ORIGINAL ARTICLE

Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study

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Objective: To investigate the associations between Parkinson's disease and other degenerative parkinsonian syndromes and environmental factors in five European countries.

Methods: A case–control study of 959 prevalent cases of parkinsonism (767 with Parkinson's disease) and 1989 controls in Scotland, Italy, Sweden, Romania and Malta was carried out. Cases were defined using the United Kingdom Parkinson's Disease Society Brain Bank criteria, and those with drug-induced or vascular parkinsonism or dementia were excluded. Subjects completed an interviewer-administered questionnaire about lifetime occupational and hobby exposure to solvents, pesticides, iron, copper and manganese. Lifetime and average annual exposures were estimated blind to disease status using a job-exposure matrix modified by subjective exposure modelling. Results were analysed using multiple logistic regression, adjusting for age, sex, country, tobacco use, ever knocked unconscious and family history of Parkinson's disease.

Results: Adjusted logistic regression analyses showed significantly increased odds ratios for Parkinson's disease/parkinsonism with an exposure–response relationship for pesticides (low vs no exposure, odds ratio (OR) = 1.13, 95% CI 0.82 to 1.57, high vs no exposure, OR = 1.41, 95% CI 1.06 to 1.88) and ever knocked unconscious (once vs never, OR = 1.35, 95% CI 1.09 to 1.68, more than once vs never, OR = 2.53, 95% CI 1.78 to 3.59). Hypnotic, anxiolytic or antidepressant drug use for more than 1 year and a family history of Parkinson's disease showed significantly increased odds ratios. Tobacco use was protective (OR = 0.50, 95% CI 0.42 to 0.60). Analyses confined to subjects with Parkinson's disease gave similar results.

Conclusions: The association of pesticide exposure with Parkinson's disease suggests a causative role. Repeated traumatic loss of consciousness is associated with increased risk.

Parkinson's disease is a neurodegenerative disease characterised by progressive degeneration of the dopaminergic neurons of the substantia nigra. It is the second commonest neurodegenerative disease after Alzheimer's disease, and in the UK has a lifetime prevalence of between 0.1 and 0.3% of the population.[1] There is evidence that both genetic and environmental factors are important determinants,[2] and a family history of the disease has been shown to be a risk factor.[3 4] It seems likely that Parkinson's disease is not a single disease but a number of phenotypically similar illnesses. A variable range of genetic and environmental interactions may produce these conditions and it may be that any individual risk factor will only affect susceptible subjects.

The discovery that 1-methyl-4-phenyl tetrahydropyridine, a contaminant of a synthetic opiate, can cause parkinsonism through its neurotoxic metabolite, 1-methyl-4-phenylpyridinium, stimulated interest in environmental chemical exposures as risk factors for Parkinson's disease.[5] Many case–control studies have investigated the association between Parkinson's disease and pesticide use and some, but not all, have found an association.[3 6 7] Use of well water, rural living and agricultural employment have also been implicated as risk factors, although studies have given conflicting results.[3 8] If there is an association with these factors it may be that they are simply surrogate measures of pesticide exposure.

A Danish cohort study found an increased risk of first hospital admission with Parkinson's disease in agricultural workers.[9] A prospective cohort study in Hawaii (the Honolulu Heart Program) found that plantation work for more than 10 years was associated with an increased relative risk of Parkinson's disease.[10] A cohort study of workers exposed to pesticides in Washington State, using detailed exposure information, found a marginally non-significant increased prevalence ratio of Parkinson's disease among those with the longest exposures.[11] A prospective cohort study in southwestern France (the PAQUID study) has reported an increased relative risk of Parkinson's disease among men with occupational pesticide exposure.[12]

Although most studies show a positive association between pesticide exposure and Parkinson's disease, no specific agent has been implicated consistently. Agriculture employs a range of pesticides and so identifying the causative agent is extremely difficult. Similarly, the degree of pesticide exposure that may lead to Parkinson's disease is unknown. Necropsy studies have found increased levels of organochlorine pesticides in the brains of patients with Parkinson's disease.[13] Acute reversible parkinsonism has been described after organophosphate pesticide poisoning.[14] One German case–control study found an association between the use of organochlorine compounds and alkylated phosphates/carbamates and Parkinson's disease.[15] Cases of parkinsonism have been reported after occupational exposure to maneb: a manganese-containing carbamate pesticide (manganese ethylene-bis-dithiocarbamate).[16] Paraquat, a widely used bipiridyl herbicide, is structurally similar to 1-methyl-4-phenylpyridinium and has been linked to parkinsonism in both epidemiological surveys[17]

Abbreviations: AAI, average annual intensity; CE, cumulative exposure; OEL, occupational exposure limit; OR, odds ratio; UK PDS, United Kingdom Parkinson's Disease Society

and laboratory work,[18] while rotenone, another insecticide, is used to induce parkinsonism in a rat model of the disease.[19]

