

Parkinson's Disease: Workplace Risk Factors

Final Report to WorkSafeBC

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Summary

- **Parkinson's disease** is a chronic disorder, characterized by muscle tremors, stiffness, and slow movements. It affects between 34,000 and 60,000 Canadians.
- The **purpose of this study** was to determine whether individuals in certain occupations or with exposures to respiratory infections, vibration, head injury, stress, pesticides, metals, or solvents have increased risks of Parkinson's disease.
- The study included 403 individuals with Parkinson's disease and a comparison group of 405 controls without the disease. They were interviewed about their lifetime job history, medical history, and lifestyle habits.
- The following were the **main findings**:
 - *Smokers* had decreased risks of the disease, as found in other studies, therefore we adjusted for smoking in our analyses.
 - *Social science, law and library* jobs and *farming and horticulture* jobs had increased risks of the disease, as found in other studies. Gas station jobs, welders, heavy equipment operators and carpenters also had increased risks.
 - There was an increased risk for *influenza*, and decreased risks for red measles and chicken pox or shingles.
 - *Whole body vibration* showed an interesting u-shaped pattern of risk: increased risk with no exposure, but also with increasing intensity of exposure.
 - *Head injuries* were associated with increased risk of Parkinson's disease, including among people who were injured at work.
 - Stress on the job was not related to Parkinson's disease.
 - There was some evidence of increased risk with exposure to *pesticides*, but it was not as convincing as the increased risk to farmers.
 - Exposures to most metals and solvents were not associated with increased risks.

Executive Summary

Context

Parkinson's disease is a chronic disorder, characterized by muscle tremors, stiffness, and slow movements. It progresses with age and impacts quality of life and independence. There is no registry of Parkinson's disease cases in Canada, so cases are difficult to identify in numbers large enough for study. The information about Parkinson's disease is so poor that estimates of the numbers of cases in Canada and elsewhere are not exact, though it is estimated that it afflicts between 34,000 and 60,000 Canadians and millions worldwide.

The difficulty in identifying cases means that the causes of Parkinson's disease have not been studied very frequently and remain largely unknown. Some cases may be inherited, but it is now considered likely that the large majority of cases have an environmental basis, that is, exposures in the workplace or elsewhere may cause the disease.

Study Purpose

The purpose of this study was to determine whether individuals in certain occupations or with exposures to respiratory infections, vibration, head injury, stress, pesticides, metals, or solvents have increased risks of Parkinson's disease and whether certain genetic susceptibilities might alter those risks.

Approach

The study had a population-based case-control design, and included Parkinson's disease cases and controls, frequency matched on age, sex, and geographic region (greater Vancouver metropolitan area and all of Vancouver Island except Victoria). Cases were selected by identifying individuals with prescriptions for anti-parkinsonian medications paid by the British Columbia (BC) PharmaCare program, and verified on physical assessment to have Parkinson's disease. Controls were a random sample from the provincial medical insurance plan. Participants were restricted to ages 40 to 69 years inclusive, as of December 31st, 2002.

All participants were interviewed using a structured questionnaire about the jobs they held since the age of 16, their exposures in those jobs, medical histories, and personal habits histories including smoking and use of alcohol, marijuana, and coffee. Each study participant was asked to provide a small sample of cells from inside the mouth to allow genetic testing for different forms of certain enzymes that detoxify chemicals in the body. Relative risks (in the form of odds ratios) were calculated for associations between Parkinson's disease and occupational categories, occupational and other exposures, and genotypes. Analyses were conducted using unconditional logistic regression, adjusting for age, sex, and cigarette smoking.

Results

The study included 403 Parkinson's disease cases with a mean age of diagnosis of 56 years and a mean age on interview of 65 years. There were 405 controls with a mean age on interview of 62 years.

As with most other studies of Parkinson's disease, *cigarette smoking* was associated with a reduced risk. *Other personal habits* were not associated with the disease: use of alcohol, marijuana, or coffee.

The following *occupations* had evidence of increased risk: social science, law and library jobs; farming and horticulture jobs; gas station jobs; welders; drivers of heavy equipment; and carpenters. The following occupations had evidence of reduced risks: management and

administration jobs; other health care jobs; repairers; and electricians.

Evidence related to *viral infectious diseases* showed a pattern consistent with increased risks for influenza, and decreased risks for other viral diseases, especially red measles and chicken pox or shingles.

Parkinson's disease showed u-shaped pattern of risk for *whole body vibration*: increased risk among those with no exposure, and among those with exposure, increasing risk with increasing intensity of exposure.

Those with prior *head injuries* had increased risk of Parkinson's disease, particularly those whose injury resulted in unconsciousness and those who were injured at work.

Most *job strain* measures (psychological job demand, physical job demand, noise) were not related to Parkinson's disease, though decision latitude was associated with a reduced risk.

Self-reported *pesticide*, insecticide, and wood preservative exposures were associated with increased risk of Parkinson's disease. The risk estimates tended to decline when exposures were restricted to those judged likely to be exposed above background levels or to specific types of chemicals.

Exposures to almost all *metals* were associated with reduced risks, counter to expectations.

Exposures to *solvents* were either not associated with Parkinson's disease or associated with reduced risks, also counter to expectations.

Most *enzyme system genetic polymorphisms* were not associated with Parkinson's disease, except cytochrome P450 2D6 A heterozygote and B mutant, which had elevated odds ratios.

Implications

The following is a brief overview of the potential implications of this research:

- Use of administrative databases for identifying and contacting potential research participants is important to allow population-based health research on diseases like Parkinson's that do not have registries.
- Smoking was associated with reduced risk of Parkinson's disease, and needs to be measured and adjusted for in research on this disease.
- Social science and farming jobs were associated with elevated risk of Parkinson's disease. The potential exposures that may cause these elevations merit further investigation.
- Influenza was associated with increased risk of Parkinson's disease and common childhood viral diseases were associated with reduced risk. Studies that measure exposures to these diseases objectively would be a valuable addition to our understanding of the exposure-response relationship.
- Whole body vibration as a potential cause of Parkinson's disease is worthy of continued investigation.
- Head injuries were associated with increased risk of Parkinson's disease. Thus workplace head injury prevention measures have additional benefits beyond preventing the acute impacts of the injury.
- Job strain was assessed for the first time in relation to Parkinson's disease, but no clear pattern of associations emerged.
- This study did not strengthen support for pesticides, metals, or solvents as risk factors for Parkinson's disease.

- Two rare genetic polymorphisms were associated with Parkinson's disease in the study population. Examination of the impact of these polymorphisms on susceptibility to chemical exposures would require pooling of datasets with other studies. This is planned for the future.
- Additional work by the study team included estimation of Parkinson's disease prevalence by three methods. Estimates remain very uncertain. They suggest that between 4,500 and 8,000 British Columbians have the disease.

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1. Context

1.1 Study purpose

This report describes the results of the study “*Parkinson’s Disease: Workplace Risk Factors and Host Susceptibility*.” The primary purpose of the study was to investigate the etiology of Parkinson’s disease by examining associations with occupational exposures.

The main exposures addressed were job categories, infections spread by respiratory droplets, and whole body vibration to test hypotheses developed subsequent to preliminary work by the study team, reported in 1999 [1]. Other exposures examined included head injuries, both on and off the job, and stress within the occupational context. We also examined exposures previously studied by others: pesticides; metals; and solvents. Finally, because of the great interest in host susceptibility in Parkinson’s research in the last decade, we examined genetic polymorphisms of the following enzyme systems involved in the activation and detoxification of chemicals: monoamine oxidase; cytochrome P450; and glutathione-S-transferase.

1.2 Previous research motivating this study

Parkinson’s disease is thought to be the second most common chronic neurological disease (after Alzheimer’s), although prevalence and incidence are difficult to establish because there are no registries or on-going surveys to document cases on a population basis. International estimates of prevalence and incidence vary by more than an order of magnitude [2,3], likely because of differences in methods of ascertainment, age distributions of the populations, and environmental exposures. Estimates of prevalence in Australia, the UK, and Canada have been in the range of 100 to 200 per 100,000 persons [3-6], suggesting that 34,000 to 70,000 Canadians and 4,500 to 9,000 British Columbians have the disease.

Parkinson’s disease is a progressive movement disorder, characterized by tremor, rigidity, slowed movement, and gait disturbance. It results from loss of dopamine-producing cells in the *substantia nigra* region of the brain. Many factors may lead to this pattern of cell loss. Age is one factor; Parkinson’s disease prevalence increases exponentially with age, for example in BC, prevalence is estimated to be about 90/100,000 in the 50-54 year age bracket and about 1,500/100,000 in the 80-84 year age bracket [6].

The cause of the disease originally postulated by James Parkinson in 1817 was anxiety. A related theory about rigid personalities was dominant for a considerable time [7]. Stress remains a hypothesis, though the evidence to date is weak, and it has never been studied using well-established instruments [7,8].

The following presents an overview of the literature on potential occupational and environmental risk factors for Parkinson’s disease at the time that this study was designed and funded.

1.2.1 Mendelian inheritance

Most published findings suggested that Mendelian inheritance probably accounted for less than 20% of cases [9-11]. Twin studies revealed little or no concordance in disease, and little difference between mono- and di-zygotic twin pairs, except at young age of onset [10-14]. Families at increased risk of parkinsonism were identified, as were genes that appear to be etiologic in these rare cases [10,11]. These cases exhibited unusual features, such as younger age of onset, relative

lack of tremor, more rapid rate of progression, and shorter survival [10,11].

1.2.2 Environmental factors

Evidence that Parkinson's disease may be caused by environmental agents arose from dramatic clusters of cases, rather than population-based epidemiological research. Although the clusters collectively represented only small numbers of cases, they were suggestive that environmental etiologies may apply to the broader population. In the decades since 1980, epidemiological research on the subject slowly increased.

The first clusters appeared in the 19th century, when parkinsonism was observed in workers exposed to manganese and carbon disulfide [15,16]. In the 1980s, a street drug (MPTP) was found to cause an acute onset of irreversible parkinsonism [17]. MPTP was subsequently used to create parkinsonism in experimental animals, to investigate the natural history and mechanisms of the disease [11,18]. The environmental risk factors studied most frequently were pesticides, heavy metals, and hydrocarbon solvents.

Some pesticides have chemical structures similar to MPTP, for example, paraquat, a herbicide for which both neurotoxic mechanisms and epidemiological associations were found with Parkinson's disease [19-21]. Rotenone, an insecticide derived from plant roots, was also shown to cause destruction of dopamine-producing neurons in rats, although whether there is selectivity for these neurons is controversial [22]. Most epidemiological studies did not study specific pesticides because of small numbers or unsophisticated exposure assessment, but increases in Parkinson's disease risks were observed with use of "herbicides" and "insecticides," increasing years of pesticide application, pesticide applicator occupations, agricultural occupations, and rural residence [20,21,23-30]. Although these findings were among the most consistent, their non-specific nature prevented reviewers from concluding they are causal [31].

Many, but not all [27], reports associated parkinsonism with manganese exposure, as in ore miners [15], smelter workers [32], those with exposure to the fungicide maneb [33] and with manganese in the diet [34]. A US study with industrial hygiene exposure review found 10-fold risk increases with more than 20 years of manganese exposure, and 2- to 5-fold increases with exposures to lead and/or copper [25,35]. A study of ethnic Chinese found a 12-fold increase in Parkinson's with exposure to heavy metals as a broad class of agents [36]. Mercury on its own was found to be both associated with parkinsonism [37], and not [35].

Organic solvents linked with parkinsonism included carbon disulfide, n-hexane, and organic solvents as a group in occupational settings [16,38,39], toluene in solvent abuse [40], and petroleum waste ingestion [41] (the latter two based on case reports). A study of 990 Parkinson's cases found that those with prior hydrocarbon solvent exposure had an earlier onset of symptoms and more severe disease [42]. In a cohort study that queried exposure by self-administered questionnaire, no association was found with exposure to the class "chemicals/acids/solvents," illustrating the non-specific nature of exposure assessment that was common in studies of this disease [43].

The role of environmental factors in the development of Parkinson's disease was also illustrated by a surprising protective exposure, cigarette smoking. Smokers were consistently shown to have risks of Parkinson's disease about half those of the non-smoking population [25,36,44-49], a risk reduction not explained by either survival of non-smokers to an older age [50] or to personality differences between these groups [51]. Nicotine was found in an animal study to reduce the toxicity of MPTP [52]. Protective effects were observed for coffee and tea, even after controlling

for smoking [36,43].

1.2.3 Respiratory infections and vibration – Previous work by the research team

In an earlier study, we examined the distribution of occupations among 447 patients with Parkinson's disease seen at the University of British Columbia Movement Disorders Clinic from 1986 to 1993, comparing it to the distribution of occupations in the 1991 Census [1]. Several odds ratios were substantially elevated and statistically significant. A prior clinical observation of an apparently elevated risk for teachers was confirmed (OR=2.5). The greatest elevation, however, was for the category "other primary occupations" which included forestry, logging, mining, and oil/gas field exploration, with an odds ratio of 3.8. There was also a substantial elevation for social service workers (OR=2.5), and medical workers (OR=2.1). On the other hand, certain groups had substantially reduced estimated risks: construction work (OR=0.31); administrative work (OR=0.48); clerical work (OR=0.58); and "occupation not applicable" which was a heterogeneous mixture, whose low OR was primarily driven by unemployed males (OR=0.16).

The overall pattern of odds ratios was not consistent with chance, even after allowing for the fact that 17 odd ratios were calculated. Many of the occupations with elevated risks were hypothesized to have higher than average exposure to respiratory infections, whereas the opposite was thought to be likely for several occupations with reduced risks. Those in the highest risk group (forestry, logging, mining, and oil/gas field exploration) might have had increased exposures to infections because of residence in industrial camps. They also might have had exposures to fuels, fuel exhausts, and vibration in common (e.g., via operation of drilling equipment, chain saws, loaders, etc.). However, we could not validate these explanations, because we had no direct information on occupational exposures of participants. Furthermore, this sample of Parkinson's disease cases may have been unrepresentative because of referral bias.

The possibility of infection as an etiologic factor in Parkinson's disease had not been adequately explored using epidemiological methods, though numerous viral infections were reported to be associated with parkinsonism, mainly in case series: encephalitis lethargica [53]; Japanese encephalitis B [54]; western equine encephalitis [55]; coxsackie B2 [56]; mycoplasma pneumoniae [57]; and influenza A [58]. A neurovirulent strain of influenza A virus was demonstrated to target the *substantia nigra* in mice [59]. Two studies replicated our findings of elevated risks in occupations with high levels of inter-personal contact such as teachers and medical personnel [30,60]. One of these used data from three US movement disorders clinics, so might also be subject to referral bias [30]. A US case-control study released in the summer of 2006 had a potentially related finding: increased risks of Parkinson's with chronic rhinitis [61].

