EVALUATING EPIDEMIOLOGIC ASSOCIATIONS BETWEEN OCCUPATIONAL WHOLE BODY VIBRATION AND PARKINSON'S DISEASE

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES

(Health Care and Epidemiology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

December 2010

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ABSTRACT

Parkinson's disease is a chronic degenerative illness, the ultimate causes of which remain largely unknown. This thesis aims to test a new etiological hypothesis: that whole body vibration exposure may be associated with Parkinson's disease. The thesis comprises three studies relevant to a test of this hypothesis. The first study concerns the methods by which cases of Parkinson's disease can be defined at a population level and the prevalence of Parkinson's disease in British Columbia. Levodopa (a drug typically used for Parkinson's treatment) was increasingly used by people without a Parkinson's diagnosis between 1996 and 2005, with non-Parkinson's users outnumbering physician diagnosed cases among women and those under the age of 65 in 2005. These changes in levodopa use could mean that relying on use of levodopa to define Parkinson's disease cases will be less efficient.

The second study developed a method for retrospectively assessing occupational whole body vibration from a detailed interview conducted in a case control sample. I combined self-reported exposure with estimates of vibration intensity (acceleration) derived from the literature to construct metrics of exposure. I concluded that three of the metrics (duration, most intense equipment exposure, and a dose calculation that combined intensity and duration in a cumulative measure after raising vibration acceleration values to the fourth power) captured sufficiently different aspects of occupational exposure for individual tests of their associations with Parkinson's disease.

The third study tested these associations using logistic regression. The metrics were categorized to enable the detection of nonlinear effects. Ever being occupationally exposed to whole body vibration was inversely associated with Parkinson's disease, as was the lowest category of most intense equipment exposure. However, the highest values of most intense equipment exposure were associated with increased odds of Parkinson's disease. Effects were strongest when exposures that occurred more recently than 20 years prior to diagnosis were excluded. A protective effect of low intensity vibration could be due to correlation with a confounding protective factor such as physical activity, while an increased risk associated with high intensity exposures could be due to mechanical stress imposed by the repetitive shocks incurred.

PREFACE

The central chapters of this thesis are constructed as scientific manuscripts that will be submitted for publication in peer-reviewed journals, although none have yet been published. Each of these manuscripts will have co-authors as detailed below. For this reason, in each of chapters 2-4 I will use "we" to describe the authors, but it should be understood that I, as primary author, take full responsibility for this thesis work. Our data collection was approved by the University of British Columbia's Behavioural Research Ethics Board (certificate number: H97-80463).

Chapter 2 (Parkinson's disease case ascertainment), first author: MAH, proposed co-authors: Mieke Koehoorn, Kay Teschke. I conceived this study after conducting preliminary analyses on the efficiency of recruitment for our case control study. I sought collaborations with researchers conducting geographic analyses of prescription drug use in British Columbia (led by Steve Morgan of the Centre for Health Services and Policy Research at UBC). With the assistance of MK, I also applied for remote access to individual level survey data from Statistics Canada. MK also provided guidance in the more arcane regulations and analyses required for use of Statistics Canada data. It is important to note that we had no direct access to individual level data for these analyses, but it was my responsibility to construct analytic programming for survey data (using simulated data) and to direct case definition construction for analyses of drug use and physician diagnoses. My co-authors assisted in analysis planning, but I conducted all of the prevalence and sensitivity analyses. I wrote the manuscript which was edited and revised with the aid of the collaborators. Overall contribution: 95%.

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Chapter 3 (Whole body vibration exposure assessment), first author: MAH, proposed coauthors: Peter Cripton, Kay Teschke. In order to test for an association between whole body vibration and Parkinson's disease we first had to construct estimates of exposure. I developed the methods detailed in this chapter after consulting the previous literature and with the exposure assessment expertise of my supervisor, along with important input on the biomechanical properties and effects of whole body vibration from PC. I constructed all variables and performed all of the statistical analyses. I wrote the manuscript, which was then refined by input from my co-authors and supervisory committee. Overall contribution: 90%.

Chapter 4 (Tests of association between whole body vibration and Parkinson's disease), first author: MAH, proposed co-authors: Stephen Marion, Joseph Tsui, John Spinelli, Kay Teschke. This is the centrepiece of this thesis and the key hypothesis to be tested by my work. The hypothesis that whole body vibration exposure could be associated with Parkinson's disease pre-dated my involvement with this study, and was considered by the investigators in designing the interview questions. However, it was my responsibility to refine this hypothesis (e.g. to construct a mechanistic rationale) and determine (with the expert guidance of my supervisor, my committee and Parkinson's disease study co-investigators) how we could best test this hypothesis with the data collected. I used the exposure variables designed in Chapter 3. My co-authors provided important guidance on the analyses and construction of covariates. I performed all analyses and wrote the manuscript with input from the co-authors. Overall contribution: 90%.

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ACKNOWLEDGEMENTS

My PhD studies were enriched and enabled by many mentors, collaborators, and organizations. Foremost, I thank my supervisor, Kay Teschke, for her patient and rigorous guidance throughout my doctoral studies. I am grateful to my committee members Peter Cripton, Stephen Marion, and John Spinelli for their contributions, as well as Joseph Tsui, co-investigator on the Parkinson's study. I thank all of the staff and participants in the Parkinson's study who gave so generously of their time to facilitate this research. The Parkinson's study was funded both by the Medical Research Council (now the Canadian Institutes of Health Research) and by WorkSafe BC, with additional support provided by the Pacific Parkinson's Research Centre.

I am appreciative of the educational environment afforded by the UBC School of Population and Public Health (formerly the Department of Health Care and Epidemiology). I thank the staff for their administrative assistance and my fellow students for the enlightening experiences we shared. I thank my professors for their patient instruction, and am particularly grateful to Mieke Koehoorn and Adrian Levy for their mentorship.

I am especially grateful for the UBC Bridge Program, which provided excellent training in research development, and provided the opportunity for interdisciplinary collaboration with a fantastic group of students and mentors. I feel particularly fortunate to have worked with such a terrific group of Bridge Fellows during my participation in this program. I would like to express my appreciation to all of the staff, faculty mentors, and trainees of the Bridge Program.

Funding for my doctoral studies was provided by the UBC Bridge Program, the UBC tuition scholarship, a UBC University Graduate Fellowship, the Michael Smith Foundation for Health Research senior graduate scholarship and the Canadian Institutes of Health Research/ Public Health Agency of Canada doctoral award. I am grateful to all of the operating and scholarship funding agencies for enabling my studies.

I owe much to the support of my health research colleagues Linda Vrbova, Nina Dobbin, Glenys Webster and Meghan Winters, who were excellent sounding boards and sources of motivation and to Conor Reynolds for his collaborative support on our cycling safety research initially developed in the Bridge Program Grant Development course. Moral support from friends from every phase of my life was called upon during these studies, and I am indebted to all of them, especially those who led the way and showed by example that PhD studies *can* end: Bronwyn Keatley, Carrie Lyons, Alexandre Poulain, Daniel Selbie, Angela Strecker and Jon Sweetman. My thanks as well to Amilynn Sharpe, Sarah Whiteford, Danielle Dezort, Brianne Kerik, Erin MacKimmie, and Wendy Kwong for their dependable encouragement and reassurance. I am grateful for the support of my family, particularly my brother Thom and my Vancouver uncles. Lastly, and most importantly, I thank my parents, Grant and Emily: my Dad for being my first and best scientific mentor, and both my Mum and Dad for their unflagging emotional support and for showing by example how to be all around classy human beings.

DEDICATION

To my Grandad, Aussie Harris, who lost his smile to Parkinson's disease but passed a muchappreciated sense of humour to his children and grandchildren.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Overview

This chapter comprises a review of relevant literature to introduce topics relevant to this thesis, broadly: Parkinson's disease, occupational whole body vibration exposure, and the potential for a relationship between the two. The intention of this chapter is not to provide a comprehensive review of the Parkinson's disease literature but instead to include a sampling of this literature so that the reader may follow the rationale for the ensuing analyses and recognize important variables for these analyses. The last section of this chapter outlines the basic rationale and objectives of the central chapters of this thesis.

Literature Review

Parkinson's disease introduction

Parkinson's disease (paralysis agitans) is a chronic neurodegenerative condition first formally described by James Parkinson in 1817 (1) and characterized by symptoms such as resting tremor, slowed movement (bradykinesia), and muscle rigidity. Parkinson's disease patients experience a progressive loss of ability to move, affecting quality of life (2). In the mid 20th century, the loss of neurons in the substantia nigra region of the brain that produce the neurotransmitter dopamine was recognized as a key feature of Parkinson's disease (3), and subsequent etiological research has attempted to explain this loss (4, 5). While some cases of Parkinson's disease run in families (6), about 90- 95% of Parkinson's disease can be

described as "idiopathic" or "sporadic" and its occurrence is not yet explained (3). Because its causes remain unknown, this thesis is concerned with idiopathic Parkinson's disease, so the use of the term "Parkinson's disease" below is intended to refer to idiopathic Parkinson's disease unless otherwise specified.

Parkinson's disease diagnosis and treatment

Parkinson's disease is diagnosed by the presence of hallmark symptoms, exclusion of other diagnoses (such as inherited Parkinson's disease or secondary parkinsonian symptoms that can arise after treatment with certain psychiatric medications), and response to antiparkinsonian medication (7, 8). The disease has an insidious onset (9, 10), which has implications for the interpretation of date of diagnosis as definitive onset in etiological research. No diagnostic tests are yet available that offer a substantial improvement over the symptom based clinical approach in living patients (11), although some imaging techniques may be useful in differential diagnosis that attempts to distinguish between subtypes or atypical presentations in early clinical visits (12). Diagnoses can only be confirmed through autopsy. Post mortem examinations of the brain seek two definitive characteristics of Parkinson's disease: i) loss of dopaminergic neurons from the substantia nigra and ii) the presence of protein aggregations called Lewy bodies in the remaining neurons (13). A review of post mortem validation studies found that the sensitivity and specificity of clinical diagnosis varied widely, but that diagnosis by a neurologist seemed the most accurate (sensitivity was 93%, while specificity was 77% upon a first visit) (8). The observations of disappointing accuracy of diagnosis in post mortem studies may be partly a result of a bias in

the selection of patients for autopsy, because those selected may represent unusual or atypical cases (8).

Since the discovery in the 1960s that Parkinson's disease is associated with loss of dopamine producing neurons, the focus of treatment has been to supplement lost dopamine production with the use of levodopa (also called L-DOPA) (14), which is a precursor to dopamine. A more recent approach has been to use a variety of drugs that can have similar effects to dopamine (called agonists)(15). Despite the advances in Parkinson's disease treatment to alleviate symptoms, the clinical course remains one of increasing disability and progression of both motor and non-motor symptoms (16).

Detecting Parkinson's disease cases for epidemiological studies

The accuracy of diagnosis of Parkinson's disease as described above imposes an upper limit on the accuracy of methods of used to locate and define Parkinson's disease cases. However, locating Parkinson's disease cases for epidemiological studies poses challenges in addition to those of clinical diagnosis. Certain epidemiological case ascertainment methods rely directly on records of clinical diagnoses (17, 18). When Parkinson's disease patients are located by a survey of physicians, researchers must consider how well the cases visiting the selected physicians represent the total population of cases. Referral bias is introduced when the case study sample is not representative of all cases. This may be of particular concern in studies including specialists only because it may be the more complicated, atypical cases who are referred to neurologists or because personal characteristics may determine who seeks a specialist referral, as has been observed with other chronic neurologic diseases (e.g. multiple sclerosis (19)). These personal characteristics may in turn be related to the types of occupations people hold, or exposures of interest. Some researchers have attempted to improve representativeness by including general practice physicians in their samples (20-22), although diagnosis by general practice physicians may be less accurate than specialist diagnosis (23). Relying on records of clinical diagnosis means that undiagnosed cases will not be detected, so other studies have attempted to approach a sample of the entire population directly to assess whether individuals have Parkinson's disease (24, 25) . The relative rarity of Parkinson's disease is a challenge to the efficiency of this approach. For example, in a study conducted in six cities in China during 1983, more than 60,000 people were approached and only 28 cases were located (26). The prevalence and incidence of Parkinson's disease are discussed further below. Other studies have employed use of antiparkinsonian medications such as levodopa or dopamine agonists to locate cases (27-29). Potential limitations of this method are addressed in Chapter 2, particularly the possibility of an increasing number of non-Parkinson's users of antiparkinsonian medications (30).

Parkinson's disease prevalence, incidence and burden of illness

Parkinson's disease is relatively rare compared with many other chronic diseases but is one of the most common neurodegenerative diseases. Prevalence observations have ranged from 50 to 250 cases per 100,000 population members (9, 17, 20, 26, 27, 29, 31). In British Columbia, a study by Lai et al. estimated crude prevalence in 1998 by the use of antiparkinsonian drugs and found it to be between 125 and 144 per 100,000 population members(29). The incidence of Parkinson's disease can be defined as the number of new cases arising in the observed population over a given period of time. A systematic review by Twelves et al. found that estimates of crude incidence ranged between 5 and 20 cases per 100,000 person-years, but that the most methodologically sound studies found incidences ranging from 16-19 cases per 100,000 (32). Many studies present age-standardized prevalence and incidence figures (e.g (9, 18)) because Parkinson's disease occurs primarily in older persons and therefore differences in age structure of populations make comparisons difficult. Age standardized estimates allow comparison between regions, but they are artificial and are not designed to characterize the actual number of cases. This means that studies reporting only age standardized prevalence and incidence are less useful for estimating the burden of illness in the population under study, if we consider the burden of illness to be a collective term describing the economic and social costs of disease (which are heavily influenced by disease prevalence). The mean age of Parkinson's disease diagnosis is approximately 65 years (summarized in (32)), although other authors have found a mean age of diagnosis as high as 76 years (33). Van den Eeden et al. (18) showed that incidence of Parkinson's disease rose dramatically after age 50, with approximately 100 cases per 100,000 person-years for those between the ages of 70 and 90.

Parkinson's disease imposes disability and loss of quality of life as patients progressively lose motor function (2, 34). In a comparison between Parkinson's disease patients and the general population, Schrag et al. recorded significant differences in self care, mobility, and social functioning (2). Depression and anxiety symptoms were also more common among Parkinson's disease patients (2). Although Parkinson's disease cases typically survive long after diagnosis and often die due to other causes (35, 36), survival and life expectancy are

lower among Parkinson's disease cases than the general population (37). There is evidence that people with Parkinson's disease are more likely to require residential care than those without the disease (37), an additional social and economic burden. Worldwide increases in life expectancy and overall greater proportion of the population who are elderly have been projected to dramatically increase the absolute burden of illness of Parkinson's disease in coming decades (38).

Known and suspected epidemiological risk factors for Parkinson's disease

The most important epidemiological predictor of Parkinson's disease is age. As described above, incidence rises dramatically with age, particularly after the age of 50 (18). Dopaminergic neuron loss is an effect of aging so an age effect could be due to individual differences in the pace of this loss, although the pattern of neuron loss appears different in Parkinson's disease than in normal aging (3). The effect of age could also be due to the years of life available to accrue "multiple hits" that each result in small increases in Parkinson's disease risk (39). While an individual may require multiple hits to acquire the disease, at a population level these will be detectable as epidemiological risk factors because they will be more common in those with the disease than those without. Below I will review several candidate "hits" that may contribute to a "multiple hit" view of the disease.