Some,[15 20] but not all,[21] case–control studies have found a moderately increased risk of Parkinson's disease in association with organic solvent exposure. In one study a job-exposure matrix failed to confirm the self-reported association between solvent exposure and Parkinson's disease.[15] Few studies have examined metal exposures as risk factors for Parkinson's disease.[8] An ecological study in Michigan found that Parkinson's disease mortality was more common in those counties with metalworking industries.[22] Some case–control studies have found associations between copper and manganese exposure and Parkinson's disease, but others have not.[8] Racette *et al* reported a higher prevalence of parkinsonism in male welders in Alabama than in the general population.[23]

The current evidence for occupational risk factors for Parkinson's disease has several weaknesses. Many studies of occupational exposures have had small sample sizes. There have been few studies of occupational exposures to solvents or metals. The exposure estimates employed in some studies have been relatively crude, sometimes as simple as *ever/never* exposed or job title classifications. It is known that such exposure surrogates may lead to misclassification of exposure.[24]

We wished to determine the increase in risk of degenerative parkinsonian syndromes, in general, and Parkinson's disease, specifically, in those exposed to solvents, pesticides, iron, copper or manganese. We included patients with other degenerative parkinsonian conditions as well as Parkinson's disease because (*a*) it allowed us to assess whether they share common environmental and genetic risk factors; (*b*) diagnosis is inaccurate: 10–20% of cases labelled as Parkinson's disease turn out to be another degenerative parkinsonian syndrome and vice versa.

METHODS

Study design

We undertook a five-centre case–control study set in northern Scotland (Grampian region and Easter Ross), southeastern Sweden (Östergötland and Jönköping counties), northern Italy (Emilia-Romagna region), eastern Romania (metropolitan Bucharest) and Malta (including the island of Gozo). In each centre we aimed at recruiting 200 prevalent cases of parkinsonism and 400 controls. Our study received approval from each centre's research ethics committee and, additionally, the full study was subject to review by a European Union research ethics panel. In Italy, cases were enrolled by neurologists as consecutive patients attending outpatients' clinics at the Neuroscience Department, University Hospital of Parma or at the Neurological Division, Hospital of Fidenza (Parma) (100 cases from each centre). In Malta, cases were either referred by neurologists or identified from a register of patients receiving L-Dopa treatment for Parkinson's disease. In Scotland, cases were identified by review of the records of patients attending neurology and medicine for the elderly outpatient clinics. In Sweden and Romania, cases were identified by neurologists from their clinic lists. Potential subjects were then approached by a research nurse or research assistant and invited to participate in the study.

Patients were classified as having Parkinson's disease or parkinsonism using the United Kingdom Parkinson's Disease Society Brain Bank (UK PDS Brain Bank) clinical diagnostic criteria.[25] Cases of vascular or drug-induced parkinsonism were excluded from the study, as were those with dementia. A neurologist confirmed the diagnosis at recruitment in two centres (Parma and Linköping), but owing to resource limitations this was not possible in the other centres where review of hospital records was employed to categorise cases. A random review of patients classified using hospital records was undertaken in one centre (Scotland).

Controls

Controls were group-matched to the cases for age and sex and were recruited from anticoagulant clinics (Italy), hospital inpatients (Romania), the community (Sweden) and a mixture of community controls and hospital outpatients (Scotland, Malta). In Scotland, the hospital outpatients were principally recruited from respiratory and orthopaedic outpatient departments and had a range of conditions. In Malta, the hospital outpatients were recruited at the bleeding room at St Luke's Hospital, which serves most outpatient departments and collects blood from those outpatients requiring blood tests. Care was taken to ensure that cases and controls were drawn from the same geographical areas. We did not tell participants the precise aims of the study to minimise recall bias.

Interviewer-administered questionnaire

A questionnaire in English was developed, piloted and translated into Italian, Swedish, Romanian and Maltese. Questionnaires were translated by bilingual physicians familiar with the relevant medical and occupational terminology and so back-translation was not employed. Interviewers, trained to minimise the risk of biased data collection, administered the questionnaire. A history of lifetime employment was gathered, together with data relating to the duration and likely intensity of occupational and hobby exposure to target agents (solvents, pesticides, iron, copper and manganese). We recorded episodes of private water supply use (well, river or spring) by both duration and geographical location. Smoking, alcohol and education histories were obtained. Inquiry as to the use of anxiolytic drugs, antidepressant drugs or sleeping tablets for more than 1 year was made. History of having been knocked unconscious (defined as any loss of consciousness) and family history of Parkinson's disease in first- and second-degree relatives was recorded. No information about the timing of either head injury or drug use was sought.

