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## Pesticide exposure and risk of Parkinson's disease – a population-based case–control study evaluating the potential for recall bias

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**Objective** The aim of this study was to investigate whether pesticide exposure was associated with Parkinson's disease in a population-based case–control study in British Columbia, Canada.

**Methods** Patients reimbursed for anti-parkinsonian agents were identified and screened for eligibility as cases. Controls were selected from the universal health insurance database, frequency-matched to the case sample by birth year, gender, and geographic region. A total of 403 cases and 405 controls were interviewed about their job, medical and personal habits histories, and beliefs about disease risk factors. Among those reporting pesticide exposure, an occupational hygiene review selected participants exposed “beyond background” (ie, above the level expected in the general population). Unconditional logistic regression was used to estimate associations for different pesticide categories.

**Results** Of the cases, 74 (18%) self-reported pesticide exposure and 37 (9%) were judged to be exposed beyond background. Self-reported exposure was associated with increased risk [odds ratio (OR) 1.76, 95% confidence interval (95% CI) 1.15–2.70], however the risk estimate was reduced following the hygiene review when restricted to those considered exposed (OR 1.51, 95% CI 0.85–2.69). When agricultural work was added to the model, the risk for hygiene-reviewed pesticide exposure was not elevated (OR 0.83, 95% CI 0.43–1.61), but agricultural work was (OR 2.47, 95% CI 1.18–5.15). More than twice as many cases as controls thought chemicals cause Parkinson's disease.

**Discussion** This study provides little support for pesticide exposure as a cause of Parkinson's disease. The observed pattern of step-wise decreases in risk estimates might indicate differential recall by case status. The relationship to agricultural jobs suggests that farming exposures - other than pesticides - should be considered as risk factors for Parkinson's disease.

**Key terms** agricultural job; British Columbia; Canada; job history; self-report.

The etiology of Parkinson's disease is partly unknown, though 5–10% of the cases are attributed to genetic mutations (1). Parkinson's disease is thought to result from an interplay between genetic susceptibility and environmental risk factors (2). An association between pesticides and Parkinson's disease was first suspected in 1983, when the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which has a chemical structure similar to the herbicide paraquat, was observed to cause acute Parkinsonism (3). Since then, exposure to pesticides and subsequent development of Parkinson's

disease has been studied intensively (eg, 4–17) and many studies (4–8, 12–17) have confirmed associations, though some were weak and not significant, and other studies did not find an effect (9, 10).

Methods of pesticide exposure ascertainment have varied from study to study, but it would be extraordinarily difficult to include direct exposure measurement due to the rarity and late-life incidence of Parkinson's disease. Retrospective self-reporting of exposures is the most commonly used method for estimation of pesticide exposure (4–10); however, this method has the

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potential for recall bias (11). Some studies have gathered self-report of exposure prospectively (12, 13) or used more objective methods, such as job exposure matrices (14–16) or combinations of geographic information and historical data on pesticide use (17).

Here we report the results of a population-based case–control study of the relationship between pesticide exposure and Parkinson's disease. Self reports in combination with an occupational hygiene review were used to estimate exposures. We also investigated whether study participants believed that chemicals, including pesticides, cause Parkinson's disease and whether such a belief may have confounded exposure–response relationships.

## Methods

### Study population

Cases and controls were sampled from two areas of the province of British Columbia, Canada: Metro Vancouver representing an urban area (2.1 million people, population density ~735 per km<sup>2</sup>); and all of Vancouver Island, except Greater Victoria, representing a rural area (400 000 people, population density ~10 per km<sup>2</sup>). The rural area was included to increase the diversity of occupations. Persons between the ages of 40–69 years inclusive (as of 31 December 2002) who were alive and residing in the study area at the time of interview and who were able to communicate with the interviewer in English were eligible. Subjects in the age group 40–69 years were chosen because they were less likely to suffer from dementia or other illnesses that could complicate an interview and because they were in, or close to, their working years and therefore more likely to recall exposures correctly.

Potential cases were identified using the PharmaCare database of the provincial prescription payment plan, which included all those who had more than CAN\$800 in prescription costs in a given year. For inclusion, individuals had to have had at least one prescription for anti-parkinsonian drugs for at least one calendar year from 1995–2002 inclusive. The following were defined as anti-parkinsonian drugs: levodopa, bromocriptine mesylate, pergolide mesylate, levodopa/benserazide hydrochloride, levodopa/carbidopa, or seligiline hydrochloride. The populations meeting the potential case definition were identified on two occasions: in 2001 (data from 1995–1998) and 2005 (data from 1999–2002). To blind the data extractors, the extract was supplemented with a 20% “camouflage” sample of other individuals in the database.

