Professional exposure to pesticides and Parkinson's disease

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Summary

Objective. We studied the relation between Parkinson's disease (PD) and professional exposure to pesticides in a community-based case-control study conducted in a population characterized by a high prevalence of exposure. Our objective was to investigate the role of specific pesticide families and to perform dose-effect analyses.

Methods. PD cases (n=224) from the *Mutualité Sociale Agricole* (MSA, France) were matched to 557 controls free of PD affiliated to the same health insurance. Pesticide exposure was assessed using a two-phase procedure, including a case-by-case expert evaluation. Analyses of the relation between PD and professional exposure to pesticides were first performed overall and by broad category (insecticides, fungicides, herbicides). Analyses of 29 pesticide families defined based on a chemical classification were restricted to men. Multiple imputation was used to impute missing values of pesticide families. Data were analyzed using conditional logistic regression, both using a complete-case and an imputed dataset.

Results. We found a positive association between PD and overall professional pesticide use (OR=1.8, 95% CI=1.1-3.1), with a dose-effect relation for the number of years of use (p=0.01). In men, insecticides were associated with PD (OR=2.2, 95% CI=1.1-4.3), in particular organochlorine insecticides (OR=2.4, 95% CI=1.2-5.0). These associations were stronger in men with older onset PD than in those with younger onset PD and were characterized by a dose-effect relation in the former group.

Interpretation. Our results lend support to an association between PD and professional pesticide exposure and show that some pesticides (i.e., organochlorine insecticides) may be more particularly involved.

Keywords : Parkinson's disease ; pesticides ; case-control ; environment.

Introduction

The etiology of Parkinson's disease (PD) is likely to be multifactorial: while genetic susceptibility plays a role, as demonstrated by familial aggregation and association studies,[1,2] twin studies and segregation analyses suggest that environmental factors are also involved.[3,4]

Studies of the relation between pesticides and PD were triggered by the description of parkinsonism in drug users exposed to MPTP,[5] which also causes degeneration of dopaminergic neurons in animals.[6] To be active, MPTP is metabolized into MPP+ that has a chemical structure similar to that of the herbicide paraquat.

Case-control and cohort studies have shown an association between pesticides and PD, and specific pesticides have been shown to be toxic for dopaminergic neurons.[7] Although accumulating data support this association, the majority of epidemiologic studies have neither implicated specific pesticides nor assessed dose-effect relations.[8]

We studied the relation between PD and pesticides in a community-based case-control study conducted in a population characterized by a high prevalence of exposure. Our objective was to study in detail the relation between PD and professional pesticide exposure, by investigating pesticide families and performing dose-effect analyses.

Methods

This study was conducted among affiliates to *Mutualité Sociale Agricole* (MSA), the French health insurance for workers in agriculture and related occupations while in activity or retired (farm owners and workers; workers in silos, agricultural cooperatives, seed shops; tertiary sector professionals).[9,10] At the time of the study, MSA counted approximately four million members and 82 offices distributed across France according to an administrative division (French "*départements*"); 62 offices agreed to participate. The research protocol was approved by the ethics committee of *Hôpital du Kremlin-Bicêtre*, and all subjects signed an informed consent.

Participants

In France, free healthcare is available for PD. Eligible patients (18-75 years) applied for free healthcare for PD to MSA (02/1998-08/1999). Patients with free healthcare for dementia were not eligible.

Patients who accepted to participate were examined by a movement disorders neurologist. When impossible, patients' neurologists were contacted. Parkinsonism was defined as the presence of ≥2 cardinal signs (rest tremor, bradykinesia, rigidity, impaired postural reflexes). PD was defined by parkinsonism after exclusion of prominent or early signs of more extensive nervous system involvement and drug induced parkinsonism.[11]

Eligible controls were affiliates who requested reimbursement for health-related expenses (02/1998-02/2000). A maximum of three controls were matched to each case (on age+/-2 years, sex, affiliation office). Subjects with free healthcare for dementia or PD were not eligible.

Data collection

A physician interviewed the participants (demographic data, smoking, well water drinking, family history),[10] examined the participants to confirm the presence (patients) or absence (controls) of parkinsonism, and administered the Mini Mental State Examination (MMSE).

Professional history and pesticide exposure

Pesticide exposure was assessed using a two-phase procedure.[12,13] First, occupational history was obtained through self-questionnaires. For each job, participants declared if they had personally sprayed pesticides. Information on pesticide use for gardening was also obtained. Questionnaires were reviewed, blinded to case-control status, to classify participants as never users of pesticides, users for gardening only, or professional users. We interviewed never users and users for gardening over the phone (n=30) to confirm that none of them had been professional users.

Second, professional users were interviewed at home by a MSA occupational health physician in order to reconstruct the history of pesticide use. Participants were asked to list each farm where they had worked (start/end years). They were asked to describe each farm in terms of land size, crops (size) and animal breeding (number) and if they had personally sprayed pesticides for each of them. For each crop/animal for which pesticides were used, detailed information was obtained: pesticides, frequency (days/year), duration (hours/year), spraying method (portable device, tractor), start/end years. In order to use as many sources of information as possible, interviewers visited the farm, discussed technical issues, looked for old pesticide containers and packages, and reviewed bills and farming calendars. Farm interviews usually lasted half a day or more. Ten subjects were re-interviewed 6 months later; agreement was excellent for all variables used in analysis.

Home interview questionnaires were reviewed by two epidemiologists, two occupational health physicians, and an agronomist blinded to disease status. Special attention was given to: pesticide availability at the reported date of use, likelihood of use for the target crop/animal, likelihood of duration/frequency of use given the land size or number of animals. In case of implausibility, the occupational health physician re-contacted the participant.

Coding of pesticides and measures of exposure

Using these questionnaires, we constructed an “exposure history” dataset consisting of multiple observations per subject, each corresponding to an instance of pesticide use. Each observation

included several variables: pesticide, crop/animal, spraying method, frequency (days/year), duration (hours/year), start/end years.

Pesticides were coded using a pesticide dictionary and were grouped into (i) 50 families based on chemical similarities (http://www.alanwood.net/pesticides): 12 insecticides (e.g., organophosphorus, organochlorines), 21 herbicides (e;g., dinitrophenol, nitrile), 17 fungicides (e.g., dithiocarbamate, triazole); and (ii) three pesticide categories: insecticides, fungicides, herbicides. Four generic "unknown" codes were used when a subject did not remember the specific pesticide used (unknown insecticide, fungicide, herbicide, pesticide). Fifty-three indicators were computed (for 50 families and three categories). When generic "unknown" codes were used, all corresponding family indicators were coded as missing, as any of them could have been used (e.g., for an "unknown insecticide" code, the "insecticide" indicator was coded "Yes", the 11 indicators for insecticide families were coded "Missing", and the indicators for "fungicide", "herbicide", and 39 families of fungicides and herbicides were coded "No").

Finally, an "exposure summary" dataset with one line/subject was obtained, including 53 yes/no indicators for pesticide use; for each indicator, we computed variables assessing exposure intensity (cumulative lifetime number of years/days/hours of exposure; cumulative hectares x years/days/hours of exposure).[14] Only exposures occurring before PD onset in cases and index age (age at onset in matched case) in controls were included.

Statistical methods

We first conducted complete-case analyses comparing the frequency of professional use of pesticides, insecticides, fungicides, herbicides, and pesticide families by disease status, using conditional logistic regression (proc PHREG, SAS v9.1).[15]. Continuous variables were dichotomized using the median of their distribution in exposed subjects; trend tests were performed using a three level variable (0 for no exposure, and midpoints of intervals below and above the median among those exposed). An indicator variable for "gardening-only" pesticide use was included in order to exclude subjects exposed exclusively through gardening from the reference group. All analyses were adjusted for MMSE and cigarette smoking (pack-years).[10]

Because exposure patterns were different in men and women, all analyses were sex-stratified. Because genetic susceptibility may depend on age at onset, we stratified analyses by median age at onset/index age. As one study found an association between pesticides and incident but not prevalent PD,[16] we also stratified analyses by median disease duration.

In complete-case analyses, observations with missing information for any of the predictors are deleted from the analyses.[17] This approach reduces the precision of parameter estimates, may introduce bias, and yields different sample sizes depending on the predictors included in the model; the problem is especially severe in matched case-control studies. Simple approaches (e.g., missing indicators method) do not in general correct this bias, and require that missingness be independent of case-control status.[18] Multiple imputation (MI) is more generally appropriate and allows asymptotically unbiased estimation of exposure effects under the weaker assumption of missing at random conditional on measured variables, including case-control status.[17]

We used MI to impute missing exposure values in the pesticide exposure history dataset. MI replaces missing values with plausible values based on observed data for that variable, case-control status, and other covariates. Across families of pesticides, the strongest predictors of pesticide use were the type of crop/animal and the time period of use. For each pesticide family indicator, we therefore imputed missing values using a logistic regression model with the following predictors: crop/animal, time period, case-control status, sex, age, MMSE.[19] For each indicator, MI was done independently of that for other indicators, as joint imputation across 50 families is computationally intractable. We used SAS PROC MI to generate 10 imputed exposure history datasets; each of these was then reduced to an exposure summary dataset. Imputed exposure summary data sets were analyzed as complete data and the 10 sets of results were pooled using SAS PROC MIANALYZE.[15] Note that MI allows multivariate exposure analyses because each of the datasets analyzed is complete.

Results

Of 352 PD patients who requested free healthcare, 292 accepted to participate (83%); 184 were examined by the study neurologist who diagnosed PD in 153. Of the remaining 108, 94 were classified as having PD based on neurologists' reports. These 247 patients were matched to 676 controls (acceptance rate, 75%). Figure 1 describes the exposure assessment procedure. We were able to obtain detailed exposure data for 224 cases and 557 matched controls.

