence was examined using multilevel Poisson regression, adjusted for smoking, neurologists' density, and deprivation index.

Results: 10,282 incident PD cases were identified. Cantons with the highest pesticides expenditures for vineyards without designation of origin were characterized by 16% (95% CI=6-28%) higher PD incidence (p-trend corrected for multiple testing=0.006). This association was significant in men and older farmers. There was no association with pesticides expenditures for other farming types, including vineyards with designation of origin.

Conclusions: PD incidence increased significantly with pesticides expenditures in vineyards without designation of origin characterized by high fungicide use. This result suggests that agricultural practices and pesticides used in these vineyards may play a role in PD and that farmers in these farms should benefit from preventive measures aiming at reducing exposure. Our study highlights the importance of considering farming type in studies on pesticides and PD and the usefulness of pesticides expenditures for exposure assessment.

INTRODUCTION

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and the neurological disease with the largest increase in age-standardized prevalence between 1990-2015 (GBD, 2017). PD etiology is considered as multifactorial, and involves both genetic susceptibility and environmental factors (Ascherio and Schwarzschild, 2016).

Among environmental risk factors, professional pesticides exposure is associated with increased PD risk, but it remains unclear whether specific products are more specifically involved due to their large variety and changes over time (van der Mark et al., 2012). Some studies have highlighted herbicides (e.g., rotenone, paraquat), insecticides (e.g., organochlorines), and fungicides (e.g., maneb) (Nandipati and Litvan, 2016; Tanner et al., 2011). Most studies used self-reported information to assess exposures, with different levels of detail ranging from a simple occupational history to information on pesticide names, frequency of use, or protective equipment (Elbaz et al., 2009; Moisan et al., 2015; Tanner et al., 2011). Self-report is prone to recall bias and can induce exposure misclassification and bias association estimates for several reasons (Blair et al., 2011): PD mainly occurs after retirement, and farmers have used a large variety of pesticides over a long period of time, often in association, making it also difficult to disentangle their effect; in addition, PD is characterized by some degree of cognitive impairment that may lead to differential recall (Bocanegra et al., 2014). One meta-analysis showed that studies that used job titles in combination with expert judgment or job-exposure matrices yielded stronger associations than studies based on self-reported exposures, thus suggesting that exposure misclassification may play a role (van der Mark et al., 2012).

Few studies used pesticides expenditures to assess pesticide exposure. This approach is not hampered by recall bias and allows to examine dose-response relationships. It was used to study congenital abnormalities (Froes Asmus et al., 2017; Markel et al., 2015; Schwartz and LoGerfo, 1988), human reproductive system disturbances (Koifman et al., 2002), and cancers (Chrisman Jde et al., 2009). To the best of our knowledge, only three studies used this approach to examine the association of pesticides with PD. In rural areas of Quebec (Canada), PD prevalence was correlated with pesticide sales (Barbeau et al., 1987). Based on California (US) pesticide use reporting data, PD mortality was higher in counties with highest pesticide use per square mile (Ritz and Yu, 2000). In Andalusia (Spain), districts with high pesticide sales were characterized by increased PD prevalence (Parron et al., 2011). These studies

focused on the general population rather than on farmers or agricultural workers. In addition, expenditures and pesticides types differ considerably by type of crops. For instance, vineyards mainly use fungicides, while cereal crops use both fungicides, herbicides, and insecticides, but with lower frequency and intensity. Therefore, crops can contribute to an indirect assessment of exposure to pesticides (Kab et al., 2017b; Moisan et al., 2011b). However, previous studies did not take into account the target of pesticides.

France is the first European consumer of pesticides, with expenditures of ~3 billion euros in 2000 (Butault et al., 2011). After accounting for the number of hectares cultivated, it ranks fourth, behind Portugal, The Netherlands, and Belgium (Cemagref, 2011). We performed a nationwide ecological study to examine the association between pesticides expenditures for the main farming types in 2000 with PD incidence (2010-2015) in French farmers.

MATERIALS AND METHODS

PD cases

The French National Health Insurance database (*Système National des Données de Santé*, SNDS) contains individual-level information on health care reimbursements and sociodemographic characteristics, including age, sex, place of residence, and health insurance scheme, for >97% of the French population. Information on health care reimbursements include consultations, medical tests, and drug claims. The latter include type of drugs, purchase date, number of boxes, medication dosage, and specialization of the prescribing physician.

We identified all persons with at least one antiparkinsonian drug reimbursement between 2009-2015, and excluded those <20y, women <50y reimbursed for bromocriptine alone (lactation suppression), persons only on anticholinergics and neuroleptics (drug-induced-parkinsonism), and those not living in metropolitan France. We used an algorithm to identify PD cases that was previously validated against a neurological diagnosis (Moisan et al., 2011a). The validation study was based on 1,114 participants (320 with PD, 794 without PD) who used antiparkinsonian drugs. This algorithm allows to estimate the probability that a person is treated for PD based on the annual pattern of antiparkinsonian drugs use (levodopa, dopamine agonists, selegiline/rasagiline, pramipexole, anticholinergics, COMT inhibitors), proportion of time treated, number of neurologist/general practitioner's visits, and sex. We used the Youden index to identify the probability cutoff that maximized sensitivity (92.5%) and specificity (86.4%) of the algorithm; antiparkinsonian drug users for whom the algorithm estimated a probability above this cutoff were considered as having PD. Incident cases a given year were persons identified by the algorithm that year and who did not have antiparkinsonian drugs reimbursements the previous year.

For these analyses, we identified persons affiliated with the *Mutualité Sociale Agricole* (MSA). It guarantees health insurance (including after retirement) for farmers, other agricultural workers, and their spouses if unemployed. In 2015, the MSA covered ~3.3 million people (5% of the French population; 42% farmers, 58% workers). The workers group is a heterogeneous one that includes farm workers (38%) and workers in agricultural cooperatives (16%), administrations (28%) and workers in other areas such as forestry work and green spaces maintenance (18%) (MSA, 2016). A MSA 2010 survey reported that 25% of workers group (farm, cooperatives, administration and others workers) was exposed to

pesticides, with around less 50% for agricultural and of green spaces maintenance workers (MSA, 2015). We were able to distinguish farmers from workers, but different types of workers could not be differentiated. Therefore, as the workers group is very heterogeneous, we restricted our analyses to farmers (i.e., farm owners).

Agricultural census

We used data from an exhaustive agricultural census carried out in France by the Ministry of Agriculture that takes place every ~10y (Agreste, 2014). Since data on pesticides expenditures were available starting on year 2000, we used the 2000 agricultural census to allow for a latency period ≥ 10 y between exposure assessment and PD incidence.

In the European Union, farms are classified according to their main farming type. A farm is considered to be specialized in a type of farming, if the standard gross production related to that type exceeds two thirds of the farm's total standard gross production (Insee, 2016). The standard gross production is the production value per hectare or animal head. This classification includes 17 farming types (cereals, general crops, fresh vegetables, flowers and ornamental plants, vineyard with designation of origin, vineyards without designation of origin, permanent crops, mixed crops, cattle milk, beef cattle, mixed cattle, sheep and goats, granivore, mixed livestock with herbivore orientation, mixed livestock with granivorous orientation, general crops and herbivore, mixed crops and mixed livestock).

Data were available at the canton-level and included the number of farms for each farming type and the corresponding area or number of animals. Data on pesticide use are not collected in the agricultural census.

Annual pesticides expenditures

Data came from the Farm Accountancy Data Network (Agreste, 2018). Since 2000, member states of the European Union carry out an annual survey on a sample of representative farms in terms of region, farming type, and economic size. Although farms of small economic size are not included, the sample covers about 90% of the total agricultural area and agricultural production after sampling weights are taken into account. Data include detailed information on location (region), agricultural activities, and economic and financial information (e.g., value of production of the different crops, sales, purchases) that are used to define farming type (as in the agricultural census). For each farm, pesticides expenditures are available

globally, i.e., they are not available for each crop. As for the agricultural census, we used data for France in 2000.

Pesticides expenditures for farms specialized in livestock were considerably lower than for other farming types (less than 100 Euros per hectare) and were similar for different types of animals; in order to reduce the number of variables included in the models from 17 to 9 farming types, we grouped together all types of livestock (cattle rearing – specialist dairying; cattle rearing and fattening; cattle-dairying, rearing and fattening combined; sheep, goats and other grazing livestock; granivores; mixed livestock, mainly grazing livestock; mixed livestock, mainly granivores; field crops-grazing livestock combined; various crops and livestock combined). Alternatively, the two types of vineyards were kept separately because their expenditures were very different. According to European rules, vineyards with a designation of origin are those that originate in a specific geographical location and produce wine whose qualities and characteristics are essentially due to their region of provenance and production method. European wine producing countries have established legal frameworks to guarantee the quality and origin of these wines. Vineyards without a designation of origin correspond to other vineyards.