To our knowledge, there had not been any investigation of vibration as a risk factor for Parkinson's disease, though major trauma to the head, from boxing and accidents, was linked to the disease [62-64]. We hypothesized that cumulative microtraumas from the acceleration forces of vibration might also contribute to Parkinson's disease.

1.2.4 Gene-environment interactions

Many investigators posited that Parkinson's disease has multifactorial causation, with genetic and environmental factors contributing in varying proportions in individual cases [7,10,11]. Genetic research identified polymorphisms in human enzyme systems that are involved in the activation and detoxification of chemicals, dopamine metabolism, and the effects of cigarette smoke. Monoamine oxidase type B (MAO-B)[65-74], cytochrome P450s (CYP) [74-77], and glutathione-S-transferase (GST) [74, 78-82] were among those postulated as potential sources of gene-

environment interaction in the etiology of Parkinson's disease. In his review of the epidemiology of Parkinson's disease, Marion concluded that examination of interactions between putative risk factors may hold the key to deepening our understanding of its etiology [12].

1.3 Rationale

The previous epidemiological studies and reviews indicated that the evidence about most environmental risk factors, other than smoking [25,36,44-49], was suggestive but weak [7,10,11,31,83]. Most studies were limited by small sample sizes and therefore small numbers exposed to any single risk factor. Even though the workplace is the most likely source of high exposures to most postulated agents of interest, few studies had gathered detailed employment histories. Exposure assessment was usually based on self-reports without hygiene review and targeted broad chemical groups (e.g., insecticides) rather than specific agents.

These problems were not surprising – epidemiological research on Parkinson's disease was (and remains) at a rather early stage compared to research on cancer and heart disease. The reason is largely the difficulty of case ascertainment; it is rarely possible on a population basis, yet accrual by other methods, such as via hospitals or health maintenance organizations, is very slow and may be subject to referral bias.

1.4 Format of this Report

This report describes the study we designed and conducted in response to the literature described above. It includes methods, results, and discussion of analyses of associations with Parkinson's disease for a wide range of exposures. For this reason, the report is written in a somewhat non-standard format.

Section 2.0 Approach describes the methods that are common to all exposures.

Section 3.0 Results and Discussion first describes study participation. Then, for each exposure evaluated, exposure-specific methods are described, followed by results of the epidemiological analyses, and discussion of those results with respect to the scientific literature updated to the time that this report was written. The literature reviewed is not comprehensive, but rather focuses on studies pertinent to the associations found in this study. The final sub-section provides an overview of the results across all exposures evaluated and a discussion of the strengths and limitations of this study.

Section 4.0 Implications discusses the importance of the results for work exposures and provides thoughts about future research.

2. Approach

We conducted a population-based case-control study, with cases and controls sampled from Metro Vancouver and all of Vancouver Island, excluding Greater Victoria. Participants from Vancouver Island were included to increase the diversity of occupations by capturing those more common to rural areas of the province (forestry, fishing, mining). Data collection started in April 2001 and was completed in July 2008.

2.1 Eligibility

Persons between the ages of 40 and 69 years inclusive (as of December 31, 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 for the study. The age restriction was applied for the following reasons: 1) the etiology of Parkinson disease may vary with age and thus the age restriction made the study population more homogenous, 2) participants above the age of 40 years would have accrued occupational exposure and the possible effects would have had time to develop, 3) patients in the age range 40-69 years were expected to be easily recruited and interviewed, and to be free from symptoms that would make the interview difficult, 4) mortality would be small in the age range 40-69 years, thus minimizing survivor bias, 5) participants would be near or in their working years, and less likely to have memory problems, thus minimizing recall difficulties.

2.2 Identifying cases with Parkinson's disease

Potential cases were individuals who for at least one calendar year from 1995 to 2002 inclusive had more than \$800 in prescription costs reimbursed by PharmaCare and at least one prescription for anti-parkinsonian medications. An anti-parkinsonian agent was defined as levodopa; bromocriptine mesylate; pergolide mesylate; levodopa/benserazide hydrochloride; levodopa/carbidopa; or seligiline hydrochloride. During the case identification period, PharmaCare paid for prescription drugs for all individuals over 65 years of age, and for those under 65, if the cost of drugs exceeded \$800 per year. Due to the high cost of antiparkinsonian drugs, and the fact that most patients are treated, we assumed that the PharmaCare database would include almost all cases of Parkinson disease.

Those who were residents of a long-term care facility were excluded. To avoid recruitment of patients with secondary parkinsonism due to antipsychotic drug use, all those who had a target drug reimbursed under PharmaCare Plan G (Mental Health Plan) and all those who filled a prescription for an antipsychotic drug in the period studied were removed.

The populations meeting the potential case definition were identified by the Ministry of Health Services on two occasions: in 2001 (data from 1995 to 1998) and in 2005 (data from 1999 to 2002). To blind the data extractors to the disease status of the potential cases, the extract was supplemented with a 20% "camouflage" random sample of other individuals in the PharmaCare database.

All potential cases were verified by an initial screening interview by phone about eligibility, including presence of chronic diseases, antiparkinsonian medications taken, and the reason for their use. This screened out those taking medications for much different purposes (e.g., bromocriptine for lactation cessation or levodopa for restless legs syndrome). For those taking the medications for known or suspected Parkinson disease, an in-person physical assessment was

conducted employing a checklist and record of symptoms, reviewed by a neurologist (JT). The following clinical criteria for Parkinson disease were used: 1) two of the following symptoms present on examination: parkinsonian tremor, rigidity, bradykinesia, masked facies, micrographia, or postural imbalance, 2) absence of specific signs of other diseases that would account for these findings. The assessment form also collected patient reports on the date of Parkinson diagnosis, date when symptoms were first noted, and the date when treatment commenced. Participants who reported a date of diagnosis that indicated disease onset prior to age 40 were excluded.

2.3 Identifying controls

Controls were recruited at the same time as cases. The control sample was frequency-matched to the case sample on age (six age groups in 5-year intervals), sex, and geographic location (two strata: Metro Vancouver and Vancouver Island areas). Controls were selected using stratified random sampling from the British Columbia Ministry of Health Services Client Registry, which includes all individuals covered by the Medical Services Plan, 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. Any who indicated Parkinson disease were excluded.

2.4 Contacting potential participants

Because of BC Ministry of Health Services policy and subsequently enacted privacy legislation, this study was required to use a two-stage process in which consent to be contacted then consent to participate were sought. The Ministry of Health Services sent out two invitation letters (one signed by Ministry personnel and one signed by University of British Columbia (UBC) research team personnel) to potential cases and controls, asking them to contact the UBC team at a toll-free number or via mail using a postage-paid envelope. 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 participant if their name could be released to the study team. Participants who agreed were then contacted by the UBC study coordinator who conducted the screening interview and requested participation in the study.

2.5 Interview questionnaire

Information about the participants was obtained via in-person interviews by trained interviewers using a standardized questionnaire (Appendix A). An interview guide was mailed to each participant before the interview to prompt recall of his or her working life starting at the age of 16 (Appendix B). The questionnaire asked about each participant's birth date, sex, marital status, ethnic heritage, highest level of education, employment history, medical history, and personal habits including smoking, coffee consumption, use of alcohol, and solvent inhalation. Standard approaches that have been employed successfully in other studies were used to obtain employment, medical, smoking, and drinking histories [84-86].

The employment history served as the framework for questions about infections, vibration, job strain, pesticides, solvents, and metals. Numerous studies have shown that work histories are well recalled, and therefore form a good "backbone" upon which to build exposure assessment [86].

The questionnaire was pre-tested, revised, and retested to ensure that all questions were unambiguous, feasible to answer, and that sensitive questions were worded in such a way that interviewees felt comfortable giving answers. The interviewers were observed during pre-testing and at least annually thereafter to allow identification and correction of problems in their techniques.

Study participants knew that we were conducting a study of neurological disease, but were not told the specific disease focus or hypotheses. The interviewers were not informed of the hypotheses or told which participants were cases or controls, however, during interviews, they could easily identify certain individuals as likely cases. The structured format of the questionnaire was designed to minimize any potential bias in the interview.

All interviews were reviewed by hygienists (blind to case status) on two occasions. The first review, after the interview, was used to ensure that exposures likely associated with specific jobs were not missed; participants with potentially missed exposures were called with clarifying questions. The second review, before data analysis, screened all exposures using information about exposure duration, job duties, and tasks to rule out unlikely or background level exposures. This was done to prevent dilution of the exposed group and minimize attenuation of risk estimates [86,87].

2.6 Taking samples for genotyping

At the end of each interview, the interviewer asked the participant whether he or she was willing to participate in the genotyping part of the study, and if so, whether he or she was willing to have cell samples taken from inside the mouth. Samples were collected according to established methods [88-92] by twisting a small brush 5 times on each inner cheek surface with an upward motion, and once across the upper and lower lip within the oral cavity. Samples were stored on ice until delivery to a freezer at UBC. When a sufficient number of samples had accumulated, they were sent on icepacks in a cooler by overnight courier to the University of Washington Molecular Biology Laboratory where genotyping was performed.

2.7 Data analysis

Initial analyses examined associations with lifestyle factors (especially smoking, but also use of alcohol, coffee, marijuana, and solvents) that might be confounders of any occupational associations.

The primary occupational analyses examined the association of Parkinson's disease with job categories, infections spread by respiratory droplets, and vibration. Additional analyses examined associations with head injuries, job strain, pesticides, solvents, metals, and genotypes.

The relationships between exposures and Parkinson's disease were assessed using unconditional logistic regression. Exposures of cases were considered up to the time of first diagnosis of Parkinson's, as well as up to earlier censoring dates to account for possible latency periods (5 and 10 years)[7]. For the purposes of establishing a "date of diagnosis" for controls, controls within an age-sex stratum were assigned the mean diagnosis date of cases in that stratum. Analyses were performed with SAS software version 9.1 (SAS Institute Inc., Cary, NC). To understand the impact of increasing levels of exposure, analyses were also performed based on duration of exposure, cumulative exposure, or tasks associated with higher levels of exposure.

Analyses are presented for each exposure separately, adjusted for age, sex, and smoking status. Only analyses of exposures experienced by at least 15 study participants up to the date of diagnosis are reported here. In this report, we focus on relationships that were statistically significant, consistent with our *a priori* hypotheses, and/or strong (odds ratios of at least 2 or 0.5 or lower).

3. Results and Discussion

3.1 Participation

A total of 3,783 potential participants 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 disease; they used anti-parkinsonian drugs for other indications or were part of the camouflage sample.

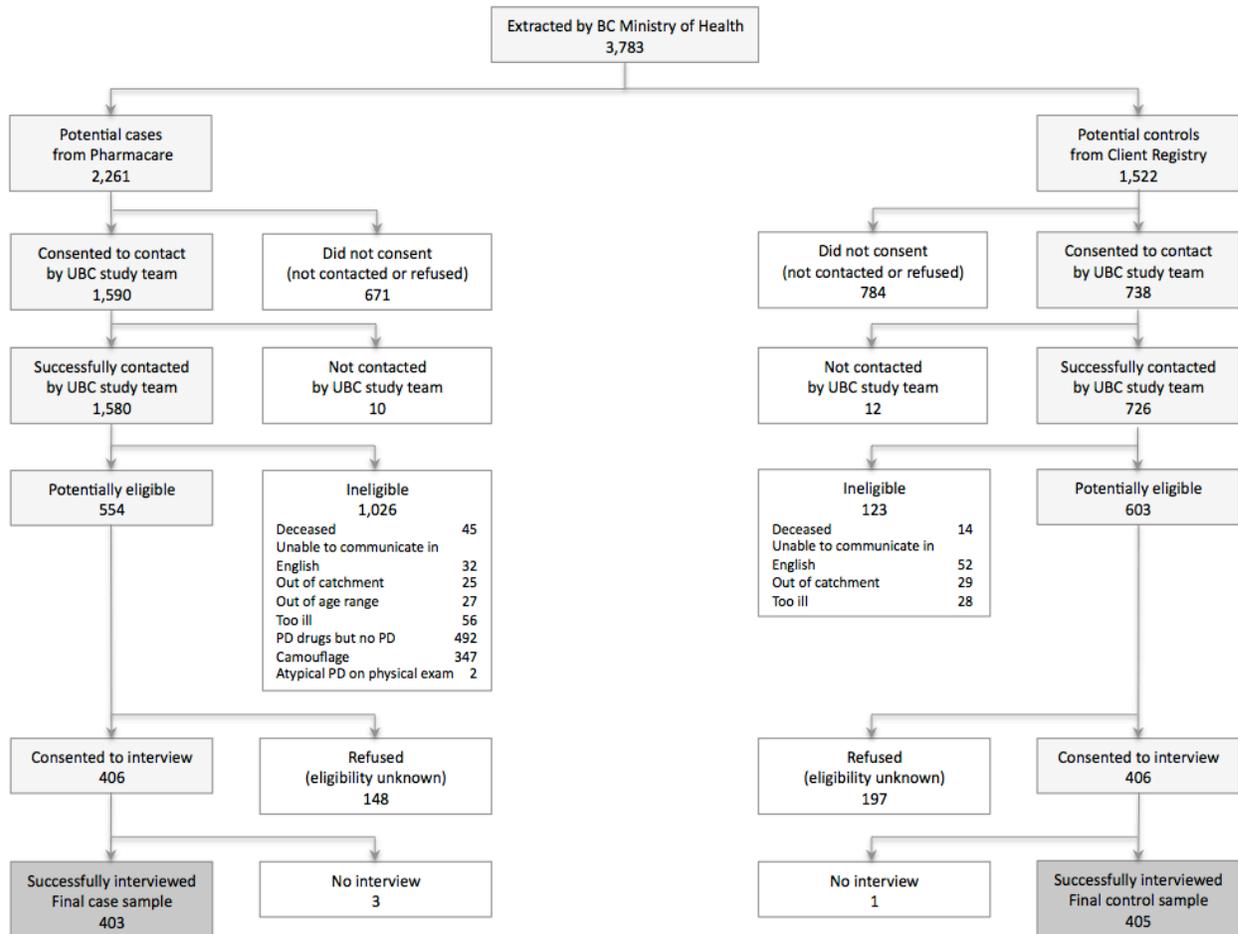


Figure 1: Chart showing the classification of potential participants from sample extract to interview

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 potentially eligible ($554/1580=0.35$ for cases, $603/726=0.83$ for controls) was the same in the initially extracted samples, we can calculate the potentially eligible numbers for the full sample ($0.35 \times 2261=791$ for cases; $0.83 \times 1522=1264$ for controls) and use these as denominators

for a conservative participation rate calculation. Using this method, the 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. Age and sex were not matched between cases and controls because the Ministry of Health Services frequency matched the “potential control” sample to the “potential case” sample, not to the actual case sample. The potential case sample included a large camouflage sample from the overall PharmaCare database and large numbers of individuals taking anti-parkinsonian medications who did not have the disease (they took the medications for restless legs syndrome, lactation cessation, smoking cessation, and other indications). These groups were younger and more likely to be female than actual cases; this distribution is reflected in the controls.