All potential cases were verified by an initial screening phone interview about chronic diseases, anti-parkinsonian drugs taken, and the reason for their use. This screened out those taking the drugs for much different

purposes (eg, bromocriptine for lactation cessation or levodopa for restless legs syndrome). Those taking the drugs for known or suspected Parkinson's disease had an in-person physical assessment employing a checklist and record of symptoms, reviewed by a neurologist with a specialty in movement disorders. The following clinical criteria for Parkinson's disease were used: (i) two of the following symptoms present on examination: Parkinsonian tremor, rigidity, bradykinesia, masked facies, micrographia, or postural imbalance; (ii) absence of specific signs of other diseases that would account for these findings. Dates of Parkinson's disease diagnosis, first symptoms, and first treatment were also recorded.

The control sample was frequency-matched to the case sample on birth year (six 5-year periods), gender, and geographic region. Controls were selected using stratified random sampling from the British Columbia (BC) Ministry of Health Services client registry, which includes all individuals covered by provincial medical insurance and represents 97.5% of the population. All potential controls were screened by phone for eligibility, including a question about whether they had any chronic diseases. Anyone who indicated Parkinson's disease were excluded.

### Subject contact procedure

This study was required to use a two-stage consent process. The BC Ministry of Health Services sent out invitation letters asking potential subjects to contact the University of BC team. If no response was received within two weeks of the mailing date, a clerk at the Ministry of Health Services phoned to ask the potential subject if their name could be released to the study team. Those who agreed were then contacted by the study coordinator who conducted the screening interview and requested study participation.

### Questionnaire information on pesticide exposure

The questionnaire was pre-tested in several steps on a sample of 40 people selected to represent the age range of the subjects. The interviewers underwent formal training about all aspects of the interview, questionnaire, and clinical examination, and were observed during mock and initial interviews to ensure consistency.

In an in-person interview, participants were asked about their job, medical, and personal habits histories. The following questions were asked for all jobs: “During this job, did you use or were you exposed to any chemicals, for example, solvents, oils, plastics, paints, metals or pesticides?” As an aid to recall, an interview guide was sent to the participants prior to the interview and was referred to during the interview. It listed chemicals with an a priori hypothesis and included common and brand names (see the appendix for the list of pesticides). If a participant

answered “yes”, the following questions were asked: “Was this substance (i) breathed in, (ii) on skin, (iii) both, (iv) no direct contact, (v) don’t know”; and “What operations were you performing when you were exposed to this substance?” for which a list of about 90 operations was provided in the interview guide. Participants were asked about weeks exposed per year, hours exposed per week, and start and end date of the exposure in that job. At the end of the interview, participants were asked: “What do you think causes Parkinson’s disease?”

Each participant’s job history was reviewed by an occupational hygienist (blind to case status) for sensitivity (ie, to check whether potential exposures of interest commonly associated with an occupation were reported). Where exposures were missed, the participant was phoned and asked about the exposures noted by the hygienist.

### Assigning exposure to pesticides

After all interviews were completed, the self-reported exposures were again reviewed, blind to case status, this time for specificity. Using defined criteria and the information on job title, job duties, mode of exposure, operations conducted during exposure, and duration of exposure, assessments were made about whether self-reported pesticide exposures were likely to be “beyond background” or above the level expected in the general population. Of 121 persons who self-reported pesticide exposures, 53 were excluded because the reported exposure was judged to be limited. For example, sales personnel handling closed containers, construction workers occasionally handling wood treated with preservatives, and restaurant workers, security guards, administrative personnel, and care aides in locations where pesticides were occasionally applied by others were all judged to have limited exposure. In comparison, those judged to have exposures above background were mainly farmers, farm workers, forestry personnel, sawmill workers applying antisapstain fungicides, florists, and kennel and stable hands. Among those judged unlikely to be exposed beyond background, only 34% named a specific pesticide, whereas among those judged exposed, 73% did. A further 8 persons were excluded due to missing information on hours per week exposed (N=7) and whether the exposure was every week (N=1); on checking the job duties, it was likely that the information was missing because the exposure was rare in the job (eg, public health nurse applying lindane for lice).” Among those reporting exposure to pesticides, 60 were judged to be exposed beyond background.

### Categorizing pesticides

Since most previous studies have categorized pesticides according to function (insecticides, herbicides, fungicides, and wood preservatives), for comparison

purposes we did the same. We also created categories by chemical class: organochlorines and organophosphates. Finally, we grouped specific pesticides reported by the participants into two categories based on neurotoxicity (18–20): (i) pesticides with evidence of human neurotoxicity: allethrin, azinphosmethyl, diazinon, dichlorodiphenyltrichloroethane (DDT), 2,4-dichlorophenoxyacetic acid (2,4-D), dieldrin, glyphosate, lindane, malathion, 2-methyl-4-chlorophenoxyacetic acid (MCPA), nicotine, paraquat, pentachlorophenol, rotenone, tetrachlorophenol, and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); and (ii) pesticides with limited or no evidence of neurotoxicity: borax, brodifacoum, calcium polysulfide, captan, copper oxychloride, creosote, chromate copper arsenate, didecyl dimethyl ammonium chloride, lime sulphur, mineral oil, simazine, and sulphur. These categories were based on available evidence for neurotoxicity in case studies, animal studies, and in vitro studies (18–20).