Annual pesticides expenditures for each farming type in French cantons were determined in two different ways:

- The first approach (“regional expenditures”) was based on expenditures at the regional level. In 22 administrative regions, we determined the weighted median pesticides expenditures per hectare for 9 farming types (cereals, general crops, fresh vegetables, horticulture, vineyards with a designation of origin, vineyards without designation of origin, permanent crops, mixed crops, livestock). Medians were calculated in each region when there were ≥ 10 farms with the corresponding activity; if there were < 10 farms, we used the median national value. Expenditures were based on regional data for 94.2% of the farms, and on national data for the remaining 5.8%. We then estimated pesticides expenditures in farms from French cantons for each farming type by multiplying the corresponding median expenditures per hectare by the average agricultural area of these farms in each canton.

- In a second approach (“national expenditures”), we took into account farms’ size as it can influence pesticides expenditures per hectare. For each farming type, we first performed a weighted linear regression of pesticides expenditures on the agricultural area of the farms. These analyses were performed at the national level in order to include a sufficient number of farms after removing outliers (Blatná, 2006). We then used the intercept and slope of these models to calculate the average pesticides expenditures per hectare for each farming type in

French cantons, using the agricultural area of these farms as explanatory variables. These values were again multiplied by the average agricultural area of each type of farming to obtain average pesticides expenditures per farm for each type of farming in each canton.

For both approaches, the annual average total pesticides expenditures by farms from a canton was calculated by summing expenditures for each type of farming (expenditures multiplied by the agricultural area of these farms) divided by the total number of farms in the canton.

PD incidence rates and standardized incidence ratios

The number of incident cases (corrected for sensitivity/specificity of the algorithm) was computed by sex/5y age groups in each canton according to the place of residence at the time of the first antiparkinsonian drug reimbursement (Couris et al., 2002). In 2000, there were 3,689 cantons in France, with an average area of 149km². Between 2010-2015, the average number of farmers in each canton was of 261. Since 118 out of 3,689 cantons had no agricultural area, analyses were therefore restricted to 3,571 cantons.

We estimated the number of farmers and the corresponding person-years (by sex/5y age groups), based on the number of farmers with any health-related expense. Analyses were restricted to persons ≥ 55 y because we previously showed that most persons in this age group have at least one health expense per year (correlation with the true number of person-years=0.97; $P < 0.001$). Below this age, health contacts may be less frequent which would lead to overestimate incidence (Kab et al., 2017a). In addition, PD is very rare below that age. Incidence rates were computed by dividing the number of incident cases by the corresponding number of person-years.

To estimate age/sex standardized PD incidence ratios (SIR) in each canton, we used indirect standardization (reference=age/sex-specific French incidence rates).

Statistical analysis

We examined the association between pesticides expenditures and PD incidence among farmers using multilevel Poisson regression with a random intercept per canton and estimated incidence rate ratios (IRR) and 95% confidence intervals (IC). Analyses were performed separately for regional and national expenditures.

We first examined the association of total expenditures with PD incidence. We then included pesticides expenditures for different farming types. Expenditures were included in

the models as categorical variables (quintiles); cantons without any expenditure were included in the first quintile. We examined dose-effect relations and tested linear trends by including ordinal variables whose levels were the medians of quintiles divided by 1-standard deviation (SD). Models were adjusted for smoking, neurologists' density, and deprivation (covariates described in Supplementary methods). All covariates were defined at the canton level.

Sensitivity analyses stratified by sex were performed, because men and women have different exposure levels. Second, we stratified analyses by median age at PD incidence (55-74/ \geq 75y) because PD etiology may depend on age. For males and the younger group, we used Poisson regression without random intercept because of small inter-canton variability. We tested interactions by comparing RRs for 1-SD (Altman and Bland, 2003). Third, to rule out a potential bias due to under-ascertainment of PD in the oldest age group, we restricted the analyses to the 75-89 years age group. Fourth, we combined the two types of vineyards in a single variable.

Third, models were adjusted for UV-B and vitamin D supplementation. Fourth, as the proportion of cantons without incident PD cases was $>20\%$ in some strata, we used binomial negative regression to estimate IRRs.

To take into account multiple comparisons, we used the false discovery rate (FDR) and computed p-values adjusted for multiple testing (q-values) for the trend and interaction tests (Benjamini and Hochberg, 1995; Storey, 2003).

All tests were two-sided and p-values <0.05 considered significant. Statistical analyses were conducted with SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The algorithm identified 17,322 persons as newly treated for PD and affiliated with the *Mutualité Sociale Agricole*. After correction for the sensitivity and specificity of the prediction model, we identified 14,661 incident PD cases. Of these, 200 did not live in metropolitan France, 417 were <55 y, 3,740 were workers, and not farmers, and 22 lived in cantons without agricultural area. Finally, we retained for our analyses, 10,282 incident PD cases among farmers aged ≥ 55 y. There were no incident cases in 654 (18.3%) cantons and the median number of cases in the remaining 2,917 cantons was 2.5 (range=1-24). **Supplementary Table 1** presents incidence rates. **Supplementary Figure 1** shows the spatial SIRs distribution.

There was considerable heterogeneity in median pesticides expenditures per hectare across farming types (**Table 1**): the five types with largest expenditures were fresh vegetables, vineyards with designation of origin, permanent crops, horticulture, and vineyards without designation of origin. **Supplementary Table 2** presents median regional expenditures. The regression coefficients from the regression of national pesticides expenditures per hectare on the area devoted to farming types (**Table 1**) show that expenditures decreased significantly when the area increased for fresh vegetables, vineyards with designation of origin, permanent crops, and vineyards without designation of origin, and increased for cereals and livestock.

Figure 1 show the spatial distribution of total expenditures and expenditures for each farming type. Correlations between expenditures for each farming type were generally weak (**Supplementary Table 3**), except moderate correlations between livestock and cereals ($r=0.482$) and between the two types of two vineyards ($r=0.459$).

Figure 2 presents the associations of total pesticides expenditures with PD incidence in French farmers (regression coefficients in **Supplementary tables 4-5**); **Supplementary table 6** provides cutoffs of quintiles. Using both approaches (regional/national expenditures), total expenditures were not associated with PD incidence neither overall nor in stratified analyses.

Regarding expenditures for farming types, PD incidence increased with increasing expenditures for vineyards without designation of origin, both using regional (q -trend=0.006, **Figure 3**) and national (q -trend=0.014, **Figure 4**) expenditures; regression coefficients are shown in **Supplementary tables 4-5**. PD incidence was 16% higher ($IRR_{Q5}=1.16$, 95% CI=1.06-1.28) in the fifth quintile compared to the lowest for regional expenditures, and 14% higher ($IRR_{Q5}=1.14$, 95% CI=1.04-1.25) for national expenditures. Expenditures for other farming types were not associated with PD.

The relation between regional/national pesticides expenditures and PD among farmers was not modified significantly by sex (q -values for interaction ≥ 0.396 ; **Supplementary tables 4-5**). In sex-stratified analyses, however, the association of expenditures for vineyards without designation of origin and PD was close to significance in men (regional expenditures, $IRR_{Q5}=1.18$, 95% CI=1.04-1.33, q -trend=0.067), but not in women ($IRR_{Q5}=1.11$, 95% CI=0.97-1.27). No tests of linear trend were significant despite some positive associations of PD with mixed crops in men and livestock in women. There was also an inverse association in women for the fifth quintile of national expenditures for vineyards with designation of origin.

Age did not modify the association between regional/national expenditures and PD (q-values for interaction ≥ 0.27 ; **Supplementary tables 4-5**). In age-stratified analyses, there was a positive association for younger farmers in the fourth/fifth quintiles without linear trend. Regarding expenditures for vineyards without designation of origin, although the interaction was not significant, a significant association was seen in the older group only (regional expenditures: $IRR_{Q5}=1.18$, 95% CI=1.06-1.31, q-trend=.006; national expenditures: $IRR_{Q5}=1.16$, 95% IC=1.05-1.28, q-trend=.014), while the association in the younger age groups was weaker and not statistically significant (regional expenditures: $IRR_{Q5}=1.09$, 95% CI=0.87-1.35, q-trend=.866; national expenditures: $IRR_{Q5}=1.05$, 95% IC=0.85-1.29, q-trend=.814). Finally, PD incidence was higher in younger farmers in the top quintile of national expenditures for livestock, but without a significant trend. A sensitivity analysis restricted to the 75-89 years age group showed the same positive association between vineyards without designation of origin and PD (regional expenditures: $IRR_{Q5}=1.17$, 95% IC=1.05-1.30, q-trend=.03; national expenditures: $IRR_{Q5}=1.14$, 95% IC=1.03-1.27, q-trend=.058). Analyses combining the two types of vineyards did not show a significant association with PD (**Figure S2**).

Analyses using negative binomial regression or adjusted for UV-B or vitamin D yielded consistent findings (data not shown).

DISCUSSION

Pesticides expenditures in 2000, regardless of farming type, were not associated with PD incidence in French farmers between 2010-2015. However, after distinguishing farming types, cantons with the highest expenditures for vineyards without designation of origin were characterized by a significantly higher PD incidence with a significant trend. In stratified analyses, this association was significant in men and above 75y.