All subsequent analyses were adjusted for birth year (in six 5-year groups) and sex.

Table 1: Characteristics of the study population: 403 cases with Parkinson’s disease and 405 population-based controls

Characteristic	Cases N (%)	Controls N (%)
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)
	Mean (SD)	Mean (SD)
Mean age at diagnosis of Parkinson disease (yr)	56.0 (7.1)	–
Mean age at the time of interview (yr)	65.0 (6.6)	62.2 (9.0)

3.2 Personal Habits

3.2.1 Methods specific to personal habits

Cigarette smoking was queried in the personal habits section of the questionnaire, using standard methods based on the American Thoracic Society and Canadian Community Health Survey questionnaires. Ever smoking was defined as smoking at least 100 cigarettes over the lifetime. Cumulative smoking exposure was calculated as the average number of packs of cigarettes smoked per day times the total number of years as a smoker, to give a result in daily pack-years.

Cannabis use was queried in the personal habits history, using an introductory sentence meant to soften the attention on cannabis use. Ever smoked marijuana was defined based on a yes/no answer to a direct question. Cumulative marijuana use was calculated as the average number of times per week smoked times the total number of years marijuana was used, to give a result in weekly event-years.

Alcohol use was queried in the personal habits history, using a standard definition of a drink (e.g., the same as the Canadian Community Health Survey: a glass of wine, a bottle of beer, or a shot of

hard liquor as one drink). Ever drinking was defined as consuming at least 2 drinks/month for a period of one year or longer. Cumulative alcohol use was calculated as the average number of drinks per week times the total number of years as a drinker, to give a result in weekly drink-years.

Coffee consumption was queried within the job history to capture variability over the lifetime. Ever drinking coffee was defined as drinking coffee during at least one job. Cumulative coffee use was calculated as the average number of drinks per week in a job times the total number of years in that job, summed over all jobs, to give a result in weekly drink-years.

3.2.2 Results and Discussion

Table 2 lists the mean cumulative lifetime consumption of cigarettes, marijuana, alcohol, and smoking among cases and controls, and the numbers of cases and controls reporting use up to the date of diagnosis. It also shows odds ratios for exposure to date of diagnosis and censored at 5 and 10 years prior to diagnosis. All analyses were adjusted for birth year and sex, and, for analyses of marijuana, alcohol and coffee consumption, also adjusted for smoking.

Table 2: Descriptive statistics for various lifestyle habits among Parkinson’s disease cases and controls, and odds ratios (OR) and 95% confidence intervals (CI) for associations between these habits and Parkinson’s disease, with exposure censoring at date of diagnosis and 5 and 10 years prior to diagnosis. Odds ratios calculated for a typical consumption amount for each habit among consumers. All analyses adjusted for gender and birth year (5-year groups). Analyses for marijuana, alcohol and coffee also adjusted for smoking (cumulative pack-years).

Personal habits variable	Cases Mean (SD)	Controls Mean (SD)	Cases / Controls N ^a	OR (95% CI) exposure up to date of diagnosis	OR (95% CI) exposure up to 5 years prior to diagnosis	OR (95% CI) exposure up to 10 years prior to diagnosis
Cigarette smoking, cumulative daily pack-years ^b	11.5 (20.1)	15.3 (21.8)	198 / 249	0.69 (0.57 - 0.83)	0.69 (0.56 - 0.84)	0.68 (0.55 - 0.85)
Marijuana smoking, cumulative weekly event-years ^c	0.37 (2.71)	1.04 (7.09)	44 / 70	0.95 (0.80 - 1.13)	0.92 (0.75 - 1.14)	0.88 (0.66 - 1.17)
Alcohol, cumulative weekly drink-years ^d	30.3 (53.4)	28.8 (54.4)	269 / 286	1.00 (0.86 - 1.16)	1.00 (0.86 - 1.16)	1.00 (0.86 - 1.22)
Coffee, weekly drink-years ^e	83.6 (97.5)	74.7(101.9)	336 / 338	1.00 (0.82 - 1.11)	0.90 (0.82 - 1.11)	0.90 (0.74 - 1.11)

^a Counts of exposures of cases and controls up to date of diagnosis (and corresponding date for controls)

^b Odds ratio calculated for 25 cumulative daily pack-years

^c Odds ratio calculated for 5 cumulative weekly event-years

^d Odds ratio calculated for 50 cumulative weekly drink-years

^e Odds ratio calculated for 100 cumulative weekly drink-years

Only cigarette smoking had a strong and statistically significant relationship to Parkinson’s disease. The relationship demonstrates a protective effect, consistent with other studies [25,36,44-49,93-96]. All subsequent analyses were adjusted for smoking, using the continuous variable, cumulative daily pack-years.

Other lifestyle exposures were not significantly associated with Parkinson’s disease. We found no other studies that examined marijuana use. Relationships between coffee drinking and Parkinson’s disease have tended to show reduced risk with increased consumption [36,43, 93,94,96-99] but

others show no association [45,95,100]. With alcohol use, more studies have found no association [93,95,96,101], though some have found reduced risk with increased consumption [45,94].

3.3 Occupations

3.3.1 Occupation-specific methods

All occupations held for at least 6 months and listed by the participants were classified to the major occupational categories used in our initial study of the UBC Movement Disorders Clinic data [1] and subcategorized using the 1980 Standard Occupational Classification [102] as a guide. The 1980 classification system was used because the retrospective nature of the study meant that the occupations of the study participants more closely conformed to those described in this classification system than newer ones.

Occupational categories were assigned by an occupational hygienist (KT) blind to case status, using all the job history data (job title, main duties and activities, employer name, and product or service provided by the employer).

3.3.2 Results and Discussion

The mean number of occupations held by each study subject was 6.3, with a standard deviation of 3.1, a minimum of 1 and a maximum of 22. Study subjects were classified into 16 major job categories (corresponding to those of our earlier study of UBC Movement Disorders Clinic data [1]) and 49 subcategories, 38 of which had sufficient study subjects to report here ($n \geq 15$).

Table 3 lists the numbers of cases and controls ever holding each occupation up to the date of diagnosis. It also shows odds ratios and confidence intervals for ever vs. never holding each occupation prior to the date of diagnosis (or the corresponding date assigned to controls), and for two censoring dates: 5 and 10 years prior to diagnosis. We also calculated odds ratios for each occupation when held for a minimum duration of 10 years, but because these analyses highlighted only a few additional associations of interest, they are reported in the text only.

Two occupations had significantly elevated odds ratios: social science, law and library jobs; and farming and horticulture jobs. Both of these had higher odds ratios with at least 10 years of employment (OR = 2.51 (95% CI: 0.88 - 7.21), OR = 5.58 (95% CI: 1.48 - 21.0), respectively). Two other occupations had odds ratios above 2, though they were not statistically significant: gas station jobs; and welders. These also had higher odds ratios with at least 10 years of employment (OR = 3.99 (95% CI: 0.42 - ∞), OR = 5.37 (95% CI: 0.58 - 49.5), respectively). Finally two jobs had odds ratios above 2, only with at least 10 years of employment: drivers of heavy equipment (OR = 6.48 (95% CI: 0.71 - 59.3)) and carpenters (OR = 11.3 (95% CI: 1.23 - 105)).

Two occupations had significantly reduced odds ratios: management and administration jobs; and other health care jobs. Two other occupations had odds ratios below 0.5, though they were not statistically significant: repairers; and electricians. None of the jobs with reduced odds ratios showed stronger relationships with at least 10 years of employment.

After Table 3, each of the jobs of interest is discussed in turn, with reference to other studies of occupations and Parkinson's disease.

Table 3: Odds ratios and 95% confidence intervals for associations between occupations held for at least 6 months and Parkinson's disease, with exposure censoring at date of diagnosis and 5 and 10 years prior to diagnosis. Each job was examined in a separate model adjusted for gender, birth year (5-year groups) and smoking (cumulative pack-years). Occupational subcategories listed only for those with at least 15 study subjects to date of diagnosis.

Major Occupational Categories & subcategories	Cases / Controls N ^a	OR (95% CI) job held prior to date of diagnosis	OR (95% CI) job held prior to 5 years prior to diagnosis	OR (95% CI) job held prior to 10 years prior to diagnosis
Management, Administration [‡]	113 / 120	0.74 (0.54 - 1.04)	0.73 (0.52 - 1.02)	0.70 (0.49 - 0.99)
Sciences, Engineering	65 / 53	1.15 (0.75 - 1.76)	1.20 (0.77 - 1.86)	1.18 (0.76 - 1.85)
Social Sciences, Law, Library [†]	34 / 28	1.73 (0.98 - 3.05)	1.76 (0.99 - 3.12)	1.82 (1.01 - 3.29)
Teaching [†]	54 / 56	0.93 (0.61 - 1.42)	0.88 (0.57 - 1.35)	0.93 (0.60 - 1.44)
Medicine, Health [†]	49 / 63	0.85 (0.55 - 1.30)	0.82 (0.53 - 1.26)	0.90 (0.58 - 1.39)
health care, other	10 / 24	0.45 (0.21 - 0.98)	0.40 (0.18 - 0.89)	0.44 (0.20 - 0.99)
lab technician	15 / 12	1.45 (0.64 - 3.30)	1.45 (0.64 - 3.29)	1.84 (0.77 - 4.40)
nursing	18 / 34	0.60 (0.32 - 1.13)	0.60 (0.32 - 1.12)	0.60 (0.32 - 1.12)
Art, Literature, Recreation, Religion	35 / 26	1.38 (0.79 - 2.39)	1.45 (0.83 - 2.53)	1.56 (0.87 - 2.78)
Clerical [‡]	138 / 164	0.95 (0.68 - 1.34)	0.94 (0.67 - 1.32)	0.92 (0.65 - 1.30)
Sales, Commodities, Services	137 / 125	1.26 (0.92 - 1.74)	1.26 (0.91 - 1.73)	1.26 (0.91 - 1.75)
gas station	14 / 5	2.66 (0.89 - 7.96)	2.55 (0.84 - 7.72)	2.55 (0.84 - 7.72)
real estate agent	8 / 10	0.84 (0.31 - 2.23)	0.99 (0.32 - 3.11)	0.84 (0.22 - 3.14)
sales	128 / 114	1.32 (0.96 - 1.83)	1.28 (0.92 - 1.78)	1.29 (0.92 - 1.80)
Service - Food, Lodging	129 / 133	1.08 (0.79 - 1.48)	1.11 (0.81 - 1.52)	1.07 (0.77 - 1.47)
cook/baker	19 / 15	1.36 (0.64 - 2.89)	1.41 (0.65 - 3.07)	1.26 (0.57 - 2.79)
food service	40 / 49	1.06 (0.66 - 1.73)	1.09 (0.67 - 1.78)	1.08 (0.66 - 1.78)
food/lodging other	8 / 7	1.03 (0.36 - 2.94)	1.02 (0.36 - 2.93)	0.77 (0.25 - 2.38)
home care	10 / 13	1.06 (0.44 - 2.58)	0.82 (0.30 - 2.22)	0.49 (0.15 - 1.63)
janitor/cleaner	26 / 24	1.34 (0.72 - 2.48)	1.69 (0.86 - 3.32)	1.77 (0.85 - 3.69)
maintenance	12 / 18	0.81 (0.36 - 1.80)	0.88 (0.37 - 2.08)	0.90 (0.33 - 2.45)
protective service	20 / 11	1.37 (0.63 - 2.96)	1.24 (0.57 - 2.72)	1.18 (0.53 - 2.60)
soldier	19 / 19	0.76 (0.38 - 1.50)	0.76 (0.39 - 1.51)	0.77 (0.39 - 1.51)
Farming, Horticulture	37 / 23	1.92 (1.05 - 3.51)	2.02 (1.09 - 3.72)	2.03 (1.10 - 3.74)
Other Primary - Forestry, Logging, Mining, Oil, Gas [†]	31 / 32	0.88 (0.50 - 1.55)	0.87 (0.50 - 1.52)	0.90 (0.51 - 1.59)
logging	14 / 19	0.66 (0.31 - 1.40)	0.65 (0.31 - 1.38)	0.60 (0.28 - 1.30)
mining	13 / 10	1.22 (0.50 - 3.02)	1.21 (0.49 - 2.97)	1.35 (0.53 - 3.41)
Processing - Ore, Metal, Glass, Stone, Rubber, Wood, etc.	98 / 73	1.14 (0.79 - 1.64)	1.09 (0.75 - 1.57)	1.07 (0.74 - 1.55)
processing - food	21 / 22	0.88 (0.46 - 1.67)	0.88 (0.46 - 1.67)	0.88 (0.46 - 1.69)
processing - metal	11 / 11	0.71 (0.29 - 1.71)	0.71 (0.29 - 1.71)	0.71 (0.29 - 1.70)
processing - other	27 / 20	1.21 (0.65 - 2.27)	1.17 (0.62 - 2.19)	1.17 (0.61 - 2.22)

Major Occupational Categories & subcategories	Cases / Controls N ^a	OR (95% CI) job held prior to date of diagnosis	OR (95% CI) job held prior to 5 years prior to diagnosis	OR (95% CI) job held prior to 10 years prior to diagnosis
processing - textile	10 / 6	1.50 (0.53 - 4.22)	1.32 (0.46 - 3.78)	1.32 (0.46 - 3.79)
processing - other wood industries	11 / 9	0.82 (0.33 - 2.06)	0.81 (0.32 - 2.03)	0.80 (0.32 - 2.00)
processing - pulp mill	15 / 11	0.90 (0.40 - 2.04)	0.83 (0.37 - 1.91)	0.75 (0.33 - 1.74)
processing - sawmill	18 / 13	1.02 (0.47 - 2.22)	1.02 (0.47 - 2.22)	1.14 (0.52 - 2.51)
Machine Related (Product Fabricating, Assembling, Repairing)	66 / 55	0.79 (0.51 - 1.21)	0.80 (0.52 - 1.24)	0.79 (0.51 - 1.22)
electronics technician	15 / 14	0.74 (0.34 - 1.60)	0.74 (0.34 - 1.59)	0.81 (0.37 - 1.79)
mechanic	23 / 23	0.66 (0.35 - 1.24)	0.57 (0.30 - 1.10)	0.54 (0.28 - 1.05)
other machine-related	12 / 8	0.85 (0.34 - 2.15)	0.99 (0.38 - 2.59)	0.92 (0.34 - 2.44)
repairer	12 / 18	0.48 (0.22 - 1.04)	0.51 (0.23 - 1.12)	0.49 (0.22 - 1.09)
welder	12 / 3	3.28 (0.87 - 12.3)	3.25 (0.87 - 12.2)	2.98 (0.78 - 11.4)
Construction[‡]	55 / 47	0.92 (0.58 - 1.45)	0.86 (0.54 - 1.37)	0.87 (0.54 - 1.38)
carpenter	13 / 10	1.18 (0.48 - 2.91)	1.17 (0.48 - 2.86)	1.15 (0.47 - 2.79)
construction - other	36 / 23	1.23 (0.69 - 2.20)	1.26 (0.70 - 2.26)	1.25 (0.69 - 2.26)
electrician	8 / 10	0.52 (0.20 - 1.38)	0.46 (0.17 - 1.27)	0.46 (0.17 - 1.26)
Transport Equipment Operating	76 / 72	0.87 (0.58 - 1.29)	0.88 (0.59 - 1.32)	0.95 (0.63 - 1.42)
driver - car, small vehicle	15 / 18	0.82 (0.39 - 1.74)	0.82 (0.39 - 1.75)	0.72 (0.33 - 1.57)
driver - heavy equipment	13 / 7	1.52 (0.58 - 4.00)	1.72 (0.62 - 4.75)	1.95 (0.66 - 5.81)
driver - truck	29 / 28	0.83 (0.47 - 1.48)	0.82 (0.46 - 1.46)	0.96 (0.53 - 1.75)
seaman/fishing	18 / 18	0.84 (0.41 - 1.71)	0.91 (0.44 - 1.86)	0.92 (0.45 - 1.89)
transport other	15 / 12	0.99 (0.45 - 2.20)	0.84 (0.37 - 1.91)	0.83 (0.37 - 1.89)
Material Handling, Printing, Utilities, Equipment Operating	59 / 58	0.84 (0.55 - 1.29)	0.86 (0.56 - 1.32)	0.89 (0.57 - 1.38)
delivery – non motorized	18 / 18	0.83 (0.41 - 1.69)	0.84 (0.41 - 1.71)	0.84 (0.41 - 1.71)
shipping/warehousing	31 / 30	0.82 (0.47 - 1.43)	0.83 (0.47 - 1.47)	0.84 (0.46 - 1.52)