Exposure estimation

The exposure estimation methodology has been described previously.[26] Briefly, a job exposure matrix was produced for the most commonly reported occupations by an occupational hygienist. Exposures were estimated with reference to the current UK occupational exposure limit (OEL) for mixed solvents, a typical pesticide employed in the task or for iron, copper or manganese, in the air.[27] This job exposure matrix allowed exposure to each target material to be categorised as zero, low, medium or high. The exposure intensity was evaluated for the three primary occupational exposure routes (inhalation, dermal, and ingestion), where applicable. The resulting exposure estimate was then modified using subjective exposure estimation techniques similar to those first used by Fidler *et al*[28] and subsequently refined.[29] Subjective exposure models employ knowledge of factors that determine exposure to estimate likely workplace exposures. These factors include ventilation, method of use (eg, spray painting may generate 10 times the solvent exposure of brush painting), and protective measures used. We partially validated this exposure assessment method using data from another study by comparing these estimates with previously validated exposure reconstructions.[26] Agreement was high, with a Spearman's correlation (r_s) of 0.89 ($p<0.01$). The results of our quality assurance system for exposure estimates show a high degree of repeatability over time (Spearman's $r_s = 0.98$, $p<0.01$) and between assessors (Spearman's $r_s = 0.88$, $p<0.01$). For repeatability over time (99 scenarios), the mean bias (second assessment/first assessment)

Table 1 Background information for cases and controls

Data	All cases (n = 959)	Cases with Parkinson's disease (n = 767)	Controls (n = 1989)	All cases vs controls (p value)
Age, mean (SD)	69.9 (9.5)	69.8 (9.2)	69.8 (10.0)	
Sex, No (%)				
Male	537 (56)	426 (56)	1057 (53)	
Female	422 (44)	341 (44)	932 (47)	
Age left school (years), mean (SD)	14.5 (2.6)	14.5 (2.6)	14.4 (2.7)	0.20†
Currently working, No (%)	90 (9)	66 (9)	334 (17)	0.001‡
Friend/relative helped with responses, No (%)	287 (30)	227 (30)	214 (11)	0.001‡
Age at diagnosis (years), mean (SD)	62.4 (10.3)	61.6 (9.9)	n/a	
Interview quality assessment, No (%)*				
Implausible	4	2	9	0.001§
Poor/confused, but plausible	176 (19)	137 (18)	253 (13)	
Good	766 (81)	616 (82)	1685 (87)	

*Interview quality was categorised by the interviewer as implausible when the subject was unable to respond to basic questioning or provided data that were illogical or implausible. Where recall was occasionally poor or confused, but in the main sounded plausible, this was coded as poor/confused, but plausible. Where the subject provided good, precise responses and the work history was well described the interview quality was categorised as good.
†t Test; ‡χ^2 test; §χ^2 test combining ''implausible'' and ''poor/confused, but plausible'' categories.

was 1.11, with both the median and mode being 1.0, and 85% of the ratios between 0.5 and 2.0. For interobserver variability (238 scenarios), the mean bias of the cumulative exposure (CE) estimates (second assessor/first assessor) was 3.7, but this figure was highly skewed by six scenarios for which the bias was >10. The median and mode figures for bias were 1.0, with over 60% of the ratios between 0.5 and 2.0.

We expressed our exposure estimation results with reference to the current UK OELs for these agents,[27] using judgment as to the most likely agents for the described task where (as was often the case) the specific chemical agent was not recalled. Exposure intensity for each job was combined with data on exposure duration (number of hours, days per year and years exposed) to calculate a job CE. This was expressed in OEL.years where 1 OEL.year is equivalent to working at the UK occupational exposure limit for 8 hours a day for 240 days a year. Job CE values were summed to provide a lifetime CE to that chemical group. The exposure metric used in the analysis is the average annual intensity (AAI) of exposure and this is derived by dividing the lifetime CE by the number of years of exposure to that material. The AAI is expressed in OEL units where, for example, 0.5 is equivalent to having worked for 240 days, 8 hours a day at 50% of the OEL for the total number of years exposed. These analyses were repeated using lifetime CE.

Statistical analysis

We undertook statistical analyses relating the various exposures to disease state (Parkinson's disease or parkinsonism versus controls). Demographic characteristics of the cases and controls were compared using t tests and χ^2 tests. For the unadjusted analysis, we tabulated the numbers of cases and controls with and without each risk factor and then calculated odds ratios (ORs) and their 95% confidence intervals. Initially we calculated the odds ratios for any exposure to solvents, pesticides and any of the three metals versus no exposure. Then, odds ratios for having high and low exposure compared with no exposure were obtained. We defined the split between high and low exposure as being the median AAI of exposure of those exposed and used AAI as the exposure metric for all analyses. The median AAI values of those exposed were: solvents 0.054 OEL units, pesticides 0.003 OEL units, iron 0.19 OEL units, manganese 0.20 OEL units, copper 0.02 OEL units.