Two previous French studies also highlighted vineyards in relation to PD using alternative exposure assessment methods (Kab et al., 2017b; Moisan et al., 2015). In a nationwide ecologic study, PD incidence in the general population increased with the area devoted to agriculture, in particular in cantons with high vineyards density (Kab et al., 2017b). This study ascertained incident PD cases from the general population between 2010-2012 and analyses were conducted overall and after excluding MSA members (farmers and workers). It focused on environmental exposure rather than professional exposure using the area of crops in the cantons of residence as a proxy. In a case-control study (incident and prevalent cases identified in 2006-2007), farmers from 5 regions were interviewed about the crops they had grown and whether they had used pesticides for each of them; farmers who used pesticides for vineyards were at increased PD risk, without association for other crops (Moisan et al., 2015). In this study, occupational exposure was measured by in-person interview and PD cases were determined by neurological examination to confirm the diagnosis. Our findings are consistent with these studies and extend them to all incident PD cases in French farmers between 2010-2015. In our study, when the two vineyards were combined, the association was no longer significant. The large difference in expenditures between the two types of vineyards explains this finding: 33% of cantons with pesticides expenditures for vineyards without designation of origin were in the first quintile, compared to 5% for vineyards with designation of origin, and few vineyards without designation of origin were included in the fifth quintile that mostly included vineyards with designation of origin.

Our findings demonstrate the importance of considering farming types to study the association between pesticides and PD. Type of products as well as the frequency, intensity, and methods of applications strongly depend on type of crops. Surveys on farming practices show major differences across agricultural activities, with higher pesticide use for vineyards, fresh vegetables, fruit or permanent crops, and flowers and ornamental plants than for other crops (Butault et al., 2011). In France, while vineyards represented ~3% of agricultural land

in 2000, they accounted for 20% of pesticides sold, of which fungicides represented 80% (Aubertot et al., 2005). In 2005, a wide range of active substances were used in vineyards: >40 insecticides and fungicides and >20 herbicides (Aubertot et al., 2005). Fungicides are the most widely used pesticides in vineyards, and their association with PD has previously been reported, both by toxicological studies showing a role of some types of fungicides (dithiocarbamates: maneb, ziram; carbamates: benomyl), and by epidemiological studies (Cao et al., 2018; Fitzmaurice et al., 2014; Pouchieu et al., 2017; Wang et al., 2011). A French case-control study in farmers reported an association between PD and duration of exposure to fungicides (Moisan et al., 2015).

A novelty of our study is the distinction between vineyards with and without designation of origin. There are important differences in their practices. Pesticides expenditures per hectare were ~1.5 times greater for vineyards with designation of origin than for those without (Agreste, 2018; Aubertot et al., 2005). Fighting against pests is a quality guarantee for vineyards with designation of origin, which leads them to increase the number of applications. Moreover, the level of technical supervision is higher for vineyards with designation of origin than for those without and it influences methods of application (e.g., use of protective equipment), but also the type of products used (Aubertot et al., 2005). In addition, since the turnover is higher for vineyards with designation of origin, more expensive pesticides are used, while mineral products (e.g., sulfur, arsenic, copper) are less likely to be used (Viel et al., 1998). One study showed that serum heavy metals (lead, arsenic, nickel, zinc, manganese, copper) levels were much higher in vineyard farmers than unexposed individuals (Rocha et al., 2015). Heavy metals are known to exert neurotoxic effects, and some pesticides contain metals; for instance, maneb, a fungicide that has been associated with PD (Bocchetta and Corsini, 1986; Nandipati and Litvan, 2016), includes manganese. Exposure to manganese is associated with parkinsonism, copper is implicated in oxidative stress, and zinc affects lysosomal function (Montes et al., 2014; Tuschl et al., 2013). One study showed higher blood levels of copper and zinc in PD patients than controls (Hozumi et al., 2011). However, in epidemiological studies, results on the association between metals and PD are heterogeneous. Available studies do not support association of welding or manganese exposure with PD (Mortimer et al., 2012; Wirdefeldt et al., 2011). Other studies are not in favor of an association with copper or zinc (Gorell et al., 1997; Lai et al., 2002). Alternatively, one ecological study showed higher PD incidence rates in US counties with high copper or manganese air concentrations (Willis et al., 2010). Finally, the median area of vineyards without designation of origin (2 ha, interquartile range (IQR)=0.6-8.3) is much

smaller than for those with designation (12 ha, IQR=5.6-20.5). Smaller farms are less mechanized, and involve more applications with backpack sprayers (rather than with tractors), leading to greater exposure during pesticide preparation/spraying. In addition, according to the agricultural census, vineyards with designation of origin employed more full-time workers (median=1.7, IQR=1.4-2.2) than those without (median=0.9, IQR=0.6-1.3). Therefore, farmers in vineyards with designation of origin may be less exposed than those without, in particular if workers engage in pesticides applications. An association between pesticides expenditures in vineyards with designation of origin and PD may in fact exist but we were unable to identify it because we only included farmers and not farm workers.

There were no significant differences between men and women for any farming type, but sex-stratified analyses showed that the association with vineyards without designation of origin was restricted to men with a weaker non-significant association in women. The weaker association and lack of significance in women may have several possible explanations: first, PD incidence is lower in women than men and there is less variability in PD incidence across cantons in women than men (data not shown); second, women in this study represent a heterogeneous group that includes farmers and spouses of farmers; third, there are sex-differences in exposure levels resulting from differences in agricultural tasks, with pesticides mainly prepared/sprayed by men (Elbaz et al., 2009; García, 2003; Moisan et al., 2015). However, the difference between men and women is not large and not statistically significant and should not be over-interpreted.

Regarding age-stratified analyses, the association with vineyards without designation of origin was present only in older farmers. This result is consistent with a previous case-control study in farmers (Elbaz et al., 2009), and an ecologic study in the general population (Kab et al., 2017b). Environmental factors are likely to play a stronger role for cases with later onset, while genetic susceptibility may play a stronger role for younger cases (Nalls et al., 2015). Longer exposure in older participants may also play a role, as well as differences in products or application methods. For instance, older persons are more likely to have been exposed to organochlorines or paraquat (Elbaz et al., 2009; Tanner et al., 2011). Again, the difference between the two age groups is not large and not statistically significant and should not be over-interpreted.

Our study's main limitation is its ecological design. To reduce ecologic bias, we used data aggregated in cantons which represent relatively small areas. In addition, contrary to other studies based on pesticides expenditures, our study is conducted among farmers, rather than the general population, who represent a more homogeneous group (Barbeau et al., 1987;

Cremonese et al., 2014; Froes Asmus et al., 2017; Parron et al., 2011; Ritz and Yu, 2000). We also adjusted for a marker of deprivation, smoking, and density of neurologists, with associations in the expected direction. Second, incident PD cases were identified through an algorithm, and were not examined in-person. However, the algorithm has previously been validated with 92.5% sensitivity and 86.4% specificity, and we corrected incidence rates for these estimates (Moisan et al., 2010). Moreover, diagnostic misclassifications is unlikely to depend on the farming type. We were not able to collect clinical information on PD patients (e.g., cardinal signs, severity scales, non-motor symptoms) other than age at PD incidence and sex, and to examine the association between pesticides exposure and different disease phenotypes. Third, a minority of farmers may live and work in different cantons; this is unlikely to represent a major source of exposure misclassification because there is a strong spatial correlation for farming types since neighboring cantons usually have similar farming types (**Supplementary Figure 3**). Fourth, we were unable to account for migration, and assumed that individuals lived in the same cantons in 2000 and 2010-2015; this is unlikely to represent a major issue for several reasons. We previously showed that the annual rate of migration from one canton to another was small in the general population. In a previous study, we excluded PD cases who moved in the 5y preceding the first reimbursement of PD drugs and results remained similar (Kab et al., 2017b). Moreover, farmers are less mobile than the general population: in 2007, 6.1% of older farmers changed municipality of residence, compared to around 10% for other professional sectors (Pistre, 2016). Cantons being geographic areas larger than the municipality (150km² vs 15km²), this percentage is even lower. Finally, our analyses rely on incidence data and it is unlikely that PD patients moved more frequently than the general population before PD onset; therefore, this bias is likely to be non-differential and would bias associations towards the null. Fifth, our analyses are restricted to farmers, and we were unable to examine associations in workers, who include a wide range of occupations that cannot be distinguished using SNDS data. Sixth, the latency period between exposure assessment and PD incidence was quite short (10-15 years), because detailed data on pesticides expenditures were available starting on year 2000. However, summary data from previous years showed that, although pesticides expenditures increased between 1989 and 2000, the same distinctions between crops persisted over time. In addition, the geographic distribution of farming types generally remains stable, in particular for vineyards. In a previous study, we showed a similar distribution of farming types across the French territory in 1988 and 2000 (Kab et al., 2017b). Therefore, cantons with high pesticides expenditures are likely to remain the same over time.

Strengths of our study include its population-based and nationwide design and large size, as well as analysis of incidence rather than prevalence data. We allowed for a long delay between exposure and disease incidence to account for a latency period. Our analyses were adjusted for several potential confounders. We used agricultural data covering all types of farming. Pesticides expenditures, as a means of assessing exposure, are not subject to recall bias and allow to investigate dose-effect relationships. We used two complementary approaches to define pesticide expenditures. While the “regional” approach takes into account that pesticides use depends on regions, the “national” approach takes into account the effect of the farms’ area on pesticides expenditures. Both approaches yielded consistent findings for vineyards without designation of origin.