### Statistical analysis

Unconditional logistic regression was used to estimate associations with Parkinson’s disease for different categories of pesticides: functional groups (insecticide, herbicide, fungicide, wood preservative); chemical groups (organophosphates, organochlorines); neurotoxic pesticides; and any specific pesticide reported by at least ten participants. In all analyses, persons reporting exposure to pesticides other than those relevant in the specific analysis were excluded.

Analyses were conducted for self-reported exposure and for hygiene-reviewed exposures beyond background. Analyses were performed for exposure via any job operation and for the subgroup reporting pesticide spraying operations. We also estimated risks with exposure duration and with censoring of exposures five and ten years prior to the date of diagnosis or the corresponding date for controls.

Finally, we estimated Parkinson’s disease risk among those with agricultural jobs. Two adjustment models were used: model 1 adjusted for gender, birth year (5-year age groups), and smoking (cumulative pack-years); and model 2 adjusted for the same variables as model 1 in addition to a variable indicating whether the subject believed Parkinson’s disease has a chemical cause.

Analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA).

## Results

A total of 3783 potential subjects were initially sent letters from the Ministry of Health Services. Figure 1 is a participation flowchart showing the classification of potential subjects. A large proportion of potential

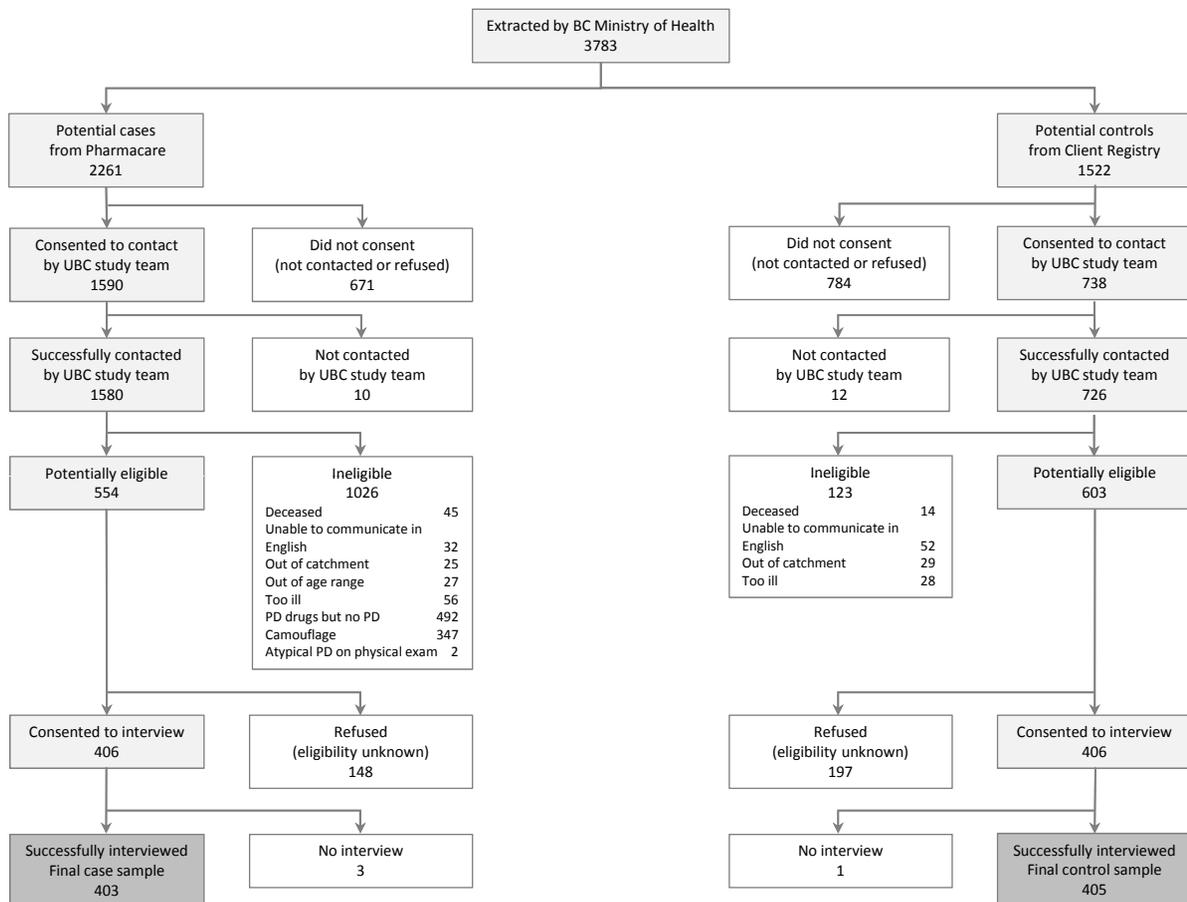
cases did not have Parkinson's disease (most used anti-parkinsonian drugs for other indications). The multi-stage consent process resulted in uncertainty about the proportion of potential subjects who were eligible to participate. However, if we assume that the proportion of contacted subjects who were eligible ( $554/1580=0.35$  for cases and  $603/726=0.83$  for controls) was the same in the initially extracted samples, we can calculate the "potentially eligible" numbers ( $0.35 \times 2261=791$  for cases;  $0.83 \times 1522=1264$  for controls) and use these as denominators for the calculation of the participation rate. Using this method, the estimated participation rate was  $403/791$  (51%) for cases and  $405/1264$  (32%) for controls. The characteristics of the final study sample of 403 cases and 405 controls are summarized in table 1.