Multiple logistic regression was used to obtain estimates of odds ratios for the same exposures adjusting for age, sex, country, ever used tobacco, ever been knocked unconscious and

Table 2 Summary of average annual intensity (AAI) of exposures by country and case–control status

	Scotland		Sweden		Romania		Italy		Malta	
	Cases (n = 202)	Controls (n = 418)	Cases (n = 201)	Controls (n = 401)	Cases (n = 178)	Controls (n = 370)	Cases (n = 200)	Controls (n = 398)	Cases (n = 178)	Controls (n = 402)
Solvents	0 (0–106) {0–2.82}	0.06 (0–100) {0–3.04}	0 (0–138) {0–0.56}	0 (0–169) {0–1.96}	0 (0–117) {0–0}	0 (0–120) {0–0}	0 (0–122) {0–0.98}	0 (0–125) {0–0.87}	0 (0–187) {0–0}	0 (0–391) {0–0}
Pesticides	0.005 (0–89.6) {0–0.18}	0 (0–50) {0–0.04}	0 (0–50) {0–0}	0 (0–29.1) {0–0}	0 (0–30) {0–0}	0 (0–25) {0–0}	0 (0–8.4) {0–0}	0 (0–10.4) {0–0}	0 (0–65) {0–0}	0 (0–61) {0–0}
Iron	0 (0–285) {0–0}	0 (0–115) {0–0}	0 (0–150) {0–0}	0 (0–150) {0–0}	0 (0–206) {0–0}	0 (0–194) {0–0}	0 (0–188) {0–0}	0 (0–146) {0–0}	0 (0–144) {0–0}	0 (0–213) {0–0}
Manganese	0 (0–285) {0–0}	0 (0–129) {0–0}	0 (0–150) {0–0}	0 (0–150) {0–0}	0 (0–206) {0–0}	0 (0–194) {0–0}	0 (0–188) {0–0}	0 (0–125) {0–0}	0 (0–144) {0–0}	0 (0–213) {0–0}
Copper	0 (0–150) {0–0}	0 (0–100) {0–0}	0 (0–20) {0–0}	0 (0–150) {0–0}	0 (0–33) {0–0}	0 (0–81) {0–0}	0 (0–100) {0–0.48}	0 (0–100) {0–0.05}	0 (0–82.5) {0–0}	0 (0–32.6) {0–0}

Figures represent exposure per year exposed: median (range) {interquartile range}.
100 = occupational exposure limit (OEL).
Not all interviews were graded for quality: the percentages shown are based on the 946 cases of PD or parkinsonism, 755 cases of PD and 1947 controls graded for quality.

Table 3 Adjusted results† (all cases vs controls)

	OR (95% CI)
Ever used tobacco containing product‡	0.50 (0.42 to 0.60)
Ever consumed beer, wine or spirits regularly	1.01 (0.83 to 1.23)
House with water supply from river or well‡§	1.18 (0.97 to 1.43)
Ever been knocked unconscious‡	1.57 (1.29 to 1.91)
Knocked unconscious:	
Once vs never	1.35 (1.09 to 1.68)
More than once¶ vs never	2.53 (1.78 to 3.59)
Ever had a general anaesthetic for an operation	0.81 (0.67 to 0.98)
Ever been treated by doctor after exposure to gas/smoke	0.99 (0.49 to 1.20)
Ever taken sleeping pills for >1 year	1.33 (1.07 to 1.65)
Ever taken medicines for anxiety for >1 year	1.95 (1.54 to 2.47)
Ever taken medicines for depression for >1 year	1.92 (1.49 to 2.49)
First-degree family history of Parkinson's disease‡	4.85 (3.43 to 6.86)
Any exposure to solvents	1.01 (0.84 to 1.23)
Any exposure to pesticides	1.29 (1.02 to 1.63)
Any exposure to iron	1.21 (0.87 to 1.44)
Any exposure to manganese	1.05 (0.81 to 1.37)
Any exposure to copper	1.00 (0.74 to 1.34)
Average annual intensity of exposure	
Solvents:	
Low exposure* vs no exposure	1.17 (0.92 to 1.50)
High exposure* vs no exposure	0.88 (0.69 to 1.12)
Pesticides:	
Low exposure* vs no exposure	1.13 (0.82 to 1.57)
High exposure* vs no exposure	1.41 (1.06 to 1.88)
Iron:	
Low exposure* vs no exposure	1.11 (0.79 to 1.56)
High exposure* vs no exposure	1.14 (0.82 to 1.59)
Manganese:	
Low exposure* vs no exposure	1.22 (0.86 to 1.73)
High exposure* vs no exposure	0.92 (0.64 to 1.32)
Copper:	
Low exposure* vs no exposure	1.05 (0.70 to 1.59)
High exposure* vs no exposure	0.94 (0.64 to 1.40)

*Cut-off point for low/high exposure taken to be median value of those exposed.
†Logistic regression adjusting for age, sex, country, ever used tobacco-containing product, ever knocked unconscious and first-degree family history of Parkinson's disease.
‡Odds ratios derived from a single logistic regression model with these factors as the only covariates.
§Excluding Malta water supply data.
¶Number of times knocked unconscious were once (n = 460), twice (n = 74), three times (n = 37), four times (n = 19), five times (n = 8), six times (n = 4), seven times (n = 1), 10 times (n = 4) and 20 times (n = 1).

first-degree family history of Parkinson's disease. We then repeated these analyses restricting cases to those with a diagnosis of Parkinson's disease. We did not adjust the p values for multiple testing.