PD incidence in French farmers was higher in cantons with higher pesticides expenditures for vineyards without designation of origin. This result suggests that pesticides used in these vineyards and/or agricultural practices may play a role in PD and that farmers in these farms should benefit from preventive measures aiming at reducing exposure. Additional studies are needed in these farmers to determine which specific products that they are exposed to and to define real-life exposure scenarios relevant for PD (Tsatsakis et al., 2019). Our study also highlights the importance of considering farming type in studies on pesticides and PD and the usefulness of pesticides expenditures for exposure assessment.

REFERENCES

- Agreste (2014). "A propos des recensements agricoles et enquêtes structures des exploitations." La statistique, l'évaluation et la prospective agricole. Retrieved 03/12/2020, 2019, from <http://46.29.123.56/enquetes/structure-des-exploitations-964/a-propos-des-recensements/>.
- Agreste (2018). "Réseau d'information comptable agricole (RICA)." La statistique, l'évaluation et la prospective agricole. Retrieved 03/12/2020, 2019, from <http://46.29.123.56/enquetes/reseau-d-information-comptable/a-propos-du-rica-978/>.
- Altman, D. G., Bland, J. M., 2003. Interaction revisited: the difference between two estimates. *Bmj*. 326, 219. 10.1136/bmj.326.7382.219.
- Ascherio, A., Schwarzschild, M. A., 2016. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol*. 15, 1257-1272. 10.1016/s1474-4422(16)30230-7.
- Aubertot, J.-N., Barbier, J. M., Carpentier, A., Gril, J.-N., Guichard, L., Lucas, P., Savary, S., VOLTZ, M., 2005. Pesticides, agriculture et environnement. Réduire l'utilisation des pesticides et en limiter les impacts environnementaux. Expertise scientifique collective Inra-Cemagref (décembre 2005).
- Barbeau, A., Roy, M., Bernier, G., Campanella, G., Paris, S., 1987. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. *Can. J. Neurol. Sci*. 14, 36-41. 10.1017/s0317167100026147.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)*. 57, 289-300. 10.1111/j.2517-6161.1995.tb02031.x.
- Blair, A., Thomas, K., Coble, J., Sandler, D. P., Hines, C. J., Lynch, C. F., Knott, C., Purdue, M. P., Zahm, S. H., Alavanja, M. C., Dosemeci, M., Kamel, F., Hoppin, J. A., Freeman, L. B., Lubin, J. H., 2011. Impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study. *Occup Environ Med*. 68, 537-41. 10.1136/oem.2010.059469.
- Blatná, D., 2006. Outliers in regression. *Trutnov*, Vol. 30.
- Bocanegra, Y., Trujillo-Orrego, N., Pineda, D., 2014. Dementia and mild cognitive impairment in Parkinson's disease: a review. *Revista de neurologia*. 59, 555-569.
- Bocchetta, A., Corsini, G. U., 1986. Parkinson's disease and pesticides. *Lancet*. 2, 1163. 10.1016/s0140-6736(86)90576-3.
- Butault, J. P., Delame, N., Jacquet, F., Zardet, G. (2011). "L'utilisation des pesticides en France : état des lieux et perspective de réduction." Notes et études socio-économiques n°35 Centre d'études et de prospective. Retrieved 03/12/2020, 2019, from http://46.29.123.56/IMG/pdf_nese111035A1.pdf.
- Cao, F., Souders Ii, C. L., Perez-Rodriguez, V., Martyniuk, C. J., 2018. Elucidating Conserved Transcriptional Networks Underlying Pesticide Exposure and Parkinson's Disease: A Focus on Chemicals of Epidemiological Relevance. *Front Genet*. 9, 701. 10.3389/fgene.2018.00701.
- Cemagref, E. s. c. I.-. Une utilisation des pesticides élevée mais très mal connue. Pesticides, agriculture et environnement. Editions Quæ, Versailles, 2011, pp. 19-28.
- Chrisman Jde, R., Koifman, S., de Novaes Sarcinelli, P., Moreira, J. C., Koifman, R. J., Meyer, A., 2009. Pesticide sales and adult male cancer mortality in Brazil. *Int J Hyg Environ Health*. 212, 310-21. 10.1016/j.ijheh.2008.07.006.
- Couris, C. M., Colin, C., Rabilloud, M., Schott, A. M., Ecochard, R., 2002. Method of correction to assess the number of hospitalized incident breast cancer cases based on claims databases. *J Clin Epidemiol*. 55, 386-91. 10.1016/s0895-4356(01)00487-5.

- Cremonese, C., Freire, C., De Camargo, A. M., De Lima, J. S., Koifman, S., Meyer, A., 2014. Pesticide consumption, central nervous system and cardiovascular congenital malformations in the South and Southeast region of Brazil. *Int J Occup Med Environ Health*. 27, 474-86. 10.2478/s13382-014-0269-5.
- Elbaz, A., Clavel, J., Rathouz, P. J., Moisan, F., Galanaud, J. P., Delemotte, B., Alperovitch, A., Tzourio, C., 2009. Professional exposure to pesticides and Parkinson's disease. *Ann Neurol*. 66, 494-504. 10.1002/ana.21717.
- Fitzmaurice, A. G., Rhodes, S. L., Cockburn, M., Ritz, B., Bronstein, J. M., 2014. Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease. *Neurology*. 82, 419-426. 10.1212/WNL.0000000000000083.
- Froes Asmus, C. I. R., Camara, V. M., Raggio, R., Landrigan, P. J., Claudio, L., 2017. Positive correlation between pesticide sales and central nervous system and cardiovascular congenital abnormalities in Brazil. *Int J Environ Health Res*. 27, 420-426. 10.1080/09603123.2017.1373272.
- García, A. M., 2003. Pesticide exposure and women's health. *American journal of industrial medicine*. 44, 584-594. 10.1002/ajim.10256.
- GBD, 2017. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 16, 877-897. 10.1016/s1474-4422(17)30299-5.
- Gorell, J. M., Johnson, C. C., Rybicki, B. A., Peterson, E. L., Kortsha, G. X., Brown, G. G., Richardson, R. J., 1997. Occupational exposures to metals as risk factors for Parkinson's disease. *Neurology*. 48, 650-8. 10.1212/wnl.48.3.650.
- Hozumi, I., Hasegawa, T., Honda, A., Ozawa, K., Hayashi, Y., Hashimoto, K., Yamada, M., Koumura, A., Sakurai, T., Kimura, A., Tanaka, Y., Satoh, M., Inuzuka, T., 2011. Patterns of levels of biological metals in CSF differ among neurodegenerative diseases. *J Neurol Sci*. 303, 95-9. 10.1016/j.jns.2011.01.003.
- Insee (2016). "Standard gross margin / SGM." from <https://www.insee.fr/en/metadonnees/definition/c1876>.
- Kab, S., Moisan, F., Elbaz, A., 2017a. Farming and incidence of motor neuron disease: French nationwide study. *Eur J Neurol*. 24, 1191-1195. 10.1111/ene.13353.
- Kab, S., Spinosi, J., Chaperon, L., Dugravot, A., Singh-Manoux, A., Moisan, F., Elbaz, A., 2017b. Agricultural activities and the incidence of Parkinson's disease in the general French population. *Eur J Epidemiol*. 32, 203-216. 10.1007/s10654-017-0229-z.
- Koifman, S., Koifman, R. J., Meyer, A., 2002. Human reproductive system disturbances and pesticide exposure in Brazil. *Cad Saude Publica*. 18, 435-45. 10.1590/s0102-311x2002000200008.
- Lai, B. C., Marion, S. A., Teschke, K., Tsui, J. K., 2002. Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism Relat Disord*. 8, 297-309. 10.1016/s1353-8020(01)00054-2.
- Markel, T. A., Proctor, C., Ying, J., Winchester, P. D., 2015. Environmental pesticides increase the risk of developing hypertrophic pyloric stenosis. *J Pediatr Surg*. 50, 1283-8. 10.1016/j.jpedsurg.2014.12.009.
- Moisan, F., Gourlet, V., Mazurie, J. L., Dupupet, J. L., Houssinot, J., Goldberg, M., Imbernon, E., Tzourio, C., Elbaz, A., 2011a. Prediction model of Parkinson's disease based on antiparkinsonian drug claims. *Am J Epidemiol*. 174, 354-363. 10.1093/aje/kwr081.
- Moisan, F., Mazurie, J. L., Dupupet, J. L., Houssinot, J., Goldberg, M., Imbernon, E., Tzourio, C., Elbaz, A., 2010. Prediction model of Parkinson's disease using antiparkinsonian drug claims. *Neurology*. 2010 annual meeting, Toronto (Canada).