### Pesticide exposure

Among cases, 74 (18%) self-reported pesticide exposure and 37 (9%) were judged to be exposed beyond background following the hygiene review. In the control

group, 47 (12%) self-reported pesticide exposure and 23 (6%) were judged to be exposed beyond background. In both the case and control groups, insecticides and herbicides were the most frequently reported types of pesticides (table 1).

Table 2, model 1 (adjusted for birth year, gender and smoking) shows the results for both self-reported and hygiene-reviewed pesticide exposure via any job operation and spraying operations. For self-reported pesticide exposure, we found a significantly increased risk of Parkinson's disease. Among those judged exposed beyond background after the hygiene review, the odds ratio (OR) was lower than among those self-reporting exposure. In the hygiene-reviewed group, exposure via spraying pesticides had a higher risk estimate than via any job operation, though neither of these risk estimates were statistically significant. The risk estimates for subcategories of pesticides tended to follow similar patterns: the highest risk estimates were for self-reports; the hygiene review resulted in reductions in risk estimates; and there were slightly higher risk estimates for spraying exposures. None



**Figure 1.** Flowchart showing the classification of potential participants in a case control study of Parkinson's disease in British Columbia, Canada. Potential cases were those with a prescription for antiparkinsonian drugs during the study period.

**Table 1.** Characteristics of the study population: 403 patients with Parkinson's disease and 405 controls. [SD=standard deviation.]

Characteristic	Cases				Controls			
	N	%	Mean	SD	N	%	Mean	SD
Men	266	66.0	.	.	204	50.4	.	.
Women	137	34.0	.	.	201	49.6	.	.
Birth year								
1929–1938	245	60.8	.	.	175	43.2	.	.
1939–1948	131	32.5	.	.	129	31.9	.	.
1949–1958	27	6.7	.	.	101	25.0	.	.
Geographic region: Metro Vancouver	263	62.3	.	.	242	59.8	.	.
Self-reported pesticide exposure	74	18.3	.	.	47	11.6	.	.
Hygiene-reviewed pesticide exposure	37	9.2	.	.	23	5.7	.	.
Insecticides	18	4.5	.	.	13	3.2	.	.
Herbicides	17	4.2	.	.	13	3.2	.	.
Fungicides	7	1.7	.	.	6	1.5	.	.
Wood preservatives	10	2.5	.	.	5	1.2	.	.
No pesticide exposure	329	81.6	.	.	358	88.4	.	.
Ever smoker <sup>a</sup>	184	45.7	.	.	226	55.8	.	.
Named chemicals as cause of Parkinson's disease	111	27.5	.	.	43	10.6	.	.
Smoking, cumulative pack-years			11.4	20.4	.	.	15.4	22.4
Mean age at diagnosis of Parkinson's disease (years)			56.0	7.1	.	.	.	.
Mean age at the time of interview (years)			65.0	6.6	.	.	62.2	9.0

<sup>a</sup> At least 100 cigarettes in the period prior to Parkinson's disease diagnosis and a corresponding period for controls.

of the OR for pesticide subcategories were statistically significant, except self-reported insecticide exposure. Risk estimates for hygiene-reviewed pesticide exposures were slightly above 1.0 in all categories of pesticides, except for organophosphates, organochlorines and DDT, however, most risk estimates had wide 95% confidence intervals (95% CI) (table 2). Censoring exposures five and ten years prior to diagnosis did not change the risk estimates markedly (data not shown) and analyses including duration of pesticide exposure showed no significant associations with Parkinson's disease (data not shown).