Cases had worked in farms more often than controls (table 1). In analyses stratified by gender, the association between farming and PD was similar in men and women (interaction, p=0.36). Cases had been professional pesticide users more often than controls; there was no significant difference in ORs between men (OR=1.8, 95% CI=0.9-3.8) and women (OR=2.4, 95% CI=1.1-5.6; interaction, p=0.54). In men, ORs increased with the number of years of professional use (p=0.05); the relation was stronger for male cases with onset > 65 years (OR=4.5, 95% CI=1.0-20.0) than in those with younger onset (OR=1.1, 95% CI=0.5-2.7; interaction, p=0.05).

Professionally exposed subjects generated a pesticide exposure history dataset with 4322 observations; the median (IQ range) number of observations/subject was 11 (13) in cases and 10 (13) in controls, was higher in men than in women, increased with MMSE, and was lower in older onset than in younger onset cases. The proportion of generic unknown codes per subject (unknown insecticide, fungicide, herbicide, or pesticide) was not significantly higher in cases (19%) than in controls (17%, p=0.24); it increased with age and lower MMSE, and was higher in women than in men, both in cases and controls (interaction p-values ranging from 0.35 to 0.46).

Table 2 shows ORs for exposure to three categories of pesticides (insecticides, fungicides, herbicides); frequencies are shown in appendix 1. Separate models were fitted for each category and strata defined by sex and age at onset. The proportion of missing values did not exceed 5% in any model. Frequency of exposure to each of three categories was lower in women than in men. Male cases had used insecticides more often than controls; this relation was stronger for older onset PD and was characterized by a dose-effect relation in this group. The relation between herbicides or fungicides (yes/no) and PD was not significant in men. There was a significant dose-effect trend for fungicides in men with older onset PD. Among women, cases

had used fungicides more frequently than controls. The number of exposed women was insufficient to perform detailed analyses.

When insecticides and fungicides were included in the same model for men with older onset PD, insecticides (OR=4.4, 95% CI=1.0-20.4) but not fungicides (OR=1.2, 95% CI=0.2-5.5) remained associated with PD. When the relation between PD and professional pesticide exposure was adjusted for insecticide use, the OR for professional pesticide exposure was 0.7 (95% CI=0.1-8.7); adjustment for fungicides yielded an OR of 2.6 (95% CI=0.3-25.6) for professional pesticide exposure. These analyses suggest that the association between PD and professional pesticide use among men with older onset PD was mainly explained by insecticide use rather than fungicide use; similar results were found among men overall (data not shown).

Appendix 2 shows frequencies in men of 29 pesticide families present in more than 5% of controls. Among controls, organochlorines, dithiocarbamates, and triazines were the most frequently reported insecticides, fungicides, and herbicides respectively. The mean percentage of missing values was: insecticides, 25%; herbicides, 21%; fungicides, 14%. When comparing controls matched to older and younger onset cases, frequencies of pesticide families were influenced by their date of marketing. The mean cumulative lifetime number of years of exposure of all families was similar in controls matched to older onset cases (13 years) and in controls matched to younger onset cases (12 years), despite having a longer period of potential pesticide exposure in the older group. The mean cumulative lifetime number of hours of exposure of all families was higher in controls matched to younger onset cases (88 hours) than in those matched to older onset cases (52 hours).

Table 3 shows ORs for pesticide families among men overall and among with older onset PD using a complete-case analysis; appendix 3 shows the corresponding dose-effect analyses. Male cases had used organochlorine insecticides and amide or dithiocarbamate fungicides more often than controls; a dose-effect relation was present for nitrile herbicides. No association with younger onset PD was present for any family (data not shown). Older onset cases had used organochlorine insecticides and nitrile or phenoxy herbicides more often than controls; dose-

effect relations were significant for organochlorine insecticides and some herbicides (nitriles, triazines, ureas), but not phenoxy herbicides.

Analyses implementing MI in men overall and in men with older onset PD are presented in table 3 and appendix 4. In men, significant ORs were found for organochlorine insecticides and sodium chlorate, without significant dose-effect relations. No associations with younger onset PD were detected (data not shown). In men with older onset PD, significant associations were found for organochlorine insecticides, nitrile herbicides, and arsenic; significant trends were observed for organochlorine insecticides and arsenic, but not for nitrile herbicides. In multivariate analyses, both in men overall and in men with older onset PD, only organochlorines remained associated with PD after adjusting for other pesticide families. When the relation between professional pesticide exposure was adjusted for organochlorines among men with older onset PD, the OR for professional pesticide use became 2.3 (95% CI=0.4-12.7).

Figure 2 shows the results of dose-effect analyses for organochlorine insecticides among men with older onset PD, using a complete-case analysis and multiple imputation; as shown in the figure, analyses using cumulative lifetime number of hours or years of exposure yielded similar results.

Figure 3 shows the relation between PD and organochlorines among men according to age at onset and period of exposure. Cases with older onset PD used orgachlorines more frequently than matched controls at each time period, while there was no difference between cases with younger onset and their matched controls. In addition, there was no difference in exposure frequencies between controls matched to each group of cases. Similar findings were observed for insecticides or professional pesticide use overall (data not shown).

Analyses stratified by median disease duration, analyses restricted to subjects with MMSE above the median, and lagged analyses excluding all exposures in the 5 years preceding onset in cases and the index date in controls led to similar results (not shown).

Discussion

As part of a community-based case-control study of PD among subjects characterized by a high frequency of professional pesticide exposure, using a detailed case-by-case expert exposure assessment, we found an association between PD and professional pesticide use with a dose-effect relation. In men, insecticides were more strongly associated with PD than fungicides and herbicides; the most robust association was found for organochlorines. Most of these associations were stronger in older onset PD and were characterized by dose-effect relations.

Previous studies suggested that pesticide exposure is associated with PD.[7,8] A meta-analysis of case-control studies found an OR of 1.9.[20] Three cohort studies reported positive associations;[21-23] in the largest, several chemical exposures were studied but only pesticides were associated with PD (RR=1.7).[21] In the Agricultural Health Study (AHS), incident (n=78) but not prevalent (n=83) self-reported PD was associated with pesticide use.[16] Specific pesticides were associated with PD; among insecticides, ORs were increased for phorate (organophosphorus) and lindane (organochlorine; OR=1.4 [0.8-2.5] for both). With the exception of the AHS,[16] most studies included limited exposure assessment and few exposed subjects, precluding detailed studies of dose-effect relations and specific pesticides, and did not distinguish men from women.

The association between PD and professional pesticide use was stronger for older males. Using different age cut-offs to define this group led to the same conclusions. This finding is consistent with the view that genetic susceptibility plays a stronger role in younger onset cases, while environmental factors play a stronger role for older onset cases.[24] Alternative explanations can be considered. First, cases with older onset may have been exposed for more years than those with a younger onset; however, the number of years of exposure was similar between both groups for specific families of pesticides, and the cumulative lifetime hours of exposure were generally greater for younger onset cases; in addition, ORs were not significantly increased in younger cases with the highest exposures. Higher exposure levels in younger onset cases are due to increasing use in more recent decades; the size of the farms of the younger cases was also larger. Second, there are time-trends in exposure frequencies of pesticide families; these

were higher in controls matched to older cases than in those matched to younger cases for products such as arsenic, copper, or sulfur, that were used before more sophisticated products became available; however, they also had lower exposure levels for these products. Alternatively, controls matched to older cases had lower exposure frequencies for the majority of other families, including organochlorines. In addition, when studying the association between PD and professional pesticides, insecticides, or organochlorines use among men, we found that associations were present in men with older onset PD for all time periods, while there was no association for younger onset cases for all periods. In addition, there were no differences in exposure rates between controls matched to younger and older onset male cases; therefore, differences in ORs were not explained by exposure differences in controls groups. Third, younger subjects may have been more educated with respect to pesticides than older subjects and may have taken more precautions while spraying.

We did not find an association between PD and paraquat (quaternary ammonium herbicide). In the AHS, paraquat was associated with prevalent but not incident PD.[16] One study reported a significant association based on four exposed cases and no exposed controls;[25] there was no association in three other studies.[26-28] A Taiwanese study found an association between PD and paraquat use for more than 20 years.[29] There are several possible reasons for these conflicting findings. First, in France, paraquat is mainly used as a non-selective herbicide to kill weeds around the fields, thus resulting in lower exposure levels compared to other herbicides. Second, if gene-environment interactions are involved, paraquat may be associated with PD only among susceptible individuals.[9,30] Third, toxicological studies have suggested that maneb (dithiocarbamate fungicide) and paraquat act synergistically.[31] We found an association between PD and dithiocarbamate fungicides among men, that was not significant in multivariable analyses or after multiple imputation of missing values; interaction analyses showed no synergy between both families (data not shown).

Among men, the most robust association with PD was for organochlorine insecticides. A German study reported an association between PD and organochlorines based on nine exposed subjects.[32] In a family-based study, organochlorines and organophosphates were associated with

PD.[33] In Greenland, PD cases had higher levels of plasma DDE than controls.[34] Post-mortem studies showed that PD brains had higher dieldrin or lindane levels than control brains.[35-37] These findings do not imply causality: they may simply reflect pesticide exposure because organochlorines are the only pesticides for which long-term biomarkers are available. Nevertheless, there is laboratory evidence in favor of dopaminergic neurotoxicity of organochlorines. Dieldrin induces apoptotic cell death, alters dopamine levels, and induces mitochondrial dysfunction and protein aggregation.[38] Endosulfan inhibits proteasomal activity.[39] Oral administration of lindane decreases dopamine levels in rats.[40] Lindane and dieldrin induce ROS production in cultured microglial cells.[41] In our study, the main organochlorine used was lindane, followed by DDT. Lindane is the most common isomer of hexachlorocyclohexane and was used as a large spectrum insecticide in agriculture in France between the early 1950s and 1998; in our study, its main target was corn, followed by potatoes. It is characterized by a high persistency in the environment, with the potential for long-range transport. Significant levels of lindane and other organochlorines are still detected in the sera of humans.[42]

A strength of our study is the use of a detailed exposure assessment method. It is however possible that farmers did not declare some products (e.g., rarely used ones). Because cognitive impairment is more frequent in PD, recall may be differential. We therefore adjusted all our analyses for MMSE and performed sensitivity analyses restricted to subjects with higher MMSE. Alternatively, some cases may have been aware of a possible link between PD and pesticides, which may affect the exposure assessment overall; however, for specific pesticides, it is more likely that recall errors were non-differential given the many pesticides reported, the lack of strong candidates, and the complex pattern of use.[14]

Most of the participants knew what crops the products they declared were used for and whether they were insecticides, fungicides, or herbicides; therefore, the proportion of missing values was low for this broad classification. Farmers were not always able to recall specific pesticides and our exposure assessment method resulted in a number of missing values for pesticide families. The proportion of missing values was variable across families and depended on disease status, MMSE, time period, age, and gender. To address this issue, we used MI to

impute missing values based on these covariates. This approach is considered to decrease bias without strongly affecting standard errors of regression parameters.[43]

We did not ask the participants to provide information on protective equipment use. This information is difficult to obtain, with farmers being likely to over-report their use when interviewed by occupational physicians. In addition, protective equipments were seldom used in France when the majority of the participants included in this study, even those with younger onset, started working; it is therefore unlikely that there have been large differences in use of protective equipments among study participants because of their period of activity and the type of farms they ran. It is only more recently, that farmers trained in agricultural schools have started using more systematically protections when handling pesticides.