Some 5-10% of cases of Parkinson's disease are inherited and their occurrence can be explained by simple Mendelian inheritance. These cases represent monogenic forms of Parkinson's disease in which the disease can be linked to mutations at a single genetic locus,

although the specific locus affected in a given line of inherited cases may be any one of several now known to be related to monogenic Parkinson's disease (40). Despite this increased understanding of the monogenic forms of Parkinson's disease, studies of twin pairs assumed to be genetically identical (monozygotic twins) show that most cases of Parkinson's disease do not occur in both twins in the pair (41, 42). These findings suggest the importance of exogenous environmental exposures in epidemiological studies of Parkinson's disease, and support the focus on such exposures in the current thesis. Nonetheless, an increasing body of literature demonstrates the possible contribution of mutations at a number of genetic loci to incremental risk of Parkinson's disease (40, 43-46). Because not all of those who possess the observed genetic variants exhibit Parkinson's disease, and because the observations of increased risk can be inconsistent (e.g. (47)), these genetic relationships are interpreted as indications of susceptibility which may interact or additively combine with exogenous exposures to produce Parkinson's disease. The remainder of this review will discuss some of the most interesting candidate non-genetic exposures.

One of the most heavily scrutinized epidemiological associations is the inverse risk relationship between smoking and Parkinson's disease. The finding that smokers are at reduced risk of Parkinson's disease has been replicated in multiple studies (eg. (48-50)). The effect has been observed in studies comparing twin pairs in which one twin has Parkinson's disease and the other does not (51). A meta-analysis of several studies examining this association conducted by Hernan et al. estimated that ever smoking was associated with a risk ratio of 0.59 (95%CI: 0.53-0.63). Given the substantial health risks associated with smoking, it was thought possible that smokers might not survive long enough to develop

Parkinson's disease. However, the inverse association has been robust even when comparisons are made between people who have survived to the same age (e.g. (51)). Furthermore, a dose-response relationship is observed: those who smoke more heavily are even less likely to develop Parkinson's disease than those who smoke less heavily (52, 53). A recent analysis by Chen et al. suggests the effect of smoking may be more attributable to years of smoking rather than the number of cigarettes smoked per day (53). One interpretation of this association is that exposure to a component of cigarette smoke (e.g. nicotine) may have a protective effect on dopaminergic neurons in the brain by provoking a detoxification response that would mitigate the risks associated with other relevant exposures (54). A second line of thinking concerns the possibility that smoking itself is related to individual differences in impulsivity and sensation seeking and that a risk averse (low impulsivity, low sensation seeking) personality may relate to Parkinson's disease susceptibility (55). Given that the brain's dopaminergic system has been implicated in mechanisms of both addiction (56) and more general impulsivity and sensation seeking (57), it is possible that smoking may both exert a direct effect on Parkinson's disease risk and also be more generally associated with other traits that influence Parkinson's disease risk. Regardless of the mechanistic explanation for the association between smoking and Parkinson's disease, smoking is an important variable to consider as a possible confounder of epidemiological analyses of occupational exposures because smoking behaviour is also related to occupation (58).

While smoking is one of the most consistent predictors of Parkinson's disease, certain studies have showed decreasing risk with increasing consumption of alcohol (59) and caffeine,

particularly from coffee consumption (59-61), which may exert influence through similar mechanisms as smoking (59). Other studies have been unable to replicate the caffeine (49) and alcohol (49, 62) inverse associations. Interestingly, Ascherio et al. have reported interactions between sex and the protective effect of caffeine, in which the protective effect was confined to men (63), and that postmenopausal hormone replacement in women reduced the protective association with caffeine (63) or indeed reversed it (64). These findings reinforce the importance of sex as a variable to consider in epidemiological analyses of Parkinson's disease.

Male sex is a risk factor for Parkinson's disease, with men being approximately 1.5 times as likely to develop Parkinson's disease (32, 65, 66). Biological differences between men and women are one possible explanation for this observation. These could include genetic mutations on the X-chromosome or effects of sex hormones. Mutations on the X-chromosome would be expected to disproportionately affect men because they lack a second X-chromosome and therefore also lack the possibility of having at least one functional gene copy. However, only one of the currently identified loci of interest in Parkinson's susceptibility is X-linked (40). A hormonal explanation may be better supported, because post-menopausal estrogenic supplementation may decrease risk (67) (although this is not consistently observed, for example see Popat et al (68)) , and seems to modify other epidemiological associations (64). A longer interval between menarche and menopause (a proxy for lifetime estrogen exposure) has also been found to be associated with decreased risk of Parkinson's disease (69). Despite the potential for these biological differences to explain at least part of the difference in risk of Parkinson's disease between men and women,

the observed strength of the association of Parkinson's disease and sex varies greatly between studies (66), which may not be consistent with hormonal or genetic differences between men and women, because these are not likely to be culturally dependent. One explanation of the heterogeneity of the observed sex ratio is that men and women experience different exogenous exposures and these sex differences in exposure may vary through place and time. The differences in environments experienced by men and women may be most apparent in a comparison of occupational exposures.

The simplest studies examining occupational risks for Parkinson's disease often examine associations with employment in specific industries or jobs. Such studies have previously found statistically significantly increased odds of Parkinson's disease among workers in the agricultural (70), construction (70), educational (70, 71) and health care (71-73) industries. Several occupation-based studies have reported no (73, 74) or only one (72, 75) statistically significant odds ratio out of more than 20 reported, suggesting that Type I error could explain the observations. There is no existing consensus on high risk or protective industries. For example work in "construction" has been found to be associated with increased (70), neutral (72-75), or even decreased (71) odds of Parkinson's disease. Similar inconsistency has been observed in the risk associated with work in agriculture (70, 73). Where cases are recruited from the population of patients of a neurological clinic (71), there is the possibility that these associations may be attributable to differences between patients of that clinic and members of the general population (19). Without knowledge of the agent of interest and a hypothesis for the mechanism of its effects, it is difficult for epidemiologists to decide how to consider work history as a potential risk factor. For example, certain previous studies

considered only current occupation (71), while others considered any occupation held for more than six months (75), and still others considered the job held longest in life (70).

The limited ability to identify agents of interest from job titles or industries with sufficient precision is perhaps the most important limitation of these studies. For example, work in agricultural environments may entail a number of potential chemical, physical, and biological hazards, so it is not clear which of the many hazards shared by agricultural workers is being measured. Furthermore, certain exposures may not always be as consistently shared as is assumed. For example, MacFarlane et al. examined the ability of farm related job title to predict pesticide exposure, and found that only 21.7% of those in the study sample who worked in agriculture were exposed to pesticides, meaning that agricultural work was a poor proxy for pesticide exposure (76). This example is from Australia, and it is reasonable to hypothesize that agricultural work would be a better proxy for pesticide exposure in other regions depending on the crops cultivated, but this is an issue to be considered in job title analyses. Nonetheless, the increased risk of Parkinson's disease associated with agricultural work did encourage studies examining the association between pesticides and Parkinson's disease risk (e.g. (77-84)), probably the most heavily studied hypothesized potential risk factor. A meta-analysis of pesticide association with Parkinson's disease found a combined odds ratio of 1.85 (95%CI: 1.31-2.60) (85). This hypothesized association has mechanistic support because certain pesticides (e.g. paraquat) bear a structural similarity to the compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a contaminant in street drugs which was found to rapidly induce parkinsonian symptoms (86). Similarly, the pesticide rotenone has been found to induce parkinsonian symptoms in animal studies (87). Despite this

biological plausibility, the effect of pesticides is not always consistently observed (87). Furthermore, researchers face the challenge of distinguishing the effects of relevant compounds with rare exposure (86). One last challenge to studies of pesticide as a risk for Parkinson's disease in case control studies is that self report of pesticide exposure may be particularly vulnerable to recall bias because the hypothesized relationship is so well known among people with Parkinson's disease (88). Recently, attention has turned to other possible exposures that may be shared by agricultural workers, such as endotoxin exposure from the decay of organic material (89).

Other occupational chemical exposures have also been linked to Parkinson's disease. From the finding that extreme exposure to hydrocarbon solvents could induce parkinsonian symptoms (90, 91), researchers hypothesized a potential causal influence of longer term, less extreme solvent exposure on the risk of Parkinson's disease. The epidemiological evidence has been inconclusive. Certain studies report an association between occupational solvent exposure and occurrence (92) or severity (93) of Parkinson's disease, but other studies (94, 95) have failed to replicate this finding. Occupational exposure to metals such as manganese (96, 97) and lead (98) have also been linked to Parkinson's disease. Interestingly, joint exposure to pairs of metals (e.g. copper-lead) can show significant associations where individual metal exposures do not (97).

Occupational physical hazards for Parkinson's disease have been less commonly studied. Previous research indicates that head injury is associated with an increased risk of Parkinson's disease (94, 99-101). While a recent study by Rugbjerg et al. suggested the possibility that

injury associations may result from impaired motor function in the early stages of disease (102), a twin study by Goldman et al. (100) found an odds ratio of 3.8 (95% CI: 1.3–11) when reports of head injury were included only if they occurred 10 years before diagnosis or earlier. Head injury may affect Parkinson's disease risk by facilitating the accumulation of the proteins that play a role in disease etiopathogenesis (103). The association of traumatic head injury (which, by definition, results from an injurious non-physiologic increase in mechanical stress in at least some components of the brain) as a risk factor for Parkinson's disease prompted the hypothesis that long-term exposure to whole body vibration (another mechanical exposure that may be transmitted to the head (104)) could also be a risk factor for Parkinson's disease.

Whole body vibration

Whole body vibration is repetitive movement of the body as it rests upon a supporting surface that is vibrating (105) (e.g. on board a ship or driving a tractor). Whole body vibration can characterized with several measures. Figure 1 shows several properties of vibration if the repetitive motion is approximated with a sine wave. The frequency describes the number of repeated motions (or cycles) per second, while amplitude describes the distance travelled from the baseline in each repetitive motion. A measure of the intensity of vibration is peak-to-peak displacement, which describes the total distance travelled between vibration peaks. This is only practicably measured when the vibration exhibits high amplitude, and low frequency (similar to waves on a ship). Higher frequency, lower amplitude vibration (such as that experienced by heavy equipment operators) requires a

different intensity measure. The most commonly used is peak-to-peak acceleration, primarily due to ease of measurement and convenient intersection with the mathematical properties of other physical measurements (105). Peak-to-peak acceleration refers to the maximum acceleration attained during travel between peaks in cyclical vibration. This peak-to-peak acceleration may fluctuate with, for example, the speed of a ship's motor or the speed of a train, and therefore a single measurement may mislead an observer. Therefore, a mean, or summary measure, is used. The standard measure is a root-mean-square measure (RMS, see Table 1) which is calculated by taking peak-to-peak acceleration measurements over time, then taking the square root of the mean value of the squared acceleration values (the values are squared because some are negative and others positive). Measures of vibration acceleration intensity are typically weighted according to the frequency of vibration, which is intended to approximate the effect of frequency on the discomfort incurred during vibration exposure (106).

As vibration occurs in 3-dimensional space, researchers also characterize the intensity experienced along three orthogonal axes. Typically, the x-axis describes motion in a line from the back to the chest, the y-axis in a line from the right to left side, and the z-axis from head to toe (105). Vibration can be summarized by summing estimates of intensity in each of the three axes, with a multiplication factor applied to each axis according to a standard (see Table 1 and (106)).

The International Organization for Standards (ISO) details the calculation of a vector sum (see Table 1 and (106)) that is the most commonly reported in the exposure measurement

literature (107-118). However, some studies report vibration dose value (VDV) as an alternative metric or in addition to RMS values (119). The VDV which is constructed similarly but raises measurements to a 4th power, averages them, and then takes the 4th root (105). Several articles (120-123) have called for a revision of the subjective comfort-based vibration standards detailed by the ISO. The current methods of evaluation are not based on health effects (in large part because these are not known), but on the perception of comfort by the exposed individual, and because the relative importance of frequency and amplitude changes is partly extrapolated from noise exposure research (105).

In occupational settings, whole body vibration occurs in the operation of vehicles (110, 124, 125) and industrial machinery (109, 126, 127). The most ubiquitous source of whole body vibration exposure is automobiles (128), which is a source of background exposure in the general population, but may be cumulatively substantial for professional drivers with a long duration of exposure (e.g. taxi drivers (124)). Conversely, the vibration intensities associated with heavy equipment use can be greater, although exposure duration may be shorter.

The health effects of long term whole body vibration exposure are not well understood. Probably the best studied relationship concerns whole body vibration exposure as a risk factor for back disorders (110-113, 116, 127). Although an association between occupational whole body vibration exposure and back pain has been consistently observed, particularly in cross-sectional studies, and there is mechanistic support for a causal interpretation of this association (129), more recent evidence from twin studies suggests this relationship may not be causal (130, 131). Exposure to whole body vibration has also been associated with

impaired gastric motility (132, 133) and disruption of vision (134). Vibration exposure can also affect vascular function and impose long term damage to this system (135). Interestingly, whole body vibration has been considered as a possible treatment for Parkinson's disease patients (albeit at much lower intensity and frequency than occupational exposures). A study by King et al. reported short term motor impairment improvements in participants exposed therapeutically to whole body vibration (136), although a placebo controlled trial by Arias et al. found no effect (137).

Few studies have examined potential associations of long term occupational whole body vibration and chronic diseases with long latency. A case control study of myocardial infarction (MI) by Bjor et al. found that exposure to whole body vibration (as assessed by experts from participant reported job histories) was associated with increased risk of MI (138). However, this association could be confounded by the correlation between noise and whole body vibration exposures, because noise has also been found to be a risk factor for MI (139).

Although occupational exposure to vibration was found to be associated with diffuse cerebral atrophy (a loss of neurons throughout the brain) in a case series analysis by Iivanainen in 1975 (140), few subsequent studies have considered whole body vibration exposure as a potential risk factor for neurodegenerative disease. To my knowledge, only one additional study has examined a risk relationship between occupational whole body vibration exposure and a neurodegenerative disease: a small case control study of Alzheimer's disease by Gun et al. (141). The study found no association, but used a simple dichotomous

construction of whole body vibration exposure as assessed by an expert with access to participants' self reported exposures. The difficulty of assigning exposure is one of the challenges of case control studies of occupational risk factors discussed below.

Using the case control study design to evaluate occupational risk factors

Case control studies compare the exposures incurred by a sample of disease cases to those incurred by a sample of control participants who do not have the disease (142). If an exposure is more commonly detected among cases than controls, it can be identified as a risk factor. The case control design is an alternative to cohort studies, which observe a large number of participants over many years and identify disease cases as they arise. Prospective cohort studies can collect data on occupational and other exposures during the course of the study and later test for associations with relevant disease outcomes as they arise. However, the rarity of Parkinson's disease poses a challenge to this type of design. As one example, Ascherio et al. analyzed data from two cohorts comprising more than 130 000 participants observed for 10 years or more and detected only 288 cases of Parkinson's disease (143). For this reason, the case control design is the most commonly used design in epidemiological studies of Parkinson's disease etiology (e.g. (67, 73, 74, 77, 93, 94, 98, 101, 102)). Although case control studies of Parkinson's disease may attempt to restrict inclusion to newly diagnosed cases only (e.g. (70)), the lack of a clear date of onset and the very long survival of Parkinson's patients are possible justifications for the inclusions of longstanding (prevalent) cases (142).

Case control studies are inherently retrospective (because participants are not recruited until their disease status is known), so determining the prior exposures of participants is an inherent challenge to this design (144). Retrospective exposure reconstructions are subject to several sources of error, most of which can be expected to be non-differential between cases and controls, making it less likely that true associations will be detected (144). Recall bias is differential misclassification of exposure that occurs when there are systematic errors in reports of exposures that are dependent on case or control status. Recall bias may occur as a result of cases more thoroughly cataloguing their exposure histories while reflecting on why they incurred the disease (145). Although this bias may not have large effects on study conclusions (146), it is a cause for concern where studies rely on self report of exposures. Where self report of exposure and occupational histories are used, both differential and nondifferential error may be reduced when participants report on exposures they can feel (such as vibrations) (144) and where they respond to lists of relevant prompts rather than responding to open ended questions (147).