RESULTS

Recruitment took place between June 2000 and September 2004. The overall response rate in Scotland, Sweden, Italy and Romania was 64% (77% for cases and 59% for controls). The response rate for cases in Malta was 66%, but no comparable figure was available for controls. A total of 959 cases of parkinsonism (of whom 767 met the UK PDS Brain Bank criteria for Parkinson's disease) and 1989 controls matched for age and gender were recruited. Table 1 shows descriptive data for all subjects. Table 2 shows a summary of the average annual intensity of exposures by country of residence and case–control status. The proportion of cases defined as parkinsonism using the UK PDS Brain Bank criteria was 10% in Romania, 16% in Scotland, 19% in Sweden, 21% in Italy and 34% in Malta. In Scotland, a centre that had employed note-based classification, a neurologist reviewed a random sample of 15 cases. All subjects examined met the UK PDS Brain Bank criteria for parkinsonism but 2/12 (17%) cases of Parkinson's disease were reclassified as having a Parkinson's plus condition.

Owing to difficulties in the interpretation of the question about water supply in Malta, the results for private water supply exclude Malta.

Initial univariate analyses for all cases and controls suggested a protective effect for subjects ever having used tobacco products (data not shown). Significantly increased odds ratios were found for private water supply, ever having been knocked unconscious, and prolonged use of hypnotic drugs, anxiolytic drugs or antidepressants, and first-degree family history of Parkinson's disease. A significant relationship was found with the frequency of having been knocked unconscious. Increased odds ratios for any exposure to solvents, pesticides, iron, manganese and copper were found, but this association was statistically significant only for pesticides. There was an exposure–response relationship between the AAI of exposure to pesticides and parkinsonism (low exposure vs no exposure, OR = 1.19, 95% CI 0.90 to 1.57, high exposure vs no exposure, OR = 1.56, 95% CI 1.19 to 2.04). The median AAI of exposure to pesticides in the low exposure group was 0.0004 OEL units (range 0.0–0.003) and in the high pesticide exposure group the median exposure was 0.019 OEL units (range 0.003–0.89).

Multiple logistic regression analyses for all cases and controls, adjusting for age, sex, country, ever having used tobacco, ever having been knocked unconscious and first-degree family history of Parkinson's disease, provided similar results (table 3) to the unadjusted analyses. Significantly raised odds ratios were found for ever having been knocked unconscious, ever having taken hypnotic drugs, anxiolytic drugs or antidepressants for more than 1 year, and for first-degree family history of Parkinson's disease. Tobacco use was shown to be protective (OR = 0.50, 95% CI 0.42 to 0.60). There was evidence of an exposure–response relationship for having been knocked unconscious (once vs never, OR = 1.35, 95% CI 1.09 to 1.68, more than once vs never, OR = 2.53, 95% CI 1.78 to 3.59). There was a weaker association for pesticide exposure (low exposure vs no exposure, OR = 1.13, 95% CI 0.82 to 1.57, high exposure vs no exposure, OR = 1.41, 95% CI 1.06 to 1.88).

Comparing only the subjects with Parkinson's disease with all controls gave very similar results for both univariate and multivariate analyses (table 4) as the all cases analyses. Analyses using the CE metric gave very similar results to those presented here.

DISCUSSION

The Geoparkinson study is one of the largest case–control studies to date of genetic, environmental and occupational risk factors for Parkinson's disease or other degenerative parkinsonian syndromes. The genetic analyses (reported separately) have examined 15 candidate polymorphisms as potential modifiers of chemical toxicity. We have used an unusually detailed method to estimate exposure, integrating data on both occupational and hobby exposure to produce estimates of total exposure to the target agents. The advantage of this approach is that it provides a quantitative measure of exposure and can provide useful information about the adequacy of current exposure standards to prevent Parkinson's disease. The results suggest that relatively low intensity exposures to pesticides may increase risks. On the contrary, they suggest that, in general, risks from solvents and metals are less important in this respect. However, we return to this in the accompanying paper, where we examine exposure–gene interactions.