We also examined the relationship between agricultural work and Parkinson's disease: 36 cases and 17 controls reported an agricultural job. Of these, 20 cases and 7 controls were exposed to pesticides. Participants who reported agricultural jobs had a significantly increased risk of Parkinson's disease (OR 2.36, 95% CI 1.23–4.55, adjusted for gender, birth year and smoking). When the hygiene-reviewed pesticide exposures were added to this model, the elevated and statistically significant OR for agricultural work remained (OR 2.47, 95% CI 1.18–5.15), but the risk for pesticide exposure was no longer elevated (OR 0.83, 95% CI 0.43–1.61). A similar pattern held for each pesticide category: when added to a model with agricultural job, the elevated risk for the job remained, but the risk estimate for the pesticide was always <1.0. There were no significant interactions between agricultural job and any of the pesticide categories.

The analyses reported above suggest that differences in exposure recall between cases and controls may have contributed to the higher risk estimates for self-reported pesticide exposures, so we examined the responses to the question about what causes Parkinson's disease. A total of 154 participants reported "chemicals" as a suspected cause of Parkinson's disease (111 cases and 43 controls). Most did not name a specific class of chemical, however 21 participants specifically mentioned "pesticides" and all of these were cases. To see whether beliefs about causes of the disease might alter the association with pesticides, we conducted an additional set of analyses with adjustment for the participants' beliefs that chemicals are a cause of Parkinson's disease (table 2, model 2). The OR for pesticides in the model 2 analyses were consistently lower than those of model 1, and none were statistically significant. In contrast, in analyses of agricultural job with adjustment for participants' beliefs that chemicals are a cause of the disease, the increased risk persisted (OR 2.28, 95% CI 1.16–4.47).

## Discussion

In this study, we observed significantly increased risks of Parkinson's disease with self-reported pesticide or insecticide exposures, but reductions in risk for those considered

**Table 2.** Odds ratios (OR) and 95% confidence intervals (95% CI) for Parkinson's disease among persons who self-reported pesticide exposure and among those judged - by a hygiene review - to have pesticide exposure beyond background. Statistically significant OR in bold. [DDT= dichlorodiphenyltrichloroethane.]

Pesticide category	Model 1 <sup>a</sup>									Model 2 <sup>b</sup>								
	Self-reported exposure, via any job operation			Hygiene-reviewed exposure, via any job operation			Hygiene-reviewed exposure, spraying operations			Self-reported exposure, via any job operation			Hygiene-reviewed exposure, via any job operation			Hygiene-reviewed exposure, spraying operations		
	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI	N	OR	95 % CI
Pesticides		<b>1.76</b>	<b>1.15–2.70</b>		1.51	0.85–2.69		1.91	0.82–4.49		1.49	0.96–2.32		1.18	0.65–2.14		1.38	0.56–3.40
Cases	74			37			20			74			37			20		
Controls	47			23			9			47			23			9		
Insecticides		<b>1.80</b>	<b>1.03–3.15</b>		1.26	0.58–2.74		1.86	0.66–5.24		1.44	0.81–2.58		0.86	0.38–1.93		1.24	0.42–3.65
Cases	40			18			13			40			18			13		
Controls	26			13			6			26			13			6		
Herbicides		1.82	0.97–3.40		1.33	0.60–2.97		1.60	0.53–4.87		1.59	0.84–3.00		1.16	0.51–2.60		1.49	0.47–4.71
Cases	33			17			10			33			17			10		
Controls	19			13			6			19			14			6		
Fungicides		0.94	0.38–2.32		1.18	0.35–4.00		·	·		0.80	0.31–2.03		0.95	0.27–3.31		·	·
Cases	11			7			3 <sup>c</sup>			11			7			3 <sup>c</sup>		
Controls	11			6			2 <sup>c</sup>			11			6			2 <sup>c</sup>		
Wood preservatives		2.20	0.90–5.34		1.56	0.51–4.77		·	·		1.80	0.70–4.62		1.34	0.42–4.28		·	·
Cases	17			10			4 <sup>c</sup>			17			10			4 <sup>c</sup>		
Controls	9			5			0 <sup>c</sup>			9			5			0 <sup>c</sup>		
Organo-phosphates		1.57	0.53–4.64		0.74	0.20–2.78		·	·		1.47	0.49–4.45		0.72	0.19–2.68		·	·
Cases	10			5			4 <sup>c</sup>			10			5			4 <sup>c</sup>		
Controls	6			5			3 <sup>c</sup>			6			5			3 <sup>c</sup>		
Organo-chlorines		1.23	0.53–2.85		0.62	0.19–2.00		·	·		1.05	0.44–2.52		0.38	0.11–1.31		·	·
Cases	16			6			5 <sup>c</sup>			16			6			5 <sup>c</sup>		
Controls	10			6			4 <sup>c</sup>			10			6			4 <sup>c</sup>		
Pesticides with neuro-toxic effects		1.76	0.95–3.25		1.08	0.49–2.36		1.34	0.53–3.40		1.48	0.78–0.80		0.86	0.38–1.93		1.06	0.40–2.82
Cases	35			17			14			35			17			14		
Controls	19			13			8			19			13			8		
DDT		1.32	0.55–3.18		0.76	0.22–2.62		·	·		1.09	0.44–2.75		0.45	0.12–1.65		·	·
Cases	15			6			5 <sup>c</sup>			15			6			5 <sup>c</sup>		
Controls	9			5			3 <sup>c</sup>			9			5			3 <sup>c</sup>		