Observational study designs such as case control studies do not permit definitive conclusions about causation, but accumulation of evidence from several studies can contribute to the construction of coherent theories of disease that can be subjected to ongoing hypothesis tests and refined accordingly. Therefore, a case control study can offer useful information to improve our understanding of the causes of Parkinson's disease.

Why a case control study should examine occupational whole body vibration as a possible risk factor for Parkinson's disease

No previous studies have examined occupational whole vibration as a risk factor for Parkinson's disease. In and of itself this is not a justification for the proposed work, but the fact that the long term heath effects of occupational whole body vibration are understudied should be relevant to the threshold of plausibility for examining its effect. One study shows a possible relationship between vibration and cell loss in the brain (140). This evidence must be considered in the context of very few neurological outcome studies. If several studies had examined vibration exposure and concluded there was no relationship with neurological health, we could more easily dismiss a single result.

Does the evidence from job or industry title risk factor studies provide any insight? Work in the construction and agriculture industries (70) has been associated with Parkinson's disease, and these industries also rely on the use of whole body vibrating equipment. But whole body vibration is a common workplace exposure (128), so job title analyses alone have limited ability to detect its effects. A further complication is the fact the when Parkinson's disease is diagnosed, many potential research participants have retired from work, so cross-sectional exposure assessments could be misleading.

Hachiya et al. (103) presented a case for the examination of mechanical stress as an environmental hazard that could impair cellular quality control mechanisms that normally deal with improperly folded proteins that may accumulate in Parkinson's disease pathology. These authors were particularly interested in the *repeated* mechanical stress experienced by athletes such as boxers and soccer players, but repetitive mechanical displacement is also the defining feature of whole body vibration. While this displacement may follow a predictable oscillatory pattern as depicted in Figure 1, exposure to whole body vibration can also entail repeated but more haphazardly distributed shock events that may provoke distinct responses from the body (148). Both of these repetitive types of displacement could constitute mechanical stressors of the type discussed by Hachiya et al.

These lines of reasoning provide support for examining a previously untested relationship, rather than themselves establishing the relationship. The limitations of job title or industry as a proxy for the variables of interest call for a targeted and detailed exposure assessment that can best be implemented in a case control study due to the rarity of Parkinson's disease.

Rationale and Objectives

Overarching objectives

The central goal of this thesis is to test an etiological hypothesis regarding a possible relationship between whole body vibration and Parkinson's disease. The chapters contained in this thesis, although independent, can be conceptualized as steps required for an epidemiological investigation of Parkinson's disease and whole body vibration:

- Justifying the hypothesis: the first chapter of this thesis presents a summary of the literature that highlights that which is known and not known, providing a rationale for the overall hypothesis and approach of the thesis work in general.
- Locating Parkinson's disease cases: this study relates to the challenges of defining and locating people with Parkinson's disease, which is necessary for all epidemiological studies.
- Retrospectively assessing exposure to whole body vibration: for any hypothesis test to proceed, the prior exposure of study participants must be characterized. The inherently retrospective nature of case control studies presents a challenge, and this study presents a new method for quantitatively assigning whole body vibration exposure.
- Testing the association between whole body vibration and Parkinson's disease: once cases are located and recruited (along with a control sample), and their occupational whole body vibration exposure has been assessed, a test of the association can proceed.
- Synthesizing the results, analyzing efficiency, and assessing future steps: the final chapter of the thesis reflects on issues raised by the thesis findings and on challenges faced during the research and how they may be addressed in future studies.

This thesis thus consists of five chapters: three research chapters constructed to allow publication as independent manuscripts, this introductory chapter, and a concluding chapter. The objectives and basic rationale of each of the research chapters are described below.
Chapter 2: Finding people with Parkinson's disease for epidemiological studies: A comparison of population-level case ascertainment methods

As discussed in the literature review above, a major challenge to epidemiological studies of Parkinson's disease is how to efficiently locate cases. The case control study of Parkinson's disease which provided the data for Chapters 3 and 4 employed drug tracer methods to locate cases. Although these methods were intended to prioritize sensitivity (detecting all eligible cases) over specificity (detecting no ineligible cases or non-cases), we found far more non-Parkinson's disease users of antiparkinsonian drugs than expected (particularly levodopa, which was expected to be fairly specific to Parkinson's disease), which compromised the efficiency of recruitment (149). This finding led to the question of how many users of antiparkinsonian drugs (especially levodopa) actually do have Parkinson's disease, and how different methods of defining cases such as records of physician diagnosis, prescription of antiparkinsonian drugs, or self report of disease status would affect estimates of prevalence. We were able to locate relevant sources which had collected data that could help address these questions: the Canadian Community Health Survey 1.1 and preparation materials for the 2009 British Columbia Prescription Drug Atlas (150). The serendipitous availability of these data sources allowed us to compare methods of ascertainment within the time scale of a PhD thesis, something that would not have been possible had we needed to conduct primary data collection or even apply for access to secondary data sources.

Chapter 3: Retrospective assessment of occupational whole body vibration exposure for an epidemiological study

Case control studies are inherently retrospective, which limits the options for exposure assessment. For example, measurements of current occupational exposures are not likely to be relevant, particularly for those who are ill. Given the limited options for retrospective exposure assessment, previous studies of the long term health effects of vibration have relied on dichotomous exposure construction (141), which limits the ability to detect dose response effects, or expert assessment (138), which may introduce non-differential misclassification of exposure (144). The objective of this chapter was to define and describe a method of producing quantitative estimates of occupational whole body vibration exposure, using a combination of participant self report and measurements of whole body vibration from the peer-reviewed literature.

Chapter 4: Association between occupational whole body vibration and Parkinson's disease in a population based case control study

Given the hypothesized relationship between mechanical stress and Parkinson's disease (100, 103), and the potential for whole body vibration to be transmitted to the head (104), we hypothesized that occupational whole body vibration could constitute a risk factor for Parkinson's disease. The objective of this chapter was to test this hypothesis using data from a case control study of Parkinson's disease and the estimates of occupational whole body vibration exposure derived in Chapter 2, while taking into account possible confounders of

this relationship such as age, sex, smoking behaviour, and head injuries (which could be more likely among workers exposed to whole body vibration).

Table 1. Methods of summarizing measurements of whole body vibration exposure intensity.

Root mean square (RMS) acceleration:

$$a_w = \left[1/T \int_0^T {a_w}^2(t) dt\right]^{\frac{1}{2}}$$

Where:

T is the duration of observation and measurement(s)

 a_w is the weighted acceleration (m/s²); as a function of time (t); the weighting is applied to the raw vibration signal according to the frequency of the vibration (weights for each frequency are defined by a function which varies depending on the standard used).

ISO 2631 Vector Sum (see (106)) :

$$a_{v} = ((1.4)^{2} a_{wx}^{2} + (1.4)^{2} a_{wy}^{2} + (1.0)^{2} a_{wz}^{2})^{\frac{1}{2}}$$

Where:

 a_{wx} is the weighted RMS acceleration (m/s²) in the x-axis (from back to chest). a_{wy} is the weighted RMS acceleration (m/s²) in the x-axis (from side to side). a_{wz} is the weighted RMS acceleration (m/s²) in the x-axis (from head to toe). The multiplying factors shown are those recommended for seated postures.



Figure 1. Properties of vibration conceptualized as a sine wave.

CHAPTER 2: FINDING PEOPLE WITH PARKINSON'S DISEASE FOR EPIDEMIOLOGICAL STUDIES: A COMPARISON OF POPULATION-LEVEL CASE ASCERTAINMENT METHODS

Synopsis

Locating Parkinson's disease cases for population-based epidemiological studies is challenging. While several drugs are used to treat Parkinson's disease, a number of these are used for other purposes. Prescriptions of levodopa have previously been considered sufficiently specific to Parkinson's disease to comprise a useful proxy for diagnosis. We sought to test this assumption and compare three methods of population-level case ascertainment. We compared Parkinson's disease prevalence estimates for British Columbia, Canada, derived from self-reports in the 2001 Canadian Community Health Survey to those obtained from administrative records of filled levodopa prescriptions and to Parkinson's disease diagnoses from physician visit billing and hospital discharge records in 1996 and 2005. We compared a case definition based on levodopa prescriptions with a definition based on records of physician diagnosis by calculating positive predictive value and sensitivity. Crude prevalence estimates ranged from approximately 100 to 200 per 100,000. Levodopabased case definitions seemed to overestimate prevalence, while physician- and hospitalrecord-based case definitions provided lower prevalence estimates compared to survey derived estimates. The proportion of levodopa users with a diagnosis of Parkinson's disease declined from 62% to 52% between 1996 and 2005. The resulting decrease in the positive

predictive value was most dramatic among women (64% to 44%) and those under age 65 (54% to 39%). Sex and age trends suggest increasing use of levodopa among patients with conditions other than Parkinson's disease, such as restless legs syndrome. Increased non-Parkinson's levodopa use decreases the efficiency of levodopa as a Parkinson's disease case tracer and may have broader public health implications.

Introduction

Parkinson's disease is a neurodegenerative disorder entailing loss of dopaminergic neurons, typically producing slowed movement, stiffness, and resting tremor (151). Partly due to the lack of a definitive laboratory test to confirm Parkinson's disease and partly to the absence of Parkinson's disease epidemiological registries, researchers must rely on proxy methods for identifying Parkinson's disease cases for population health studies. With typical crude prevalence estimates ranging from 100 to 200 cases per 100,000 population members (9, 27, 29), further challenges to locating Parkinson's disease cases are posed by the relative rarity of Parkinson's disease is considered to be the second-most common neurodegenerative disease (after Alzheimer's disease) (37). Two commonly used methods to locate cases for estimating prevalence are drug tracer analyses (based on prescriptions of anti-Parkinson's disease medication), and population-based surveys.

Population-based surveys might be considered the ideal method for ascertaining disease prevalence. Other methods, such as large cohort studies (152) or surveys of physicians (20),

face the difficulty that the underlying subgroups studied (i.e., the cohort or sampled physician practices) may not be representative of the larger population of interest. Sampling the population directly poses different challenges. In population-based surveys, it can be difficult to attain sufficient sample size to produce meaningful results, particularly if participants are clinically evaluated to validate Parkinson's disease self-report. A recent door-to-door in-depth and clinically validated survey conducted in Australia sampled 501 people aged 55 and over (24), and a similar study in Israel sampled 918 residents aged 65 and over (25). The authors of both studies noted unusual or unexpected (e.g. prevalence of Parkinson's disease compared to other conditions, or in the magnitude of prevalence), which could be partially attributable to sampling error because the expected number of cases would be so small. Increasing the sample size of surveys can increase the stability and precision of estimates for rare diseases. However, larger sample sizes can be expensive and even with tens of thousands of participants and unusually high response rates could still locate fewer than 100 cases (26). Other survey designs may reduce costs by relying on participant self-report, but introduce another potential source of error.

The use of drug-tracer analyses has held great promise for epidemiological studies of Parkinson's disease. Using the consumption of anti-Parkinson's disease medication as an indicator of Parkinson's disease has the advantage of being inexpensive and relatively simple to analyze on a large scale (for example, by examining bulk sales records). This method does assume that all cases are diagnosed and treated, and therefore newly incident cases not receiving treatment will not be detected. Furthermore, drug tracer methods require that anti-Parkinson's disease drugs are relatively specific to Parkinson's disease, little used for other

indications. Although many drugs used for Parkinson's disease are used for other purposes, the assumption of specificity might be met by levodopa, a drug commonly used among Parkinson's patient to replace the lost neurotransmitter production unique to Parkinson's disease. Indeed, a study conducted in 1998 in Italy estimated that greater than 75% of patients treated with levodopa were true Parkinson's disease cases (27). However, a more recent study using drug-tracer methodology to estimate Parkinson's disease prevalence in Denmark noted a higher than expected estimate which the authors speculated could have been affected by the use of anti-Parkinson's disease medications for other indications such as restless legs syndrome (RLS)(153).

In British Columbia, Canada, a levodopa drug-tracer analysis estimated crude prevalence of Parkinson's disease to be 144 per 100,000 in 1998 (29). This estimate relied on the assumption of highly specific levodopa use. The current study attempts to test the assumption that levodopa use is specific to Parkinson's disease patients by comparing British Columbia prevalence estimates derived from three population-based secondary data sources to contrast the efficiency/accuracy trade-offs entailed in the various methods of identifying Parkinson's disease cases: a national population-based survey conducted in 2001; 1996 and 2005 records of filled prescriptions for anti-Parkinson's disease drugs; and 1996 and 2005 clinical diagnoses of Parkinson's disease in physician service and hospital discharge records. These secondary data sources were serendipitously available and the years included do not reflect the choices of the investigators. For example, a question about Parkinson's disease was included only once on a population-based nation-wide Canadian survey.

Materials and methods

Data sources

Data were drawn from three sources outlined in Table 2: 1) a national survey of the Canadian population which asked participants to self report on a number of chronic conditions (as diagnosed by physicians); 2) records of filled prescriptions for levodopa maintained by the British Columbia College of Pharmacists; and 3) records of physician diagnosis from hospital discharges and outpatient physician visits billed to the near universal public insurer. Please see Table 2 for specific details on case definitions. No individual personal records were obtained by the authors for these analyses.

The Canadian Community Health Survey (CCHS) cycle 1.1 was a comprehensive and nationally representative survey conducted by Statistics Canada as mandated by the Statistics Act (154). The CCHS uses a complex sampling strategy to ensure coverage of approximately 98% of the Canadian population with approximately 130 000 respondents. The CCHS 1.1 had an estimated response rate of 84.7% (155). To access CCHS data, we created and tested analytical programming using officially released artificial data and submitted these programs to Statistics Canada whose analysts then applied the programs to the actual survey data. Aggregate results only were then released to us by Statistics Canada after meeting standards of anonymity (unweighted cell sizes larger than 30) and estimate stability (coefficient of variation less than 33.3%).

In British Columbia, records of all filled prescriptions (regardless of payer) are maintained by the College of Pharmacy to ensure patient safety in case of recalls. The single-payer public health insurance provided by the province is intended to be universal. All family practice physicians and neurologists treating Parkinson's disease bill the public insurer, and therefore may not issue any private billings, effectively ensuring universal public treatment of Parkinson's disease. This allows studies using such records of physician treatment to be truly population-based. Physicians bill the provincial insurer for services, citing reasons for treatment using International Classification of Disease (ICD) codes. The same coding is found in records of hospital discharges. Both of these data sources can be analyzed for diagnostic codes of interest and linked to prescription records via patient Personal Health Numbers. For this study, tabulations of records of levodopa prescription, physician billing (for outpatient visits), and hospital discharge diagnoses of Parkinson's disease were obtained from a draft version of the British Columbia Prescription Drug Atlas, 2nd Edition (150), a project that conducted the linkage after approval by the Behavioural Research Ethics Board of the University of British Columbia and contained relevant cross tabulations of prescription by indication for 1996 and 2005. In the preparation of this atlas, only those with some prescription treatment were included for the "Physician diagnosis" definition of Parkinson's disease (see footnote to Table 2 for the possible treatments that acted as a gate before any records of diagnosis from physician billing were recorded). However, all users of levodopa preparations were identified as a distinct group (see Table 2), and no requirements for other treatment existed for this group.