A major problem in case–control studies is that of recall bias. We have tried to deal with this by the use of lifetime occupational histories, the use of prompts (''In this job was there use of…?'') and the production of detailed exposure estimates. Recall bias is most likely to lead to differential reporting for brief exposures. Under-reporting of short-term

Table 4 Adjusted results† (Parkinson's disease only vs controls)

	OR (95% CI)
Ever used tobacco containing product‡	0.48 (0.40 to 0.58)
Ever consumed beer, wine or spirits regularly	0.92 (0.74 to 1.15)
House with water supply from river or well‡§	1.23 (1.00 to 1.52)
Ever been knocked unconscious‡	1.52 (1.23 to 1.88)
Knocked unconscious:	
Once vs never	1.28 (1.01 to 1.62)
More than once vs never	2.56 (1.78 to 3.69)
Ever had a general anaesthetic for an operation	0.74 (0.61 to 0.91)
Ever been treated by doctor after exposure to gas/smoke	1.24 (0.60 to 2.57)
Ever taken sleeping pills for >1 year	1.38 (1.10 to 1.75)
Ever taken medicines for anxiety for >1 year	2.00 (1.55 to 2.57)
Ever taken medicines for depression for >1 year	1.90 (1.44 to 2.51)
First-degree family history of Parkinson's disease‡	4.63 (3.21 to 6.69)
Any exposure to solvents	1.06 (0.86 to 1.30)
Any exposure to pesticides	1.25 (0.97 to 1.61)
Any exposure to iron	1.07 (0.82 to 1.40)
Any exposure to manganese	0.98 (0.73 to 1.31)
Any exposure to copper	1.01 (0.73 to 1.39)
Average annual intensity of exposure to:	
Solvents:	
Low exposure* vs no exposure	1.21 (0.93 to 1.57)
High exposure* vs no exposure	0.94 (0.72 to 1.21)
Pesticides:	
Low exposure* vs no exposure	1.09 (0.77 to 1.55)
High exposure* vs no exposure	1.39 (1.02 to 1.89)
Iron:	
Low exposure* vs no exposure	1.05 (0.73 to 1.51)
High exposure* vs no exposure	1.10 (0.77 to 1.59)
Manganese:	
Low exposure* vs no exposure	1.10 (0.75 to 1.62)
High exposure* vs no exposure	0.88 (0.59 to 1.30)
Copper:	
Low exposure* vs no exposure	1.09 (0.71 to 1.69)
High exposure* vs no exposure	0.94 (0.61 to 1.43)

*Cut-off point for low/high exposure taken to be median value of those exposed.
†Logistic regression adjusting for age, sex, country, ever used tobacco-containing product, ever knocked unconscious and first-degree family history of Parkinson's disease.
‡Odds ratios derived from a single logistic regression model with these factors as the only covariates.
§Excluding Malta water supply data.

exposures among controls would have little impact on our quantitative exposure estimates. This is in contrast to the large effect recall bias might have in studies that use exposure metrics such as *ever/never* exposed. More cases than controls had the assistance of a relative or friend in completing the interview. This, together with the proportion of cases whose interview responses were held to be poor/confused but plausible (18% of Parkinson's disease cases vs 13% of controls), suggests that cognitive impairment was commoner among cases. This would tend to lead to under-reporting of exposures among cases and so bias the study downwards. However, cases may have been more likely than controls to reflect on past exposures because of concern about their illness, so leading to over-reporting of exposures among cases.

In this study some subjects clinically held to have Parkinson's disease were classified as having parkinsonism when the UK PDS Brain Bank criteria were applied. As a result, the category parkinsonism comprised a mixture of patients with Parkinson's disease and other degenerative parkinsonian syndromes. The numbers of subjects, classified as parkinsonism, with a Parkinson's plus condition such as progressive supranuclear palsy or multisystem atrophy was too small for further study. The variation in the numbers of subjects with parkinsonism across the five centres may, in part, reflect differing methods of case ascertainment (neurologist review versus note-based classification).

We found an increased odds ratio for work with pesticides, with a significant exposure–response relationship. Many previous studies have found such an association, but few have established an exposure–response relationship,[17] perhaps owing to small sample size[6] or poor exposure assessment. One limitation of this study (and in most previous retrospective case–control studies) was our inability to establish which pesticides subjects had been exposed to, as most participants were unable to provide this information. Our estimates were generated for typical pesticides used for the agricultural class or activity described. For example, we used paraquat dichloride (OES: 0.1 mg/m^3 8 hour time-weighted average exposure) for herbicidal tasks in gardening hobbies or jobs. We acknowledge that many pesticides do not have UK occupational exposure limits and that our method of using a generic ''pesticide'' metric to describe exposure to a diverse range of chemicals is based on the assumption that all pesticides act in an additive manner with respect to Parkinson's disease. While we recognise the limitations of this approach, we believe that the quantitative values assigned to pesticide exposures represent a considerable improvement on simpler classification systems.