Accounting for exposure to multiple pesticides is a challenge for the analysis. We defined a priori pesticide families using a traditional chemical classification. This approach defines groups of subjects exposed to pesticides sharing chemical characteristics and leads to groups of larger size than if we had considered pesticides separately; to further reduce the number of exposure variables, we restricted our analyses to families with at least 5% of controls exposed. However, the relation with the disease may be heterogeneous within a family and this approach may suffer from a dilution of effects. Multivariable analyses identified organochlorines as the main variable associated with PD. This family had the highest frequency among all variables included in the model; therefore, it is possible that the lack of association with other less frequently used families may be due to insufficient power of the study.

To perform dose-effect analyses for pesticide families, we used the cumulative lifetime hours of exposure. In comparison to variables defined by the number of years or days of exposure, this variable captures information about duration of spraying (which is related to land size or type of spraying). Nevertheless, using number of years or days of exposure led to similar findings. Because owners of small farms may be more likely to spray pesticides using portable devices or small tractors compared to owners of larger farms, we performed analyses using hectares-years, days, or hours, with similar results.

The timing of exposure may be important but it remains challenging to define the appropriate exposure window since it has been suggested that even developmental exposures may be relevant in PD.[31] In order to exclude exposures that may have occurred during the pre-symptomatic phase, we performed lagged analyses and found results similar to the overall ones.

In this study, we included cases with a recent diagnosis of PD (median disease duration since diagnosis of 1.5 years). We also performed analyses stratified by median disease duration and found that association measures were similar in cases with shorter and longer disease duration; these findings are not in favor of a prevalence-incidence bias.[44]

In conclusion, professional pesticide use was associated with PD in a population characterized by a high prevalence of exposure. These findings may provide leads for further toxicological studies. Our findings for organochlorine insecticides may be particularly important since they are highly persistent in the environment; however, they exclusively concern professional pesticide exposure and no conclusion can be drawn regarding other sources of exposure.

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Figure legends

***Figure 1*. Flow chart for the assessment of exposure to pesticides.**

***Figure 2*. Association between Parkinson's disease and exposure to organochlorine insecticides among men with onset of PD above 65 years and matched controls: dose-effect analysis using a complete-case analysis and multiple imputation of missing variables.**

Odds ratios (OR, 95% CI) were computed using conditional logistic regression models for matched sets. The reference category included subjects not exposed to organochlorine insectides; subjects exposed to any pesticide for gardening exclusively are included in the analysis, but are treated as their own exposure group and excluded from the reference group. Analyses are adjusted for MMSE and cigarette smoking (in pack-years). The median of the distribution of the cumulative lifetime number of hours of exposure to organochlorines was 70 (IQ range=159) hours in exposed cases and controls combined; the median of the distribution of the cumulative lifetime number of years of exposure to organochlorines was 16 (IQ range=26) years in exposed cases and controls combined.

***Figure 3*. Association between Parkinson's disease and exposure to organochlorine insecticides among men by period of exposure and according to age at onset.**

Panels A and B show the frequency of exposure to organochlorines by time period in male cases with age at onset below and above 65 years and in their matched controls. Panels C and D show the corresponding odds ratios computed using conditional logistic regression models for matched sets, based on a complete case analysis or multiple imputation of missing variables. The reference category is represented by subjects not exposed to organochlorine insectides; subjects exposed to any pesticide for gardening exclusively are included in the analysis, but are treated as their own exposure group and excluded from the reference group. Analyses are adjusted for MMSE and cigarette smoking (in pack-years).

***Table 1*. General characteristics of PD patients and controls**

General characteristics	Controls n=557	Cases n=224	OR (95% CI)[a]	p[a]
Median age at onset of PD, years (IQ range)[b]	--	65 (11)	--	--
Median age at diagnosis of PD, years (IQ range)	--	66 (10)		
Median age at the time of the study, years (IQ range)	68 (9)	69 (10)	--	--
Median lag time between diagnosis study, years (IQ range)	--	1.5 (2.3)	--	--
Male sex, % (n)	52 (291)	53 (118)	--	--
Median MMSE (IQ range)	28 (3)	27 (5)	--	<0.001
Cigarette smoking, % (n)[c]				
Never cigarette smoking	69 (380)	77 (172)	1.0 (ref.)	--
Ever cigarette smoking	31 (170)	23 (50)	0.5 (0.4-0.8)	0.003
Ever cigarette smoking, pack-years ≤ 17	16 (85)	15 (32)	0.6 (0.4-1.1)	0.06
Ever cigarette smoking, pack-years > 17	15 (85)	8 (18)	0.4 (0.2-0.7)	0.002
Farming, % (n)[d]				
Never farming	29 (161)	18 (40)	1.0 (ref.)	--
Ever farming	71 (396)	82 (184)	1.9 (1.3-2.9)	0.003
Farming: no. of years ≤ median (41 yrs)[e]	36 (200)	33 (75)	1.4 (0.9-2.2)	0.15
Farming: no. of years > median (41 yrs)[e]	35 (196)	49 (109)	2.7 (1.7-4.3)	<0.001
Pesticide exposure[f, g]				
No pesticide exposure	38 (211)	31 (69)	1.0 (ref.)	-
Exposure for gardening	22 (121)	21 (48)	1.4 (0.9-2.3)	0.18
Professional exposure	40 (225)	48 (107)	1.8 (1.1-3.1)	0.02
Professional exposure: no. of years ≤ median (38 yrs)[e]	21 (116)	24 (54)	1.7 (1.0-2.9)	0.05
Professional exposure: no. of years > median (38 yrs)[e]	19 (109)	24 (53)	2.1 (1.1-3.9)	0.02
Ever well-water drinking, % (n)[h]	64 (353)	65 (144)	1.0 (0.7-1.5)	0.83
Family history of PD (parents, siblings), % (n)[h]	5 (27)	9 (20)	2.1 (1.1-3.9)	0.02

[a]We used conditional logistic regression for matched sets with a varying number of controls to compute ORs (95% CI). MMSE was categorized according to the quartiles of its pooled distribution to perform a trend test.
[b]IQ range: interquartile range.
[c]Values were missing for 7 controls and 2 cases. Trend test for pack-years, p=0.0008.
[d]Farming included farm owners, farm workers, and farm helpers. ORs increased with the number of years of farming (trend, p<0.001).
[e]ORs were computed for each exposure category compared to the reference group (persons who were not farmers or who never used pesticides).
[f]Analyses for pesticides are based on the comparison of exposure status in 224 cases and 557 controls, since it was known for all cases and controls included in this paper.
[g]After adjustment for MMSE level and cigarette smoking (pack-years), the ORs were: professional pesticide exposure, OR=1.7 (95% CI=1.0-2.9); professional exposure ≤ 38 yrs, OR=1.6 (95% CI=0.9-2.8); professional exposure > 38 yrs, OR=2.0 (95% CI=1.0-3.5); trend, p=0.05). ORs increased with the number of years of professional exposure (trend, p=0.01).
[h]Values were missing for 2 controls and 2 cases for both variables.

***Table 2*. PD and professional exposure to three broad categories of pesticides: insecticides, fungicides, and herbicides**

	Insecticides			Fungicides			Herbicides		
Professional pesticide exposure, % (n)	**OR (95% CI)**	**p**	**p[a]**	**OR (95% CI)**	**p**	**p[a]**	**OR (95% CI)**	**p**	**p[a]**
Men									
No	1.0 (reference)	--		1.0 (reference)	--		1.0 (reference)	--	
Yes	2.2 (1.1-4.3)	0.03		1.5 (0.8-3.0)	0.22		1.4 (0.7-2.6)	0.35	
Women									
No	1.0 (reference)	--		1.0 (reference)	--		1.0 (reference)	--	
Yes	1.4 (0.5-3.8)	0.49		3.5 (1.2-10.3)	0.02		1.2 (0.4-3.8)	0.72	
Men, age at onset ≤ median (65 yrs)									
No	1.0 (reference)	--		1.0 (reference)	--		1.0 (reference)	--	
Yes	1.2 (0.5-2.8)	0.67		1.2 (0.5-2.7)	0.72		0.9 (0.4-2.1)	0.81	
No of cumulative hours < median	1.5 (0.6-3.9)	0.39		1.5 (0.6-3.8)	0.35		0.8 (0.3-2.0)	0.59	
No of cumulative hours ≥ median	0.9 (0.3-2.3)	0.77	0.44	0.7 (0.2-2.0)	0.49	0.17	0.9 (0.3-2.2)	0.75	0.95
Men, age at onset > median (65 yrs)									
No	1.0 (reference)	--		1.0 (reference)	--		1.0 (reference)	--	
Yes	4.9 (1.4-17.3)	0.01		2.7 (0.8-8.6)	0.10		2.1 (0.8-5.7)	0.13	
No of cumulative hours < median	4.4 (1.2-16.8)	0.03		2.0 (0.6-7.0)	0.28		2.0 (0.7-6.0)	0.21	
No of cumulative hours ≥ median	5.4 (1.5-20.0)	0.01	0.04	4.8 (1.2-19.3)	0.03	0.02	2.2 (0.8-6.4)	0.14	0.24

ORs are based on separate conditional logistic regression models for matched sets comparing subjects exposed to any of the three broad pesticide categories to subjects who did not report that category of pesticide use (reference group); corresponding exposure frequencies and medians of the distributions of the cumulative lifetime number of hours of exposure in cases and controls are shown in Appendix 1. Subjects exposed to any pesticide for gardening exclusively are included in analyses, but are treated as their own exposure group. All analyses are adjusted for MMSE and cigarette smoking (in pack-years).