Prevalence analyses

Prevalence was calculated as x/n, where x is the number of observed disease cases (according to definitions listed in Table 2) and n is the total number of persons in the relevant populations during the index year. Crude prevalence was calculated for British Columbia for each ascertainment method. Age and sex specific prevalence estimates were available from British Columbia administrative data sources. However, due to Statistics Canada precisionbased restrictions on information release, for age and sex prevalences we were not able to obtain British Columbia specific estimates and instead were provided Canada-wide age and sex prevalences. Additionally, only a very crude age stratification was available (ages less than 65 versus ages 65 and over). To account for the sampling strategy used to conduct the CCHS, bootstrapped confidence intervals were calculated for the estimates (154). Confidence intervals on physician diagnosis- and drug-based case definitions were calculated using the Wald approximation (156). Due to the age restrictions on the CCHS survey population (ages 12 years and over), a correction factor based on 2001 Canadian census data was applied to survey-based point estimates to account for the proportion of the population under 12 years of age who must be included in the denominator for a true crude prevalence estimate. We assumed that there were no cases of Parkinson's disease in those under 12, so no adjustment of the numerator was required.

Secondary parkinsonism and ICD coding precision

In British Columbia, physician billing ICD coding for outpatient visits requires less precision than hospital billing ICD coding for hospital visits. For example a physician billing the public insurer using ICD-9 codes uses the code 332 to identify patients with Parkinson's disease, while hospital discharge records distinguish between codes 332.0 (Idiopathic paralysis agitans) and 332.1 (Secondary parkinsonism). Where precision was available, we included only idiopathic cases and excluded secondary cases. To determine the potential impact of reduced precision in physician billing records, we used hospital discharge records to calculate the proportion of patients who would be classified as 332 under less precise classifications who could be identified as 332.1 (Secondary parkinsonism) given full precision (that is, the proportion of all cases who are secondary cases).

Levodopa as Parkinson's disease case definition

To evaluate the agreement of a Parkinson's disease case definition from levodopa prescription records with a Parkinson's disease diagnosis recorded in physician billing and hospital discharge records we calculated:

- The percentage of those with at least one prescription of levodopa who also had a physician diagnosis of Parkinson's disease (as defined in Table 2). This is the positive predictive value of levodopa prescription, assuming the physician diagnosis case definition as the gold standard.
- The percentage of those clinically diagnosed and treated for Parkinson's disease (as defined in Table 2) for whom each drug definition also applied. This is the sensitivity of levodopa prescription, assuming physician diagnosis case definition as the gold standard.

Results

Prevalence analyses

Crude prevalence estimates are compared by method in Table 3. Physician billing and hospital discharge (physician diagnosis) prevalence estimates tended to be the lowest, while levodopa-prescription-based estimates were the highest. Prevalence among males was greater than prevalence among females for all estimation methods except for 2005 levodopaprescription-based estimates, which were approximately equal for males and females. Prevalence was greater among the population aged 65 and over. Levodopa-based estimates consistently exceeded physician diagnosis-based estimates of Parkinson's disease in the population under aged 65, and indeed in 2005 the levodopa-based estimate was more than twice the physician diagnosis-based estimate in this population. The survey-based prevalence point estimate was comparable to levodopa-based estimates in the population under age 65, but the survey estimate lacked precision due the small number of expected cases (Table 3).

Secondary parkinsonism and ICD coding precision

Of the 2,368 cases (ICD-9: 332) identified by hospital discharge records alone, 39 (1.6 %) were identified as secondary parkinsonism (ICD -9: 332.1) and excluded from further analyses. A further 19 (0.8%) had diagnoses of both secondary parkinsonism (ICD -9: 332.1) and idiopathic PD (ICD -9: 332.0) and were included as cases.

Levodopa as Parkinson's disease case definition

Table 4 compares prescription levodopa-based definitions of Parkinson's disease to clinical physician diagnosis definitions. Levodopa prescription was highly sensitive to Parkinson's disease physician diagnosis status, with more than 95% of Parkinson's disease diagnosed individuals also having a prescription for levodopa. Sensitivity increased modestly from 1996 to 2005 in all strata except among those under age 65. Conversely, the proportion of people with a prescription for levodopa who also had a recorded physician diagnosis of Parkinson's disease (positive predictive value of levodopa prescription) declined from 1996 to 2005 in all strata (Table 4). This decrease was most dramatic among females and among those under age 65. Whereas Parkinson's disease diagnosed users of levodopa outnumbered non-diagnosed users in all other strata, in 2005 there were more non-diagnosed users than diagnosed users among women and those under age 65 (Table 4).

Discussion

The observed crude prevalence estimates of Parkinson's disease of 100 to 200 cases per 100,000 population straddle those from a previous report that used drug tracer methods to identify Parkinson's disease cases in British Columbia between 1996 and 1998 (29). However, that report assumed that 75% of levodopa prescriptions were to people with Parkinson's disease. Our results suggest this proportion could now be an overestimate. We observed that the proportions of those with a levodopa prescription who also had a Parkinson's disease diagnosis based on physician billing/ hospital discharge records ranged from 39% to 66%,

and decreased from 1996 to 2005. A previous study of levodopa use in Denmark also concluded that levodopa prescriptions overestimated Parkinson's disease prevalence (153).

Most cases identified by the physician diagnosis definition also had a levodopa prescription. The first explanation of this finding has to do with a methodological limitation with the algorithmic procedure used in the BC Prescription Drug Atlas creation: in order for diagnoses to be recorded, participants had to be taking at least one of the study drugs (at least one prescription for dopa or dopa derivatives, dopamine agonists: bromocriptine, cabergoline, apomorphine MAO-B inhibitors, or amantadine). Therefore, untreated patients or those treated with other drugs were not detected by the physician diagnosis based algorithm. However, the sensitivity of levodopa to ascertain Parkinson's disease cases may have additional explanations. Most cases of Parkinson's disease in any population are prevalent, rather than incident. New (incident) cases are rarer than long-standing (prevalent) cases, so most detectable cases could be expected to have progressed to levodopa use. A second possible explanation is that the guideline to delay treatment is not as widely adhered to as one might expect. Generalizable studies on actual (rather than intended or hypothetical) prescribing practices among physicians treating Parkinson's disease are rare. Studies conducted in Italy suggest deviation from guidelines on antiparkinsonian prescribing practices (157, 158). Tan et al. (159) conducted a study of actual prescribing practices in Singapore, and found that 92.3% of Parkinson's disease patients were receiving levodopa. The neurologists surveyed cited the need to maximize treatment efficacy as the reason for selecting levodopa over agonists.

Our physician diagnosis based estimates of prevalence were lower than expected, and lower than the survey estimates. Some of this difference is likely due to the omission of untreated patients from the physician diagnosis definition, or those treated with dopamine agonists not included in the algorithm. These limitations are illustrated in Figure 2. However, our physician diagnosis based estimates are similar to those observed in a 1989 study conducted in a rural population of southern British Columbia that located cases by family and specialist physicians (21). Although records of ICD diagnoses of Parkinson's disease were found to be highly predictive of Parkinson's disease in a previous study of nursing home patients in the United States (160), sensitivity at the population level could be impaired by inconsistent recording and selection of ICD diagnoses by physicians in their billing records for individual treatment sessions. It is possible that when physicians treat longstanding Parkinson's disease patients they are more likely to record proximate reasons for treatment via ICD codes (e.g. incontinence, dyskinesia) rather than Parkinson's disease itself, especially when only one diagnosis code is recorded per billing record as is the case in British Columbia. If so, extending the period in which a Parkinson's disease diagnosis is recorded in billing records for positive case definition from three years to five or more could increase diagnosis based prevalence estimates. We might have expected out physician diagnosis based estimates to have overestimated prevalence if they did not appropriately distinguish between idiopathic Parkinson's disease and secondary parkinsonism arising as a side effect of treatment with antipsychotic medications. The imprecision of billing codes used for outpatient treatment would not allow such a distinction. However, in the hospital discharge records, where precision was available, only a small percentage of cases were identified as having "secondary parkinsonism" (1.6%). This percentage should not be misinterpreted as the prevalence of secondary parkinsonism in our sample or in the population: it likely reflects the use of diagnostic codes in practice. For example, patients treated for psychotic symptoms would likely prompt treating physicians to record ICD codes such as "F20: Schizophrenia" (in ICD-10), even if the current reason for treatment was secondary parkinsonian symptoms. As a result, codes for secondary parkinsonism would be very rarely used, consistent with our observations. Therefore, even when precision of ICD coding does not allow for distinction of idiopathic Parkinson's disease and secondary parkinsonism, the billing and recording practices used in both outpatient and inpatient treatment may distinguish these two groups.

In contrast to possible underestimates from physician diagnosis records, survey self-report could overestimate Parkinson's disease prevalence. Self-report diagnoses based on symptoms have been found to be sensitive (89-95%) but somewhat less specific (88-89%) when compared to Parkinson's disease physician diagnosis (161, 162), suggesting some overestimation in self-reports, perhaps due to the confusion of parkinsonism with idiopathic Parkinson's disease. A simple yes/no report of disease status (even with the qualifier that the condition has been diagnosed by a physician), as used in the CCHS, could be more vulnerable to misclassification error.

Parkinson's disease is generally found to be more common among men than women (151). The sex ratio in Parkinson's disease prevalence we observed also showed male prevalence exceeding female prevalence in all estimates except the 2005 levodopa-based estimate. The latter anomaly suggests increased use of levodopa among women without Parkinson's disease in British Columbia in recent years. This is further supported by the dramatically decreased positive predictive value (PPV) of levodopa among females from 1996 to 2005. The trend in prevalence estimates and decline in PPV of levodopa among those under age 65 further indicates increasing numbers of younger non-Parkinson's disease users of levodopa. While some levodopa prescriptions could have been used to diagnose Parkinson's disease and withdrawn when ineffective, it would be surprising if this practice alone would explain the pronounced gap between levodopa use and diagnosed cases among the younger and female populations or the fact that the gap widened between 1996 and 2005. It is also possible that increasing use of drugs not included in this study could have occurred, because cases treated with other drugs (or those untreated) were not detected by physician diagnosis identification algorithms. However, decreased reliance on levodopa is not consistent with the observation that per capita levodopa use actually increased from 1996 to 2005, particularly among women and those under 65. Furthermore, this does not address the decrease in the proportion of persons using levodopa who do have a physician diagnosis of Parkinson's disease (decreased PPV). We posit that the increase in levodopa prescriptions among younger and female populations reflects a trend of increasing diagnosis and treatment of restless legs syndrome (RLS). RLS is a disorder in which patients experience an urge to move causing discomfort during rest (163). Use of levodopa to treat non-Parkinson's disease conditions such as RLS would explain the reduced positive predictive value of levodopa. Literature reviews suggest that RLS is more commonly diagnosed in women (163), consistent with our observation of increased non-Parkinson's disease female users of levodopa.

Dopamine agonists are considered the most appropriate first line treatment for RLS, rather than levodopa, but levodopa has also been examined and discussed as a potential intervention for RLS (164). Reviews and advertisements report favorable results of treatment of RLS by levodopa and other antiparkinsonian agents (165-167), which could affect prescribing practices. Furthermore, levodopa preparations may be attractive because they are available as generics, and therefore less expensive. The symptom-based criteria for RLS have been found to be present in approximately 10% of adults (165), and therefore RLS diagnosis and treatment could dwarf Parkinson's disease prevalence (approximately 0.1-0.2%). If we assume that even a small proportion of RLS patients receive levodopa as treatment, this would dramatically affect the proportion of non-Parkinson's levodopa users because there are so many more RLS patients than PD patients. It is interesting to note that a study of population wide drug sales in Sweden found that increased use of dopamine agonists were not associated with any reduction in use of levodopa (30), suggesting that the dopaminergic treated population has expanded, rather than increasing dopamine agonist use resulting in reduced reliance on levodopa.

Increased use of levodopa for non-Parkinson's conditions poses a methodological challenge to drug tracer Parkinson's disease case identification, but could also have public health implications in young treatment populations (168). Future studies could examine the range of ICD diagnosis codes present in administrative records of all patients filling prescriptions for levodopa to evaluate the hypothesis of increased use among RLS patients, though this will be challenged by the fact that RLS is not distinguished by a unique code in the ICD-10.

This study is limited by the lack of a perfect "gold standard" Parkinson's disease case definition. Ideally, all survey-based, physician diagnosis-based, and levodopa-based case definitions would be validated with clinical assessment or postmortem examination (8) but this is not feasible for truly population-based estimates of prevalence. Despite the limitations of each case definition, definitions combining prescription and diagnosis records are commonly used in etiological research concerning Parkinson's disease, particularly in large anonymized studies using data held by administrative bodies (169, 170). Our observation of the decreased utility of levodopa drug use to predict diagnosed Parkinson's disease will be important to consider in future studies relying on drug use for case ascertainment. It is possible that these studies could employ additional requirements, such as a minimum age or a minimum duration of use, to improve case ascertainment from drug records. Our study indicates that tracking trends in prescription use by indication will provide important information for all studies using administrative data to trace cases for epidemiological research.

	Data source	Index year(s)	Method of Access	Linkage	Population	Parkinson's Disease Case Definition
Survey	Canadian Community Health Survey (CCHS) 1.1	2001	Statistics Canada remote access	None	Canadians over the age of 12 years living in private dwellings. (Restricted to British Columbia residents for overall estimate, but age and sex specific estimates are for all of Canada)	Answered "Yes" to question CC_Q231: "Do you have Parkinson's disease?" ^a
Levodopa Prescription	Records of filled outpatient prescriptions maintained by British Columbia College of Pharmacists	1996, 2005	British Columbia Prescription Drug Atlas (10)	Physician diagnosis	British Columbia residents registered with provincial health insurer (Medical Services Plan, MSP) for \geq 275 days of index year.	At least one prescription for levodopa (all preparations, including those with decarboxylase inhibitors) during index year.
Physician Diagnosis	Physician billing (visits data) and hospital discharge records (ICD Diagnoses) maintained by British Columbia. Ministry of Health.	1996, 2005	British Columbia Prescription Drug Atlas (10)	Levodopa prescription	British Columbia residents registered with provincial health insurer (Medical Services Plan, MSP) for ≥ 275 days of index year.	Among treated patients ^b , those with at least one hospital discharge or two MSP billing records ^C for Parkinson's disease (ICD-9:332.0, ICD-10: G20) during index year or previous two years.

Table 2. Details of data sources and definitions used to identify Parkinson's disease cases.

^aA preamble to chronic disease questions in the CCHS reads "We are interested in long-term conditions which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional".

^bTreated patients were those with at least one prescription for dopa or dopa derivatives, dopamine agonists (bromocriptine, cabergoline, apomorphine) MAO-B inhibitors, or amantadine.

^cThe number of records required by this algorithm is based on the standard methodology of the BC Prescription Drug Atlas. The rationale is that hospital discharge diagnoses are considered to be more accurate than records of diagnosis from billing of a single visit to a physician.

Table 3. Crude prevalence estimates obtained using three different methods of case ascertainment: a
national survey, diagnoses in records of physician billing and hospital discharge and
filled prescriptions of levodopa. All estimates apply to the population of British
Columbia, except for the age and sex specific estimates from the CCHS survey, which
apply to all of Canada.

	Crude Prevalence Estimates per 100,000					
	(95% CI)					
	CCHS Survey	Levodopa	a Prescription	Physician	Diagnosis	
	2001	1996	2005	1996	2005	
Overall	175	152	218	99	116	
	(101-249)	(148-156)	(213-223)	(96-102)	(113-119)	
Female	146	140	215	87	97	
	(110-182)	(134-146)	(208-222)	(83-91)	(93-101)	
Male	189	164	220	112	136	
	(127-251)	(158-170)	(213-227)	(107-117)	(131-141)	
Age <65	64	33	58	19	24	
0	(35-93)	(31-35)	(55-61)	(17-21)	(22-26)	
Age 65+	978	882	1143	594	652	
-	(792-1164)	(855-909)	(1116-1170)	(572-616)	(631-673)	

	Index	Index2x2 table elements					Indices of agreement	
	Year	Diagnosis+ Levodopa+	Diagnosis– Levodopa+	Diagnosis+ Levodopa–	Diagnosis– Levodopa–	Sensitivity ^c	Positive Predictive Value ^d	
Overall	1996	3,247	1,942	139	3,410,987	95.9	62.6	
	2005	4,455	4,083	99	3,911,134	97.8	52.2	
Female ^b	1996	1,450	797	64	1,745,958	95.8	64.5	
	2005	1,878	2,387	44	1,974,526	97.7	44.0	
Male ^b	1996	1,787	932	74	1,660,505	96.0	65.7	
	2005	2,578	1,675	54	1,933,342	97.9	60.6	
Age <65	1996	518	45 0	27	2,936,936	95.0	53.5	
	2005	752	1,186	42	3,340,215	94.7	38.8	
Age 65+	1996	2,729	1,492	112	474,051	96.1	64.7	
~	2005	3,712	2,888	53	573,808	98.5	56.2	

Table 4. Comparison of Parkinson's disease cases defined by levodopa prescription with treated^a Parkinson's disease cases defined by physician billing/hospital discharge diagnosis in British Columbia, Canada.