- Moisan, F., Spinosi, J., Delabre, L., Gourlet, V., Mazurie, J. L., Benatru, I., Goldberg, M., Weisskopf, M. G., Imbernon, E., Tzourio, C., Elbaz, A., 2015. Association of Parkinson's Disease and Its Subtypes with Agricultural Pesticide Exposures in Men: A Case-Control Study in France. *Environ. Health Perspect.* 123, 1123-1129.
- Moisan, F., Spinosi, J., Dupupet, J. L., Delabre, L., Mazurie, J. L., Goldberg, M., Imbernon, E., Tzourio, C., Elbaz, A., 2011b. The relation between type of farming and prevalence of Parkinson's disease among agricultural workers in five French districts. *Mov. Disord.* 26, 271-279. 10.1002/mds.23370.
- Montes, S., Rivera-Mancia, S., Diaz-Ruiz, A., Tristan-Lopez, L., Rios, C., 2014. Copper and copper proteins in Parkinson's disease. *Oxid Med Cell Longev.* 2014, 147251. 10.1155/2014/147251.
- Mortimer, J. A., Borenstein, A. R., Nelson, L. M., 2012. Associations of welding and manganese exposure with Parkinson disease: review and meta-analysis. *Neurology.* 79, 1174-80. 10.1212/WNL.0b013e3182698ced.
- MSA (2015). "Les expositions professionnelles des salariés agricoles à des agents chimiques." Retrieved 11/01/2021, 2021, from <https://ssa.msa.fr/wp-content/uploads/2019/04/11595-Fiche-4-Expositions-professionnelles-des-salari%C3%A9s-agricoles-%C3%A0-des-agents-chimiques.pdf>.
- MSA (2016). "Chiffres utiles de la MSA - Edition 2016." Retrieved 11/01/2021, 2021, from <https://statistiques.msa.fr/publication/chiffres-utiles-de-msa-edition-nationale-2016/>.
- Nalls, M. A., Escott-Price, V., Williams, N. M., Lubbe, S., Keller, M. F., Morris, H. R., Singleton, A. B., 2015. Genetic risk and age in Parkinson's disease: Continuum not stratum. *Mov Disord.* 30, 850-4. 10.1002/mds.26192.
- Nandipati, S., Litvan, I., 2016. Environmental Exposures and Parkinson's Disease. *Int J Environ Res Public Health.* 13. 10.3390/ijerph13090881.
- Parron, T., Requena, M., Hernandez, A. F., Alarcon, R., 2011. Association between environmental exposure to pesticides and neurodegenerative diseases. *Toxicol. Appl. Pharmacol.* 256, 379-385. 10.1016/j.taap.2011.05.006.
- Pistre, P., 2016. Géographies des groupes socioprofessionnels retraités en France métropolitaine : structures spatiales, migrations et trajectoires résidentielles Cahiers de démographie locale. 21-49.
- Pouchieu, C., Piel, C., Carles, C., Gruber, A., Helmer, C., Tual, S., Marcotullio, E., Lebailly, P., Baldi, I., 2017. Pesticide use in agriculture and Parkinson's disease in the AGRICAN cohort study. *Int J Epidemiol.* 10.1093/ije/dyx225.
- Ritz, B., Yu, F., 2000. Parkinson's disease mortality and pesticide exposure in California 1984-1994. *Int. J. Epidemiol.* 29, 323-329. 10.1093/ije/29.2.323.
- Rocha, G. H., Lini, R. S., Barbosa, F., Jr., Batista, B. L., de Oliveira Souza, V. C., Nerilo, S. B., Bando, E., Mossini, S. A., Nishiyama, P., 2015. Exposure to heavy metals due to pesticide use by vineyard farmers. *Int Arch Occup Environ Health.* 88, 875-80. 10.1007/s00420-014-1010-1.
- Schwartz, D. A., LoGerfo, J. P., 1988. Congenital limb reduction defects in the agricultural setting. *Am J Public Health.* 78, 654-8. 10.2105/ajph.78.6.654.
- Storey, J. D., 2003. The positive false discovery rate: a Bayesian interpretation and the q - value. *Ann. Statist.* 31, 2013-2035. <https://doi.org/10.1214/aos/1074290335>.
- Tanner, C. M., Kamel, F., Ross, G. W., Hoppin, J. A., Goldman, S. M., Korell, M., Marras, C., Bhudhikanok, G. S., Kasten, M., Chade, A. R., Comyns, K., Richards, M. B., Meng, C., Priestley, B., Fernandez, H. H., Cambi, F., Umbach, D. M., Blair, A., Sandler, D. P., Langston, J. W., 2011. Rotenone, Paraquat and Parkinson's Disease. *Environ. Health Perspect.* 119, 866-872. 10.1289/ehp.1002839.

- Tsatsakis, A., Goumenou, M., Liesivuori, J., Dekant, W., Hernández, A. F., 2019. Toxicology for real-life risk simulation - Editorial preface to this special issue. *Toxicol Lett.* 309, 33-34. 10.1016/j.toxlet.2018.12.003.
- Tuschl, K., Mills, P. B., Clayton, P. T., 2013. Manganese and the brain. *Int Rev Neurobiol.* 110, 277-312. 10.1016/b978-0-12-410502-7.00013-2.
- van der Mark, M., Brouwer, M., Kromhout, H., Nijssen, P., Huss, A., Vermeulen, R., 2012. Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. *Environ Health Perspect.* 120, 340-7. 10.1289/ehp.1103881.
- Viel, J. F., Challier, B., Pitard, A., Pobel, D., 1998. Brain cancer mortality among French farmers: the vineyard pesticide hypothesis. *Arch Environ Health.* 53, 65-70. 10.1080/00039899809605690.
- Wang, A., Costello, S., Cockburn, M., Zhang, Z., Bronstein, J., Ritz, B., 2011. Parkinson's disease risk from ambient exposure to pesticides. *Eur J Epidemiol.* 26, 547-555. 10.1007/s10654-011-9574-5.
- Willis, A. W., Evanoff, B. A., Lian, M., Galarza, A., Wegrzyn, A., Schootman, M., Racette, B. A., 2010. Metal emissions and urban incident Parkinson disease: a community health study of Medicare beneficiaries by using geographic information systems. *Am J Epidemiol.* 172, 1357-63. 10.1093/aje/kwq303.
- Wirdefeldt, K., Adami, H. O., Cole, P., Trichopoulos, D., Mandel, J., 2011. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur. J Epidemiol.* 26 Suppl 1, S1-58. 10.1007/s10654-011-9581-6.

Author's contribution

LP, FM and AE: designed the research; FM and AE: conducted the research; LP: performed statistical analysis and drafted the manuscript; FM and AE: supervised statistical analysis and the writing; LP, JS, LC, SK, FM and AE: contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. AE had primary responsibility for the final content, he is the guarantor.

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Table 1. Annual pesticides expenditures by farming type (Agreste)

Farming type	National median in Euros per hectare (IQR)	National mean in Euros per hectare (SD)	Regression on area ^a	
			Intercept (SE)	Slope (SE)
Cereals ¹	120 (61)	122 (288)	126 (1)	19 (6)*
General crops ²	162 (85)	178 (678)	170 (3)	-7 (16)
Fresh vegetables ³	626 (1,336)	824 (9,514)	877 (62)	-1,226 (284)*
Horticulture ⁴	322 (850)	426 (2,192)	723 (63)	-251 (420)
Vineyards with designation of origin ⁵	512 (559)	1,091 (6,671)	647 (15)	-1,156 (101)*
Vineyards without designation of origin ⁶	313 (193)	202 (1,815)	333 (7)	-177 (52)*
Permanent crops ⁷	327 (499)	46 (346)	425 (17)	-327 (83)*
Mixed crops ⁸	144 (103)	727 (4,925)	167 (9)	-107 (60)
Livestock ⁹	34 (57)	327 (1,220)	40 (1)	22 (4)*

IQR= interquartile range, SD, standard deviation, SE= standard error.

^a We regressed pesticides expenditures (PE) per hectare for each type of farming on the average agricultural area of the farms with that type of farming (A, in hectares) ($PE = \text{Intercept} + \text{Slope} \times A$). Positive slopes indicate that average pesticides expenditures per hectare for a given type of farming increase with the area of farms devoted to that type of farming, while negative coefficients indicate the opposite.

* $p < .05$.

¹ Including cereals, oilseed and protein plants, rice.

² Including field crops, root crops, cotton, tobacco.

³ Including outdoor and under glass fresh vegetables, mushrooms.

⁴ Including outdoor and under glass flowers and ornamental plants.

⁵ Including quality wine with label.

⁶ Including wine other than quality, table grapes.

⁷ Including fruits, citrus fruits, nuts.

⁸ Including field crops and horticulture, field crops and permanent crops, field crops and vineyard, horticulture and permanent crops, mixed crops.

⁹ Including cattle rearing – specialist dairying; cattle rearing and fattening; cattle-dairying, rearing and fattening combined; sheep, goats and other grazing livestock; granivores (e.g. pigs, poultry); mixed livestock, mainly grazing livestock; mixed livestock, mainly granivores; field crops-grazing livestock combined; various crops and livestock combined.

Figure 1. Spatial distribution of annual regional pesticides expenditures for all farming types combined (total) and each farming type in French cantons (2000).