[a]P-value for trend (no exposure, < median, ≥ median).

Table 3. **PD and exposure to 29 families of pesticides in men: complete-case analysis and multiple imputation of missing values**

		Complete case analysis		Multiple imputation	
		Men	Men, AO>65 y	Men	Men, AO>65 y
Exposure		**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Insecticides	Carbamate	1.6 (0.7-3.7)	1.2 (0.3-4.7)	1.3 (0.6-2.7)	1.5 (0.4-5.0)
	Organochlorine	2.4 (1.2-5.0)[a]	4.2 (1.5-11.9)[a]	1.9 (1.1-3.5)[a]	3.0 (1.2-7.9)[a]
	Organophosphorus	1.8 (0.9-3.7)	2.9 (0.9-9.1)	1.3 (0.7-2.3)	1.6 (0.7-3.7)
	Pyrethroid	1.4 (0.7-2.8)	1.8 (0.6-5.1)	1.0 (0.6-1.7)	1.1 (0.5-2.6)
	Arsenic	1.5 (0.6-3.7)	1.6 (0.5-5.1)	1.6 (0.8-3.3)	2.7 (1.0-7.3)[a]
Fungicides	Amide	3.1 (1.2-8.3)[a]	4.7 (0.9-23.0)	2.3 (0.9-5.9)	4.0 (0.9-19.1)
	Aromatic	0.6 (0.2-2.3)	Not estimable	0.5 (0.1-1.8)	Not estimable
	Carbamate	1.3 (0.6-2.6)	1.2 (0.3-5.4)	1.0 (0.5-1.8)	0.9 (0.3-2.8)
	Dicarboximide	1.2 (0.4-3.0)	0.8 (0.2-3.4)	0.9 (0.4-2.0)	0.8 (0.2-2.9)
	Dithiocarbamate	2.1 (1.0-4.3)[a]	2.5 (0.8-7.8)	1.6 (0.9-2.9)	2.2 (0.8-5.7)
	Triazole	0.8 (0.4-1.7)	0.8 (0.2-3.5)	0.7 (0.4-1.5)	0.7 (0.2-2.5)
	Copper	1.8 (0.8-3.7)	3.0 (0.8-11.7)	1.5 (0.8-2.8)	2.0 (0.7-6.1)
	Sulfur	1.4 (0.7-3.0)	2.4 (0.7-8.6)	1.3 (0.7-2.5)	1.7 (0.6-4.8)
Herbicides	Amide	1.5 (0.7-3.3)	1.6 (0.5-5.4)	1.5 (0.7-3.1)	1.4 (0.5-4.3)
	Aryloxyphenoxypropionate	1.7 (0.5-5.5)	1.1 (0.1-12.9)	2.0 (0.7-5.8)	1.1 (0.1-14.8)
	Benzoïc acid	0.5 (0.1-1.9)	0.2 (0.1-2.1)	0.5 (0.1-1.7)	0.3 (0.1-2.5)
	Carbamate	0.8 (0.3-2.2)	0.5 (0.1-2.4)	0.7 (0.3-2.1)	0.4 (0.1-1.8)
	Dinitroaniline	0.6 (0.2-1.4)	0.5 (0.1-3.7)	0.7 (0.3-1.6)	0.7 (0.2-3.7)
	Dinitrophenol	1.1 (0.6-2.3)	1.9 (0.7-5.0)	1.3 (0.8-2.3)	1.9 (0.9-4.1)
	Nitrile	2.7 (0.9-7.5)	11.4 (1.4-93.7)[a]	2.2 (0.9-5.6)	5.8 (1.1-29.0)[a]
	Organophosphorus	1.5 (0.8-2.7)	2.4 (0.9-6.0)	1.5 (0.8-2.5)	2.0 (0.8-4.6)
	Phenoxy	1.8 (0.9-3.3)	2.9 (1.1-7.3)[a]	1.7 (0.9-3.0)	2.3 (0.9-5.3)
	Picolinic acid	1.7 (0.8-3.7)	3.0 (0.7-11.8)	1.5 (0.8-3.1)	2.3 (0.8-7.0)
	Quaternary ammonium	1.1 (0.6-2.0)	1.4 (0.6-3.1)	1.2 (0.7-2.1)	1.6 (0.7-3.4)
	Triazine	1.1 (0.6-1.9)	1.9 (0.8-4.3)	1.2 (0.7-2.1)	2.1 (0.9-4.7)
	Triazole	0.8 (0.3-2.1)	1.0 (0.2-4.9)	0.9 (0.4-2.1)	1.2 (0.3-5.0)
	Uracil	1.2 (0.5-3.0)	0.2 (0.1-2.2)	1.2 (0.5-2.8)	0.3 (0.1-2.9)
	Urea	1.1 (0.6-2.1)	2.4 (0.9-6.8)	1.2 (0.7-2.2)	2.0 (0.8-5.0)
	Sodium chlorate	2.5 (0.9-7.6)	2.2 (0.6-8.2)	2.9 (1.0-8.2)[a]	2.7 (0.8-9.3)

ORs are based on separate conditional logistic regression models for matched sets comparing subjects exposed to each pesticide family to subjects who did not report that pesticide use (reference group); corresponding exposure frequencies in cases and controls are shown in Appendix 3. Subjects exposed to any pesticide for gardening exclusively are included in the analysis, but are treated as their own exposure group. All analyses are adjusted for MMSE and cigarette smoking (in pack-years). Arsenic, copper, sulfur, and sodium chlorate are inorganic compounds.

[a]$P < 0.05$.

Appendix 1. Frequency of professional exposure to insecticides, fungicides, and herbicides in PD cases and controls.

	Insecticides		Fungicides		Herbicides	
Exposure, % (n)[a]	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Men (118 cases, 291 controls)						
Missing	3 (3)	3 (8)	3 (3)	2 (6)	1 (1)	0 (1)
No exposure	14 (14)	26 (63)	17 (17)	27 (67)	18 (18)	24 (58)
Professional exposure	83 (84)	71 (176)	80 (81)	70 (174)	81 (82)	76 (188)
Hours (median, IQ range)[b]	158 (340)	175 (286)	308 (679)	375 (964)	317 (555)	276 (440)
Men, age at onset ≤ median (65 yrs; 61 cases, 147 controls)						
Missing	4 (2)	2 (2)	-	2 (2)	2 (1)	-
No exposure	21 (11)	25 (29)	23 (12)	29 (34)	23 (12)	22 (26)
Professional exposure	76 (40)	74 (86)	77 (41)	69 (81)	76 (40)	78 (91)
Hours (median, IQ range)	175 (331)	223 (294)	295 (645)	496 (1633)	407 (596)	326 (501)
Men, age at onset > median (65 yrs; 57 cases, 144 controls)						
Missing	2 (1)	5 (6)	5 (3)	3 (4)	-	1 (1)
No exposure	6 (3)	26 (34)	10 (5)	25 (33)	13 (6)	25 (32)
Professional exposure	92 (44)	69 (90)	83 (40)	72 (93)	88 (42)	75 (97)
Hours (median, IQ range)	147 (368)	129 (195)	322 (768)	210 (895)	214 (417)	234 (345)
Women (106 cases, 266 controls)						
Missing	1 (1)	1 (1)	1 (1)	1 (2)	-	-
No exposure	85 (64)	89 (169)	84 (63)	93 (176)	92 (69)	94 (178)
Professional exposure	13 (10)	10 (19)	15 (11)	6 (11)	8 (6)	6 (11)
Hours (median, IQ range)	52 (687)	78 (147)	95 (680)	264 (490)	48 (30)	80 (349)
Women, age at onset ≤ median (65 yrs; 57 cases, 143 controls)						
Missing	-	1 (1)	3 (1)	2 (2)	-	-
No exposure	83 (33)	86 (85)	83 (33)	90 (89)	90 (36)	92 (91)
Professional exposure	18 (7)	13 (13)	15 (6)	8 (8)	10 (4)	8 (8)
Hours (median, IQ range)	39 (70)	78 (212)	67 (126)	217 (610)	60 (52)	196 (403)
Women, age at onset > median (65 yrs; 49 cases, 123 controls)						
Missing	3 (1)	-	-	-	-	-
No exposure	89 (31)	93 (84)	86 (30)	97 (87)	94 (33)	97 (87)
Professional exposure	9 (3)	7 (6)	14 (5)	3 (3)	6 (2)	3 (3)
Hours (median, IQ range)	698 (717)	69 (84)	140 (680)	264 (336)	37 (6)	42 (61)

[a]Subjects exposed for gardening exclusively are not included in the "No exposure" group. There were 17 male cases (8 ≤ 65 years, 9 > 65 years), 44 male controls (30 ≤ 65 years, 14 > 65 years), 31 female cases (17 ≤ 65 years, 14 > 65 years), 77 female controls (44 ≤ 65 years, 33 > 65 years) who were exposed through gardening exclusively.
[b]Cumulative lifetime number of hours of exposure in professionally exposed subjects. IQ range: interquartile range.

Appendix 2. Frequency of 29 families of pesticides in male cases and controls.