^aTreated patients were those with at least one prescription for dopa or dopa derivatives, dopamine agonists (bromocriptine, cabergoline, apomorphine) MAO-B inhibitors, or amantadine.

^b 26 individuals with unrecorded sex were excluded from sex stratified analyses.

^c Sensitivity – Percentage treated Parkinson's disease cases with a diagnosis from physician billing and hospital discharge records, with a levodopa prescription.

^d Positive predictive value – Percentage of those with a levodopa prescription, with a Parkinson's disease diagnosis from physician billing and hospital discharge records.



This scaleless Venn diagram describes populations relevant to a study comparing levodopa use to physician diagnosis as a way of detecting Parkinson's disease cases. In our data sources, population **B** is well identified, as is the intersection between **A** and **B**, so we can address the question of the proportion of levodopa users who are Parkinson's disease patients. However, the identification of population **A** itself (outside of the intersection of **A** and **B**) has limitations, because only the treated population was included, which limits the accuracy of our prevalence estimates. To fully characterize off-label antiparkinsonian use, future work should seek to define population **C**, not described by our study and identify the intersection of **B** and **C**, which our study suggests may be larger than was previously suspected.

Figure 2. Comparison of populations relevant to comparisons between levodopa drug use and physician diagnosis as methods of identifying Parkinson's disease cases.

CHAPTER 3: RETROSPECTIVE ASSESSMENT OF OCCUPATIONAL WHOLE BODY VIBRATION EXPOSURE FOR AN EPIDEMIOLOGICAL STUDY

Synopsis

Occupational whole body vibration has most often been studied as a risk factor for conditions which may arise during or soon after exposure, but only rarely have studies examined associations with conditions which arise long after occupational exposure has ceased. Our objective was to develop of method of constructing previous occupational whole body vibration exposure metrics from self reported data collected for a case control study. A detailed job history and exposure interview was designed and administered to 808 residents of British Columbia, Canada. Participants were prompted to report exposure to whole body vibrating equipment. We limited the data to exposure reports deemed to be above background exposures. We used the whole body vibration measurement literature to assign intensity (acceleration) values to each type of equipment reported. We created four metrics of exposure (duration of exposure, most intense equipment exposure, and two dose metrics combining duration and intensity) and examined their distributions and correlations. We tested the role of age and sex in predicting whole body vibration exposure 36% of participants were found to have at least one previous occupational exposure to whole body vibrating equipment. Because less than half of participants reported exposure, all continuous metrics exhibited positively skewed distributions, although the distribution of most intense equipment exposure was more symmetrically distributed among the exposed. Among the exposed, the arithmetic mean (SD) of duration of exposure among those exposed was 7.5 (10.1) work years, while the geometric mean (geometric SD) was 2.6 (5.5). For most intense equipment exposure (among the exposed), the arithmetic mean (SD) was 0.9 (0.3) m⁻s⁻² and the geometric mean (geometric SD) was 0.8 (1.4). Male sex and older age were both associated with exposure, although the effect of age was attenuated when adjusted for sex. The methods developed allowed us to create continuous metrics of whole body vibration retrospectively. The metrics displayed variation useful for epidemiological studies and identified age and sex as important variables to consider in future analyses.

Introduction

Exposure to whole body vibration occurs in the operation of vehicles and heavy equipment. While all persons living in developed countries are likely to have at least some level of whole body vibration exposure, occupational exposure may be more intense and less common than this background level of exposure. In a population-based survey of UK residents, Palmer et al. found that 56% of employed men and 19% of employed women reported at least one source of occupational whole body vibration exposure in the week prior to the survey (128). This study also found that the variation in vibration dose (a combination of intensity and duration) was more attributable to variation in occupational exposure than to leisure or background exposure (128), suggesting that occupational exposure is the logical target for epidemiologic study of vibration's potential health effects. Occupational vibration exposure has been linked to chronic back pain (108, 111, 171), impaired gastric motility (132), and disrupted vascular function (135). Previous studies have related measured exposure to possible intermediate outcomes which may lie on the causal pathway of health effects such as back pain (172). Studies of lower back pain are focused on the potential for whole body vibration exposure to cause conditions that may arise during the period of use of the equipment. In such cases, there is the potential that measurements of current exposure could be relevant and representative of the entire period of exposure. This assumption underlies studies measuring vibration exposure and potential health outcomes simultaneously (e.g. (112)). Although some investigators have performed retrospective assessments (109, 113), rarely have epidemiologists attempted to link whole body vibration exposure to health outcomes arising many years after exposure has ceased. This type of assessment poses particular challenges in that contemporary measurements at the time of the study may not accurately reflect lifelong exposures, and records of previous exposure may not exist. As a result, exposure assessments may have to rely on proxy measures or expert assessment. A previous case control study of whole body vibration exposure and myocardial infarction relied entirely on expert assessment of intensity and duration of exposure based on job description (138), meaning that variance in exposure within similar jobs might not be fully represented by assigned exposures. A case control study of Alzheimer's disease employed expert assessment using job exposure matrices, but used a simple "ever/never" construction of vibration exposure (141), precluding the examination of a dose-response relationship.

We are interested in the potential for cumulative whole body vibration exposure to increase the risk of Parkinson's disease, perhaps through mechanisms analogous to the effects of head injury events, a previously identified risk factor (100). Parkinson's disease is a relatively rare neurological disorder that affects people later in life (151), so epidemiological studies frequently rely on retrospective assessment of occupational risk factors. This methodological paper describes our construction of continuous metrics of whole body vibration to be applied to our case control study to allow the examination of dose-response relationships. Parkinson's disease is not the focus of the current paper, but it is the intended application of the method developed here. We used detailed self-reports of vibrating equipment use over the job history, industrial hygiene review of these reports, and whole body vibration measurements from the literature to assign and calculate exposure duration, intensity and dose.

Materials and methods

Questionnaire development

A detailed and structured occupational history questionnaire was created to query respondents on several variables, including those related to whole body vibration exposure. The interview was pre-tested for clarity and terminology among a convenience sample of approximately 30 people representing a broad range of occupational backgrounds. Interviews were conducted by trained interviewers. Respondents were first asked to report details of their job history. For each job held, participants reported job title, employer information, a description of duties, dates held, and hours worked per week. For each job held, participants were then asked to report exposure to any vibrating equipment types listed in an interview guide mailed to each participant in advance and present during the interview. This list was generated through examination of the vibration exposure measurement literature as reviewed for a study of back injury (173) and pilot testing among residents of British Columbia. Equipment types were listed in four categories: "off-road and earth-moving equipment, "road vehicles", "off-road vehicles not listed elsewhere" and "whole-body vibrating equipment not listed elsewhere". Exposure to other (unprompted) equipment types was also recorded. For each reported equipment exposure, participants reported on the date range of exposure, the hours exposed per week, and the weeks exposed per year, and the operations conducted with the equipment from a prompted list of operations such as "digging", "filling", "mowing", "driving", "operating", "refuelling", or "working near equipment but no direct contact".

Application to case control study sample

The questionnaire was administered to 808 participants in a case control study conducted in British Columbia, Canada (403 cases, 405 controls) by trained interviewers. The study population included people between the ages of 40 and 69 residing in greater Vancouver and Vancouver Island, excluding the city of Victoria. 403 Parkinson's disease cases were located via their use of anti-Parkinson's drugs from 1995-2002. 405 controls were randomly selected from enrolees in the universal provincial health insurance program. This case control sample was comprised of 338 women and 470 men. Year of birth in this sample ranged from 1929 to 1958, with a mean of 1940. Due to the visible symptoms of Parkinson's disease, interviewers could not be blinded to case status. However, the details of study hypotheses were withheld from interviewers and a highly structure questionnaire was used to elicit exposure information. Any participants not cognitively able to participate in the interview were excluded. Communication assistance was occasionally provided by family members when physical difficulties made participants' speech difficult to understand.

Post-interview reviews

After each interview, occupational hygienists reviewed responses to ensure all exposures expected (given job description) were included (a sensitivity check). If expected exposures were not reported, participants were called back and again prompted to report exposures. If participants could not be reached or denied experiencing the expected exposures, no adjustments were made. Only four calls were made to check for possible unreported whole vibration exposures, for the most part the hygienists found that those with occupations suggesting vibration exposure reported it.

Prior to data analysis, a second hygiene review (a specificity check) excluded exposures not likely to reflect more than background exposure. We selected minimum weekly exposures to be beyond background use of vehicles by the general population (e.g. average commuting times). The following exclusions were applied:

• Reported exposures for which the operation did not involve direct contact with the equipment while it was on (e.g. "refuelling" or "working near equipment but no direct contact").

- Reported exposures to any equipment for 0.5 hours per week or less because this was the lower limit of exposure duration queried.
- Reported exposures to cars for 10 hours per week or less.
- Reported exposures to buses, vans, and light trucks for 5 hours per week or less.

We also performed logic checks on durations of exposure. For example, if the total weekly hours of exposure to multiple types of equipment were greater than the number of hours worked per week, we divided the total hours worked between each reported equipment type, maintaining the proportion of hours each type of equipment contributed to total exposure. All reviews and consistency checks were performed while blinded to case and control status.

Vibration intensity extraction from literature

We obtained acceleration values for each type of equipment from literature sources, retrieving sources from previous reviews (173) and additional searching on specific equipment names and the terms "whole body vibration" and "vibration exposure" in ISI Web of Science and Google Scholar. Articles presenting measurement data using the ISO 2631 guidelines (106) for frequency and axis weighting were preferred, but any articles providing acceleration intensity assessments were sought. For each equipment type, we extracted values from the articles reporting acceleration measurements for that equipment. Where multiple values were located for a single equipment type, we calculated the mean of the abstracted values. We found insufficient consistency of reporting of sample size and variability measures to allow us to incorporate these into our combined estimates of intensity, and also did not find sufficient description of the exact location of accelerometers during measurement to allow us to evaluate the effect of this factor.

Creation and evaluation of whole body vibration metrics

We calculated descriptive statistics for each equipment type, including the mean reported number of hours per week each was used, and the number and percentage of participants reporting exposure to each type. Among participants with occupational whole body vibration exposure, we created four metrics of exposure (defined in Table 5) over all jobs for each participant: duration of exposure, most intense equipment exposure, and two dose metrics. The two dose calculations differ on the exponents of acceleration (intensity, $m \cdot s^{-2}$) values. The first applied a power of two (as used by Boshuizen et al. (111)), while the second dose metric applied a power of four (similar to Griffin (105), p. 859). Acceleration values (in $m \cdot s^{-2}$) are often squared in the calculation of dose to make dose estimates proportionate to the energy absorption power of whole body vibration (106). Raising acceleration values to a higher power places a greater emphasis on extreme values of intensity, which could be important for whole working life observations where durations of exposure would otherwise overwhelm intensity in estimates of dose. To evaluate the metrics and their relation to each other, we calculated descriptive statistics for each metric and compared them directly using Spearman rank correlation. We conducted these analyses only among the exposed, such that the large number of background exposed individuals did not unduly influence the results. Among all participants, we also conducted linear regressions of age and sex with the most

intense equipment exposure metric. All analyses were performed using SAS 9.1 (©SAS Institute Inc., 2002–2003).

Results

Vibration intensity extraction from literature

The 15 literature sources for whole body vibration acceleration values are listed in Table 6. While most sources reported measured acceleration as the root mean square vector sum (as per (106)), Paddan et al. reported root mean square values for the axis with the most severe acceleration (rather than a vector sum) (174). Omitting estimates from axes with less intense accelerations was unlikely to have rendered these measurements uninformative because the correlation between estimates reported by Paddan et al. and means of the estimates provided by other articles reporting on vector sums was r=0.46. Because this article did report on primary measurements, we concluded it was important to include in our overall estimates.

All of the included articles except for that by Palmer et al. (128) were primary sources that reported on directly measured acceleration values, whereas Palmer et al. derived z-axis acceleration estimates from a combination of sources including previous measurements and expert assessment. For the 18 equipment types included by Palmer et al. and also studies reporting vector sum measurements, we found that Palmer's estimates were strongly related to the mean of vector sum intensity values reported in primary measurement studies

(r=0.77). However, because we could not tell how much of each reported estimate was derived from primary measurement, we conducted an additional test to confirm that the scale would be comparable and these estimates would be relevant to include. In a simple linear regression, the intercept was not significantly different from zero, while the coefficient was 1.1 (p<0.001, R²=0.59, df=17). Therefore, we included the estimates reported by Palmer et al. (128) in our own mean intensity estimates.

Acceleration values assigned to each equipment type derived from the mean of all reported measurements in all literature sources are listed in Table 7.

Creation and evaluation of whole body vibration metrics

A total of 292 (36%) participants were occupationally exposed to at least one piece of whole body vibrating equipment. Light trucks, planes and forklifts were the most commonly reported occupational exposures (Table 7). Among reports of exposure, semi-trailer trucks had the greatest mean reported hours of occupational exposure per week, while motorized dirt bikes and helicopters had the least (Table 7). If the number of people exposed and the average hours of use per week are multiplied, we can identify the equipment types associated with the most occupational exposure in the sample. These were light trucks, cars, semi-trailer trucks, dump trucks, forklifts, and vans.

Histograms of the four exposure metrics are shown in Figures 3-6, while descriptive statistics for participants with exposure above background are compared in Table 8. The skewness of
duration and dose metrics (Equations 1-3 in Table 5) is apparent in the distributions shown in Figures 3, 5 and 6, as well as the high geometric standard deviations observed (Table 8), even among this group exposed above background. By contrast, the vibration intensity metric (Equation 4, Table 5) was more symmetrically distributed among those with exposure above background (Figure 4); geometric standard deviation < 1.5.

As expected, raising intensity values to the 4th power in the calculation of dose (instead of squaring) increased the variance and mean estimates of exposure (Table 8). However, the two dose metrics were highly correlated (Table 9). The 2nd power dose metric was also correlated with total duration of exposure, but the 4th power dose metric was less so, illustrating its increased emphasis on exposure intensity.

Linear regression showed that most intense equipment exposure was 0.43 m·s⁻² greater in men than women (p<0.0001, R²=0.20). Year of birth was more weakly inversely associated with most intense equipment exposure in simple linear regression, with an average decrease of 0.008 m·s⁻² for each year increase in birth year (p<0.01, R²=0.02). However, when both year of birth and sex were included in the same regression model, the effect of age was weakened to a decrease of 0.003 m·s⁻² for each year increase in birth year increase in birth year, and was no longer statistically significant (p<0.15). The effect of sex remained significant with exposure in men 0.42 m·s⁻² higher than in women (p<0.0001).