^a Counts of jobs of cases and controls up to date of diagnosis (and corresponding date for controls)

[‡] Occupational categories that had statistically significantly reduced odds ratios in the analysis of the Movement Disorders Clinic database by the study team, reported in 1999 [ref]

[†] Occupational categories that had statistically significantly elevated odds ratios in the analysis of the Movement Disorders Clinic database by the study team, reported in 1999 [ref]

Social science, law and library jobs. Elevated risks of Parkinson's disease in such occupations is a consistent finding, in studies of clinic data [103], hospitalizations [104], proportionate mortality [60,105], and cases and controls [96,106], though in the latter two studies, the elevations were not statistically significant. This major job category also had significantly elevated odds ratios in our study of data from the UBC Movement Disorders Clinic [1], a basis for our interest in infectious diseases spread by respiratory droplets as a potential cause. However other occupations that contributed to this hypothesis in the earlier study (teaching, medicine and health) did not have elevated risks in this study.

Farming and horticulture jobs. Farming occupations are among the most studied with respect to Parkinson's disease and have consistently demonstrated elevated risks [20,23,24,29,60,106-115], a result supported here. A few studies have not found increased risk in this occupational category or found mixed results [116-118]. The associations with farming have often been attributed to pesticide exposure, an exposure we examine in section 3.8. We were not able to examine pesticide applicators as a separate job category, since that occupation was rare in this study. Sawmill workers, many of whom have exposures to anti-sapstain fungicides, did not show excess risks here.

Gas station jobs. We found only one other study that listed gas station employment as an identifiable job category, in this case in combination with automotive dealers. Park *et al.* [118] found a non-significant but strongly elevated odds ratio, similar to our result. The potential exposure of interest could be solvents and other volatile hydrocarbons, an exposure we examine in section 3.10. Other occupations expected to have hydrocarbon exposures would include mechanics, but this occupation did not show elevated risk here.

Welders. Welding has been a frequently studied occupation with regards to Parkinson's disease because of the potential for high exposures to manganese and other metals that have been associated with the disease in the past [15, 25, 32-35]. Most studies have not found elevated risks [60,104,111,117,119,120], though one of these studies did find a significantly elevated risk in welders under the age of 65 [60]. Other occupations in our study with potential exposures to metals, including metal processors, electronics technicians, mechanics, and repairers did not have elevated risks. Metals exposures are examined in section 3.9.

Drivers of heavy equipment. A few studies have examined driving occupations. Those grouping all drivers or transport occupations together have not reported elevated risks [96,104,118]. One study separated bus drivers and excavating or grading operators, but still did not find excess risks [60]. Our study found elevated risks only in this one segment of driving occupations, but not for car, truck, boat or other transportation occupations. Hypothesized exposures for this group include whole body vibration and hydrocarbons, discussed in sections 3.5 and 3.10 respectively.

Carpenters. A few studies have examined wood-working occupations, and all have identified elevated risks [29,96,104,105]. In our study, the elevated risk was isolated to carpenters with at least 10 years of employment, but was not seen in sawmill, pulp mill, or other wood industry employees. This suggests that the exposure of interest may not be wood, but perhaps glues, head injuries, or other exposures that might differ in carpenters. These exposures are addressed in sections 3.6 and 3.10.

Management and administration jobs. Other studies of Parkinson's disease that have examined managerial jobs have usually found odds ratios near 1.0, without significant elevations or reductions in risk [96,107,113,118], except one study that found a slightly and significantly elevated risk [104]. In the current study and in our initial study of the UBC Movement Disorders Clinic data [1], we found significantly reduced odds ratios.

Other health care jobs. In our study, this mixed group (dentistry, physiotherapy, occupational therapy, care aides, and x-ray technicians) had significantly reduced risks. Other studies found odds ratios near 1.0, without significant elevations or reductions in risk for other health and medical workers, and dentists [104], and health care support, and health care practitioner and technical jobs [96]. Park *et al.* [60] included separate estimates for several of the professions included here, and found slightly elevated risks for dental assistants, dentists, dental laboratory personnel, and x-ray

technicians, significant only for the first job group.

Repairers. This was another mixed group (locksmiths, elevator mechanics, service technicians, shoe repairers, appliance technicians). They had strongly reduced risks, but not statistically significant. Similar occupations were difficult to identify in other studies. Park *et al.* [118] found a very similar reduced risk estimate for technicians, and Schulte *et al.* [105] found a significantly increased odds ratio for technicians and related support occupations.

Electricians. The only other study we found that examined electrical workers found an odds ratio near 1.0 [104], providing little support for the non-significant protective effect we observed.

In our earlier study of the UBC Movement Disorders Clinic data [1], 4 of 16 major occupational categories had significantly elevated risks and 3 had significantly reduced risks. In this population-based study, only one of these categories had a significantly elevated risk (social science, law, library) and only one a significantly reduced risk (management, administration), suggesting that our concern about potential referral bias in the initial clinic-based study was well founded.

3.4 Infections

3.4.1 Infection-specific methods

Viral infections spread by respiratory droplets were assessed in two ways: 1) within the job history, via questions about sick days taken and their causes, the number of people typically contacted, the type of living accommodations, and contact with animals; and 2) within the medical history, via a questions asking about flu shots and whether a doctor said the subject had any of a list of communicable diseases.

3.4.2 Results and Discussion

Table 4 provides the odds ratios and confidence intervals for associations between the variables considered potentially related to infections and Parkinson's disease, in three groupings: influenza; other viral communicable diseases; and contact with people or animals during the job.

The variables related to influenza have a pattern suggesting increased risk of Parkinson's disease, though only severe influenza was statistically significant. Absence from work for at least 5 days per year within at least one job and cumulative days absent over all jobs showed slight elevations, which increased in strength with censoring of episodes 5 and 10 years prior to diagnosis. Flu shots were increasingly protective with censoring at 5 and 10 years prior to diagnosis. Another study examining influenza in a case-control study reported a slight non-significant elevation [121]. There do not appear to be other epidemiological studies that have examined this exposure, though there have been case reports of acute onset Parkinsonism and hypotheses about potential causal mechanisms [58].

Unlike the results for influenza, absence from work for colds (for at least 5 days per year within at least one job and cumulative days absent over all jobs) showed non-significantly reduced risks. Most other viral diseases queried in the medical history also had reduced risks, with statistically significant reductions for red measles and chicken pox or shingles. Reduced risk of Parkinson's disease with measles, mumps and chicken pox has been reported previously [121,122], though a small study examining measles antibodies in cases and controls did not observe a difference [123].

Our analyses examining the average number of people contacted within a working day showed no association with Parkinson's disease, but parallel to our findings related to non-influenza viral

infections, having lived in a dormitory during a job showed a significant reduction in risk. The major occupational categories involving dormitory living included: service - food or lodging; other primary - forestry, logging, mining, oil or gas; medicine or health; and transport equipment operating.

In contrast to human contact, animal contact on the job was associated with increased risks of Parkinson's disease, with significant elevations for cats, cattle, pigs, sheep or goats, and chickens, ducks, or geese. The major occupational categories involving contact with these animals were farming or horticulture, and food processing. Few other studies have examined animal contact. Lee *et al.* [109] found significantly elevated proportionate mortality for Parkinson's disease in livestock farmers, whereas Firestone *et al.* [117] found no association for animal or dairy farmers, and Kuopio *et al.* [116] found significant reductions in risk with childhood exposures to the same animals investigated in our study. Two potential mechanisms for the elevated risks observed with animal exposures are flu viruses and endotoxin. Influenza A viruses have their origin in wild waterfowl, are mainly transmitted to humans via domestic poultry and pigs, and have been found in other domestic animals including cats, dogs and horses [124]. Endotoxins, the lipopolysaccharide components of cell walls of Gram-negative bacteria, can be found in organic dust (e.g., from grains) and plant matter (e.g., hay) [125] and could also be related to these animal exposures (e.g., via fodder for livestock or via cats used to control pests in grain stores). Endotoxin has been hypothesized as a potential cause of Parkinson's disease based on toxicological evidence [126]. Direct tests of the epidemiological association in humans are awaited.

Table 4: Odds ratios and 95% confidence intervals for associations between variables potentially related to infections and Parkinson disease. Each was analyzed in a separate model adjusted for gender, birth year (5-year groups) and smoking (cumulative pack-years). Exposure censored at date of diagnosis and 5 and 10 years prior to diagnosis. Disease and contact categories listed only for those with at least 15 study subjects to date of diagnosis.

Category and variable	Cases / Controls N ^a	OR (95% CI) exposure up to date of diagnosis	OR (95% CI) exposure up to 5 years prior to diagnosis	OR (95% CI) exposure up to 10 years prior to diagnosis
Influenza				
Ever absent from work for more than five days per year for flu	40 / 33	1.21 (0.73 - 2.02)	1.30 (0.76 - 2.20)	1.38 (0.80 - 2.38)
Cumulative days absent from work for flu ^b	-	1.06 (0.98 - 1.17)	1.08 (0.98 - 1.20)	1.10 (0.98 - 1.22)
Ever had a flu shot	104 / 102	1.07 (0.77 - 1.50)	0.97 (0.61 - 1.53)	0.85 (0.46 - 1.60)
Ever had severe influenza	43 / 26	2.01 (1.16 - 3.48)	2.02 (1.14 - 3.59)	1.74 (0.97 - 3.12)
Other viral communicable diseases				
Ever absent from work for more than five days per year for colds	23 / 32	0.71 (0.40 - 1.27)	0.71 (0.40 - 1.27)	0.79 (0.44 - 1.43)
Cumulative days absent from work for cold ^b	-	0.94 (0.87 - 1.04)	0.94 (0.85 - 1.06)	0.94 (0.83 - 1.06)
Ever had croup	23 / 30	0.74 (0.41 - 1.34)	0.73 (0.40 - 1.33)	0.73 (0.40 - 1.33)
Ever had herpes simplex	43 / 49	0.96 (0.60 - 1.53)	1.00 (0.62 - 1.61)	1.01 (0.63 - 1.63)

Category and variable	Cases / Controls N ^a	OR (95% CI) exposure up to date of diagnosis	OR (95% CI) exposure up to 5 years prior to diagnosis	OR (95% CI) exposure up to 10 years prior to diagnosis
Ever had German measles	53 / 41	1.27 (0.77 - 2.08)	1.27 (0.78 - 2.08)	1.28 (0.78 - 2.09)
Ever had red measles	242 / 291	0.65 (0.48 - 0.90)	0.65 (0.47 - 0.90)	0.65 (0.47 - 0.89)
Ever had mumps	208 / 232	0.76 (0.56 - 1.02)	0.76 (0.56 - 1.02)	0.76 (0.57 - 1.03)
Ever had chicken pox or shingles	252 / 296	0.75 (0.54 - 1.03)	0.73 (0.53 - 1.00)	0.73 (0.53 - 1.00)
Contact with people or animals during job				
Average number of people contacted on a typical working day ^c	-	1.06 (0.94 - 1.20)	1.06 (0.94 - 1.20)	1.06 (0.94 - 1.20)
Ever lived in a dormitory	100 / 122	0.53 (0.38 - 0.74)	0.54 (0.38 - 0.75)	0.55 (0.39 - 0.78)
Ever had contact with cats	19 / 31	2.06 (1.09 - 3.92)	2.74 (1.38 - 5.47)	2.92 (1.40 - 6.07)
Ever had contact with dogs	46 / 50	1.16 (0.74 - 1.83)	1.22 (0.77 - 1.94)	1.11 (0.69 - 1.79)
Ever had contact with fish, frogs, turtles	17 / 17	0.85 (0.41 - 1.76)	0.87 (0.41 - 1.83)	0.87 (0.41 - 1.85)
Ever had contact with gerbils, hamsters, mice, rats	11 / 15	1.95 (0.82 - 4.65)	1.86 (0.77 - 4.47)	2.14 (0.87 - 5.30)
Ever had contact with cattle	19 / 44	2.23 (1.22 - 4.09)	2.39 (1.29 - 4.41)	2.36 (1.28 - 4.35)
Ever had contact with horses	22 / 25	1.12 (0.59 - 2.13)	1.20 (0.63 - 2.29)	1.14 (0.59 - 2.19)
Ever had contact with pigs	9 / 20	1.97 (0.85 - 4.58)	2.27 (0.95 - 5.44)	2.23 (0.93 - 5.32)
Ever had contact with sheep, goats	5 / 13	1.88 (0.64 - 5.52)	2.46 (0.77 - 7.91)	2.46 (0.77 - 7.91)
Ever had contact with chickens, ducks, geese	13 / 27	1.77 (0.87 - 3.58)	2.07 (0.98 - 4.39)	2.00 (0.94 - 4.24)
Ever had contact with other birds	7 / 9	1.16 (0.42 - 3.23)	1.60 (0.50 - 5.11)	1.62 (0.51 - 5.17)

- not applicable

^a Counts of exposures of cases and controls up to date of diagnosis (and corresponding date for controls)

^b Odds ratio calculated for 20 cumulative days absent from work for cold or flu (4 weeks away from work)

^c Odds ratio calculated for average number of people contacted on a typical working day = 30 (~ size of public school class)

3.5 Whole Body Vibration

3.5.1 Vibration-specific methods

Whole body vibration exposure was queried within the job history. Subjects were asked to report use of any vehicle types presented in the interview guide, the operations performed during use, weeks of use per year, hours of use per week, and month and year of start and end of use.