Exposure, % (n)[a]		Men		Men, AO ≤ 65 years		Men, AO > 65 years	
		Cases	Controls	Cases	Controls	Cases	Controls
Insecticides							
Carbamate	Missing	33 (33)	28 (68)	25 (13)	24 (28)	42 (20)	31 (40)
	No exposure	50 (50)	57 (141)	55 (29)	57 (67)	44 (21)	57 (74)
	Professional exposure	18 (18)	15 (38)	21 (11)	19 (22)	15 (7)	12 (16)
Median (IQ range)[b]	Years[c]	15 (13)	10 (11)	15 (13)	12 (12)	15 (19)	10 (8)
Median (IQ range)[b]	Hours[c]	45 (90)	37 (78)	64 (227)	37 (88)	22 (85)	39 (60)
Organochlorine	Missing	32 (32)	26 (63)	28 (15)	20 (23)	35 (17)	31 (40)
	No exposure	24 (24)	39 (96)	30 (16)	41 (48)	17 (8)	37 (48)
	Professional exposure	45 (45)	36 (88)	42 (22)	39 (46)	48 (23)	32 (42)
Median (IQ range)	Years	15 (16)	15 (18)	12 (9)	15 (14)	18 (27)	15 (26)
Median (IQ range)	Hours	45 (80)	60 (108)	40 (82)	58 (82)	72 (248)	60 (142)
Organophosphorus	Missing	37 (37)	27 (67)	30 (16)	20 (23)	44 (21)	34 (44)
	No exposure	26 (26)	39 (96)	30 (16)	39 (45)	21 (10)	39 (51)
	Professional exposure	38 (38)	34 (84)	40 (21)	42 (49)	35 (17)	27 (35)
Median (IQ range)	Years	14 (16)	15 (27)	14 (12)	14 (27)	20 (19)	19 (26)
Median (IQ range)	Hours	75 (145)	90 (214)	75 (150)	90 (218)	60 (110)	72 (199)
Pyrethroid	Missing	25 (25)	20 (50)	15 (8)	16 (19)	35 (17)	24 (31)
	No exposure	46 (46)	52 (129)	51 (27)	50 (59)	40 (19)	54 (70)
	Professional exposure	30 (30)	28 (68)	34 (18)	33 (39)	25 (12)	22 (29)
Median (IQ range)	Years	13 (10)	13 (7)	14 (9)	14 (7)	11 (9)	12 (7)
Median (IQ range)	Hours	72 (124)	60 (100)	82 (156)	66 (102)	53 (101)	30 (78)
Arsenic	Missing	15 (15)	13 (33)	6 (3)	13 (15)	25 (12)	14 (18)
	No exposure	65 (66)	72 (177)	77 (41)	74 (87)	52 (25)	69 (90)
	Professional exposure	20 (20)	15 (37)	17 (9)	13 (15)	23 (11)	17 (22)
Median (IQ range)	Years	17 (16)	9 (15)	18 (16)	12 (17)	14 (15)	7 (14)
Median (IQ range)	Hours	80 (118)	53 (334)	149 (156)	288 (655)	62 (62)	40 (52)
Fungicides							
Amide	Missing	16 (16)	15 (36)	17 (9)	10 (12)	15 (7)	19 (24)
	No exposure	71 (72)	77 (191)	68 (36)	78 (91)	75 (36)	77 (100)
	Professional exposure	13 (13)	8 (20)	15 (8)	12 (14)	10 (5)	5 (6)
Median (IQ range)	Years	12 (7)	8 (9)	13 (9)	8 (5)	10 (6)	5 (13)
Median (IQ range)	Hours	72 (136)	50 (203)	90 (219)	83 (246)	72 (108)	23 (56)
Aromatic	Missing	16 (16)	16 (40)	15 (8)	13 (15)	17 (8)	19 (25)
	No exposure	79 (80)	76 (188)	76 (40)	74 (87)	83 (40)	78 (101)
	Professional exposure	5 (5)	8 (19)	9 (5)	13 (15)	-	3 (4)
Median (IQ range)	Years	6 (4)	9 (11)	6 (4)	6 (8)	6 (4)	16 (14)
Median (IQ range)	Hours	100 (72)	50 (134)	100 (72)	50 (150)	100 (72)	53 (95)

Appendix 2 follows.

Exposure, % (n)		Men		Men, AO ≤ 65 years		Men, AO > 65 years	
		Cases	Controls	Cases	Controls	Cases	Controls
Fungicides (follows)							
Carbamate	Missing	18 (18)	14 (34)	13 (7)	12 (14)	23 (11)	15 (20)
	No exposure	60 (61)	69 (170)	57 (30)	64 (75)	65 (31)	73 (95)
	Professional exposure	22 (22)	17 (43)	30 (16)	24 (28)	13 (6)	12 (15)
Median (IQ range)	Years	9 (11)	10 (15)	10 (11)	10 (17)	6 (7)	8 (16)
Median (IQ range)	Hours	38 (152)	73 (114)	43 (225)	78 (127)	23 (36)	63 (124)
Dicarboximide	Missing	16 (16)	13 (33)	17 (9)	11 (13)	15 (7)	15 (20)
	No exposure	72 (73)	75 (184)	68 (36)	74 (87)	77 (37)	75 (97)
	Professional exposure	12 (12)	12 (30)	15 (8)	15 (17)	8 (4)	10 (13)
Median (IQ range)	Years	15 (16)	12 (16)	21 (18)	12 (19)	9 (12)	8 (14)
Median (IQ range)	Hours	117 (216)	134 (405)	160 (416)	176 (508)	93 (77)	48 (188)
Dithiocarbamate	Missing	21 (21)	16 (40)	19 (10)	15 (17)	23 (11)	18 (23)
	No exposure	46 (46)	58 (144)	43 (23)	54 (63)	48 (23)	62 (81)
	Professional exposure	34 (34)	26 (63)	38 (20)	32 (37)	29 (14)	20 (26)
Median (IQ range)	Years	12 (19)	17 (21)	10 (15)	15 (21)	18 (37)	19 (22)
Median (IQ range)	Hours	93 (238)	136 (426)	93 (119)	155 (480)	99 (386)	117 (154)
Triazole	Missing	11 (11)	12 (29)	4 (2)	13 (15)	19 (9)	11 (14)
	No exposure	69 (70)	70 (174)	66 (35)	59 (69)	73 (35)	81 (105)
	Professional exposure	20 (20)	18 (44)	30 (16)	28 (33)	8 (4)	9 (11)
Median (IQ range)	Years	5 (7)	7 (6)	6 (6)	7 (5)	3 (10)	6 (7)
Median (IQ range)	Hours	46 (127)	38 (92)	64 (209)	40 (76)	18 (65)	30 (230)
Copper	Missing	14 (14)	10 (25)	13 (7)	9 (10)	15 (7)	12 (15)
	No exposure	24 (24)	33 (82)	30 (16)	40 (47)	17 (8)	27 (35)
	Professional exposure	62 (63)	57 (140)	57 (30)	51 (60)	69 (33)	62 (80)
Median (IQ range)	Years	29 (31)	28 (26)	25 (30)	27 (21)	35 (35)	30 (30)
Median (IQ range)	Hours	160 (509)	201 (550)	126 (904)	256 (776)	180 (318)	177 (440)
Sulfur	Missing	13 (13)	11 (26)	9 (5)	9 (10)	17 (8)	12 (16)
	No exposure	27 (27)	34 (85)	34 (18)	40 (47)	19 (9)	29 (38)
	Professional exposure	60 (61)	55 (136)	57 (30)	51 (60)	65 (31)	59 (76)
Median (IQ range)	Years	35 (49)	38 (48)	30 (43)	31 (52)	37 (57)	41 (44)
Median (IQ range)	Hours	217 (724)	316 (857)	180 (1446)	408 (1531)	252 (428)	210 (584)
Herbicides							
Amide	Missing	25 (25)	28 (68)	17 (9)	21 (25)	33 (16)	33 (43)
	No exposure	55 (55)	56 (139)	57 (30)	58 (68)	52 (25)	55 (71)
	Professional exposure	21 (21)	16 (40)	26 (14)	21 (24)	15 (7)	12 (16)
Median (IQ range)	Years	11 (10)	10 (14)	11 (17)	10 (13)	11 (7)	11 (16)
Median (IQ range)	Hours	30 (43)	34 (98)	33 (48)	25 (81)	20 (39)	58 (100)

Appendix 2 follows.