Discussion

In this retrospective assessment, we created metrics of whole body vibration exposure with the use of a detailed occupational questionnaire and the vibration intensity measurement literature. The positive skew we observed in the dose and duration metrics is typical of the positively skewed distributions often observed in occupational exposures (for examples, see (175)). The skewness of duration means that variance in dose (with acceleration values squared) is more attributable to variance in duration, as reflected by the high correlation between these metrics. However, the relative contributions of intensity and duration were closer when the contribution of intensity to the dose calculations is increased by a larger exponent (4th power dose estimates). Because the relationship between Parkinson's disease has not been previously tested, we do not have a priori assumptions about whether duration of exposure, intensity of exposure, or some combination of these would best be able to identify the posited risk relationship. Therefore we think it reasonable to test for independent effects of duration, intensity, and dose. To select a dose variable, we noted that the 4th power dose estimate was less correlated with duration than was the 2nd power dose estimate, suggesting that this 4th power estimate would allow the examination of an effect different from that of simply examining duration. We also note that duration and most intense equipment exposure were correlated, indicating that participants with long histories of exposure were also more likely to be exposed to more intensely vibrating equipment.

The prevalence of exposure in our sample was comparable to that observed by Palmer et al. in a UK study (128), although as that survey included only the employed, assessed a different time scale (the previous week, rather than lifetime) and did not apply the same restrictions to distinguish above-background exposure, we may reasonably suggest that our study sample represents a more highly exposed population, perhaps due to the prevalence of primary industry (e.g. fishing, forestry) employment among British Columbia workers, especially during the historical period captured by the lifetime exposures of our participants (176). The fact that men had greater exposure to whole body vibration to women was not surprising (128). Historical changes in primary industry employment (176) or decreased enrolment in armed forces (177) may explain our observation than intensity of exposure was greater among older participants in our study. The fact that this effect was partly attributable to sex (it was attenuated when adjusted for sex) could be due to generational changes in work role sex segregation (178). Both age and sex are therefore important variables to consider as potential confounders in epidemiological analyses of the health effects of whole body vibration.

This exposure assessment has several limitations. Firstly, we were not able to directly assess reliability and validity of our metrics. Although we drew our intensity values from the published literature, the variance observable over measurements of even single equipment types indicate that many factors contribute to total exposure other than equipment types. Error in these estimates may also be introduced by measurement technique (e.g. placement of accelerometer on the seat). Furthermore, factors such as road surface (114), seat type (179) and equipment size (180) have all been previously found to be determinants of vibration

intensity, but these items may not be practicable to include in a retrospective assessment, constraining the observable variance in intensity of exposure in our estimates. While limiting observable variance also limits the ability to detect epidemiological risk relationships, our metrics do exhibit more variance than would simple ever/never assessments of exposure, suggesting they will be useful in our epidemiological analyses.

We do not know which aspect of whole body vibration exposure may affect risk of neurological disease. While the measurement literature is focused on accelerative intensity values, it is possible that vibration frequency could be an equally important variable to explicitly consider, particularly when vibration exposure occurs at a resonant frequency of the skull. However, these resonant frequencies vary between individuals and are determined by numerous personal features and characteristics (181) that may not be readily assessed retrospectively.

We did not assess non-occupational exposure. This means that a varying level of background exposure is not captured by our metrics. However, if we are concerned with testing the health effects associated with whole body vibration exposure, the logical target is occupational exposure because previous studies suggest that non-occupational exposure to whole body vibration is distributed more equitably in the population, while variance in occupational exposure is much greater (128).

We are limited by our reliance on self reported equipment exposures. We attempted to improve the accuracy and reliability of self-reports by using equipment type prompts, using

names that participants would recognize (144). A validity study by Palmer (182) showed good correlation of self-report with researcher observations, although this study took place over much shorter periods of recall. Given that some misclassification due to recall is unavoidable, we must consider whether we would expect this to be differential between disease cases and controls. We have no reason to expect recall bias in this case, because whole body vibration exposure is not a well known hypothesized cause of Parkinson's disease. Indeed, our questionnaire asked participants to identify what they suspect are causes of Parkinson's disease. Only one participant identified vibration exposure as a suspected cause, compared to 154 participants who suspected "chemical" causes.

A future study could address some of the limitations of our study by conducting a validation study over longer observation periods than have been previously used (182) in studies of selfreport in vibration exposure. Such a study could attempt to incorporate some of the additional factors that can affect the actual exposure incurred such as seat type and construction, body size, and driving surface, particularly to determine if these variables can be validly assessed retrospectively. It would also be interesting to examine effects of different frequencies incurred during exposure. Despite the limitations of this assessment, if future epidemiologic analyses employ the metrics reported here to assess risk relationships and detect an effect, this would support the conclusion that these metrics are capturing real and meaningful variance in exposure. The methods presented here offer a novel way to retrospectively assign whole body vibration exposure for dose response epidemiologic investigations of chronic disease arising many years after exposure.

Whole Body Vibration Metric	Formula	Units
Duration	Equation 1.	work-years
	n	
	$\sum t_i$	
	$\sum_{i=1}^{n}$	
	For <i>n</i> equipment sources, where:	
	<i>i</i> =Each individual equipment source of exposure.	
	t= Total time exposed to source in full-time working	
	year equivalents (2000 hours). Calculated by multiplying	
	total weeks of exposure by the number of hours per	
	week the equipment was used.	
Most Intense	Equation 2.	m·s ⁻²
Equipment		
Exposure	$Max(a_i) = 1,, n$	
	For <i>n</i> equipment sources, where:	
	<i>i</i> =Each individual equipment source of exposure.	
	a = Intensity of vibration (acceleration in m/s^2) of source	
	(mean of abstracted literature values).	
Dose	Equation 3.	m ² ·s ⁻⁴ ·work-years
2 nd power	n	
	$\sum a_i^2 t_i$	
	$\sum_{i=1}^{j}$	
	For <i>n</i> equipment sources, where:	
	<i>i</i> =Each individual equipment source of exposure.	
	a = Intensity of vibration (acceleration in m/s^2) of source	
	(mean of abstracted literature values).	
	t= Total time exposed to source in full-time working	
	year equivalents (2000 hours). Calculated by multiplying	
	total weeks of exposure by the number of hours per	
	week the equipment was used.	
Dose	Equation 4.	m ⁴ ·s ⁻⁸ ·work-years
4 th power	$\sum_{n=1}^{n}$	
	$\sum a_i^4 t_i$	
	$\overline{i=1}$	
	For <i>n</i> equipment sources, where:	
	<i>i</i> =Each individual equipment source of exposure.	
	a= Intensity of vibration (acceleration in m/s^2) of source	
	(mean of abstracted literature values).	
	t= Total time exposed to source in full-time working	
	year equivalents (2000 hours). Calculated by multiplying	
	total weeks of exposure by the number of hours per	
	week the equipment was used.	

Table 5. Description of metrics used to characterize whole body vibration exposure.

Authors and Citation	Study Location	Assessment approach	Vibration measure reported	Relevant Equipment Measured	Number of pieces of equipment	Extracted acceleration value (in m·s ⁻²)	Relevant Variability measure (in m·s ⁻²)
Anttonen and Niskanen 1994 (107)	Finland	Triaxial seat acceleration measurements conducted over multiple years among reindeer herders.	Frequency weighted RMS as per ISO 2631 vector sum ^a	Snowmobile	11	Average of 3 reported averages from different years of measurements: 1.9	Range 1.1-6.1
Boshuizen, Bongers et al. 1990 (111)	Netherlands	Reported estimates of intensity based on measurements of vehicles at two companies by the Institute for Mechanical Constructions	Frequency weighted RMS as per ISO 2631 vector sum	Tractor Caterpillar Combine Bulldozer Van Car Excavator	Not reported	Tractor (in fields): 0.6 Tractor (on road): 1.1 (averaged to 0.9) Caterpillar: 0.6 Combine: 0.3 Bulldozer: 0.6 Van: 0.4 Car: 0.3 Excavator: 0.4	Not reported
Boshuizen, Bongers et al. 1992 (112)	Netherlands	Seat accelerometer measurements during normal work operations at five participating companies.	Frequency weighted RMS as per ISO 2631 vector sum	Forklift	Not reported	Forklift (small): 0.80 Forklift (large): 0.79 Averaged to 0.8	Not reported

Table 6. Literature sources yielding estimates of vibration intensity (acceleration) for a retrospective whole body vibration exposure assessment.

Authors and Citation	Study Location	Assessment approach	Vibration measure reported	Relevant Equipment Measured	Number of pieces of equipment	Extracted acceleration value (in m·s ⁻²)	Relevant Variability measure (in m·s ⁻²)
Bovenzi and Zadini 1992 (183)	Italy	Sample of city bus drivers. Seat accelerometer measurements in a mixture of old and new city buses.	Frequency weighted RMS as per ISO 2631—each of 3 axes	Bus	6	Summed axes using ISO 2631 weighting $[(1.4x)^2 + (1.4y)^2 + z^2]^{1/2}$, average of 6 vector sums: 0.44	Range: 0.24-0.71
Bovenzi and Betta 1994 (184)	Italy	Seat acceleration in representative sample of vehicles driven under various conditions (e.g high and low speed, different terrains)	Frequency weighted RMS as per ISO 2631 vector sum	Tractor	6 models 53 vehicles	Average of six model average vector sums: 1.11	Range : 0.36-2.03
Cann.	Canada	Sample of male	Frequency	Bulldozer :			SD
Salmoni et		construction workers.	weighted RMS	Small	4	1.11	0.35
al. 2003		Measured vibration	as per ISO	Large	9	0.92	0.14
(115)		intensity using triaxial seat	2631 vector	C		Averaged to 1.01	
		pad accelerometer during	sum	Crane	2	0.15	0.07
		20 minute driving samples		Dump Truck	2	1.21	0.70
		over various representative		Excavator	14	0.51	0.51
		surfaces.		Forklift			
				Regular	1	0.37	
				Variable	3	0.65	0.12
						Averaged to 0.51	
				Grader	4	0.55	0.15

Authors and Citation	Study Location	Assessment approach	Vibration measure reported	Relevant Equipment Measured	Number of pieces of equipment	Extracted acceleration value (in m·s ⁻²)	Relevant Variability measure (in m·s ⁻²)
				Loader: Crawler Wheel	3 2	1.01 1.16 Averaged to 1.09	0.18 0.70
Cann, Salmoni et al. 2004 (114)	Canada	Sample of male highway transport truck operators. Seat accelerometer measures during 30 minutes of representative highway driving. Tested differences in mean intensity between old and new trucks, road types, truck design, seat types, and driver experience.	Frequency weighted RMS as per ISO 2631 vector sum	Semi-trailer truck	68	Average of reported means over all categories and conditions: 0.59	Range of combined values: 0.51- 0.73
Futatsuka, Maeda et al. 1998 (127)	Japan	Among agricultural workers, triaxial seat accelerometer measurements during normal operating conditions	Frequency weighted RMS as per ISO 2631 vector sum	Combine Tractor	3 2	Means: 0.67 0.66	Range: 0.414-1.026 0.426-0.890
Griffin 1990 (105)	U.K.	Presents examples of triaxial seat measured vibration exposures in vehicles under standard conditions.	Frequency weighted RMS as per ISO 2631 vector sum or z-axis only as indicated	Car Van Truck Train Tractor	1 1 1 Unknown, 4 conditions tested	0.43 0.892 1.056 0.368 2.10 (mean of all 4 conditions)	 Range of combined values: 1.195-2.984

Authors and Citation	Study Location	Assessment approach	Vibration measure reported	Relevant Equipment Measured	Number of pieces of equipment	Extracted acceleration value (in m·s ⁻²)	Relevant Variability measure (in m·s ⁻²)
				Tank (over rough course)	1	1.748	
				Helicopter	7	0.596 (mean of 7 values)	Range of combined values: 0.343-1.227
				Fixed-wing aircraft (z-axis only)	3	0.858 (mean of 3 z-axis measurements)	Range of combined values: 0.356-1.247
				Ships (z-axis only)	2	0.297 (mean of 2 z- axis measurements)	Range of combined values: 0.113-0.481
Johanning U 1991 (116)	U.S.	Among subway conductors, triaxial seat accelerometer measurements during normal operation.	Frequency weighted RMS as per ISO 2631 vector sum	Subway	5 car classes	Mean: 0.55	Range of combined values: 0.32- 099
Johanning, U Fischer et al. 2002 (185)	U.S.	Among locomotive engineers, triaxial seat accelerometer measurements during normal operation.	Frequency weighted RMS as per ISO 2631 vector sum	Train	14 locomotive types (some multiple measurements)	Mean:0.59	SD: 0.26
Paddan and U	U.K.	Seat accelerometer	Frequency				SD
Griffin		measurements over	weighted RMS	Car	25	0.39	0.14
2002 (174)		relevant (but not	as per ISO	Excavator	4	0.91	1.23
(1,1)		conditions.	most severe	Dumper	4	1.28	0.62

Authors and Citation	Study Location	Assessment approach	Vibration measure reported	Relevant Equipment Measured	Number of pieces of equipment	Extracted acceleration value (in m·s ⁻²)	Relevant Variability measure (in m·s ⁻²)
			axis	Lift truck (forklift)	11	0.74	0.16
				Tractor	7	0.73	0.15
				Lorry	16	0.50	0.26
				Van	9	0.45	0.07
				Armoured vehicle	4	0.85	0.51
				Helicopter	1	1.08	
				Bus	10	0.56	0.16
Palmer, Griffin et	U.K.	Reported estimates derived from a combination of grey	Estimated z- axis	Armoured vehicle (tank)	Not reported	1.2	Not reported
al. 2000		literature measurements	acceleration	Boat		0.2	
(128)		and expert assessments.		Bulldozer		0.75	
				Bus		0.6	
				Car		0.5	
				Dumper		1.2	
				Excavator		0.6	
				Forklift truck		0.9	
				Grader		0.75	
				High speed boat		1.5	
				Loader		1.2	
				Lorry (truck)		0.7	
				Crane		0.3	
				Motorcycle		1.0	
				Off-road		0.75	
				forestry vehicle			

Authors and Citation	Study Location	Assessment approach	Vibration measure reported	Relevant Equipment Measured	Number of pieces of equipment	Extracted acceleration value (in m·s ⁻²)	Relevant Variability measure (in m·s ⁻²)
				Aircraft		0.5	
				Quad bike		1.5	
				Tractor		0.75	
				Train		0.5	
				Van		0.7	
				Helicopter		0.8	
Rehn, Nilsson et al. 2005 (118)	Sweden	Triaxial seat accelerometer measurements during occupational use of vehicles (for energy company and ski hill operation)	Frequency weighted RMS as per ISO 2631 vector sum	Snowmobile	6	1.7 (mean)	Range: 1.3-2.1
Teschke,	Canada	Triaxial seat accelerometer	Frequency				SD^{b}
Trask et al.		measurements on 50	weighted RMS	Ferry	1	0.37	
2008		British Columbia worksites.	as per ISO	Bus	2	0.48	0.07
(186)			2631 vector	Forklift	22	0.66	0.33
			sum	Forest machines	3	1.22	0.20
				Semi-trailer trucks	4	0.51	0.22
				Tug boat (boom boat)	2	0.64	0.10

^a Reported figures assumed to be vector sums because of the description of triaxial measurements, and the separate reporting of a subset of individual axis measurements.

^b Individual entries used for the calculation of means and standard deviations were measurement session results (as opposed individual vehicle results).

Table 7. Equipment types reported in an assessment of whole body vibration exposure. Intensity values were assigned from the mean of the acceleration values reported in the listed literature sources. Numbers of exposed participants (out of 808) and the mean hours of use per week among those exposed are derived from application to a case control sample.