On occupational hygiene review, certain exposures were excluded: exposures to vehicles that were indirect only (i.e., “working near equipment but no direct contact”); very short exposures, i.e., those less than 30 minutes per week; exposures considered no different from typical background exposures in the general population, i.e., those less than 10 hours per week in cars, or less than 5 hours per week in vans and light trucks.

Four metrics of whole body vibration were assigned following a literature review [3] of vibration exposures associated with the range of vehicles reported by study subjects:

- *ever vs. never exposed*;
- *most intense whole body vibrating vehicle exposure*, derived as the mean vector sum acceleration of the vehicle with the highest vibration level over the working life;
- *total duration of exposure*, calculated as the sum, over all vehicles used, of the hours of exposure in each vehicle, divided by 2000 hours per working year;
- *whole body vibration dose*, calculated as the sum, over all vehicles used, of the product of the acceleration to the 4th power of each vehicle used and the duration of its use.

The latter 3 metrics were categorized into 5 groups: no exposure and quartiles of exposure.

3.5.2 Results and Discussion

Table 5 lists the numbers of cases and controls exposed and the odds ratios and confidence intervals for each of the metrics of vibration exposure. Ever having occupational whole body vibration exposure was associated with non-significantly decreased odds of Parkinson's disease, an effect that persisted even when exposures were censored at 5 and 10 years before diagnosis.

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) for Parkinson disease for occupational whole body vibration exposure, with exposure censoring at date of diagnosis and 5 and 10 years prior to diagnosis. All analyses adjusted for gender, birth year (5-year groups) and smoking (cumulative pack-years).

Vibration metric		Cases / Controls N ^a	OR (95% CI) exposure up to date of diagnosis	OR (95% CI) exposure up to 5 years prior to diagnosis	OR (95% CI) exposure up to 10 years prior to diagnosis
Ever occupationally exposed to whole body vibration		145 / 147	0.73 (0.52-1.03)	0.71 (0.50-1.001)	0.72 (0.50-1.02)
Most intense whole body vibrating vehicle exposure (m·s ⁻²)	No exposure	258 / 258	1.75 (1.09 - 2.79)	1.85 (1.16 - 2.97)	1.93 (1.19 - 3.13)
	>0 to 0.68	44 / 61	ref	ref	ref
	>0.68 to 0.88	42 / 44	1.19 (0.65 - 2.20)	1.24 (0.67 - 2.32)	1.37 (0.73 - 2.56)
	>0.88 to 1.19	23 / 17	1.92 (0.87 - 4.25)	2.00 (0.92 - 4.36)	2.28 (1.01 - 5.15)
	>1.19	36 / 25	1.71 (0.88 - 3.34)	1.80 (0.90 - 3.57)	1.86 (0.91 - 3.77)
Total duration of whole body vibration exposure (work-years ^b)	No exposure	258 / 258	1.49 (0.57 - 3.88)	1.78 (0.68 - 4.69)	1.37 (0.54 - 3.50)
	>0 to 0.68	9 / 12	ref	Ref	ref
	>0.68 to 2.99	26 / 29	1.10 (0.37 - 3.27)	1.35 (0.45 - 4.07)	1.49 (0.52 - 4.30)
	>2.99 to 10.99	45 / 37	1.50 (0.53 - 4.24)	1.56 (0.55 - 4.42)	0.81 (0.29 - 2.22)
	>10.99	65 / 69	0.89 (0.33 - 2.40)	1.07 (0.39 - 2.95)	0.87 (0.32 - 2.35)
Whole body vibration dose (m ⁴ ·s ⁻⁸ ·work-years ^b)	No exposure	258 / 258	2.15 (0.98 - 4.73)	2.32 (1.03 - 5.24)	1.54 (0.70 - 3.42)
	>0 to 0.16	11 / 23	ref	ref	ref
	>0.16 to 0.91	29 / 23	2.04 (0.78 - 5.32)	2.00 (0.76 - 5.24)	1.34 (0.53 - 3.39)
	>0.91 to 4.16	49 / 47	1.62 (0.68 - 3.88)	1.58 (0.64 - 3.87)	0.94 (0.39 - 2.25)
	>4.16	56 / 54	1.55 (0.66 - 3.65)	1.80 (0.74 - 4.42)	1.19 (0.49 - 2.88)

ref = reference group (OR = 1.00)

^a Counts of exposures of cases and controls up to date of diagnosis (and corresponding date for controls)

^b Work-year = 2000 working hours of exposure

However, among those with occupational exposure to whole body vibration, there were increasing odds of Parkinson’s disease with increasing intensity of exposure and with increasing censoring of exposure in the years prior to diagnosis. The odds ratio was statistically significant in the second highest intensity category, for exposures up to 10 years prior to diagnosis. Duration and dose of whole body vibration exposure were not associated with Parkinson’s disease. We found no other studies that have examined this exposure.

3.6 Head Injuries

3.6.1 Head injuries-specific methods

In the medical history section of the questionnaire, participants were asked to report any injury event for which they visited a physician. They were asked the part of the body injured, whether the injury event took place at work, in a motor vehicle, or during sports, and the severity and circumstances of the injury. The data were used to identify all injuries involving the face or head. These were classified in categories of increasing severity: those involving stitches to the face or head; those involving a concussion; and those involving unconsciousness (all also included in the concussion category).

3.6.2 Results and Discussion

Prior concussions and unconsciousness were both associated with Parkinson’s disease, with a higher risk for the latter more severe injury category (Table 6). We were able to consider numbers of concussions and found higher risks with more concussions: 1 concussion, OR = 1.90 (95% CI: 1.15 - 3.13) vs. 2 or more concussions, OR = 2.54 (95% CI: 0.76 - 8.48). Odds ratios were very similar or slightly higher when events were censored at 5 and 10 years prior to diagnosis, indicating that the injuries were not likely to be a consequence of the disease in its early stages (data not shown).

Sub-classifications by where the injury event took place all showed elevated risks, but not statistically significant because of smaller numbers (Table 6). Injuries involving concussions and unconsciousness at work had the highest risk estimates. This could be due to greater severity of such injuries, or due to enhanced recall of such injuries because they usually involve accident reporting and investigation.

Table 6: Odds ratios (OR) and 95% confidence intervals (CI) for Parkinson disease, among persons self-reporting injuries involving stitches to the face or head, concussion, or unconsciousness, with sub-classifications by the circumstance location. Analyses for exposures up to the date of diagnosis. Each variable was analyzed in a separate model adjusted for gender, birth year (5-year groups) and smoking (cumulative pack-years).

Type of head injury	Cases / Controls N ^a	All Circumstances OR (95% CI)	At work OR (95% CI)	In motor-vehicle crash OR (95% CI)	During sports OR (95% CI)
Stitches to face or head	30 / 24	1.31 (0.72 - 2.38)	1.08 (0.59 - 2.00)	1.17 (0.62 - 2.21)	1.41 (0.72 - 2.77)
Concussion	65 / 35	1.97 (1.23 - 3.16)	2.01 (0.64 - 6.33)	1.66 (0.85 - 3.25)	1.29 (0.45 - 3.66)
Unconsciousness	39 / 15	2.45 (1.29 - 4.66)	2.63 (0.65 - 10.6)	1.88 (0.78 - 4.52)	1.90 (0.44 - 8.20)

^a Counts of exposures of cases and controls up to date of diagnosis (and corresponding date for controls)

Numerous studies have identified a relationship between trauma to the head and Parkinson's disease [62,64-66,96,110,127-130], though a few have not [122,131,132].

3.7 Job Strain

3.7.1 Job strain-specific methods

Job strain was queried within the job history. The statements offered were a subset of those used in the demand-control model developed by Karasek and Theorell [133], and each was assigned a score of 1 (strongly agree) to 4 (strongly disagree). The data were summarized and scored in four dimensions, as follows [133]:

- $decision\ latitude = [(5 - a) + b + (5 - h) + (5 - j)] * 6/4 + [(5 - g) + i + (5 - k)] * 2$
 - a. This job required that you learn new things.
 - b. This job required a lot of repetitive work.
 - g. This job allowed you to make a lot of decisions on your own
 - h. This job required high degree of skill
 - i. In this job, you had very little freedom to decide how to do your work.
 - j. You got to do a variety of different things in this job
 - k. You had a lot of say about what happened in this job
- $psychological\ job\ demands = [(5 - c) + (5 - e)] * 3 + [(5 - f) + l + m] * 2$
 - c. This job required working very fast.
 - e. This job required working very hard
 - f. In this job, you were asked to do an excessive amount of work.
 - l. In this job you had enough time to get the job done
 - m. In this job you were free from conflicting demands
- $physical\ job\ demands = 5 - d$
 - d. This job required lots of physical effort.
- $noise = 5 - o$
 - o. This job was noisy

The mean score for each dimension was calculated across all jobs held. A cumulative measure was also calculated, as the sum over all jobs of the product of the job strain score times the duration in each job.

3.7.2 Results and Discussion

Table 7 lists the odds ratios for the mean job strain measures. The cumulative measures all had odds ratios of 1 and confidence intervals of 0.995 to 1.008 or narrower, so are not presented here. None of the job strain measures were significantly related to Parkinson's disease, and odds ratios did not change with censoring of exposures 5 and 10 years prior to diagnosis. Decision latitude had a strongly reduced odds ratio, supporting the reduced risks found for management jobs. Psychological job demand showed no association with Parkinson's disease, physical job demand showed slightly reduced risk and noise somewhat elevated risk.

Though stress is a hypothesized etiology for Parkinson’s disease [12,13], we found only one other study that examined job strain or other measures of stress before diagnosis. Kuopio *et al.* [116] examined physical strain of work, and found reduced risks for heavy versus light work, but significantly increased risks for very heavy work. Related theories about personality types have also been studied. For example, Bower *et al.* [134] found increased risk for anxious and pessimistic, but not depressive, personalities. In general, most such studies have been small and have not found convincing associations [7].

Table 7: Odds ratios and 95% confidence intervals for associations between four dimensions of job strain (mean score over all jobs held) and Parkinson’s disease, with exposure censoring at date of diagnosis and 5 and 10 years prior to diagnosis. Each was analyzed in a separate model adjusted for gender, birth year (5-year groups) and smoking (cumulative pack-years).

Job strain variable	Cases Mean (SD)	Controls Mean (SD)	OR (95% CI) exposure up to date of diagnosis	OR (95% CI) exposure up to 5 years prior to diagnosis	OR (95% CI) exposure up to 10 years prior to diagnosis
Decision latitude ^a	33.5 (3.9)	33.4 (4.1)	0.40 (0.16 - 1.35)	0.40 (0.16 - 1.35)	0.40 (0.16 - 1.35)
Psychological job demand ^a	31.0 (3.9)	31.2 (4.4)	1.00 (0.29 - 2.43)	1.00 (0.40 - 3.24)	1.00 (0.40 - 3.24)
Physical job demand ^b	2.6 (0.6)	2.6 (0.6)	0.81 (0.44 - 1.54)	0.79 (0.42 - 1.45)	0.79 (0.42 - 1.45)
Noise ^b	2.5 (0.6)	2.5 (0.6)	1.42 (0.73 - 2.80)	1.42 (0.73 - 2.80)	1.39 (0.71 - 2.66)

^a Odds ratio calculated for a score of 30, approximately the mean score

^b Odds ratio calculated for a score of 2.5, approximately the mean score

3.8 Pesticides

3.8.1 Pesticide-specific methods

Pesticide exposures were queried within the job history. Subjects were asked to review the list of pesticides presented in the interview guide and asked to report any exposure, whether the substance was breathed in or on the skin or both, the operations performed during use, weeks of use per year, hours of use per week, and month and year of start and end of use.

Pesticide analyses were conducted based on participants’ self-reported exposures, as well as exposures assessed to be plausible after exclusions made following hygiene review. Exposures were excluded because they were judged not to be above background in the general population: exposures that were indirect only (i.e., “working near chemical but no direct contact”); very short exposures, i.e., those less than 1 hour per week; and exposures judged to be limited (e.g., sales personnel handling closed containers, construction workers occasionally handling wood treated with preservatives, administrative personnel working in areas where pesticides were occasionally applied by others). Additional analyses were done with a further restriction meant to represent higher exposures: those that occurred during spraying operations.

Pesticide exposures were classified as the most specific possible agent with at least 15 participants exposed. Only one individual pesticide (DDT) included enough exposed subjects for analysis using this criterion. Other analyses were done for pesticide groups: all pesticides; functional groups (insecticides, herbicides, fungicides, wood preservatives); and chemical classes (organophosphates, organochlorines). A further grouping was created based on a literature review of potential

neurotoxicity of the pesticides reported by study participants:

- *pesticides with evidence of neurotoxicity*: allethrin, azinphosmethyl, diazinon, DDT, 2,4-D, dieldrin, glyphosate, lindane, malathion, MCPA, nicotine, paraquat, pentachlorophenol, rotenone, tetrachlorophenol, 2,4,5-T.

Total duration of exposure was calculated as the sum of the hours of exposure, divided by 2000 hours per working year.

3.8.2 Results and Discussion

Table 8 shows the results for self-reported pesticide exposure and for hygiene-reviewed pesticide exposure via any job operation and via spraying operations. Self-reported exposure to “pesticides” as a group had a significantly increased risk of Parkinson disease. Among those judged exposed beyond background after hygiene review, the odds ratio 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 operation, though not significant.

Table 8: Odds ratios (OR) and 95% confidence intervals (CI) for Parkinson disease, among persons self-reporting pesticide exposure and among those judged by hygiene review to have pesticide exposures above background, for any operation or for operations involving pesticide spraying. Analyses for exposures up to date of diagnosis. Pesticide categories listed only for those with at least 15 study subjects to date of diagnosis.

Pesticide variable	Cases / Controls N ^a	Self-reported pesticide exposure, any job operation OR (95% CI)	Hygiene-reviewed pesticide exposure, any job operation OR (95% CI)	Hygiene-reviewed pesticide exposure, spraying operations OR (95% CI)
Pesticides	74 / 47	1.76 (1.15 - 2.70)	1.51 (0.85 - 2.69)	1.91 (0.82 - 4.49)
Insecticides	40 / 26	1.80 (1.03 - 3.15)	1.26 (0.58 - 2.74)	1.86 (0.66 - 5.24)
Herbicides	33 / 19	1.82 (0.97 - 3.40)	1.33 (0.60 - 2.97)	1.60 (0.53 - 4.87)
Fungicides	11 / 11	0.94 (0.38 - 2.32)	1.18 (0.35 - 4.00)	1.09 (0.17 - 7.08)
Wood preservatives	17 / 9	2.20 (0.90 - 5.34)	1.56 (0.51 - 4.77)	>1000^b (<0.001 - >1000)
Organophosphates	10 / 6	1.57 (0.53 - 4.64)	0.74 (0.20 - 2.78)	0.88 (0.19 - 4.16)
Organochlorines	16 / 10	1.23 (0.53 - 2.85)	0.62 (0.19 - 2.00)	0.75 (0.20 - 2.87)
Pesticides with evidence of neurotoxicity	35 / 19	1.76 (0.95 - 3.25)	1.08 (0.49 - 2.36)	1.34 (0.53 - 3.40)
DDT	15 / 9	1.32 (0.55 - 3.18)	0.76 (0.22 - 2.62)	1.02 (0.24 - 4.42)

^a Counts of self-reported pesticide exposures of cases and controls up to date of diagnosis (and corresponding date for controls).