<sup>a</sup> Model 1: Adjusted for gender, birth year (5-year age groups), smoking (cumulative pack-years).

<sup>b</sup> Model 2: Adjusted for gender, birth year (5-year age groups), smoking (cumulative pack-years), and naming chemicals as a cause of Parkinson's disease.

<sup>c</sup> Fewer than ten subjects exposed, odds ratios and confidence intervals not reported.

exposed based on the hygiene review and when more specific categories of pesticides were mentioned. There were no increases in risk with censoring of exposures five and ten years prior to diagnosis, nor increasing risks with increasing duration of exposure. Only one pattern was suggestive of an association: the increases in risk for hygiene-reviewed exposures from "any job operation" to "spraying operations," though none of these OR were statistically significant. In analyses with agricultural job, pesticide exposures no longer had elevated OR. This pattern of results does not add convincing support to the proposed association between pesticides and Parkinson's disease and, for the most part, was counter to what would be expected to support pesticides as a cause.

Two patterns suggested the potential for recall bias

to explain at least a portion of the observed associations between pesticide exposure and Parkinson's disease: decreases in risk between self-reported and hygiene-reviewed exposures and decreases in risk after adjustment for participants' belief that chemicals were a cause. In our study, 27.5% of cases with Parkinson's disease reported chemicals (including pesticides) as a cause of Parkinson's disease; the corresponding percentage for controls was 10.6%. This difference indicates a greater suspicion of a chemical cause among cases than controls; the risk estimates for pesticide exposures decreased when controlling for this factor, meaning that suspecting a chemical cause was also associated with reporting pesticide exposure.

Evidence of recall bias in case-control studies has generally been sparse, except with open-ended

questioning of exposure or where participants suspect a disease cause (22, 23). Difficulties in recall of pesticides have been shown to differ between cases and controls in a general population sample (24). Adjusting for suspicions of hypothesized causation may be inadvisable as a routine practice, particularly if knowledge is causally related to exposure or if exposed cases become knowledgeable about the hypotheses post-diagnosis (25). The former seems unlikely in our study, although the latter is possible, so we cannot know with certainty that the effect we observed was indeed due to recall bias.

Our results raise the question of whether the prior studies may have been subject to recall bias. Previous studies that, like ours, obtained information on exposure to pesticides from interviews have this potential (4–11, 21). Nevertheless, two cohort studies using prospective self-reports of exposure, which should not be prone to recall bias, found associations between exposure to pesticides as a group and risk of Parkinson's disease (12, 13).

Non-differential misclassification of exposure to pesticides is also an important issue, which could exist in our study and thus bias our results towards the null (26). Reducing non-differential misclassification of exposure was one of the purposes of the industrial hygiene review of exposures. We expected risk estimates to be higher for hygiene-reviewed than self-reported exposures, but the opposite was the case, initiating our suspicion of recall bias.

#### Agricultural employment versus pesticide exposure: what is measured?

We observed a significantly increased risk of Parkinson's disease among those reporting an agricultural job, with a risk estimate higher than those for pesticides. The finding for agricultural jobs was little influenced by adjustment for pesticide exposure or participants' beliefs that chemicals are a cause.

This raises the question of whether there is something else about agricultural work that might be related to Parkinson's disease. A number of studies (27–29), though not all (30), have reported associations between agricultural jobs and Parkinson's disease. Most investigators have related these associations to the use of pesticides in these jobs. However, a recent Australian study investigated the extent to which farm-related jobs indicated pesticide exposure (31) and found that only 22% likely had exposure. In our study, 51% of those in agricultural jobs were classified as "pesticide exposed". Farming jobs may share many other potential exposures, including solvents, fuels, fuel exhaust, dusts, micro-organisms, and traumatic injuries, many of which would be useful to examine in the context of Parkinson's disease. An exposure of particular interest could be endotoxin, a lipopolysaccharide

component of gram-negative bacterial cell walls. Lange and coworkers (32) are among the researchers who have posited that part of the elevated risk of Parkinson's disease associated with agriculture could be explained by exposure to endotoxin because exposure is common in the agricultural sector and there is mechanistic support from animal experiments (33).