Exposure, % (n)		Men		Men, AO ≤ 65 years		Men, AO > 65 years	
		Cases	Controls	Cases	Controls	Cases	Controls
Herbicides (follows)							
Aryloxyphenoxypropionate	Missing	18 (18)	20 (50)	15 (8)	19 (22)	21 (10)	22 (28)
	No exposure	75 (76)	75 (185)	74 (39)	74 (87)	77 (37)	75 (98)
	Professional exposure	7 (7)	5 (12)	11 (6)	7 (8)	2 (1)	3 (4)
Median (IQ range)	Years	3 (5)	6 (3)	2 (5)	5 (4)	4 (0)	6 (3)
Median (IQ range)	Hours	10 (38)	22 (26)	19 (37)	31 (25)	4 (0)	14 (67)
Benzoïc acid	Missing	21 (21)	21 (52)	17 (9)	17 (20)	25 (12)	25 (32)
	No exposure	75 (76)	74 (182)	77 (41)	78 (91)	73 (35)	70 (91)
	Professional exposure	4 (4)	5 (13)	6 (3)	5 (6)	2 (1)	5 (7)
Median (IQ range)	Years	9 (6)	9 (3)	10 (7)	9 (6)	5 (0)	9 (2)
Median (IQ range)	Hours	20 (7)	44 (56)	20 (13)	54 (50)	20 (0)	35 (63)
Carbamate	Missing	23 (23)	23 (57)	17 (9)	18 (21)	29 (14)	28 (36)
	No exposure	69 (70)	68 (167)	74 (39)	74 (86)	65 (31)	62 (81)
	Professional exposure	8 (8)	9 (23)	9 (5)	9 (10)	6 (3)	10 (13)
Median (IQ range)	Years	9 (21)	10 (11)	7 (9)	10 (11)	19 (24)	9 (7)
Median (IQ range)	Hours	9 (30)	28 (170)	7 (6)	34 (166)	19 (49)	25 (34)
Dinitroaniline	Missing	23 (23)	22 (53)	15 (8)	20 (23)	31 (15)	23 (30)
	No exposure	65 (66)	65 (161)	66 (35)	60 (70)	65 (31)	70 (91)
	Professional exposure	12 (12)	13 (33)	19 (10)	21 (24)	4 (2)	7 (9)
Median (IQ range)	Years	13 (10)	8 (14)	13 (11)	10 (15)	13 (9)	8 (10)
Median (IQ range)	Hours	41 (63)	21 (51)	37 (51)	31 (82)	70 (64)	12 (9)
Dinitrophenol	Missing	27 (27)	26 (64)	19 (10)	23 (27)	35 (17)	29 (37)
	No exposure	46 (46)	51 (126)	57 (30)	53 (62)	33 (16)	49 (64)
	Professional exposure	28 (28)	23 (57)	25 (13)	24 (28)	31 (15)	22 (29)
Median (IQ range)	Years	17 (15)	12 (17)	16 (9)	16 (19)	17 (20)	11 (17)
Median (IQ range)	Hours	72 (91)	54 (99)	88 (150)	65 (123)	65 (85)	51 (61)
Nitrile	Missing	23 (23)	21 (52)	17 (9)	18 (21)	29 (14)	24 (31)
	No exposure	67 (68)	73 (181)	72 (38)	74 (86)	63 (30)	73 (95)
	Professional exposure	10 (10)	6 (14)	11 (6)	9 (10)	8 (4)	3 (4)
Median (IQ range)	Years	8 (7)	4 (5)	9 (13)	3 (4)	7 (5)	6 (5)
Median (IQ range)	Hours	38 (70)	23 (42)	65 (639)	18 (32)	24 (43)	38 (47)
Organophosphorus	Missing	20 (20)	17 (42)	13 (7)	11 (13)	27 (13)	22 (29)
	No exposure	48 (48)	52 (129)	51 (27)	50 (59)	44 (21)	54 (70)
	Professional exposure	33 (33)	31 (76)	36 (19)	39 (45)	29 (14)	24 (31)
Median (IQ range)	Years	10 (10)	8 (6)	10 (15)	7 (5)	11 (7)	10 (5)
Median (IQ range)	Hours	30 (43)	20 (52)	33 (76)	21 (68)	25 (33)	20 (25)
Phenoxy	Missing	21 (21)	17 (41)	15 (8)	18 (21)	27 (13)	15 (20)
	No exposure	36 (36)	46 (114)	45 (24)	49 (57)	25 (12)	44 (57)
	Professional exposure	44 (44)	37 (92)	40 (21)	33 (39)	48 (23)	41 (53)
Median (IQ range)	Years	26 (18)	25 (19)	31 (22)	22 (19)	24 (15)	27 (16)
Median (IQ range)	Hours	139 (194)	121 (213)	168 (190)	122 (211)	86 (199)	96 (215)

Appendix 2 follows.

Exposure, % (n)		Men		Men, AO ≤ 65 years		Men, AO > 65 years	
		Cases	Controls	Cases	Controls	Cases	Controls
Herbicides (follows)							
Picolinic acid	Missing	24 (24)	26 (64)	17 (9)	16 (19)	31 (15)	35 (45)
	No exposure	59 (60)	61 (150)	62 (33)	63 (74)	56 (27)	59 (76)
	Professional exposure	17 (17)	13 (33)	21 (11)	21 (24)	13 (6)	7 (9)
Median (IQ range)	Years	8 (9)	9 (11)	7 (11)	10 (13)	9 (8)	9 (9)
Median (IQ range)	Hours	21 (30)	32 (74)	12 (37)	32 (71)	21 (25)	27 (74)
Quaternary ammonium	Missing	20 (20)	22 (53)	15 (8)	16 (19)	25 (12)	26 (34)
	No exposure	54 (54)	53 (132)	62 (33)	60 (70)	44 (21)	48 (62)
	Professional exposure	27 (27)	25 (62)	23 (12)	24 (28)	31 (15)	26 (34)
Median (IQ range)	Years	14 (11)	13 (11)	15 (12)	11 (14)	14 (7)	14 (8)
Median (IQ range)	Hours	43 (120)	35 (57)	50 (165)	40 (78)	42 (54)	31 (54)
Triazine	Missing	11 (11)	13 (33)	8 (4)	9 (11)	15 (7)	17 (22)
	No exposure	35 (35)	35 (87)	42 (22)	32 (37)	27 (13)	39 (50)
	Professional exposure	55 (55)	51 (127)	51 (27)	59 (69)	58 (28)	45 (58)
Median (IQ range)	Years	20 (16)	19 (17)	20 (18)	20 (20)	21 (14)	18 (12)
Median (IQ range)	Hours	69 (180)	61 (115)	70 (181)	100 (160)	58 (147)	55 (94)
Triazole	Missing	18 (18)	13 (31)	11 (6)	7 (8)	25 (12)	18 (23)
	No exposure	72 (73)	75 (184)	76 (40)	74 (87)	69 (33)	75 (97)
	Professional exposure	10 (10)	13 (32)	13 (7)	19 (22)	6 (3)	8 (10)
Median (IQ range)	Years	15 (17)	13 (12)	14 (14)	13 (13)	24 (21)	14 (11)
Median (IQ range)	Hours	100 (128)	71 (139)	118 (144)	98 (144)	100 (140)	48 (50)
Uracil	Missing	19 (19)	20 (50)	9 (5)	15 (18)	29 (14)	25 (32)
	No exposure	68 (69)	68 (169)	70 (37)	69 (81)	67 (32)	68 (88)
	Professional exposure	13 (13)	11 (28)	21 (11)	15 (18)	4 (2)	8 (10)
Median (IQ range)	Years	13 (6)	8 (13)	11 (9)	8 (9)	18 (5)	10 (14)
Median (IQ range)	Hours	30 (41)	26 (40)	20 (42)	41 (41)	55 (50)	20 (17)
Urea	Missing	23 (23)	26 (64)	17 (9)	18 (21)	29 (14)	33 (43)
	No exposure	49 (49)	49 (121)	53 (28)	46 (54)	44 (21)	52 (67)
	Professional exposure	29 (29)	25 (62)	30 (16)	36 (42)	27 (13)	15 (20)
Median (IQ range)	Years	15 (15)	9 (14)	21 (16)	8 (14)	13 (5)	11 (14)
Median (IQ range)	Hours	65 (134)	35 (122)	108 (161)	60 (149)	36 (80)	17 (33)
Sodium chlorate	Missing	4 (4)	4 (10)	-	1 (1)	8 (4)	7 (9)
	No exposure	88 (89)	91 (224)	96 (51)	96 (112)	79 (38)	86 (112)
	Professional exposure	8 (8)	5 (13)	4 (2)	3 (4)	13 (6)	7 (9)
Median (IQ range)	Years	10 (13)	6 (7)	11 (14)	3 (2)	10 (13)	10 (7)
Median (IQ range)	Hours	15 (34)	13 (9)	11 (14)	7 (10)	15 (57)	14 (4)

[a]Subjects exposed for gardening exclusively are not included in the "No exposure" group. There were 17 male cases (8 ≤ 65 years, 9 > 65 years) and 44 male controls (30 ≤ 65 years, 14 > 65 years) who were exposed through gardening exclusively.
[b]IQ range = interquartile range.
[c]Cumulative lifetime number of years and hours of exposure in professionally exposed subjects computed for each pesticide family.

Appendix 3. Relation between PD and cumulative lifetime hours of pesticide use for 29 families of pesticides in men.

Exposure		Cumulative lifetime number of hours	Men		Men, AO > 65 years	
			OR (95% CI)	Trend[a]	OR (95% CI)	Trend[a]
Insecticides	Carbamate	< median	1.5 (0.5-4.7)		3.5 (0.3-40.9)	
		≥ median	1.6 (0.5-4.8)	0.40	0.6 (0.1-4.0)	0.65
	Organochlorine	< median	2.7 (1.2-6.2)		3.2 (0.9-11.5)	
		≥ median	2.2 (0.9-5.1)	0.19	5.0 (1.6-16.2)	0.01
	Organophosphorus	< median	1.7 (0.8-4.0)		3.4 (0.9-13.3)	
		≥ median	1.9 (0.8-4.4)	0.22	2.4 (0.6-9.1)	0.38
	Pyrethroid	< median	1.5 (0.6-3.6)		1.6 (0.4-6.9)	
		≥ median	1.4 (0.6-3.2)	0.46	1.9 (0.5-6.8)	0.35
	Arsenic	< median	0.9 (0.3-2.9)		0.7 (0.1-4.8)	
		≥ median	2.6 (0.7-9.4)	0.13	3.0 (0.7-12)	0.12
Fungicides	Amide	< median	3 (0.8-10.9)		5.0 (0.4-61.2)	
		≥ median	3.2 (0.9-11.4)	0.10	4.5 (0.6-34.0)	0.13
	Aromatic	< median	0.3 (0.1-2.6)		Not estimable	
		≥ median	1.2 (0.2-6.7)	0.87	Not estimable	--
	Carbamate	< median	2.9 (1.0-8.4)		2.3 (0.4-13.3)	
		≥ median	0.6 (0.2-1.7)	0.36	0.5 (0.1-4.6)	0.40
	Dicarboximide	< median	1.6 (0.4-5.5)		0.3 (0.1-3.3)	
		≥ median	0.9 (0.3-3.0)	0.80	1.5 (0.3-6.8)	0.57
	Dithiocarbamate	< median	2.6 (1.1-6.1)		2.2 (0.6-7.7)	
		≥ median	1.5 (0.6-4.0)	0.60	3.2 (0.7-14.8)	0.17
	Triazole	< median	0.7 (0.2-1.8)		1.5 (0.2-9.8)	
		≥ median	1.0 (0.4-2.4)	0.97	0.4 (0.1-4.0)	0.48
	Copper	< median	1.9 (0.8-4.2)		2.4 (0.6-10.2)	
		≥ median	1.6 (0.7-3.9)	0.74	4.4 (1.0-20.2)	0.08
	Sulfur	< median	1.6 (0.7-3.6)		1.9 (0.5-7.5)	
		≥ median	1.2 (0.5-2.9)	0.90	3.3 (0.8-13.2)	0.11

Appendix 3 follows.