^b Based on very small numbers: 4 cases and 0 controls.

The risk estimates for insecticides, herbicides and pesticides with evidence of neurotoxicity tended to follow similar patterns: the highest risk estimates for self-reports; reductions in risk estimates with hygiene review; and slightly higher risk estimates for spraying exposures. For organochlorines and organophosphates, there were no increases in risk after hygiene review. None of the odds ratios for pesticide subgroups were statistically significant, except self-reported insecticide exposure. Wood preservatives had strongly elevated odds ratios, though not statistically significant.

Censoring exposures at 5 and 10 years prior to exposure tended to reduce risk estimates (data not shown). Analyses of duration of exposure showed no significant associations with Parkinson disease (data not shown). The increased risk for all pesticides is consistent with the elevated risk we found in farming and horticulture occupations. However, the reductions in risk after hygiene review and the lack of increases in risk for more specific subgroups of pesticides, exposure censoring prior to diagnosis, and duration of exposure cast doubt on the relationship between pesticides and Parkinson's disease in this study sample.

Certain pesticides (rotenone, paraquat, maneb) have been used to induce Parkinsonian symptoms in animals, as a way to study the disease [135]. In our study, 1 case and 4 controls reported exposure to rotenone, 3 cases and 3 controls reported exposure to paraquat, and no one reported exposure to maneb.

Pesticide exposure has been frequently studied as a potential cause of Parkinson's disease [21,22,24-32]. In recent studies, Elbaz *et al.* [136] found increased risks with professional pesticide use, especially insecticides, and Tanner *et al.* [96] found increased risks for self-reported use of pesticides, increasing with restriction to eight specific pesticides with high neurotoxic plausibility (very similar to our classification). In a study in nearby Washington state, Firestone *et al.* [117] found no significant association with self-reported exposure to pesticides. Different methods of assessing exposure and actual differences in exposure over time or between regions might partly explain these inconsistent results.

3.9 Metals

3.9.1 Metals-specific methods

Metal exposures were queried within the job history. Subjects were asked to review the list of metals presented in the interview guide and asked to report any exposure, whether the substance was breathed in or on the skin or both, the operations performed during use, weeks of use per year, hours of use per week, and month and year of start and end of use.

Metals analyses were conducted based on participants' self-reported exposures, as well as exposures assessed to be plausible after exclusions made following hygiene review. Exposures were excluded because they were judged not to be above background in the general population: exposures that were indirect only (i.e., "working near chemical but no direct contact"); very short exposures, i.e., those less than 1 hour per week; and exposures judged to be limited (e.g., sales or administrative personnel working in office areas of a production facility).

Metal exposures were classified as the most specific possible agent with at least 15 participants exposed to the date of diagnosis. Metals were listed in the interview guide and therefore reported by study participants mainly by common names of composites (e.g., Babbitt, mild steel, brass, tungsten carbide). The elemental metal constituents of each composite material was sought via a review of material safety data sheets and other industry sources. Each composite exposure was thus assigned to one or more component metals for analysis. In addition, metal exposures were classified by type of operation:

- *all hot metal operations:* brazing, casting, molding, smelting, soldering, welding;
- *all machining operations:* grinding, machining, drilling, milling turning.

Total duration of exposure was calculated as the sum of the hours of exposure, divided by 2000 hours per working year.

3.9.2 Results and Discussion

Table 9 reports analyses for metal exposures in the occupational setting. None of the exposures had elevated risks. Several exposures had strong reductions in risk, though none were statistically significant. This result has not been shown before and is in the opposite direction of hypotheses. Duration of exposure did not appreciably change the estimates, except in the case of welding: hygiene-reviewed welding exposures of at least 10 years had an increased odds ratio, though not statistically significant: OR = 1.77 (95% CI: 0.43 - 7.24), consistent with our result for welders as an occupational group.

A number of earlier studies have found elevated risks with exposures to manganese [15,32,33,35] and other metals [35-37,137], though these results have not been consistent [27,35]. Other studies, most more recent, have had results more consistent ours, with null results for metal workers [106], welders [60,104,111,117,119,120], and the specific metals manganese, lead and copper [117,137]. These differences may represent changes in exposure patterns over time, or different exposure patterns in the different areas where the studies took place.

Table 9: Odds ratios (OR) and 95% confidence intervals (CI) for Parkinson disease, among persons self-reporting workplace exposure to metals and among those judged by hygiene review to have such exposures above background. Additional analyses for machining and hot metal operations. All analyses adjusted for gender, birth year (5-year groups) and smoking (cumulative pack-years). Analyses for exposures up to date of diagnosis. Metal categories listed only for those with at least 15 study subjects to date of diagnosis.

Category of metal or metal operation	Cases / Controls N ^a	Self-reported metal exposure OR (95% CI)	Hygiene-reviewed metal exposure OR (95% CI)
Any metal	72 / 62	0.83 (0.55 - 1.26)	0.69 (0.40 - 1.21)
Aluminum	18 / 19	0.77 (0.38 - 1.56)	0.79 (0.29 - 2.17)
Chromium	21 / 21	0.75 (0.39 - 1.45)	1.11 (0.47 - 2.65)
Copper	26 / 30	0.62 (0.35 - 1.11)	0.60 (0.29 - 1.26)
Iron/steel	39 / 35	0.81 (0.49 - 1.36)	0.70 (0.37 - 1.32)
Lead	25 / 24	0.80 (0.43 - 1.49)	0.56 (0.25 - 1.24)
Manganese	8 / 11	0.58 (0.22 - 1.52)	0.46 (0.14 - 1.51)
Mercury	7 / 9	0.49 (0.18 - 1.37)	0.35 (0.06 - 1.99)
Molybdenum	6 / 10	0.49 (0.17 - 1.43)	0.32 (0.08 - 1.34)
Nickel	10 / 10	0.75 (0.30 - 1.91)	0.67 (0.21 - 2.10)
Tin	18 / 23	0.53 (0.27 - 1.03)	0.51 (0.23 - 1.14)
Tungsten	11 / 12	0.67 (0.28 - 1.60)	0.67 (0.23 - 1.98)
Zinc	16 / 22	0.52 (0.26 - 1.04)	0.64 (0.26 - 1.60)
All hot metal operations	32 / 26	0.88 (0.50 - 1.57)	0.81 (0.43 - 1.51)
Soldering, brazing	16 / 15	0.78 (0.36 - 1.68)	0.80 (0.33 - 1.94)
Welding	15 / 12	0.87 (0.39 - 1.95)	0.82 (0.36 - 1.84)
All machining operations	11 / 12	0.63 (0.27 - 1.49)	0.62 (0.24 - 1.59)

^a Counts of exposures of cases and controls up to date of diagnosis (and corresponding date for controls)

3.10 Solvents

3.10.1 Solvents-specific methods

Solvent intoxication was queried in the personal habits history. Ever intoxicated was defined ever 2 or more times in a year. Cumulative intoxication was calculated as the average number of times per week intoxicated times the total number of years, to give a result in weekly event-years.

Solvent exposures were queried within the job history. Subjects were asked to review the list of solvents presented in the interview guide and asked to report any exposure, whether the substance was breathed in or on the skin or both, the operations performed during use, weeks of use per year, hours of use per week, and month and year of start and end of use.

Solvent analyses were conducted based on participants' self-reported exposures, as well as exposures assessed to be plausible after exclusions made following hygiene review. Exposures were excluded because they were judged not to be above background in the general population: exposures that were indirect only (i.e., "working near chemical but no direct contact"); very short exposures, i.e., those less than 1 hour per week; and exposures judged to be limited (e.g., sales or administrative personnel working in office areas of a production facility).

Solvent exposures were classified as the most specific possible agent with at least 15 participants exposed prior to age of diagnosis. Solvents were listed in the interview guide and reported by study participants both as individual chemicals (e.g., carbon tetrachloride, toluene) as well as by common names of composites (e.g., oil-based paints, jet fuel). Because many solvents with different names have overlapping constituents, they were grouped according to common components, following a review of material safety data sheets and other industry sources, as follows:

- *aliphatic hydrocarbons with volatile constituents*: naphtha; Stoddard solvent, mineral spirits, paint thinner, white spirits, lacquer thinner, WD40; gasoline; kerosene; diesel fuel;
- *turpentine*
- *glues, adhesives*;
- *oil-based paints and inks*: epoxy paints and resins; isocyanate paints; oil paints and inks; other paints, paint thinners; polyurethane paints;
- *aromatic hydrocarbons*: toluene or toluol; benzene; xylene or xylol; phenol;
- *oils, greases*: crude oil; motor oil; lubricants and greases; coal oil; bunker C; stove oil; gun oil;
- *creosote*;
- *chlorinated hydrocarbons*: perchloroethylene; trichloroethylene; methylene chloride; ethylene dichloride; chloroform; carbon tetrachloride; anaesthetic gases; dry-cleaning agents;
- *machining fluids*: soluble, straight and synthetic;
- *hydraulic fluids*;
- *alcohols*;
- *combustion byproducts*: gasoline exhaust; diesel exhaust; jet fuel exhaust; coal fire exhaust.

In addition, solvent exposures were classified by type of operation:

- *refueling operations*: fueling, filling, pouring, pumping;
- *painting operations with oil-based paints*: brushing; spray; staining;
- *spraying operations*.

Total duration of exposure was calculated as the sum of the hours of exposure, divided by 2000 hours per working year.

3.10.2 Results and Discussion

Solvent intoxication was reported by 16 cases and 29 controls, resulting in an adjusted OR = 0.82 (95% CI: 0.57 - 1.17). This result did not change with censoring of exposures 5 or 10 years prior to diagnosis.

Table 10 reports analyses for solvent exposures in the occupational setting. Consistent with our finding for solvent intoxication, none of the occupational exposures were shown to be associated with elevated risks. A few exposures had statistically significant reductions in risk (glues, aromatic hydrocarbons, oils and greases); this result has not been shown before and is in the opposite direction of hypotheses.

Earlier studies have shown increases in risk with solvent exposure [16,38,39,41,63,117,137], but several recent studies have found little or no elevation in risk [60,96,117]. As with metals, these differences may represent changes in exposure patterns over time, or different exposure patterns in the different areas where the studies took place.

Table 10: Odds ratios (OR) and 95% confidence intervals (CI) for Parkinson disease, among persons self-reporting workplace exposure to solvents or aliphatic hydrocarbons and among those judged by hygiene review to have such exposures above background. Additional analyses for refueling, painting, and spraying operations. All analyses adjusted for gender, birth year (5-year groups) and smoking (cumulative pack-years). Analyses for exposures up to date of diagnosis. Solvent categories listed only for those with at least 15 study subjects to date of diagnosis.

Category of solvent or solvent operation	Cases / Controls N ^a	Self-reported solvent exposure OR (95% CI)	Hygiene-reviewed solvent exposure OR (95% CI)
Any solvent	293 / 269	1.14 (0.82 - 1.57)	1.08 (0.78 - 1.47)
Aliphatic hydrocarbon with volatile constituents	142 / 131	0.88 (0.62 - 1.24)	0.95 (0.66 - 1.36)
Turpentine	83 / 90	0.84 (0.48 - 1.47)	0.99 (0.55 - 1.78)
Glues, adhesives	20 / 33	0.50 (0.29 - 0.88)	0.59 (0.31 - 1.11)
Oil-based paints & inks	44 / 44	0.89 (0.61 - 1.30)	0.90 (0.60 - 1.37)
Aromatic hydrocarbons	18 / 13	0.54 (0.29 - 0.99)	0.51 (0.27 - 0.98)
Oils and greases	30 / 32	0.66 (0.45 - 0.97)	0.67 (0.45 - 0.99)
Creosote	24 / 26	1.23 (0.56 - 2.70)	1.14 (0.49 - 2.66)
Chlorinated hydrocarbons	95 / 78	0.79 (0.49 - 1.26)	0.76 (0.45 - 1.26)
Machining fluids	80 / 75	0.68 (0.37 - 1.25)	0.79 (0.42 - 1.48)
Hydraulic fluids	23 / 40	0.71 (0.42 - 1.22)	0.72 (0.42 - 1.26)
Alcohol	33 / 34	0.98 (0.57 - 1.69)	0.94 (0.51 - 1.74)
Combustion by- products	30 / 33	1.03 (0.71 - 1.50)	1.07 (0.71 - 1.59)
Refueling operations	108 / 112	0.78 (0.56 - 1.10)	0.87 (0.60 - 1.27)
Painting operations with oil-based paints	55 / 54	0.81 (0.53 - 1.25)	0.82 (0.52 - 1.30)
Spraying operations	39 / 40	0.87 (0.53 - 1.41)	0.97 (0.56 - 1.70)

^a Counts of exposures of cases and controls up to date of diagnosis (and corresponding date for controls)

3.11 Genetic polymorphisms

3.11.1 Genetic polymorphisms-specific methods

Genotyping was performed at the University of Washington Molecular Biology Laboratory. There, each buccal sample was placed in a 1.5 mL microcentrifuge tube containing 540 μ L of high-performance-liquid-chromatography-grade water. The buccal cells were lysed by adding 60 μ L of 500 mM NaOH and vortexing the tube. The tube was incubated at 95 °C for 5 minutes, then the brush was removed. The remaining liquid was neutralized and used for genotyping.

Genotyping of single nucleotide polymorphisms was done by the oligonucleotide ligation assay (OLA) method [138]. Samples were identified as wild type, mutant, or heterozygote according to their absorbance ratios. The single nucleotide variants that were identified by specific OLAs included the MAO-B intron 13 G/A polymorphism [139], the A and B alleles of CYP2D6 [140], the CYP2E1 5'-flanking region C/T polymorphism [141], and the two nucleotide transitions in exons 5 (A/G) and 6 (C/T) in the GSTP1 gene [142-144]. Genotyping of the GSTM1 and GSTT1 homozygous deletion polymorphisms, the CYP2E1 regulatory region insertion variant, and the CYP2D6 D allele were done using specific PCRs followed by agarose gel electrophoresis analyses of the PCR products. For detection of GSTM1 and GSTT1 deletion homozygotes, modifications of other methods were used [145-147]. Identification of the CYP2D6 D allele and the CYP2E1 regulatory region insertion variant that enhances enzyme activity were also conducted using revisions of other assays [148,149].