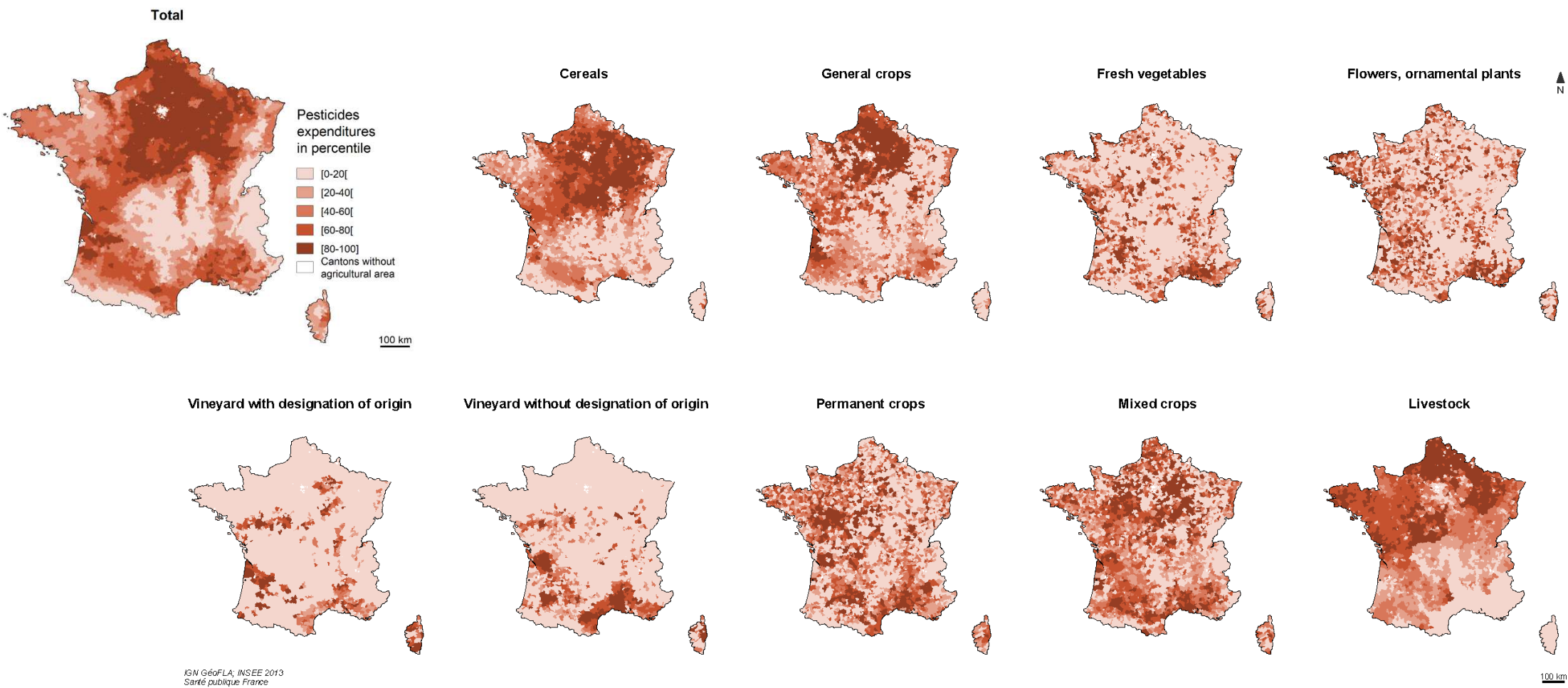
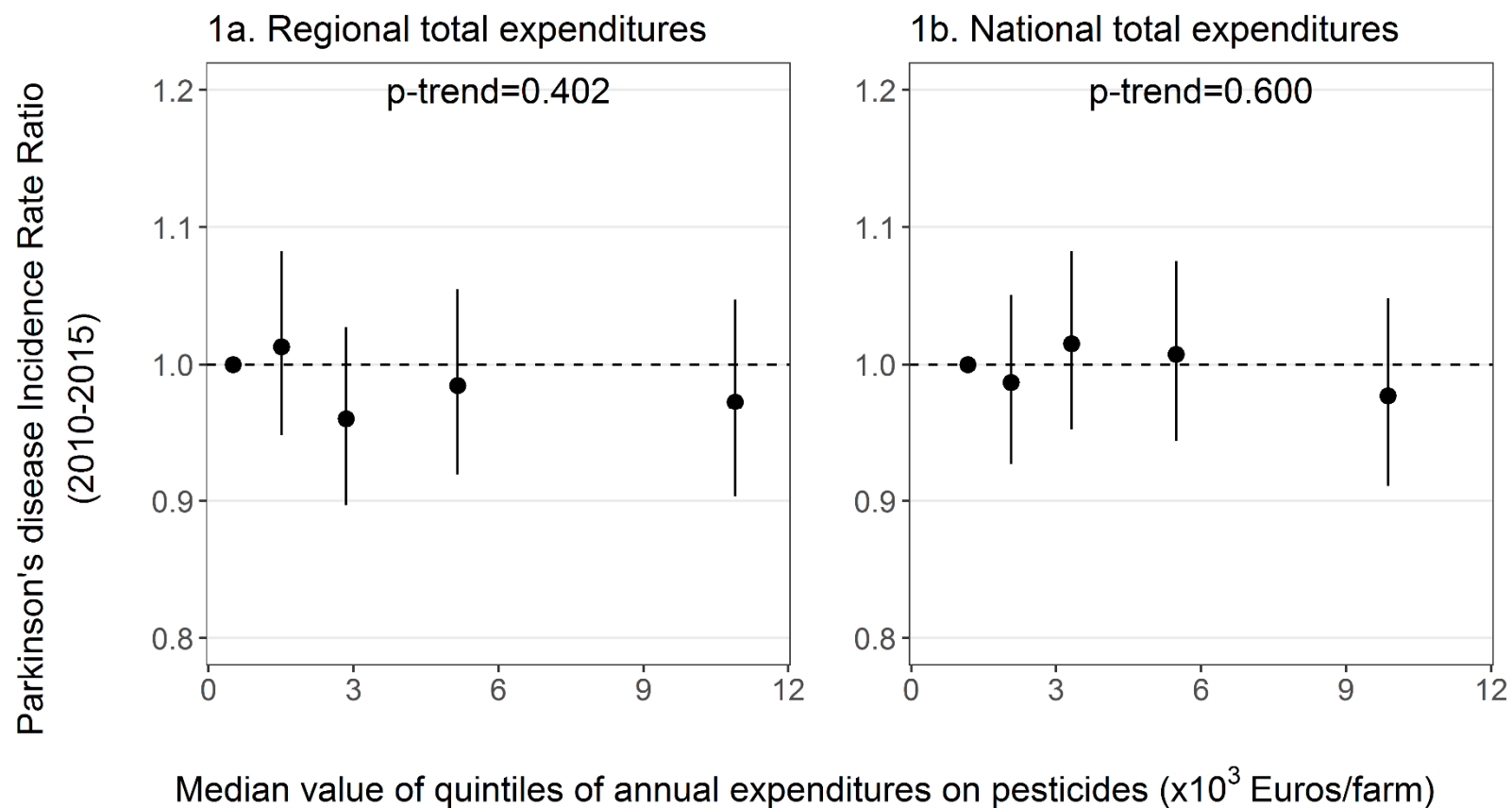
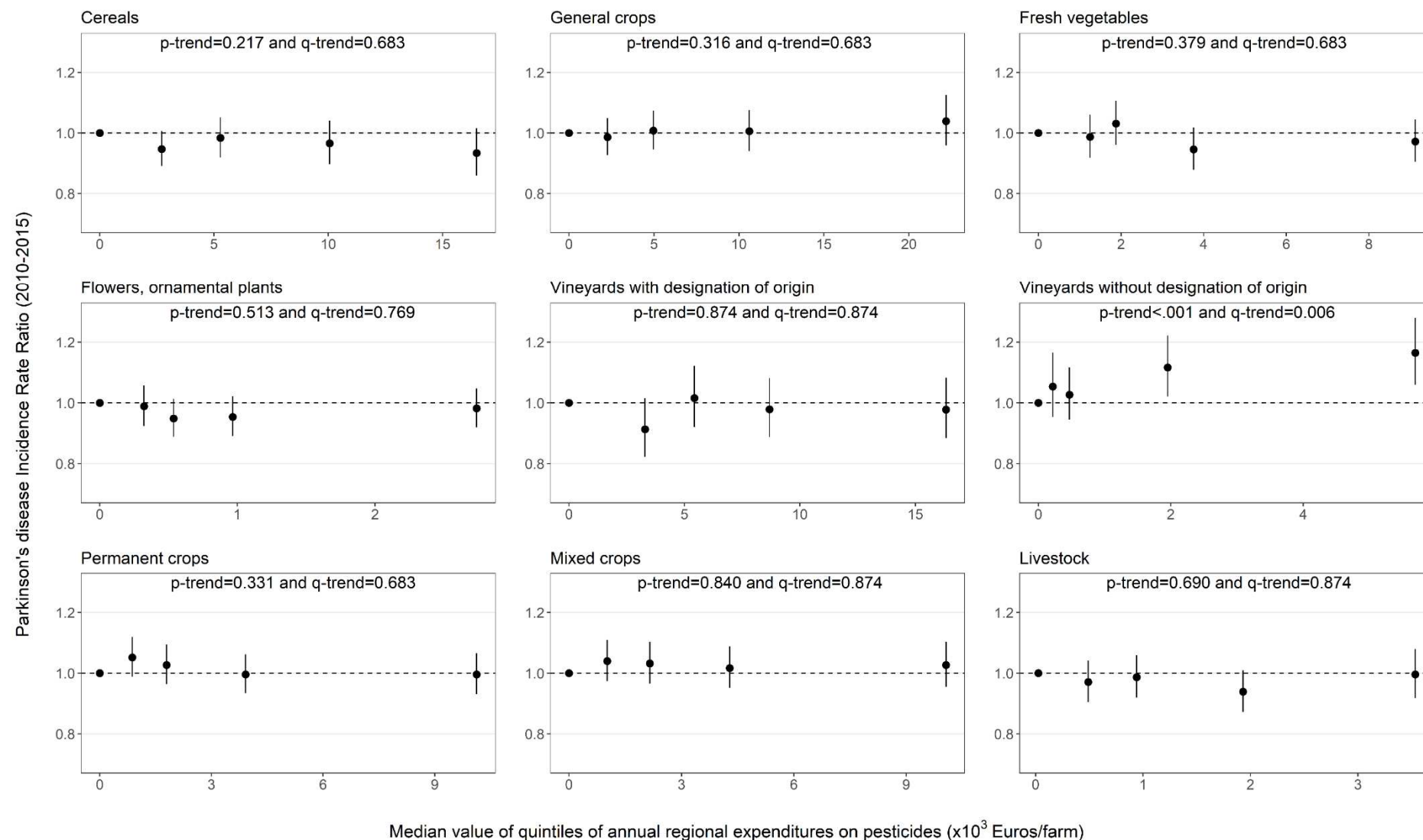