Our use of the AAI as our exposure metric allows us to classify exposure according to intensity and is much less prone to exposure misclassification than cruder metrics such as *ever/never* exposed or number of years of exposure. We acknowledge that the AAI is not a cumulative metric and will not differentiate between a person who works at 50% of the OEL for 1 year or 20 years. However, the AAI quantifies exposure intensity and we believe that this is a more useful measure than cruder metrics when setting exposure standards.

A specific weakness of our exposure metric (AAI) is that it tends to underestimate pesticide exposure owing to the seasonal nature of pesticide use. We found that pesticide exposure was generally intermittent, both for recreational (4–8 days a year for an hour or less) and occupational applications (10–40 days a year; 4–8 hours a day). In contrast, solvent and metal exposures typically arose from regular and often, daily, occupational use. As a result, caution must be exercised in interpreting the pesticide results in comparison with those for solvents and metals. A recreational user with an AAI of 0.0004 OEL units is likely to have been exposed to pesticides at about 10% of the OEL for 1 hour in each of 6 days per year. A farmer with an AAI of 0.05 OEL units, exposed to pesticides for 20 days per year, will have been exposed to approximately 50% of the OEL for that pesticide on each of those 20 days.

No associations were found with solvent exposure; however, we report our finding of gene–solvent interactions in our accompanying paper. Evidence that metal exposures were risk factors for parkinsonism or Parkinson's disease was lacking.

Head injury (defined as frequency of ever having been knocked unconscious) showed an exposure–response relationship with Parkinson's disease, and this, if confirmed, has

Policy implications

- Pesticide use is associated with Parkinson's disease and this has implications for occupational and, perhaps, recreational users of these agents. Further research is needed to establish which pesticides are associated with this effect.
- Head injury, as measured by episodes of being knocked unconscious, is associated with Parkinson's disease. This finding, if confirmed, has implications for all contact sports and, in particular, combat sports such as boxing.

Main messages

- Parkinson's disease is associated with pesticide use.
- A positive family history of Parkinson's disease is associated with an increased odds ratio of developing the disease.
- A history of ever having been knocked unconscious is associated with Parkinson's disease and this shows an exposure–response relationship, but it is unclear whether such head injuries predates disease onset.
- Use of psychoactive medication is associated with Parkinson's disease, although it is unclear whether this use predates disease onset.

implications for contact sports. Head injury has previously been linked to an increased risk of Parkinson's disease, but the results have been inconsistent.[8] Use of antidepressant, anxiolytic or hypnotic drugs also appeared to be associated with Parkinson's disease. One explanation for this finding is that depression has been associated with an increased risk of Parkinson's disease later in life.[4 30] However, no information as to the timing of head injury, or use of medication was sought and accordingly we cannot state that these exposures predate symptom onset. Thus, the observed association with head injury may be due to recall bias or to an increased risk of falls in Parkinson disease. Equally, the use of psychotropic medication may simply reflect the well recognised psychiatric effects of Parkinson's disease. The largest odds ratio was for a positive family history of Parkinson's disease. Whether this reflects shared environment or genetic predisposition or even bias is unclear.[31] Without neurological examination of family members we cannot comment on the accuracy of self-reported family history of Parkinson's disease in patients and controls.

This large study confirms the previously described[20 21 32] negative association between tobacco smoking and Parkinson's disease, which is probably owing to a true neuroprotective effect of tobacco smoke constituents.[33] In agreement with previous studies, we found no evidence that alcohol consumption was associated with disease.[34 35]

In conclusion, this study has provided important evidence of the increased risk of Parkinson's disease in relation to exposure to pesticides. The exposure–response relationship suggests that pesticide exposure may be a causative and potentially modifiable risk factor.