Exposure		Cumulative lifetime number of hours	Men		Men, AO > 65 years	
			OR (95% CI)	Trend[a]	OR (95% CI)	Trend[a]
Herbicides	Amide	< median	1.8 (0.7-4.8)		2.7 (0.6-11.3)	
		≥ median	1.3 (0.5-3.4)	0.70	0.7 (0.1-4.3)	0.69
	Aryloxyphenoxypropionate	< median	4.1 (0.6-30.1)		2.7 (0.1-63.4)	
		≥ median	1.1 (0.3-4.8)	0.77	Not estimable	0.66
	Benzoïc acid	< median	1.6 (0.2-10.2)		0.6 (0.1-7.9)	
		≥ median	Not estimable	0.12	Not estimable	0.30
	Carbamate	< median	1.0 (0.3-3.8)		0.7 (0.1-4.1)	
		≥ median	0.5 (0.1-2.9)	0.46	0.3 (0.1-3.9)	0.34
	Dinitroaniline	< median	0.4 (0.1-1.6)		Not estimable	
		≥ median	0.7 (0.2-2.3)	0.60	1.4 (0.2-12.4)	0.68
	Dinitrophenol	< median	1.1 (0.5-2.5)		2.5 (0.7-9.2)	
		≥ median	1.2 (0.5-2.9)	0.63	1.7 (0.5-5.2)	0.39
	Nitrile	< median	1.2 (0.3-4.8)		7.3 (0.7-77.6)	
		≥ median	7.9 (1.6-38.3)	0.01	22.7 (1.4-365.9)	0.05
	Organophosphorus	< median	1.0 (0.4-2.2)		2.0 (0.6-6.8)	
		≥ median	2.1 (0.9-4.6)	0.08	2.8 (0.8-9.8)	0.09
	Phenoxy	< median	1.7 (0.8-3.7)		4.0 (1.3-12.5)	
		≥ median	1.9 (0.9-3.8)	0.13	2.2 (0.7-6.4)	0.42
	Picolinic acid	< median	2.3 (0.8-6.5)		4.7 (0.7-29.3)	
		≥ median	1.2 (0.4-3.4)	0.75	1.8 (0.3-11.8)	0.51
	Quaternary ammonium	< median	0.9 (0.4-2.0)		0.9 (0.3-2.9)	
		≥ median	1.3 (0.5-3.1)	0.63	1.8 (0.5-6.1)	0.39
	Triazine	< median	0.9 (0.4-1.7)		1.3 (0.5-3.6)	
		≥ median	1.4 (0.7-2.9)	0.21	2.8 (1.0-7.8)	0.04
	Triazole	< median	0.4 (0.1-1.7)		0.8 (0.1-11.7)	
		≥ median	1.2 (0.4-4.1)	0.71	1.1 (0.1-8.8)	0.98
	Uracil	< median	1.1 (0.3-3.9)		Not estimable	
		≥ median	1.3 (0.4-4.2)	0.69	1.0 (0.1-25.2)	0.46
	Urea	< median	0.9 (0.4-2.2)		0.9 (0.2-4.4)	
		≥ median	1.3 (0.6-2.8)	0.44	4.9 (1.3-18.8)	0.02
	Sodium chlorate	< median	1.9 (0.4-8.0)		2.1 (0.4-11.0)	
		≥ median	3.7 (0.8-17.4)	0.07	2.5 (0.4-16.4)	0.23

ORs are based on the comparison of subjects exposed to each of the pesticide families with subjects who did not report that pesticide use (reference group); subjects exposed for gardening exclusively are not included in the reference group. Exposure frequencies and medians of the distributions in cases and controls are shown in Appendix 2. ORs, 95% CI, and p-values were computed using conditional logistic for matched sets with a varying number of controls per set; all analyses are adjusted for MMSE and cigarette smoking (in pack-years).

[a]P-value for trend (no exposure, < median, ≥ median).

Appendix 4. Relation between PD and cumulative lifetime hours of pesticide use for 29 families of pesticides in men (multilple imputation).

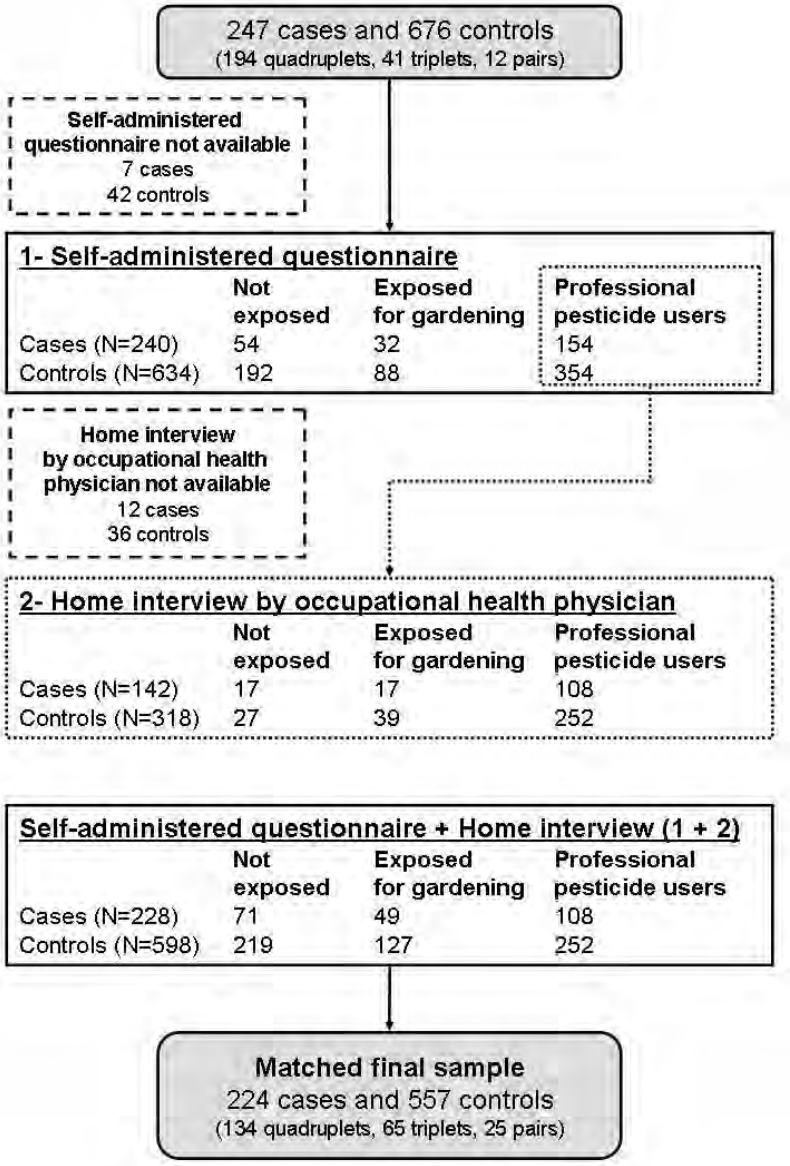
Exposure		Cumulative lifetime number of hours	Men		Men, AO > 65	
			OR (95% CI)	Trend[a]	OR (95% CI)	Trend[a]
Insecticides	Carbamate	< median	1.5 (0.6-3.7)		1.8 (0.4-8.1)	
		≥ median	1.1 (0.4-2.9)	0.82	1.2 (0.3-5.7)	0.78
	Organochlorine	< median	2.1 (1.0-4.3)		2.5 (0.8-8.3)	
		≥ median	1.8 (0.9-3.5)	0.22	3.5 (1.3-9.6)	0.03
	Organophosphorus	< median	1.2 (0.5-2.5)		1.5 (0.5-4.6)	
		≥ median	1.4 (0.7-2.7)	0.41	1.7 (0.7-4.1)	0.34
	Pyrethroid	< median	0.9 (0.4-1.9)		0.7 (0.2-2.9)	
		≥ median	1.0 (0.5-2.1)	0.92	1.6 (0.5-4.7)	0.41
	Arsenic	< median	1.1 (0.4-2.8)		1.4 (0.3-6.8)	
		≥ median	2.1 (0.9-5.4)	0.19	4.3 (1.3-14)	0.03
Fungicides	Amide	< median	2.2 (0.7-7.1)		4.6 (0.4-52.2)	
		≥ median	2.5 (0.7-8.3)	0.19	4.2 (0.4-44.4)	0.25
	Aromatic	< median	0.2 (0.1-2.0)		Not estimable	
		≥ median	0.8 (0.2-4.0)	0.78	Not estimable	--
	Carbamate	< median	1.5 (0.6-3.4)		1.4 (0.3-5.9)	
		≥ median	0.6 (0.2-1.5)	0.25	0.6 (0.1-3.0)	0.48
	Dicarboximide	< median	0.7 (0.2-2.2)		0.5 (0.1-3.4)	
		≥ median	0.9 (0.3-2.9)	0.92	1.2 (0.3-5.4)	0.78
	Dithiocarbamate	< median	2.0 (1.0-4.1)		2.5 (0.8-7.7)	
		≥ median	1.2 (0.5-2.8)	0.80	1.9 (0.5-7.3)	0.45
	Triazole	< median	0.6 (0.2-1.5)		1.1 (0.2-6.5)	
		≥ median	0.9 (0.4-2.1)	0.81	0.4 (0.1-3.1)	0.39
	Copper	< median	1.7 (0.8-3.3)		1.6 (0.5-5.5)	
		≥ median	1.1 (0.5-2.6)	0.72	3.2 (0.9-12.1)	0.08
	Sulfur	< median	1.5 (0.7-3.1)		1.6 (0.5-5.1)	
		≥ median	1.2 (0.5-2.5)	0.90	2.6 (0.7-8.8)	0.18

Appendix 4 follows.