It would be worthwhile to consider the potential for other etiological exposures to explain at least some portion of the increased risks of Parkinson's disease observed among farmers or those assessed as being exposed to pesticide due to farming jobs (12, 14–16).

#### Recent case-control studies

In other recent case-control studies, the diversity of results related to pesticide exposures and agricultural work has continued. Elbaz and colleagues (4) found increased risks with professional pesticide use, especially insecticides, though they mentioned the possibility of increased awareness among cases of the possible link between Parkinson's disease and pesticides (4). Tanner et al (8) found increased risks for self-reported use of pesticides, increasing when restricted to eight specific pesticides with high neurotoxic plausibility (very similar to our classification), but agricultural work was not found to be a risk factor. Firestone and colleagues (10) found no significant association between self-reported exposure to pesticides or agricultural work and Parkinson's disease. Regional differences in exposure patterns between study populations and methodological differences (eg, different methods of ascertaining exposure) might partly explain these inconsistent results.

Despite the large number of studies investigating the possible association between pesticide exposure and Parkinson's disease, few epidemiological studies have found associations between exposure to a specific pesticide and Parkinson's disease. In a study using geographic information systems and historic information on pesticide use, exposure to the pesticides maneb and paraquat was found to be associated with risk of Parkinson's disease (17). To pinpoint specific pesticides in an interview based case-control study, the participants' memories need to be exceptional and the number of study participants needs to be very large. To illustrate the number of subjects needed to detect a significantly increased risk of Parkinson's disease for a specific pesticide, we calculated the sample size needed, using the pesticide with the highest proportion of controls exposed in this study [DDT (5 of 405)]. With a significance level of 5%, power of 80% and equal numbers of cases and controls, 1500 cases and controls would be needed to detect an OR of 2.0.

## Strengths and limitations

Like most case-control studies, we had an in-person physical assessment of potential cases and included assessments of participants' lifestyle habits to allow control for smoking's negative association with Parkinson's disease (34). The assessment of pesticide exposure collected detailed information on the type of contact and operations performed enabling two hygiene reviews on sensitivity and specificity, respectively, both blind to case status. A list of pesticides with common names and brand names were provided to participants in advance to improve recall (see appendix) (22). Our study appears to be the only one to date that has attempted to evaluate recall bias based on participants' beliefs about the causes of Parkinson's disease.

A limitation of our study was the potential for participation bias, since those agreeing to take part in the study might differ from those refusing. Our study population was restricted to those in the age group 40–69 years, potentially limiting the generalizability of our results to older Parkinson's patients.

Further, our study was underpowered to detect 2-fold-difference associations between subcategories of pesticide exposure with a prevalence of <4% in controls. Most of our pesticide groups had sufficient power, but the number of participants who reported exposure to individual pesticides was very small, preventing analyses of most individual pesticides. The diversity of pesticide-active ingredients used by this study sample reflects the diversity of farming in the province, including fruit (apple, peaches, cherries, grapes, plums, blueberries, raspberries, cranberries), market vegetable (lettuce, tomatoes, sweet peppers, cucumbers, mushrooms), grain, and flower crop farming, as well as cattle ranching and dairy farming. The resulting variety of pesticides used is another factor that lessens the likelihood that pesticides are an important cause of Parkinson's disease in this population; there is little specificity of the chemicals. In addition, few of the study subjects had exposures to the pesticides used in animal models of Parkinson's disease (35): one case and four controls reported exposure to rotenone; three cases and three controls reported exposure to paraquat; and no one reported exposure to maneb.

In summary, the results of this study do not lend support for an association between pesticide exposure and Parkinson's disease. Our results emphasize the importance of considering recall bias via a hygiene review to ensure specificity of exposure ascertainment and by considering the participants' beliefs about the disease cause. The results related to agricultural work suggest that it would be valuable for future studies to explore other exposures of this occupational group that may be related to Parkinson's disease, such as bacterial endotoxin (32, 36).

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**Appendix.** List of pesticides sent out to the participants prior to the interview.