Equipment Type	Intensity	Literature Sources	Application to Study Sample		
	(m·s ⁻²)		N (%)	Mean	
			exposed	hours per	
				week	
Ferry	0.29	(105, 128, 186)	9 (1.1)	21	
Cranes	0.35	(115, 128, 174)	6 (0.7)	9	
Cars	0.41	(105, 113, 128, 174)	45 (5.6)	26	
Combines and Harvesters	0.49	(113, 127)	9 (1.1)	8	
Railways, Trains	0.49	(105, 128, 185)	20 (2.5)	20	
Buses	0.52	(128, 174, 183, 186)	19 (2.4)	29	
Semi-trailer Trucks	0.53	(114, 174, 186)	22 (2.7)	42	
Subways	0.55	(116)	2 (0.2)	6	
Caterpillars	0.60	(113)	16 (2.0)	20	
Excavators	0.61	(113, 115, 128, 174)	7 (0.9)	11	
Vans	0.61	(105, 113, 128, 174)	37 (4.6)	19	
Tug Boats	0.64	(186)	12 (1.5)	32	
Graders	0.65	(115, 128)	11 (1.4)	7	
Planes	0.68	(105, 128)	73 (9.0)	5	
Forklifts	0.72	(112, 115, 128, 174, 186)	66 (8.2)	13	
Bulldozers	0.79	(113, 115, 128)	18 (2.2)	7	
Helicopter	0.83	(105, 128, 174)	8 (1.0)	3	
Light Trucks	0.88	(105, 128)	77 (9.5)	17	
Forest Machines	0.99	(128, 186)	5 (0.6)	16	
Motorcycles	1.00	(128)	6 (0.7)	15	
Tractors	1.05	(105, 113, 127, 128, 174, 184)	46 (5.7)	10	
Loaders	1.15	(115, 128)	19 (2.4)	9	
Dump Trucks	1.23	(115, 128, 174)	41 (5.1)	21	
Tanks	1.27	(105, 128, 174)	11 (1.4)	13	
High-speed Marine Craft	1.50	(128)	11 (1.4)	9	
Motorized dirt bikes	1.50	(128)	3 (0.4)	3	
Snowmobiles	1.80	(107, 118)	9 (1.1)	4	

Exposure Metric	Arithmetic Mean	Arithmetic SD	Geometric Mean	Geometric SD	Min	Max
Duration (work-years) ^b	7.5	10.1	2.6	5.5	0.01	51.3
Most Intense Equipment Exposure (m·s- ²)	0.9	0.3	0.8	1.4	0.3	1.80
Dose (2 nd power) (m ² ·s ⁻⁴ ·work- years)	4.6	7.2	1.4	6.1	0.01	57.0
Dose (4 th power) (m ⁴ ·s ⁻⁸ ·work- years)	4.9	11.6	0.8	8.8	0.003	125

Table 8. Descriptive statistics of metrics used to summarize whole body vibration exposure amongthe 292 participants exposed to whole body vibration in a case control study.

^bOne work year is the equivalent of a year of full time working exposure (2000 hours).

Table 9. Spearman rank correlation matrix of var	riables used to summarize whole body vibration
exposure among the 292 occupation	onally exposed to whole body vibration in a case
control study.	

	Dose (4 th power)	Duration	Most Intense Equipment Exposure
Dose (2 nd power)	0.96	0.93	0.53
Desa (Ath power)	p<0.0001	p<0.0001	p<.0001
Dose (4 power)		0.80 p<0.0001	p<0.0001
Duration		r	0.28
			p<0.01



Figure 3. Distribution of duration of occupational whole body vibration among 808 participants in a case control study. A work-year is 2000 working hours of exposure, as though exposure occurred for 8 hours each working day for one year. Those labelled "background only" had no sources of occupational exposure. Maximum value was 51.3 work-years.



Figure 4. Distribution of values of most intense whole body vibrating equipment exposure among 808 participants in a case control study. Those labelled "background only" had no sources of occupational exposure.



Figure 5. Distribution of occupational whole body vibration dose among 808 participants in a case control study. Dose calculations sum the product of acceleration of each vibrating equipment exposure and the duration of its use, with acceleration values raised to the second power. Those labelled "background only" had no sources of occupational exposure. Maximum value was 57 m²·s⁻⁴·work-years.



Figure 6. Distribution of occupational whole body vibration dose among 808 participants in a case control study. Dose calculations sum the product of acceleration of each vibrating equipment exposure and the duration of its use, with acceleration values raised to the fourth power. Those labelled "background only" had no sources of occupational exposure. Maximum value was 125 m⁴·s⁻⁸·work-years.

CHAPTER 4. ASSOCIATION BETWEEN OCCUPATIONAL WHOLE BODY VIBRATION AND PARKINSON'S DISEASE IN A POPULATION-BASED CASE CONTROL STUDY

Synopsis

The finding that head injury events increase risk of Parkinson's disease suggests that physical hazards such as whole body vibration should be examined as potential risk factors. This study is the first to evaluate the relationship between whole body vibration exposure and Parkinson's disease. A population-based case control study was conducted in British Columbia, Canada with 403 cases and 405 controls recruited between 2001 and 2008. From detailed occupational histories and measurements of whole body vibration in the published literature, metrics of occupational whole body vibration exposure were constructed and tested for associations with Parkinson's disease using logistic regression analyses while adjusting for possible confounders. While an ever/never construction of occupational whole body vibration exposure was inversely associated with Parkinson's disease (adjusted OR [95%CI]: 0.73 [0.52-1.04]), the greatest values of the most intense equipment exposure were associated with increased odds of Parkinson's disease, particularly among those with some exposure 20 years or more prior to diagnosis (adjusted OR [95%CI]: 2.02 [1.00-4.36]). Possible mechanisms of an inverse relationship between low levels of whole body vibration exposure could include direct protective effects or correlation with other protective effects such as physical activity. The relationship between high intensity of whole body vibration and Parkinson's disease could result from vascular or inflammatory effects of vibration exposure.

Introduction

Parkinson's disease is a neurodegenerative disorder that involves loss of dopamine producing neurons resulting in tremors, rigidity and impaired mobility (187). The ultimate causes of this loss of neurons are not known (188). Twin studies do not suggest that genetics alone can explain Parkinson's disease occurrence, and instead indicate environmental exposures as targets for etiological research (41, 42, 174). Previous epidemiological research has focused extensively on potential chemical, rather than physical hazards (80, 85, 86, 169, 189). But there is good reason to explore the risks of physical hazards. Head injury is associated with increased risk of Parkinson's disease (94, 100), possibly attributable to its neuroinflammatory effects when incurred early in life (190). This relationship led to the hypothesis that exposure to whole body vibration could also be a risk factor for Parkinson's disease.

Whole body vibration exposure is repetitive physical displacement in any of three dimensions. The motion can be sinusoidal or regular (e.g. from engine vibration) and can also include intermittent shocks (e.g. from travelling over uneven surfaces). Exposure most often occurs in the operation of heavy equipment and vehicles (115, 127), when the body rests on a supporting surface that itself is vibrating (105). Nearly all residents of industrialized countries will incur some exposure to whole body vibration, but the variation in total exposure intensity and duration is most attributable to variation in occupational exposures (128), suggesting that such exposures would be most important to consider in epidemiological studies. Occupational exposure to whole body vibration is fairly common,

though more common in men than women (128). A case series evaluation by Iivananen in 1975 found a correlation between occupational vibration exposure and diffuse cerebral atrophy (140). However, to our knowledge, only one subsequent study examined a potential neurological risk relationship: a small case control study of Alzheimer's disease found no effect given a simple expert assessed dichotomous construction of whole body vibration exposure. The current study is the first to examine a relationship between Parkinson's disease and whole body vibration. We conducted a population based case control study of occupational exposures and used a combination of self-report and literature derived measurements of whole body vibration to construct quantitative exposure metrics (191).

Materials and methods

The study source population included the 2.1 million residents of greater Vancouver and the 400,000 residents of Vancouver Island (excluding the city of Victoria). The latter more rural island residents were included to increase variation in occupational exposures. Living persons between the ages of 40-69 with sufficient English language skills, health, and stamina to complete the interview were eligible. The upper age limit was applied to reduce challenges to self report, including cognitive impairment and length of recall. The study used a two-stage contact and consent procedure: the potential cases were identified by the methods described below and first contacted by the data custodians (the British Columbia Ministry of Health) to obtain their permission for their contact information to be released to our study team at the University of British Columbia. Those who agreed were then contacted by our

study team to screen for eligibility and then invited to participate in an in depth occupational history interview. This study was evaluated and approved by the University of British Columbia Behavioural Research Ethics Board. Interviews were conducted between 2001 and 2008.

Cases: users of antiparkinsonian medications

We used drug tracer methodology to detect PD cases. During the study period, the British Columbia government offered a PharmaCare program to reimburse annual drug costs over \$800. We identified cases from this list of reimbursements: anyone who claimed at least one prescription for the antiparkinsonian medications levodopa, bromocriptine mesulate, pergolide mesylate, levodopa/benserazide hydrochloride, levodopa/carbidopa, or seligiline hydrochloride between 1995 and 2002. Patients who also filled prescriptions for antipsychotic drugs (who might have had secondary parkinsonism due to those drugs) or were in assisted care facilities were excluded. The extraction process also included a random sample of other individuals in the database not meeting extraction criteria. This 20%"camouflage" sample was intended to disguise the disease status of list members to protect their privacy. Identified and consenting potential cases were contacted by our study team to determine eligibility. Those who reported taking the drugs for a purpose other than Parkinson's disease were excluded. Those who reported Parkinson's disease were included, and at the interview a detailed physical assessment checklist was administered. The checklist included items such as first symptoms noticed by the patient, their family history, the use of antiparkinsonian medications and when last dose was taken. The form also asked participants

about the presence of symptoms including resting tremor, stiffness, slowness of movements, lost of dexterity, changes in writing, loss of balance and reduced facial expressions. Interviewers were also asked to observe whether resting tremor and masked face were present, and trained by a neurologist (Joseph Tsui, also a study investigator) to administer simple tests for stiffness (a wrist flexibility test), and bradykinesia (a finger-tapping test). The last item was a writing sample. Completed forms were individually reviewed by Dr. Tsui to confirm Parkinson's disease status and to identify those presenting with atypical disease.

Controls: registrants of the provincial health insurer

Controls were identified from the list of those insured by the British Columbia Medical Services Plan. This public insurer covers approximately 97% of residents of the province. We applied the same age and geographic restrictions as the cases, and attempted frequency matching with the extracted potential case sample. Each control was randomly assigned a "diagnosis" date (constrained by age and sex stratum) to censor exposures for comparability to the cases.

Exposure assessment

A detailed description of the exposure assessment is available elsewhere (191). Briefly, interviews were conducted by trained interviewers. While interviewers were not blinded to disease status due to the evident symptoms of Parkinson's disease, interviewers were not informed of study hypotheses to minimize potential for bias. Only those participants with sufficient cognitive and physical stamina to complete the interview were included. Where physical difficulties impaired speech, a family member occasionally helped to interpret. Participants reported their complete job histories for all jobs held longer than six months and were prompted on potential sources of whole body vibration exposure by a list of equipment and vehicles. For each reported equipment exposure, participants were asked to report of potential operations (from a list provided) conducted during use of the equipment, as well as weeks per year and hours per week it was used. Occupational hygienists reviewed each participant's job history (while blinded to case or control status) to ensure all relevant exposures were reported, then restrictions were applied to ensure reported exposures were likely to be above background. We excluded reports of exposure to vehicles which were indirect only (e.g. "working near equipment but no direct contact"). We also restricted all reports to exposures longer than 30 minutes per week, 10 hours per week for cars, and 5 hours per week for vans and light trucks. To construct metrics of exposure we obtained measurements of vibration intensity for each equipment type from the peer-reviewed literature (see Chapter 3). We employed three metrics to capture different elements of lifetime equipment exposures: a duration metric (see Equation 1 in Table 5), a greatest intensity metric (see Equation 2 in Table 5), and a dose metric (combining intensity and duration). We employed the 4th power dose metric (Equation 4 in Table 5). The metrics were initially calculated to include all exposures up to the year of diagnosis, and were then recalculated to exclude any exposures occurring less than 10 and less than 20 years before diagnosis.

Statistical analyses

Unconditional logistic regression models were constructed to compare odds of Parkinson's disease in those deemed to be occupationally exposed to vibration to the odds in those not exposed above background, and to examine dose-response relationships using categorized metrics of exposure. Categories for each metric were based on the quartiles among the exposed, and we used the lowest non-zero exposure quartile as a reference group. We adjusted each analysis for age (year of birth in 10 year categories) and sex. We also adjusted for smoking (in pack years) because occupation can be related to smoking behaviour (58) and smoking is associated with an inverse risk of Parkinson's disease (52). Previous head injury (ever-never) was also included as a covariate, because it is associated Parkinson's disease (100) and could be related to employment in vibration exposed industries. Due to the insidious onset of Parkinson's disease, we were interested in the effect of only including exposures that occurred long before diagnosis. Therefore, we constructed additional regression models to test relationships when exposure and covariates were censored at 10 and 20 years prior to diagnosis. Lastly, we conducted parallel analyses where only those with occupational exposure were included. Analyses were performed using SAS 9.2 (©SAS Institute Inc., 2002–2008).

Results

We recruited and interviewed 808 participants: 403 cases and 405 controls. Figure 7 is a participation flowchart showing the fates and classification of all potential participants.

Eligibility is unknown for the potential participants who refused further contact or were uncontactable by the Ministry of Health or the UBC Study Team. Therefore it is difficult to estimate a single participation rate that is not unfairly penalized by the imperfect specificity of the drug tracer case ascertainment method and the camouflage sample. However, we could assume that the proportion of contacted subjects who were eligible was the same in the samples initially extracted by the Ministry of Health (554/1580=0.35 for cases, 603/726=0.83 for controls). From this proportion we can estimate the total number of eligible potential participants ($0.35 \times 2261=791$ for cases; $0.83 \times 1522=1264$ for controls) to use as denominators. Given these assumptions, the participation rate was 403/791 (51%) for cases and 405/1264 (32%) for controls.

The average age of cases at the time of interview was 65.0 years (SD 6.6 years) and for controls was 62.2 (SD 9.0 years). The average age at Parkinson's disease diagnosis among cases was 56.0 years. Table 10 shows the characteristics of the study sample for covariates such as age and sex. Although the initially extracted potential case and control samples were frequency matched on age and sex, Table 10 shows that the final sample was not frequency matched. Many of the potential cases we contacted were ineligible to participate because they used antiparkinsonian drugs for reasons other than Parkinson's disease (see Figure 7). This ineligibility was related to age and sex: the non-Parkinson's users of antiparkinsonian drugs were more likely to be younger and female, therefore adjustment for these variables was particularly important. We found that 36% of both cases and controls were deemed to be occupationally exposed to whole body vibration (Table 10). The distribution of cases and controls between categories of exposure magnitude for each metric are also shown in Table

10, while Table 11 shows descriptive statistics for the three metrics of vibration exposure, calculated in those deemed to be exposed above background.

The results of logistic regression analyses are shown in Table 12. Ever having occupational exposure to whole body vibration was not associated with Parkinson's disease in unadjusted analyses, but upon adjustment an inverse relationship was revealed (because exposure was more common in men, and there were more male cases than controls. The inverse relationship was marginally statistically significant when only those exposures experienced more than 20 years before diagnosis were considered (Table 12). When examining quantitative categories of exposure, a similar effect is observed: those with no occupational exposure had greater odds of Parkinson's disease than those in the lowest categories of exposure for all three metrics. However, only one of these observations was statistically significant: no history of occupational whole body vibration exposure was associated with an OR of 1.70 (95%CI: 1.03-2.81) when compared to the lowest nonzero category of the most intense equipment exposure.