Figure 2. Association of annual pesticides expenditures (1a. regional, 1b. national) with Parkinson's disease incidence in farmers from French cantons (2010-2015).



Incidence rate ratios are plotted at the median of each quintile.

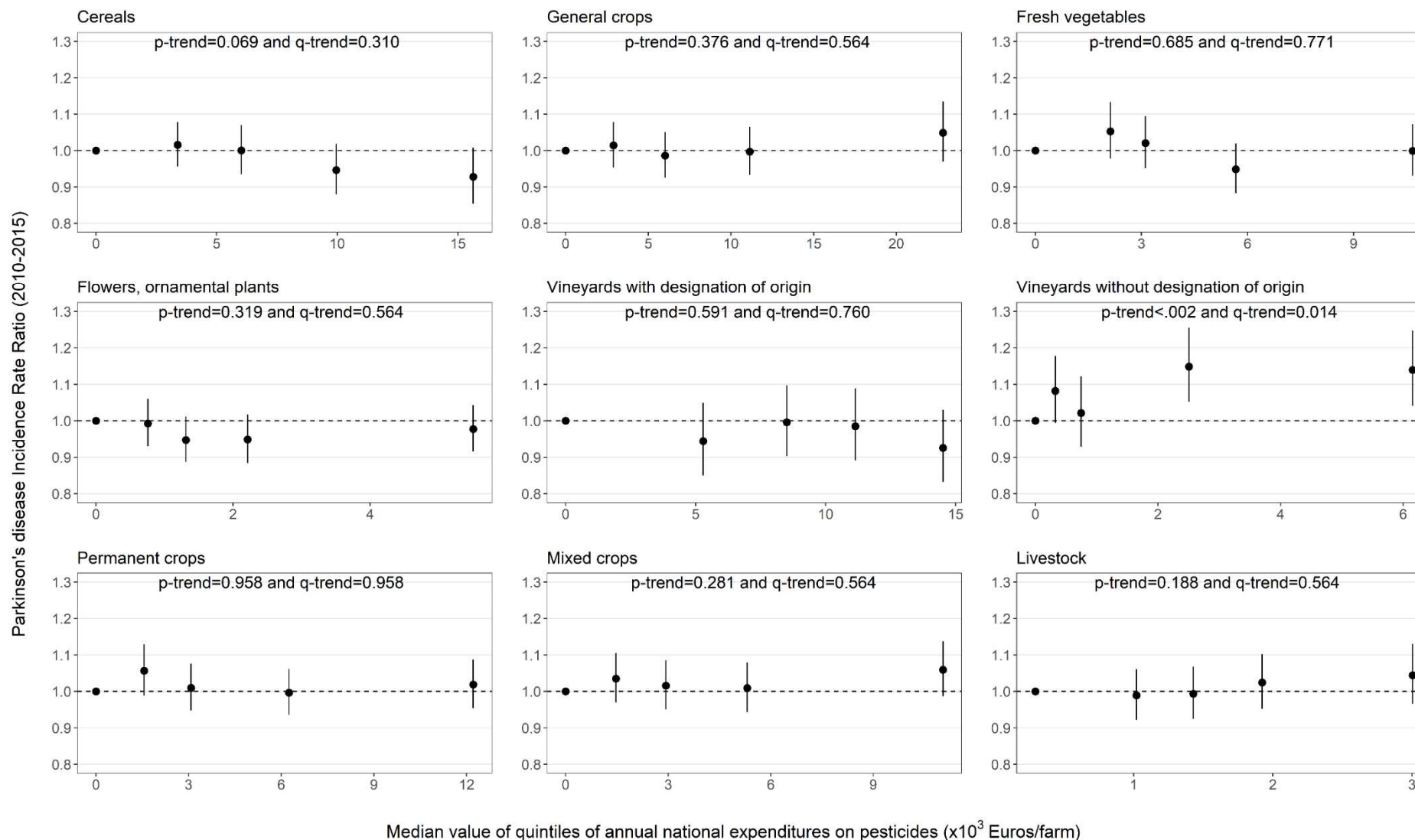
Figure 3. Multivariable association of annual pesticides regional expenditures for nine farming types with Parkinson's disease incidence in farmers from French cantons (2010-2015).



Incidence rate ratios are plotted at the median of each quintile.

Test of linear trend: p-values non-adjusted for multiple comparisons; q-values adjusted for multiple comparisons using a false discovery rate (FDR) approach.

Figure 4. Multivariable association of annual pesticides national expenditures for nine farming types with Parkinson's disease incidence in farmers from French cantons (2010-2015).

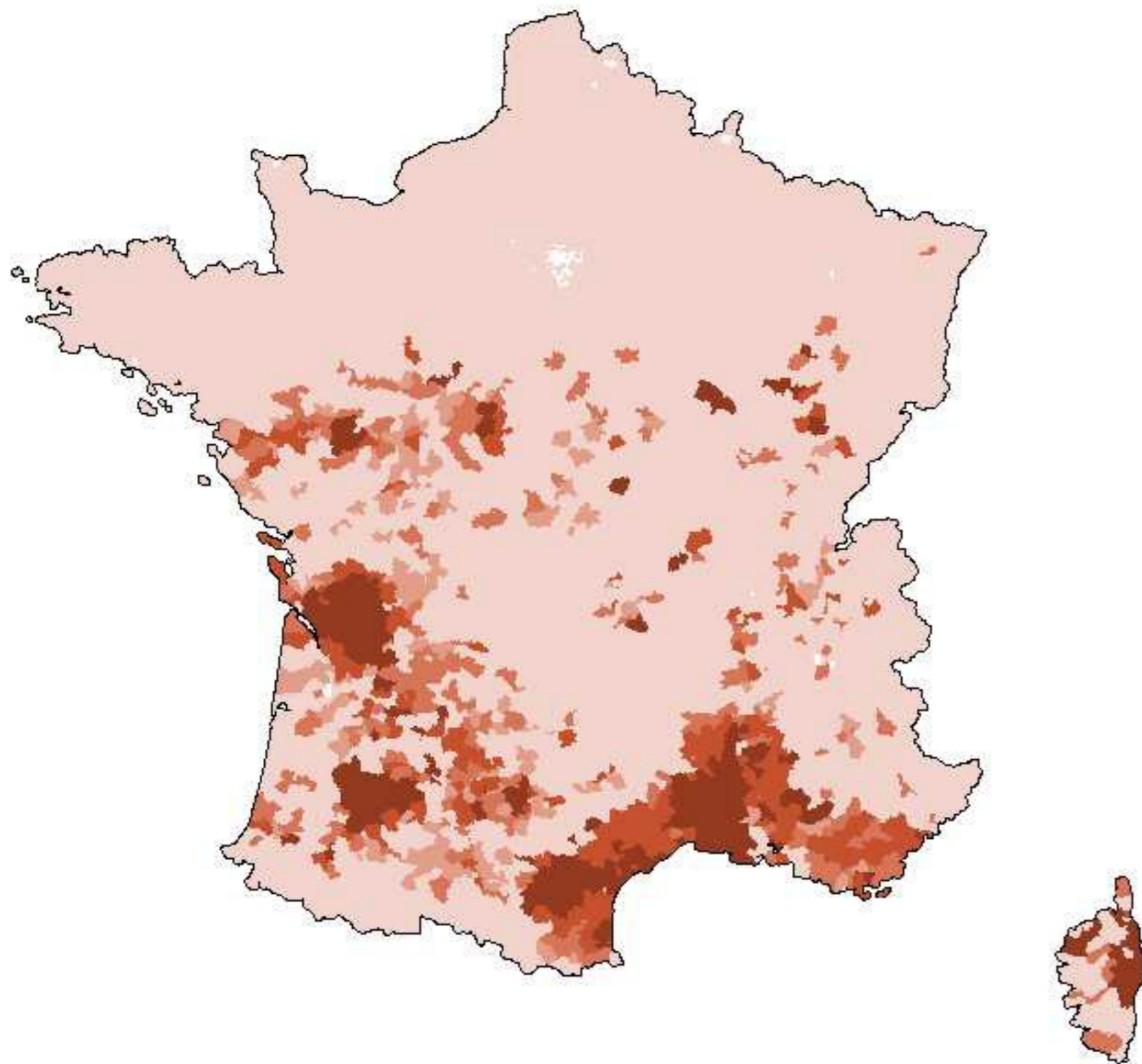


Incidence rate ratios are plotted at the median of each quintile.