Chemical name	Brand and common names
<b>Fungicides</b>	
Captan	Agrox D-L Plus, Orthocide
Chlorothalonil	Bravo, daconil 2787, Exotherm Termil, Termil
Copper oxychloride	Basicop, Coprantol, Fixed copper, mar-cop, neutron-Cop, Tri-Cop
Dodine	Cyprex, Equal
Formaldehyde	Formalin, Methanol
Lime sulphur or calcium polysulphide	Orthorix
Mancozeb	Dithane M-45, manzate 200
Maneb	Co-op DP, Ditane M-22, Mantox, Manzae, Mergamma, Pool NM Dual, Tersan LSRF
Metam	Pole-Fume, SMDC, Unifume Soil, Vapam, VPM, Woodfume
Metiram	Polyram
Quintozene	Brassicol, PCNB, terrachlor
Sulphur	Flortex, Giant Destroyer, Gopher Gasser, Kolodust, Kolospray, Magnetic 6, Ortho Flotox, Woodchuck Bombs
Ziram	Zerate
<b>Herbicides and plant growth regulators</b>	
2,4,5-T	Dacamine-4T, Esteron 2,4,5-T, Poison Ivy and Brush Killer, Reddox, Trinoxol, Veon, Verton 2T, Weedone 2,4,5-T
2,4-D	2,4-D, Amkil, Aqua-Kleen, Calmix, Chlorxone, Dacamine, Desormone 7, Diachlorprop, Driamine, Estakil, Estasol, Estemine 500, Esteron, Esteron 64, Foestamine, For-ester, Formula 40-F, Herbate, Hoe-Grass, Kilmor, Rustler, Salvo, Silvaprop, Sure-Shot Forest amine, Target, Ten-Ten, Verton, Weedar, Weedar-64, Weedaway, Weed-B-Gone, Weedex, Weedone, Weed-Rhap
Atrazine	Aatrex, Atra-Mix, Eramox 80W, gesaprim, Laddox, Marzone, Primatol A, Primextra, Vectal Atrazine
Bifenox	Modown
Chlormequat	Cycocel
Difenzoquat	Avenge
Diquat	Reglone, Reglone-A, Weedrite
Ethalfuralin	Edge
Glyphosate	Roundup, Rustler, Side-Kick, Vision
MCPA amine	Agritox, Agroxone, Bromox, Bucril, Estemine MCPA, Estakil MCPA, MCP, Mephanac, Methoxone Amine 500, No Weed, Sabre, Weedar MCPA, Weedgone MCPA
Metolachlor	Dual, Primextra
Morfamquat	Morfoxone
Norflurazon	Evitol, Zorial
Paraquat	Gramoxone, Gramoxone S, Paraquat CL, Sweep, Terraklene, Weed Rite
Simazine	Gestatop, Primatol S, Princep, Simmaprim, Simadex
Sodium chlorate	Atlacide, Atratol, Chlorax, Monobor-Chlorate, Ureabor
Sodium metaborate tetrahydrate	Borate, Ureabor
Triallate	Avadex-BW
<b>Insecticides</b>	
Allethrin	Allethrin, Synthetic Pyrethrin
Azinphos-methyl	APM, Gurhion
Cypermethrin	Ripcord
Dichlorodiphenyltrichloroethane	DDT
Diazinon	Basudin
Dieldrin	Dieldrin
Heptachlor	Heptachlor
Lindane	Agrox D-L Plus, Benolin, Co-op DP, Gamma BHC, Gammasan, Mergamma, Pool NM Dual, Thiralin, Vitaflor DP, Vitavax
Malathion	Cythion
Mineral oil	Agricultural Weedkiller #1, Dormant Oils, Petroleum Oils, Petroleum Solvents, Stoddart Solvents, Summer Oil, Superior Oil, Supreme Oil, Volck Oil, Weed Oils
Nicotine	Black Leaf 40, Nicotine, Nicotine Sulfate
Rotenone	Atox, Deritox, Derris, Noxfish Fish Toxicant, Rotenone Fish Poison
<b>Wood preservatives</b>	
3-iodo-2-propyl butyl carbamate	IPBC, NP-1, Troysan Polyphase P 100, Troysan Polyphase
Borax	Borascu, Boron, Ecobrite, Ecobrite A, Ecobrite B, Ecobrite C, Ecobrite II, Ecobrite III, F-2, Pole-Peg
Chromated copper arsenate	CCA
Creosote	Coal Tar Creosote, Pole-Peg
Didecyl dimethyl ammonium chloride	DDAC, Ecobrite III, F-2, NP-1, Timbercote II, Timbercote 2000
Pentachlorophenol	Alchem, Dowwicide, Diatox, PCP, Penta, Pole-Peg, Santobrite, Woodbrite, Woodsheath
Sodium carbonate	Ecobrite, Ecobrite A, Ecobrite B, Ecobrite C, Ecobrite II, SCB
<b>Rodenticides</b>	
Brodifacoum	Ratak, Talon
Bromadiolone	
<b>Fumigants</b>	
Methyl bromide	Brom-O-Gas, Dowfume, Dowfume MC-2, Meth-O-Gas, Sanex MB-C-2, Terr-O-Gas 67
Carbon disulfide	Dowfume, FIA 80-2, Kenfume bin fumigant, Sanifume
Hydrogen cyanide	Cyanogas, calcium cyanide, HCN