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REFERENCES

1 **MacDonald BK**, Cockerell OC, Sander JW, *et al.* The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;**123**:665–76.
2 **Di Monte DA**, Lavasani M, Manning-Bog AB. Environmental factors in Parkinson's disease. *Neurotoxicology* 2002;**23**:487–502.
3 **Zorzon M**, Capus L, Pellegrino A, *et al.* Familial and environmental risk factors in Parkinson's disease: a case-control study in north-east Italy. *Acta Neurol Scand* 2002;**105**:77–82.
4 **Taylor CA**, Saint-Hilaire MH, Cupples LA, *et al.* Environmental, medical, and family history risk factors for Parkinson's disease: a New England-based case control study. *Am J Med Genet* 1999;**88**:742–9.
5 **Langston JW**, Ballard P, Tetrud JW, *et al.* Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983;**219**:979–80.
6 **Priyadarshi A**, Khuder SA, Schaub EA, *et al.* A meta-analysis of Parkinson's disease and exposure to pesticides. *Neurotoxicology* 2000;**21**:435–40.
7 **Firestone JA**, Smith-Weller T, Franklin G, *et al.* Pesticides and risk of Parkinson disease: a population-based case-control study. *Arch Neurol* 2005;**62**:91–5.
8 **Lai BCL**, Marion SA, Teschke K, *et al.* Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism Relat Disord* 2002;**8**:297–309.
9 **Tuchsen F**, Jensen AA. Agricultural work and the risk of Parkinson's disease in Denmark, 1981–1993. *Scand J Work Environ Health* 2000;**26**:359–62.
10 **Petrovitch H**, Ross GW, Abbott RD, *et al.* Plantation work and risk of Parkinson disease in a population-based longitudinal study. *Arch Neurol* 2002;**59**:1787–92.
11 **Engel LS**, Checkoway H, Keifer MC, *et al.* Parkinsonism and occupational exposure to pesticides. *Occup Environ Med* 2001;**58**:582–9.
12 **Baldi I**, Lebailly P, Mohammed-Brahim B, *et al.* Neurodegenerative diseases and exposure to pesticides in the elderly. *Am J Epidemiol* 2003;**157**:409–14.
13 **Corrigan FM**, Wienburg CL, Shore RF, *et al.* Organochlorine insecticides in substantia nigra in Parkinson's disease. *J Toxicol Environ Health A* 2000;**59**:229–34.
14 **Bhatt MH**, Elias MA, Mankodi AK. Acute and reversible parkinsonism due to organophosphate pesticide intoxication: five cases. *Neurology* 1999;**52**:1467–71.
15 **Seidler A**, Hellenbrand W, Robra BP, *et al.* Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. *Neurology* 1996;**46**:1275–84.
16 **Meco G**, Bonifati V, Vanacore N, *et al.* Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). *Scand J Work Environ Health* 1994;**20**:301–5.
17 **Liou HH**, Tsai MC, Chen CJ, *et al.* Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. *Neurology* 1997;**48**:1583–8.
18 **McCormack AL**, Thiruchelvam M, Manning-Bog AB, *et al.* Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. *Neurobiol Dis* 2002;**10**:119–27.
19 **Betarbet R**, Sherer TB, MacKenzie G, *et al.* Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci* 2000;**3**:1301–6.
20 **Smargiassi A**, Mutti A, De Rosa A, *et al.* A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. *Neurotoxicology* 1998;**19**:709–12.
21 **De Palma G**, Mozzoni P, Mutti A, *et al.* Case-control study of interactions between genetic and environmental factors in Parkinson's disease. *Lancet* 1998;**352**:1986–7.
22 **Rybicki BA**, Johnson CC, Uman J, *et al.* Parkinson's disease mortality and the industrial use of heavy metals in Michigan. *Mov Disord* 1993;**8**:87–92.
23 **Racette BA**, Tabbal SD, Jennings D, *et al.* Prevalence of parkinsonism and relationship to exposure in a large sample of Alabama welders. *Neurology* 2005;**64**:230–5.
24 **Checkoway H**, Savitz DA, Heyer NJ. Assessing the effects of nondifferential misclassification of exposures in occupational studies. *Appl Occup Environ Hygiene* 1991;**6**:528–33.
25 **Hughes AJ**, Daniel SE, Kilford L, *et al.* Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;**55**:181–4.
26 **Semple SE**, Dick F, Cherrie JW. Exposure assessment for a population-based case-control study combining a job-exposure matrix with interview data. *Scand J Work Environ Health* 2004;**30**:241–8.
27 **HSE**. EH40/2002 Occupational Exposure Limits 2002. *EH40* 2002:7–28.
28 **Fidler AT**, Baker EL, Letz RE. Estimation of long term exposure to mixed solvents from questionnaire data: a tool for epidemiological investigations. *Br J Ind Med* 1987;**44**:133–41.
29 **Cherrie JW**, Schneider T. Validation of a new method for structured subjective assessment of past concentrations. *Ann Occup Hyg* 1999;**43**:235–45.
30 **Schuurman AG**, van den Akker M, Ensinck KT, *et al.* Increased risk of Parkinson's disease after depression: a retrospective cohort study. *Neurology* 2002;**58**:1501–4.

31 **Elbaz A**, McDonnell SK, Maraganore DM, *et al*. Validity of family history data on PD: evidence for a family information bias. *Neurology* 2003;**61**:11–17.
32 **Benedetti MD**, Bower JH, Maraganore DM, *et al*. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. *Neurology* 2000;**55**:1350–8.
33 **Quik M**. Smoking, nicotine and Parkinson's disease. *Trends Neurosci* 2004;**27**:561–8.
34 **Checkoway H**, Powers K, Smith-Weller T, *et al*. Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. *Am J Epidemiol* 2002;**155**:732–8.
35 **Fall PA**, Fredrikson M, Axelson O, *et al*. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. *Mov Disord* 1999;**14**:28–37.

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