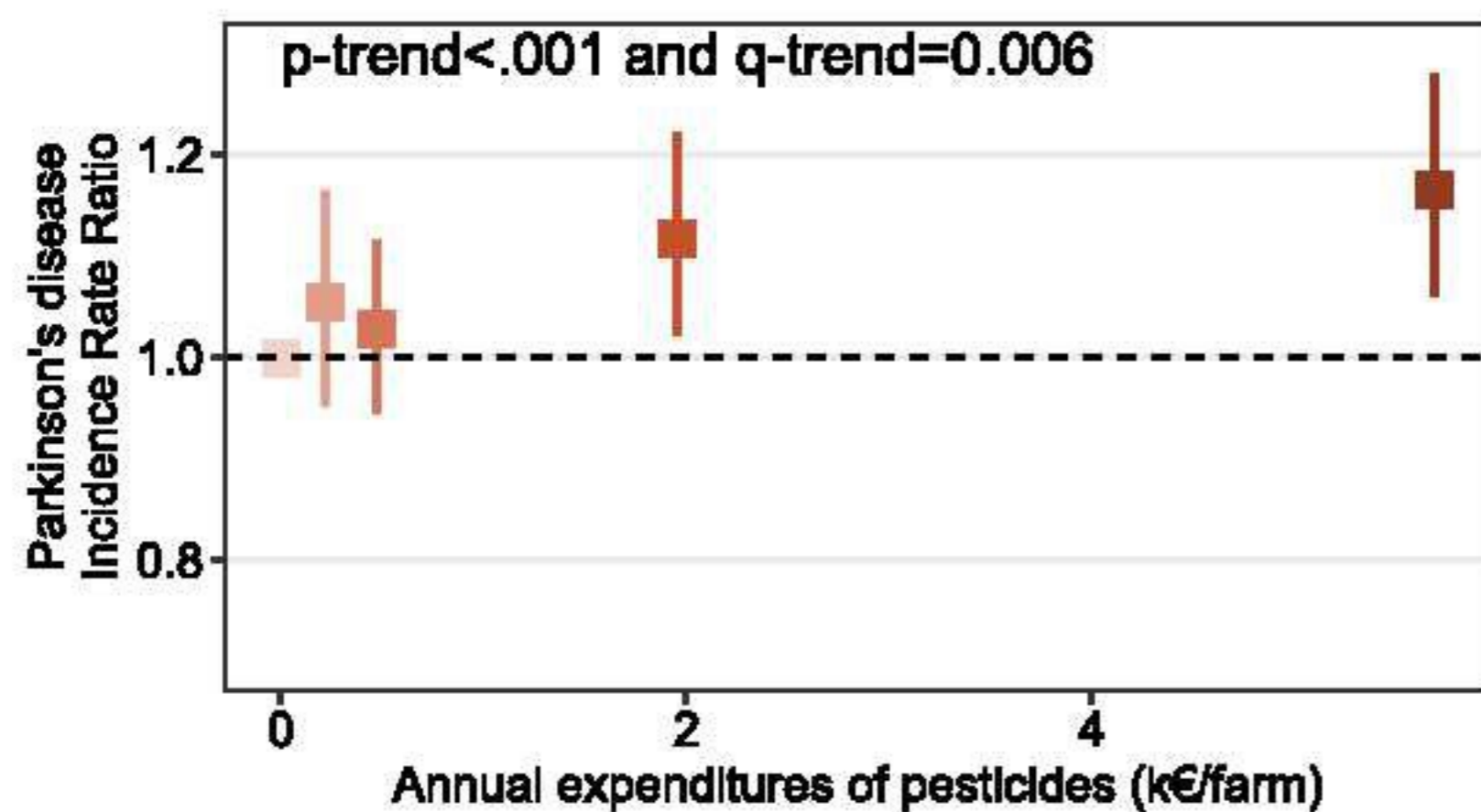
Test of linear trend: p-values non-adjusted for multiple comparisons; q-values adjusted for multiple comparisons using a false discovery rate (FDR) approach.

Vineyards **without** designation of origin

— Spatial distribution of pesticides expenditures —

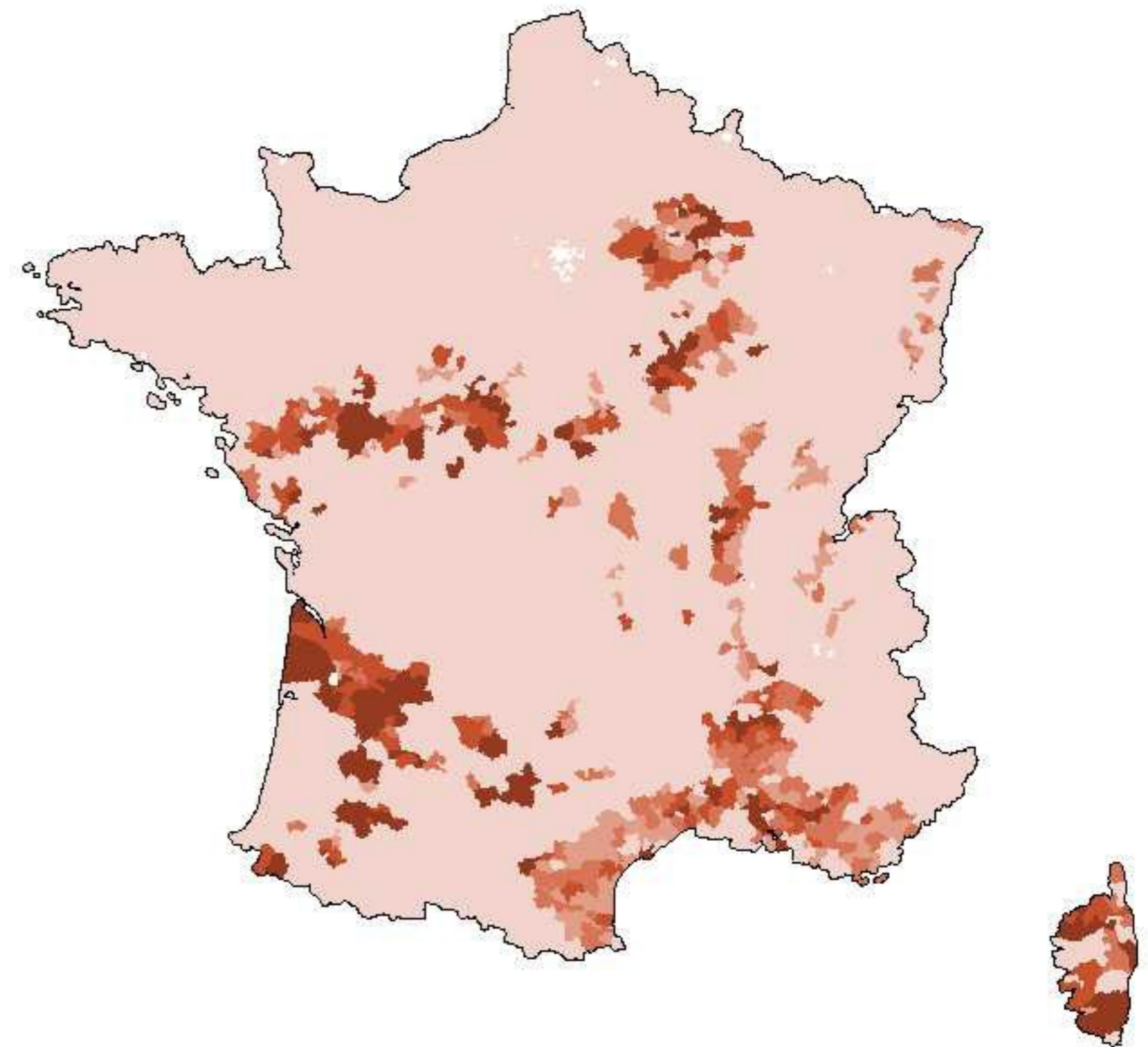


— Association with Parkinson's disease —



Vineyards **with** designation of origin

— Spatial distribution of pesticides expenditures —



— Association with Parkinson's disease —