3.11.2 Results and Discussion

Table 11 lists the odds ratios and 95% confidence limits for the relationship between various genetic polymorphisms and Parkinson's disease. Most varied little from the null value. The exceptions were cytochrome P450 2D6 (CYP 2D6) A and B, which included approximately 2-fold elevated odds ratios for the heterozygote and mutant genotypes respectively, though neither was statistically significant.

Cytochrome P450s have been postulated as potential sources of gene-environment interaction in the etiology of Parkinson's disease [74-77], though to date there have been very inconsistent relationships between these polymorphisms and the disease itself, weakening the potential for them to explain any relationship between Parkinson's disease and chemical exposures [75,77]. However, there is some evidence of gene-environment interactions between poor metabolizer status and pesticide exposures [74].

The small numbers of cases and controls with the CYP 2D6 mutant and heterozygote genotypes in this study mean that, as expected, examinations of potential gene-environment relationships will require that this study dataset be combined with data from other studies.

Table 11: Odds ratios (OR) and 95% confidence intervals (CI) for relationship between Parkinson disease and various enzyme polymorphisms (among N=763 participants who had buccal samples taken). All analyses adjusted for gender, birth year (5-year groups) and smoking (cumulative pack-years). Genotypes listed only for those with at least 15 study subjects.

Enzyme system	Genotype	Cases / Controls		OR	95% CI
		N			
Monoamine oxidase B i13	Mutant	168 / 192		0.96	(0.68 - 1.35)
	Heterozygote	89 / 62		0.95	(0.57 - 1.59)
	Wild type	116 / 136		ref	
Ubiquitin carboxyl-terminal esterase L1	Mutant	14 / 16		0.99	(0.46 - 2.15)
	Heterozygote	114 / 119		1.05	(0.76 - 1.46)
	Wild type	245 / 255		ref	
Glutathion S transferase piA	Mutant	45 / 35		0.82	(0.48 - 1.37)
	Heterozygote	168 / 187		1.12	(0.81 - 1.54)
	Wild type	160 / 167		ref	
Glutathion S transferase piB	Heterozygote	68 / 62		0.97	(0.65 - 1.45)
	Wild type	303 / 326		ref	
Glutathion S transferase ø	(+)	303 / 319		1.03	(0.74 - 1.55)
	(-)	69 / 68		ref	
Glutathion S transferase µ	(+)	184 / 176		0.89	(0.66 - 1.20)
	(-)	188 / 211		ref	
Cytochrome P450 2D6 A	Heterozygote	9 / 17		2.09	(0.86 - 5.10)
	Wild type	363 / 373		ref	
Cytochrome P450 2D6 B	Mutant	11 / 20		1.97	(0.88 - 4.42)
	Heterozygote	101 / 122		1.24	(0.89 - 1.73)
	Wild type	261 / 246		ref	
Cytochrome P450 2D6 D	(+)	15 / 11		0.70	(0.30 - 1.54)
	(-)	357 / 378		ref	

ref = reference group (OR = 1.00)

3.12 Summary of results

3.12.1 Overview of the results across all exposures

This study identified a number of Parkinson's disease risk factors that have consistently been observed by others, including

- decreased risk for smokers [25,36,44-49,93- 96] and
- elevated risks for
 - farming and horticulture occupations [20,23,24,29,60,106-115],
 - social sciences, law and library occupations [1,60, 96,103-106], and
 - head injuries [62,64-66,96,110,127-130].

These results add to the weight of evidence about these risk factors and provide new data showing their potential to be risk factors in the British Columbia population.

The risks associated with the two occupations listed above raise the question of what exposures might play a part in the elevated risks. For farming jobs, the traditional hypothesis has been

pesticides [21,22,24-32,96,136,150], however the results from our pesticide analyses were not as strong or convincing as for the occupational group itself and a recent study in Washington State also found little support for pesticides as a cause [117]. Other exposures of interest for farmers include animal contact, influenza, head injuries, vibration from heavy equipment, all studied here and found to have elevated risks. Another farming exposure, not included in our study, but beginning to receive attention is endotoxin from Gram-negative bacteria cell walls, associated with grains [125,126]. For social science occupations, the hypothesized risk is most commonly interpersonal contact leading to increased incidence of influenza. Influenza was found to have elevated risks in this study, but other occupational groups with similar or even more frequent interpersonal contact, including teaching and medicine or health, did not have elevated risks. Teaching might be influenced by the reduced risks conveyed by the childhood diseases (measles, chickenpox), and the medical professions may be more likely to be vaccinated for influenza, reducing risk. Because some of our findings on these other exposures are either the first of their kind (vaccination) or have only been reported rarely (measles, chickenpox), these explanations can be considered hypotheses only.

We provided the first analyses of head injuries in the occupational context. Parkinson's disease was shown to have strongly elevated risks subsequent to head injuries, including those incurred at work. An occupation that might be considered at higher risk of such injuries, construction work, did not show elevations in risk. However there are many sub-trades in construction that might not have high head injury risk, and there are many occupational groups beyond construction that could be subject to such injuries (including agriculture, other primary, and materials handling).

The relationship between head injuries and Parkinson's disease provided the basis for the hypothesis for examining the risk of vibration (another potential source of trauma to the brain). The relationship between vibration and Parkinson's disease has not been studied elsewhere. The u-shaped pattern of risk observed here (higher risks for those not in exposed jobs and for those most highly exposed) is sufficiently interesting to investigate in future studies. Dr. Carolyn Tanner, a highly regarded Parkinson's disease epidemiologist in California, has seen our results and is interested in examining this hypothesis in her research.

This study also examined other exposures that have only rarely been studied or are unique to this study, especially in the occupational context. Job strain, which is a measure of stressors at work, showed slightly lower risks for decision latitude, consistent with the reduced risks identified for management and administration jobs. Neither association was particularly convincing because most of the estimates were not statistically significant.

The pattern observed for viral illnesses is particularly intriguing, though its interpretation remains uncertain. Work absences for flu had a weak, non-significant, elevation in risk and was interesting mostly in the context of other analyses (reduced risk with flu vaccination, and strongly elevated risks for physician-diagnosed severe influenza). Contact with animals (cats, cattle, pigs, sheep, and fowl) at work showed strong elevations in risk. This has only rarely been studied [109,116,117], but deserves further examination as a potential explanation of the consistently elevated risks to farmers and as an adjunct to our understanding of the risks of various communicable diseases. Dormitory living and viral infectious diseases other than influenza both showed strongly reduced risks. Is it possible, as others who observed the same pattern have hypothesized, that changes in immune response related to the "childhood" diseases reduces the susceptibility to or severity of influenza and therefore its impact on Parkinson's disease? [121]

Finally, our study did not find elevated risks for occupational exposures to metals or solvents.

Metals in particular have proven less interesting than originally thought [15,32,33,35-37,137], with numerous studies now shedding doubt [60,104,106,111,117,119,120,137] on the importance of these exposures as risk factors for Parkinson's disease. Most of the metal-exposed occupations in this study also showed no elevations in risk (machine-related technicians, mechanics, repairers). The exception was welders, who had elevated risks, though welding operations (which includes welding performed by workers in other jobs) had elevated risks only with at least 10 years of exposure. The extreme temperatures achieved in welding certainly produce some of the highest metals exposures, with metal oxide fumes being easily released into the breathing zone, though the specific metals used can be very variable. Unfortunately the numbers of welders and others engaged in welding was small in this population-based study, making analyses of specific welded metals impossible. Solvents, on the other hand, were a nearly ubiquitous exposure in this study, but they too did not show elevations in risk, even when restricted to high exposure scenarios such as intoxication, refueling and spraying. As with metals, most solvent-exposed occupational groups did not show elevations in risk (mechanics, repairers, maintenance), but one with potentially high exposures did: gas station attendants. It is difficult to draw conclusions here since many other studies have shown elevated risks [16,38,39,41,63,117,137], though the paucity of evidence of a risk in this study is supported by results in other studies, including a concurrent one in neighbouring Washington state [60,96,117]. It is possible that changing exposure patterns over time or regional differences in exposures may have resulted in differences in risk.

This study also examined the associations between several genotypes and Parkinson's disease. At the time the study was designed, the genotypes hypothesized were related to enzymes responsible for dopamine metabolism (MAO-B) and detoxification of chemicals in the body (cytochrome P450, glutathion S tranferase) and there was some evidence to support associations [65-82]. The last decade has been a period of rapidly changing techniques in genotyping and examinations of gene-environment interactions. Since our original proposal, results of other studies of the genotypes we examined have not been found to be consistently related to Parkinson's disease [74,77]. Our results showed two genotypes of cytochrome P450 2D6 to be associated with Parkinson's disease. Both have shown interactions with certain pesticides in some populations [76,77]. They had very low prevalence in the study sample, therefore to examine gene-environment interactions with these genotypes, our results will be combined with datasets from studies conducted in the United States, to allow a sufficient sample size. In addition, our study included a second sample of cells from each participant. These samples are being stored to allow additional genotyping to be conducted in the future (informed consent was obtained from study participants to do so). This will allow the many new hypotheses about genetic polymorphisms that have been developed subsequent to our original design [74] to be examined in our study subjects.

3.12.2 Strengths and limitations of the study

To our knowledge, this study is the largest case-control study of Parkinson's disease conducted in Canada to date, though our final sample size was smaller than originally planned, in part because of its population-based design. The population-based design of the study was a strength compared to those based in tertiary referral centres, but it brought with it challenges of working under new policies and laws that necessitated a two-stage recruitment procedure. As a result, the study recruited smaller numbers, the participation rate was less than ideal, and the study took much longer than originally planned. Of these limitations, the greatest concern was the risk of bias from a low participation rate. Therefore we were pleased to observe the consistency in results between our study and others for certain exposures that might be considered markers of external validity, in particular, cigarette smoking and other lifestyle exposures.

Our study included both incident (newly diagnosed) and prevalent (ongoing) cases of Parkinson's disease, as is apparent from the difference between the average age at the time of interview (65 years) and the average age at diagnosis (56 years). In studies of most diseases, it is preferable to include only incident cases, because prevalent cases may represent a special group with long survival. However, Parkinson's disease patients survive long after diagnosis, so survival bias is less likely [151]. Furthermore, it is often difficult to locate truly incident cases of Parkinson's disease because it has a slow insidious onset. We censored exposures at 5 and 10 years prior to diagnosis to take the uncertain onset and a latency period into account. A recent study of Parkinson's disease and pesticide exposures suggests there should still be caution about including prevalent cases, since it found different results among incident and prevalent cases, though the samples of each were small ($N \sim 80$) and confidence intervals overlapped [150].

Our study included a restricted age range of Parkinson's disease cases – those diagnosed from ages 40 through 69 years of age – and thus does not represent the entire spectrum of Parkinson's disease cases. The lower age limit was meant to exclude those with very early onset disease, who are more likely to have disease attributable to Mendelian inheritance [10,11]. We did include cases diagnosed between ages 40 and 50, who might also be somewhat more likely to have genetic Parkinson's disease, but this was a small proportion of the study sample. The exclusion of older cases was meant to reduce the potential for survivor bias, given that prevalent and incident cases were included in the study, and to minimize difficulties with recall of working lifetime exposures, given the retrospective nature of the exposure assessment.

This study emphasized occupational exposures, because most exposures of interest were more likely to occur at work than at home (e.g., welding fumes, pesticide spraying). We did collect information on exposures during hobbies and unpaid work, but these exposures were not included in the analyses reported here. Our initial review of hobby and unpaid work exposures suggests that there were few and so are unlikely to change results, but future analyses that include them will provide better evidence in this regard. Some exposures were queried only within the work context, e.g., coffee consumption, days away sick from flu and colds, communal living. We felt that jobs would provide a structure for participants to provide responses about these exposures in defined time periods. However, this aid-to-recall technique did not allow individuals to denote differences in exposures within a job period, a particular problem in long duration jobs.

This study was retrospective, and exposure assessment was not done via direct measurements of exposure, but was based on self-reports of prior occupations and specific exposures. This type of exposure assessment is very common in case-control studies of chronic diseases of later life, but it may be subject to difficulties in recall and potentially recall bias (differences in recall between cases and controls). We used a variety of techniques to improve on self-reports alone, based on evidence from studies examining the validity and reliability of exposure assessment methods for case-control studies [86]. We used an interview guide with prompted lists of common names of the agents of interest to enhance recall. We used a two-stage industrial hygiene review: the first to enhance sensitivity of recall (i.e., ensure exposures were reported); and the second to enhance specificity (i.e., ensure that only relevant exposures beyond background in the population were considered in our "hygiene-reviewed" subsets) [87]. Few other studies of occupational exposure and Parkinson's disease reported to date have used such extensive hygiene review of exposures [23,25,35].

4. Implications

Use of administrative databases for identifying and contacting potential research participants is important to allow population-based health research.

This study demonstrated the value of population-based research in studies of Parkinson's disease. The results of the occupational analyses confirmed only 2 of the 7 statistically significant major occupational categories identified in the clinic-based study we conducted in the 1990s [1]. This confirmed our suspicion that clinic data may be subject to referral bias. Since there is no registry of Parkinson's disease cases, the only way to identify cases on a population basis is via physician visit, hospitalization, or prescription data held by the province.

This research was able to use administrative data of these types to identify cases. However, the procedures required to protect privacy (camouflaging of potential cases by including 20% known non-cases in the sample, and a two-stage contact procedure requiring potential participants to be contacted first by government personnel then by the research team) greatly increased the time and expense of the study, and likely contributed to the estimated low participation rate.

The difficulties experienced in subject contact during this study inspired a population-based survey of opinions about participating in health research [152; Appendix C]. The results indicated that the vast majority of the public are willing to participate in health research, that they value it because of its potential to improve their own health and that of others, and that they are comfortable responding to research requests from universities and hospitals, somewhat less so to those from government, and they are uncomfortable with requests from private research firms.

The survey results and the problems with subject contact experienced in this Parkinson's disease study and other research led to lobbying of the provincial government by the University of British Columbia study team and researchers at the BC Cancer Agency and the BC Centre for Disease Control. In response, in May 2008 the Freedom of Information and Protection of Privacy Act was amended to explicitly allow use of administrative data for subject contact. The amendment set out a new system for making decisions on individual research projects. The implementation of this legal change is currently underway, and should be monitored to ensure that it facilitates, rather than hinders, excellent quality research in the public interest.

Prescriptions of anti-parkinsonian medications for other indications was common in British Columbia.