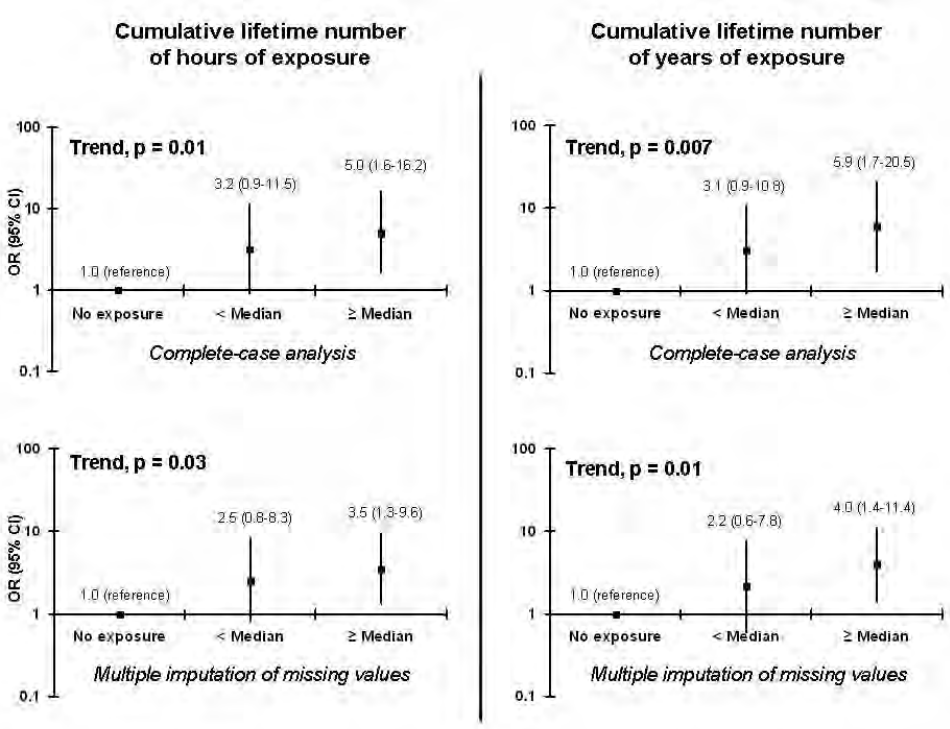
Exposure		Cumulative lifetime number of hours	Men		Men, AO > 65	
			OR (95% CI)	Trend[a]	OR (95% CI)	Trend[a]
Herbicides	Amide	< median	1.5 (0.6-4.0)		1.9 (0.4-8.4)	
		≥ median	1.5 (0.5-3.9)	0.48	1.1 (0.2-5.0)	0.90
	Aryloxyphenoxypropionate	< median	2.6 (0.5-13.1)		2.8 (0.1-63.0)	
		≥ median	1.7 (0.4-6.4)	0.38	Not estimable	0.74
	Benzoïc acid	< median	1.0 (0.2-6.0)		Not estimable	
		≥ median	Not estimable	0.18	Not estimable	0.44
	Carbamate	< median	1.1 (0.3-4.1)		0.5 (0.1-3.1)	
		≥ median	0.4 (0.1-2.0)	0.29	0.3 (0.1-2.9)	0.29
	Dinitroaniline	< median	0.6 (0.2-2.0)		Not estimable	
		≥ median	0.8 (0.3-2.1)	0.63	1.2 (0.2-6.4)	0.89
	Dinitrophenol	< median	1.2 (0.6-2.6)		1.9 (0.7-4.9)	
		≥ median	1.4 (0.7-3.0)	0.34	2.0 (0.7-5.9)	0.19
	Nitrile	< median	1.6 (0.4-6.3)		6.3 (0.8-48.7)	
		≥ median	3.0 (0.9-10.0)	0.07	5.1 (0.5-52.3)	0.17
	Organophosphorus	< median	1.1 (0.5-2.3)		1.9 (0.6-5.9)	
		≥ median	1.8 (0.8-4.0)	0.13	2.0 (0.6-6.5)	0.20
	Phenoxy	< median	1.6 (0.8-3.2)		2.7 (1.0-7.1)	
		≥ median	1.8 (0.9-3.6)	0.13	1.8 (0.7-5.0)	0.57
	Picolinic acid	< median	2.0 (0.8-5.3)		2.3 (0.5-9.9)	
		≥ median	1.1 (0.4-3.0)	0.76	2.3 (0.4-11.8)	0.26
	Quaternary ammonium	< median	0.9 (0.4-2.1)		1.4 (0.5-4.0)	
		≥ median	1.4 (0.6-2.9)	0.43	1.6 (0.6-4.5)	0.36
	Triazine	< median	1.0 (0.5-2.0)		1.7 (0.6-4.4)	
		≥ median	1.4 (0.7-2.7)	0.25	2.7 (1.0-7.4)	0.07
	Triazole	< median	0.5 (0.1-1.9)		0.6 (0.1-6.9)	
		≥ median	1.3 (0.4-4.1)	0.59	2.3 (0.3-16.3)	0.44
	Uracil	< median	1.3 (0.4-4.1)		Not estimable	
		≥ median	1.1 (0.4-3.6)	0.78	0.4 (0.1-5.5)	0.38
	Urea	< median	1.0 (0.5-2.3)		1.3 (0.3-5.4)	
		≥ median	1.4 (0.6-2.9)	0.42	2.7 (0.7-10.5)	0.19
	Sodium chlorate	< median	2.8 (0.7-11.2)		3.3 (0.7-15.7)	
		≥ median	3.0 (0.7-13.1)	0.07	2.1 (0.4-12.8)	0.20

ORs are based on the comparison of subjects exposed to each of the pesticide families with subjects who did not report that pesticide use (reference group). Subjects exposed for gardening exclusively are not included in the reference group. Medians of the distributions in cases and controls are shown in Appendix 2. ORs, 95% CI, and p-values were computed using conditional logistic for matched sets with a varying number of controls per set; all analyses are adjusted for MMSE and cigarette smoking (in pack-years).

[a]P-value for trend (no exposure, < median, ≥ median).



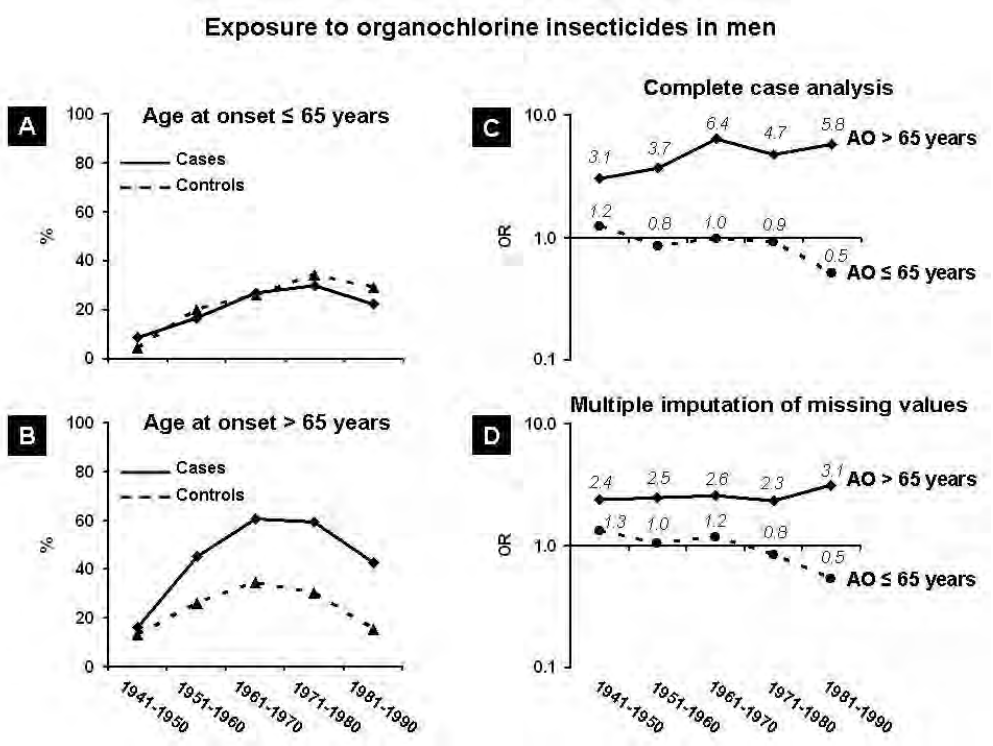
Flow chart for the assessment of exposure to pesticides
190x285mm (96 x 96 DPI)



Association between Parkinson's disease and exposure to organochlorine insecticides among men with onset of PD above 65 years and matched controls: dose-effect analysis using a complete-case analysis and multiple imputation of missing variables.

Odds ratios (OR, 95% CI) were computed using conditional logistic regression models for matched sets. The reference category included subjects not exposed to organochlorine insectides; subjects exposed to any pesticide for gardening exclusively are included in the analysis, but are treated as their own exposure group and excluded from the reference group. Analyses are adjusted for MMSE and cigarette smoking (in pack-years). The median of the distribution of the cumulative lifetime number of hours of exposure to organochlorines was 70 (IQ range=159) hours in exposed cases and controls combined; the median of the distribution of the cumulative lifetime number of years of exposure to organochlorines was 16 (IQ range=26) years in exposed cases and controls combined

254x190mm (96 x 96 DPI)



Association between Parkinson's disease and exposure to organochlorine insecticides among men by period of exposure and according to age at onset.
Panels A and B show the frequency of exposure to organochlorines by time period in male cases with age at onset below and above 65 years and in their matched controls. Panels C and D show the corresponding odds ratios computed using conditional logistic regression models for matched sets, based on a complete case analysis or multiple imputation of missing variables. The reference category is represented by subjects not exposed to organochlorine insectides; subjects exposed to any pesticide for gardening exclusively are included in the analysis, but are treated as their own exposure group and excluded from the reference group. Analyses are adjusted for MMSE and cigarette smoking (in pack-years).
254x190mm (96 x 96 DPI)