In this study, potential cases of Parkinson's disease were identified via the provincial PharmaCare database, as those reimbursed by PharmaCare for at least one prescription for an anti-parkinsonian medication (levodopa; bromocriptine mesylate; pergolide mesylate; levodopa/benserazide hydrochloride; levodopa/carbidopa; or seligiline hydrochloride). Of 1233 non-camouflage potential cases contacted by the study team, 492 (40%) took the drugs for purposes other than Parkinson's disease. Thus prescription-based identification of potential Parkinson's disease cases captures many individuals without the disease, a built-in camouflage that blinds data extractors to the disease status of the potential cases.

Smoking was associated with reduced risk of Parkinson's disease.

As in other studies, we found that smoking cigarettes conveyed a significantly reduced risk of Parkinson's disease, confirming that smoking should be measured and adjusted for in research on this disease. Other lifestyle habits often associated with cigarette smoking, including drinking

alcohol, drinking coffee, or smoking marijuana, were not associated with increases or decreases in risk.

Social science and farming jobs were associated with elevated risk of Parkinson's disease.

Two occupations had significantly elevated odds ratios and increasing risks with increasing duration of exposure: social science, law and library jobs; and farming and horticulture jobs (each estimated as held by ~7% of the source population, i.e., controls). These jobs have been consistently found to have elevated risks in other studies. The exposures that might contribute to these increased risks have not been confirmed, but both jobs may have exposure to influenza viruses beyond background in the population. This suggests that flu vaccination may be a way to reduce the risk in these occupations.

Farming jobs have other potential exposures of interest, including pesticides, endotoxins, and head injuries. Although many previous studies have examined pesticide exposures and Parkinson's disease and found increased risks, recent studies have found weaker or no associations with pesticides, similar to the results of this study. These more recent results suggest that a broader set of potential exposures should be examined to understand the association between farming jobs and Parkinson's disease.

Four less common occupations had associations with the disease: gas station jobs; welders; drivers of heavy equipment; and carpenters. The associations were less convincing because most were not statistically significant, in part because these jobs were less common in the study population. These jobs have also not been as consistently found to be associated with Parkinson's disease in other studies, though in part this may be because occupational analyses are rare. Among studies that have examined jobs, grouping of jobs is often not consistent from study to study, making it more difficult to replicate findings.

Influenza was associated with increased risk and common childhood viral diseases with reduced risk of Parkinson's disease.

About 8% of controls reported at least 5 days absence from work because of the flu and about 6% reported severe influenza. This study found a pattern of associations consistent with increased risk of the disease with influenza. Absenteeism for flu, cumulative days off work for flu, severe influenza, average numbers of people contacted on the job, and contact with animals that may be associated with influenza viruses all were associated with increased risk, and flu vaccination was associated with decreased risk.

In contrast, dormitory living and having had the common childhood illnesses, measles and chicken pox, were associated with reduced risks of Parkinson's disease.

These results support older research on Parkinson's disease, examining infectious disease hypotheses that seem to have faded from popularity in the Parkinson's research community. They suggest that future research should continue to examine influenza as a potential cause and other viral diseases as potentially protective. The latter group of diseases might be examined serologically in Parkinson's disease cases and controls, since most people experience lifelong antibody immunity. Another approach might be to identify large populations with medical records of vaccinations, and compare Parkinson's disease incidence or prevalence in those vaccinated and not vaccinated.

Whole body vibration as a potential cause of Parkinson's disease is worthy of continued investigation.

Whole body vibration was a common exposure, with 36% of controls exposed and about 7% in

the most intense exposure group. Whole body vibration exhibited a u-shaped pattern of association with Parkinson's disease, with the highest risks among those not exposed at all and those with the highest intensities of exposure. The pattern of increasing odds of Parkinson's disease with increasing intensity of exposure and with increasing censoring of exposure in the years prior to diagnosis suggest that this exposure is worthy of further examination. To our knowledge, this was the first study to examine this exposure, and the results should be treated as preliminary.

Head injuries were associated with increased risk of Parkinson's disease.

Concussions had been experienced by about 9% of controls, and unconsciousness by about 4%. Our study found an increased risk of Parkinson's disease with head injuries, consistent with the results of most other studies (though not all). Our results showed that the risk increased with increasing severity and number of injuries. It may be the first to have estimated the risk with head injuries at work.

The results underscore the importance of head injury prevention measures in workplaces, beyond preventing the acute effects of the injury. The results suggest that it would be worthwhile for WorkSafeBC to evaluate whether the accumulated evidence on head injuries is sufficient to offer compensation benefits to those who have experienced unconsciousness or concussion in a workplace setting and who subsequently develop Parkinson's disease.

Job strain was assessed for the first time in relation to Parkinson's disease, but no clear pattern of associations emerged.

Four dimensions of job strain were assessed as quantitative measures for all jobs held. Decision latitude showed strongly decreased risk, consistent with the decreased risk for management jobs. No association was seen with psychological job demand, weak associations were seen for the physical demand and noise dimensions, and no associations were observed for increasing cumulative exposures.

This study did not strengthen support for pesticides, metals, or solvents as risk factors for Parkinson's disease.

Pesticides (12%), metals (15%), and solvents (66%) were commonly reported exposures among controls. After hygiene review, the numbers judged to be truly exposed to each of the three chemical exposures, beyond background levels in the population, fell by about half.

Self-reported exposures to pesticides, insecticides, and wood preservatives had increased risks of Parkinson's disease, but risks decreased when restricted to hygiene-reviewed exposures, when more logical and specific chemical groupings were examined, and when exposures were censored 5 and 10 years prior to diagnosis. This pattern does not lend strong support to pesticides as a cause of Parkinson's disease. The results illustrate the importance of hygiene review of self-reported exposures and of sub-analyses that look for patterns of association.

Neither metal nor solvent exposures were associated with increased risks of Parkinson's disease.

These results are consistent with those of other recent studies.

Two rare genetic polymorphisms were associated with Parkinson's disease in the study population.

Certain cytochrome P450 2D6 (CYP 2D6) A and B genotypes were associated with increases in Parkinson's disease risk. These polymorphisms were rare in the population, at 4 to 5% prevalence in controls. They have been found to have interactions with pesticides and the disease in some subpopulations in other studies.

Examination of the impact of these polymorphisms on susceptibility to chemical exposures would require pooling of datasets with other studies. We have an agreement with a study team at the University of Washington in Seattle, led by Harvey Checkoway, to do so in the future.

Additional work by the study team included estimation of Parkinson's disease prevalence by three methods.

As part of her doctoral thesis, Anne Harris estimated Parkinson's disease prevalence using three methods: the 2001 Canadian Community Health Survey; levodopa prescriptions in British Columbia in 1996 and 2005; and British Columbia physician diagnoses from hospitalization and physician visit data in 1996 and 2005 [3].

- The Canadian Community Health Survey yielded an estimate of 175/100,000 (95% CI: 101-249/100,000) for Canada as a whole.
- Levodopa prescriptions yielded estimates for British Columbia of 152/100,000 (95% CI: 148-156/100,000) and 218/100,000 (95% CI: 213-223/100,000) in 1996 and 2005 respectively. The change over time is believed to reflect increasing levodopa prescriptions for people who do not have Parkinson's disease.
- Physician diagnosis data yielded estimates for British Columbia of 99/100,000 (95% CI: 96-102/100,000) and 116/100,000 (95% CI: 113-119/100,000) in 1996 and 2005 respectively.

Men had slightly higher prevalence than women (ratios of 1.2:1 to 1.4:1). Those 65 and older had much higher prevalence than younger people (ratios of 15:1 to 30:1).

These widely varying prevalence estimates reflect the ongoing uncertainty in our understanding of Parkinson's disease. They suggest that between 4,500 and 8,000 British Columbians and between 34,000 and 60,000 Canadians have the disease.

5. Dissemination

5.1 Publications in peer-reviewed scientific journals

The following articles related to prior epidemiological evidence about occupational and environmental factors, participation in health research, and Parkinson's disease prevalence, have been published:

- Lai BCL, Marion SA, Teschke K, Tsui JKC. Occupational and environmental risk factors for Parkinson's disease. [Review] *Parkinsonism and Related Disorders* 2002;8:297-309
- Lai BCL, Schultzer M, Marion SA, Teschke K, Tsui JKC. The prevalence of Parkinson's disease in British Columbia, Canada, estimated by using tracer methodology. *Parkinsonism and Related Disorders* 2003;9:233-238
- Harris MA, Levy AR, Teschke KE. Personal privacy and public health: Potential impacts of privacy legislation on health research in Canada. *Canadian Journal of Public Health* 2008;99:293-296
- Harris MA. Too soon for dopaminergics in the treatment of restless legs syndrome in children (letter). *Sleep Medicine Reviews* 2009;13: 299-300.
- Teschke K, Marino S, Chu R, Tsui JKC, Harris MA, Marion SM. Public opinions about participating in health research. *Canadian Journal of Public Health* 2010;101:159-164
- Harris MA. Invited commentary: Evaluating epidemiologic research methods – the importance of response rate calculation. *American Journal of Epidemiology* 2010;172(6):645-7.

The following articles on our results have been published to date:

- Rugbjerg K, Harris MA, Shen H, Marion SA, Tsui JKC, Teschke K. Pesticide exposure and risk of Parkinson's disease – a population-based case control study evaluating the potential for recall bias. *Scandinavian Journal of Work, Environment and Health* 2011;37:427-36
- Harris MA, Koehoorn M, Teschke K. Ongoing challenges to finding people with Parkinson's disease for epidemiological studies: A comparison of population-level case ascertainment methods. *Parkinsonism & Related Disorders* 2011;17:464-9

Anne Harris defended her doctoral dissertation on December 6, 2010. It included three articles that have been submitted for publication:

- Harris MA. *Evaluating Epidemiologic Associations Between Occupational Whole Body Vibration and Parkinson's Disease*. Vancouver, BC: University of British Columbia, 2010. 150 pp. https://circle.ubc.ca/bitstream/handle/2429/30483/ubc_2011_spring_harris_margaret.pdf?sequence=1
 - Harris MA, Koehoorn M, Teschke K. Ongoing challenges to finding people with Parkinson's disease for epidemiological studies: A comparison of population-level case ascertainment methods.
 - Harris MA, Cripton P, Teschke K. Retrospective assessment of occupational exposure to whole body vibration for a case-control study.

- Harris MA, Marion SA, Spinelli JJ, Tsui JKC, Teschke K. Occupational whole body vibration exposure and Parkinson's disease: Results from a population-based case-control study.

Other articles are in the planning stages, with the following foci: occupations; head injuries; infections; solvents and metals; job strain.

5.2 Presentations at conferences and workshops

The results will be reported at conferences with a wide variety of audiences, including the following to date:

- Lai BCL, Schultzer M, Marion SM, Teschke K, Tsui JKC. The prevalence of Parkinson's disease in British Columbia, Canada, as estimated by using drug tracer methodology. XIV International Congress on Parkinson's Disease, Helsinki, Finland, July, 2001.
- Harris A, Marion SA, Tsui JKC, Teschke K. Drug tracer estimates of Parkinson's disease prevalence in British Columbia (Canada): Validation of specificity. American Public Health Association 135th Annual Meeting & Exposition, Washington, DC, November, 2007
- Harris A, Levy A, Teschke K. Personal privacy policy and public health: Impacts of privacy legislation on the validity of health research studies. American Public Health Association 135th Annual Meeting & Exposition, Washington, DC, November, 2007
- Harris MA, Marion S, Tsui JK, Teschke K. Descriptive analyses of occupational whole-body vibration exposure among participants in a case-control study of Parkinson's disease. American Industrial Hygiene Conference and Exhibition. Toronto, June 2009
- Harris MA, Koehoorn M, Morgan S, Marion S, Tsui JK, Teschke K. A comparison of Parkinson's disease prevalence estimates derived from multiple ascertainment methods. Canadian Society of Epidemiology and Biostatistics Conference. Ottawa, June 2009
- Harris MA, Cripton PA, Marion SA, Tsui JKC, Teschke K. Assessments of occupational whole body vibration exposure for a case-control study of Parkinson's disease. BC Environmental and Occupational Health Research Network Conference. Vancouver, November 2009
- Harris M.A., Harris G.T. 2008. Conceptual models of adaptive dispositional correlates of Parkinson's disease susceptibility. American College of Epidemiology, Tucson, September 2008
- Harris MA, Marion SA, Tsui JCK, Spinelli JJ, Teschke K. Occupational whole body vibration exposure and Parkinson's disease: Results from a case-control study. 15th International Congress of Parkinson's Disease and Movement Disorders. Toronto, June 2011
- Harris MA, Shen H, Marion SA, Tsui JCK, Teschke K. Associations between viral infections and Parkinson's disease in a case-control study. 15th International Congress of Parkinson's Disease and Movement Disorders. Toronto, June 2011
- Harris MA, Marion SA, Tsui JCK, Spinelli JJ, Teschke K. Associations between Occupational Whole Body Vibration Exposure and Parkinson's Disease in a Population-Based Case-Control Study. Third North American Congress of Epidemiology. Montreal, June 2011

The investigators also welcome opportunities to speak at BC work and policy related forums, including the following to date:

- Teschke K. Parkinson's disease: environmental associations. Environmental Contaminants Subcommittee, BC Medical Association. Vancouver, BC, January 31, 2002
- Teschke K. BC Parkinson's disease case-control study. Annual Vancouver/Seattle Occupational and Environmental Health Conference. Semiahmoo, WA, January 8, 2004
- Teschke K. Studying Parkinson's disease and privacy legislation, or Who can call you at dinnertime? Occupational Safety and Health Association for Healthcare, Vancouver, February 4, 2008
- Harris MA. Comparing Methods of Parkinson's Disease Prevalence Estimation: Surveys vs. Administrative Data, School of Environmental Health, Seminar Series, Vancouver, February 27, 2009
- Harris MA. Panelist, Administrative Data-Based Research and Privacy Legislation. Population Data BC Public Workshop: Public Value, Personal Data: How personal information furthers research and influences policy. March 17, 2009.
- Harris MA. Occupational Whole Body Vibration Exposure and Parkinson's Disease. American Industrial Hygiene Association BC-Yukon Section Invited Speaker. September 15, 2010.
- Harris MA. Results from a Case Control Study of Parkinson's Disease: Occupational Whole Body Vibration and Pesticide Exposure. School of Population and Public Health, Grand Rounds, Vancouver, October 22, 2010

5.3 Lay-language publications

This report was prepared for distribution by WorkSafeBC. Additional publications will be prepared for distribution by the researchers and the Parkinson Society Canada. The content will address what is known to date about Parkinson's disease risk factors and potential control strategies. The Communications Manager of the School of Population and Public Health will provide assistance with lay writing and a dissemination strategy.

5.4 Media releases

The School of Population and Public Health, the Pacific Parkinson's Research Institute, and UBC Public Affairs will distribute media releases about the results of the research.

5.5 Website

The Communications Manager and the Systems and Network Manager of the School of Population and Public Health will provide staff support, software resources, and server space for the development of a study web presence to aid in the dissemination of results. It will include our scientific and lay publications, and will serve as a centralized link to other pertinent web sites.

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