While we observed increased odds for those with no occupational history of exposure, the greatest intensities of exposure were associated with increased odds of Parkinson's disease when compared to the lowest nonzero intensities of exposure (Table 12). While the unadjusted effect was statistically significant (OR=1.93, 95%CI: 1.04-3.58), the association was attenuated after adjustment for age, sex, smoking and previous head injury. However, the effect was greater when exposures occurring closer to diagnosis were excluded. When subanalyses were performed including only in those with some exposure, we found that the

effect was stronger and was marginally statistically significant for exposures incurred 20 years or more before diagnosis (OR=2.02, 95%CI=1.00-4.36).

None of the estimated associations for duration of occupational whole body vibration or cumulative whole body vibration dose were statistically significant (Table 12), although the point estimates followed similar patterns to those observed for most intense equipment in that no history of exposure was associated with increased odds compared to low duration and dose, while the greatest exposure duration and dose was associated with increased odds, particularly when exposure was censored at 20 years prior to diagnosis.

Discussion

Our results suggest a possible nonlinear relationship between occupational whole body vibration exposure and Parkinson's disease, in which those with low levels of whole body vibration exposure may be at reduced risk, while those with the highest intensities of exposure may be at increased risk. To put these preliminary findings in context, we must consider potential causal and non-causal explanations for our observations and take into account the limitations of our analyses.

The finding that a lack of occupational whole body vibration exposure was associated with Parkinson's disease compared to ever being exposed or compared to low but non-zero values of most intense equipment exposure has several possible explanations. Perhaps low intensity whole body vibration exposure could be protective against Parkinson's disease. It may be relevant that very low intensity and frequency whole body vibration exposure has been examined as a treatment for Parkinson's disease, with the hypothesized effect of improvements in proprioception and ease of movement (e.g. (136, 192)). However, a trial that included a placebo found no benefit (137). Furthermore, even a clear treatment benefit of vibration might not be associated with a protective effect if applied before disease is initiated.

A second possibility is that those who work in vibration exposed industries may share an exposure other than vibration itself that could be protective. One example could be physical activity. Physical activity has been hypothesized as a protective factor for Parkinson's disease because forced exercise in parkinsonian animal models was found to spare dopamine production (e.g. (193)). In epidemiological cohort studies, greater levels of physical activity long before diagnosis were associated with lower risk of Parkinson's disease (194, 195). Some vibration exposed work could be hypothesized to entail physical activity above the population background level (such as agricultural and construction work). However, the correlation is imperfect, because other vibration exposed work would be considered sedentary (drivers of buses or semi-trailer trucks). Furthermore, there is evidence that those who work in exposed industries may be less likely to participate in leisure (non work related) physical activity (196), so it is not clear that whole body vibration exposure would be a good proxy for total physical activity. Future studies could attempt to measure and adjust for physical activity to evaluate its potential as a confounder of the observed inverse association.

A third possible explanation of the inverse relationship between ever having occupational whole body vibration exposure and Parkinson's disease is that those susceptible to the effects of vibration may be more sensitive to and subsequently avoid exposure. This could entail a trend in which those most sensitive to whole body vibration exposure leave the exposed workforce earlier or do not enter the exposed work force. An analogous effect has been observed in respiratory epidemiology, where those most sensitive to exacerbating exposures modify their occupations to avoid exposure (197). The increasing strength of the protective association as exposures were restricted to those incurred long before diagnosis is consistent with this hypothesis in that those most sensitive to the exposure and its effects may have departed the exposed work force to avoid whole body vibration, weakening the inverse effect as exposures incurred closer to diagnosis are included. The possibility that those never exposed could represent a different susceptibility to Parkinson's disease was the reason we pursued analyses among the exposed only and set the lowest nonzero exposure group as the reference category, to ensure similar patterns would be observed.

In contrast to the inverse relationship between low levels of whole vibration exposure and Parkinson's disease, we found that the greatest values of the most intense equipment exposure were associated with approximately twice the odds of Parkinson's disease as the lowest (but non-zero) values. The effect was strongest when only those exposures incurred 20 years or more before diagnosis were included, and when only those with some history of exposure were included in analyses. This observation suggests that high intensities of whole body vibration exposure experienced earlier in life may increase Parkinson's disease risk. The opposing effects of background only exposure and very high intensities of exposure highlight the importance of examining dose response relationships and may be one reason that a previous study of Alzheimer's disease and whole body vibration using a dichotomous construction of exposure did not detect an effect (141).

If high intensities of whole body vibration could be causally related to Parkinson's disease, what is the mechanism of this effect? Previous studies of whole body vibration have found that the accelerative forces associated with whole body vibration are indeed transmitted to the head (198-200). Transmissibility is affected by the axis in which vibration occurs (198-200), body posture (198-200), and the presence of head rests (200) and back rests (201). The effect of this transmission on the brain itself is not as well-studied. However, increases in cerebral blood flow and oxygenation have been observed in men exposed to whole body vibration at frequencies comparable to vehicle exposures (202). Although this increased blood flow may not be a hazardous effect, it demonstrates that brain tissue does respond to whole body vibration exposure. Vascular impairment is a known risk of vibration exposure, particularly in the extremities (203). Curry et al. (135) found that high intensity vibration exposure damaged rat arterial cells after only 9 hours of exposure. Other animal studies suggest a possible immunoreactive response to vibration stress (204, 205), which may relate to an inflammatory response (206). Neuroinflammation, particularly when incurred early in life, has been suggested as an important factor in the development of Parkinson's disease (190). Liu et al. discussed neuroinflammation as a mechanism by which both infection and injury may increase risk of Parkinson's disease (190). The emphasis on early exposures is consistent with our observation of strengthened associations as exposures are restricted to those incurred long before diagnosis. Hachiya et al. wrote of their hypothesis that mechanical

stress may stimulate the production of protein aggregates which are associated with Parkinson's disease (103). Although this mechanical stress might be typically thought to be produced by head injury events, it is possible that the large and repetitive shocks associated with the highest intensities of vibration exposure could have effects comparable to single head injury events. Clearly, further study is required to attempt to replicate the association between occupational whole body vibration exposure and Parkinson's disease and to elucidate the mechanism of action. For example, it would be useful to study the acute effects of whole body vibration exposure of differing intensities on biomarkers of neuroinflammation (207).

Because this study indicates intensity of vibration as more relevant that duration of exposure, future studies attempting to replicate our findings will need to carefully construct metrics of exposure that distinguish those exposed to high intensities. Job titles or expert assessments that depend on job title and industry to make judgements about exposure may be particularly challenged. For example, those in the highest category of vibration intensity were exposed to equipment such as snowmobiles, high speed marine craft, tanks, and motorized dirt bikes (191) while working in a diverse array of jobs. Where exposure might be specific to job title or industry (e.g. tank use was military), job title or industry may not be exposed. Job title and industry (or expert assessment that relies on these) might not be able identify exposure to equipment items such as snowmobiles and marine craft, which were used during work in recreation, law enforcement, conservation, and even the arts (film). No single industry dominated among those exposed to high intensity equipment. While this highlights the

limitations of job title as an exposure variable, it also suggests that it is unlikely that another exposure shared by the diverse group of workers represented could straightforwardly confound and explain the findings presented here.

We found that the greatest values of most intense equipment exposure were associated with increased odds of Parkinson's disease. However, we did not detect a statistically significant effect of duration of exposure or vibration dose (which combines intensity and duration estimates in a cumulative metric), although both of these metrics showed a similar pattern in effect sizes to that observed for intensity. Our findings certainly point to intensity of whole body vibration as the best candidate for future etiological study. However, we should not yet conclude that duration is not relevant to the effects of whole body vibration on risk of Parkinson's disease. Our study restricted reports of exposures to jobs held longer than six months and to exposures of at least one half hour per week. Although these were important criteria for distinguishing occupational exposure above background, it also restricted the observable variation in duration of exposure (because very short durations of exposure were not considered).

The current study has a number of limitations. We included prevalent cases of Parkinson's disease, as is apparent from the difference between the average age at the time of interview (65.0 years) and the average age at diagnosis (56.0 years). Although it is preferable to include only incident cases, the term "incident" can be misleading due to the insidious onset of Parkinson's disease. Furthermore, Parkinson's disease patients survive long after diagnosis so survival bias is less likely (36). However, even the differential mortality experienced by

Parkinson's disease patients compared to the general population (37) would have to also be correlated with whole body exposures incurred long before diagnosis to influence the results we observed. We are also limited by possible confounding. Although we adjusted for possible confounders such as age, sex, smoking, and previous head injury, it is possible that whole body vibration exposure was correlated with other relevant exposures that we did not measure, which themselves could independently increase risk of Parkinson's disease such as noise or manganese in exhaust (169). However, we note that duration of whole body vibration exposure, which could be expected to better correspond to correlated exposures than intensity of exposure, was not significantly associated with Parkinson's disease.

This study was retrospective, meaning that direct measurements of whole body vibration exposure were not possible. Relying on self-report of equipment exposures may have introduced error into our exposure assessment, although we attempted to minimize this by the use of recognizable prompts (191). A test of the validity of self-reported whole body vibration exposure suggests that self reports are fairly accurate (182), but the periods of recall tested were much shorter than in the current study of complete occupational history. Although there are no studies of the reliability and accuracy of self reported whole body vibration exposure in Parkinson's disease study participants, a study of self reported environmental exposures and Parkinson's disease showed high reliability with no differences in reliability between cases and controls (208). The imperfections in the use of self report are likely to introduce non-differential misclassification of exposure rather than recall bias, partly because very few participants were aware of any suspected relationship between whole body vibration and Parkinson's disease. Our interview included an open ended question: "What do

you think causes Parkinson's disease?", and only one participant made reference to vibration in their response, whereas 154 participants reported "chemicals" as a suspected cause (88). To address the non-differential errors associated with retrospective and self-report based exposure assessment, a future cohort study could incorporate contemporary measurements of occupational whole body vibration exposure.

This study is the first to examine a relationship between occupational whole body vibration exposure and Parkinson's disease. Our results suggest that this relationship warrants further scrutiny in the continuing effort to explain the occurrence of Parkinson's disease and prevent future cases.
			Cases N (%)	Controls N (%)
	Sex	Men	266 (66.0)	204 (50.4)
		Women	137 (34.0)	201 (49.6)
	Year of Birth	1929 to 1938	245 (60.8)	175 (43.2)
Covariates		1939 to 1948	131 (34.0)	129 (31.9)
		1949 to 1958	27 (6.7)	101(25.0)
	Head injury	Ever	92 (22.8)	51 (12.6)
		Never	311 (77.2)	354 (87.4)
	Smoking (cumulative pack-years)	Mean (SD)	11.4 (20.4)	15.4 (22.4)
	Occupational whole	Ever	146 (36.2)	146 (36.0)
	body vibration	Never	257 (63.8)	259 (64.0)
	Most intense whole body	No occupational exposure	257 (63.8)	259 (64.0)
on exposure	vibrating equipment exposure $(m \cdot s^{-2})$	>0 to 0.68	46 (11.4)	52 (12.8)
		>0.68 to 0.88	36 (8.9)	50 (12.3)
		>0.88 to 1.19	18 (4.5)	17 (4.2)
		>1.19	46 (11.4)	27 (6.7)
	Total duration of whole	No occupational exposure	257 (63.8)	259 (64.0)
brati	body vibration exposure (work-years ^a)	>0 to 0.68	34 (8.4)	39 (9.6)
ly vil		>0.68 to 2.99	36 (8.9)	37 (9.1)
s bod		>2.99 to 10.99	38 (9.4)	35 (8.6)
/hole		>10.99	38 (9.4)	35 (8.6)
M	Whole body vibration	No occupational exposure	257 (63.8)	259 (64.0)
	dose (m ⁴ ·s ⁻⁸ ·work-years)	>0-0.16	35 (8.7)	38 (9.4)
	,	>0.16-0.91	39 (9.7)	34 (8.4)
		>0.91-4.16	27 (6.7)	46 (11.4)
		>4.16	45 (11.2)	28 (6.9)

Table 10. Sample characteristics of a case control study of Parkinson's disease (403 cases and 405 controls).

^aA work-year of exposure is 2000 working hours of exposure (as though exposure occurred for 8 hours for every day at work in a single year).

		Cases				Controls							
		N	Arithmetic Mean	Geometric Mean	Geometric SD	Min	Max	Ν	Arithmetic Mean	Geometric Mean	Geometric SD	Min	Max
	Total duration of whole body vibration exposure (work-years ^a)	146	8.05	2.69	5.66	0.032	51.3	146	7.0	2.5	5.4	0.012	45.8
Exposure metric	Most intense whole body vibrating equipment exposure (m·s ⁻²)	146	0.94	0.88	1.45	0.29	1.80	146	0.87	0.81	1.43	0.29	1.80
	Whole body vibration dose (m ⁴ ·s ⁻⁸ ·work- years)	146	6.44	0.98	9.29	0.003	125.0	146	3.4	0.7	8.3	0.003	43.7

Table 11. Descriptive statistics of occupational whole body vibration exposure among participants in a case control study of Parkinson's disease. Only the 292/808 participants with occupational exposure above background are described.

^aA work-year of exposure is 2000 working hours of exposure (as though exposure occurred for 8 hours for every day at work in a single year).

			All	Exposed Only					
Unadjusted			Adjusted ^a			Adjusted ^a			
ÓR			OR			OR			
		(95% CI)		(95% CI)		(95% CI)			
Exposure censored at:		Diagnosis	Diagnosis	10 years	20 years	Diagnosis	10 years	20 years	
				before	before		before	before	
				diagnosis	diagnosis		diagnosis	diagnosis	
Ν		808	808	808	808	292	269	225	
Occupational whole	Ever	1.01	0.73	0.74	0.70				
body vibration		(0.76-1.34)	(0.52 - 1.04)	(0.52-1.06)	(0.49-1.00)				
			p=0.07		p=0.05				
	Never	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)				
Most intense whole	No occupational	1.12	1.45	1.55	1.70				
body vibrating	exposure	(0.73-1.73)	(0.90-2.34)	(0.95-2.53)	(1.03-2.81)				
equipment exposure	_			p=0.08	p=0.04				
$(m \cdot s^{-2})$	>0 to 0.68	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	
	>0.68 to 0.88	0.81	0.81	1.04	1.17	0.79	1.05	1.22	
		(0.45-1.46)	(0.43-1.50)	(0.55-1.97)	(0.58-2.35)	(0.42-1.47)	(0.55-2.00)	(0.60-2.47)	
	>0.88 to 1.19	1.20	1.05	1.03	0.87	1.04	1.08	0.96	
		(0.55 - 2.59)	(0.47-2.36)	(0.45-2.35)	(0.36-2.13)	(0.46-2.33)	(0.48-2.45)	(0.39-2.33)	
	>1.19	1.93	1.68	1.74	1.90	1.66	1.86	2.02	
		(1.04-3.58)	(0.87 - 3.25)	(0.88-3.44)	(0.91-3.95)	(0.86-3.19)	(0.94-3.68)	(1.00-4.36)	
		p=0.04			p=0.08		p=0.07	p=0.05	

Table 12. Results of logistic regression analyses relating Parkinson's disease to occupational whole body vibration exposure among participants in a case control study. Odds ratios with p-values ≤ 0.05 are highlighted, while all p-values ≤ 0.10 are shown.

			All		Exposed Only			
		Unadjusted OR (95% CD)		Adjusted ^a OR (95% CD)			Adjustedª OR (95% CD)	
E	Exposure censored at:	Diagnosis	Diagnosis	10 years	20 years	Diagnosis	10 years	20 years
	1	0	8	before	before	0	before	before
				diagnosis	diagnosis		diagnosis	diagnosis
Total duration of	No occupational	1.14	1.42	1.34	1.53			
whole body vibration	exposure	(0.70-1.86)	(0.83-2.42)	(0.78-2.30)	(0.88-2.65)			
exposure (work- vears ^b)	>0 to 0.68	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
, , , , , , , , , , , , , , , , , , ,	>0.68 to 2.99	1.12	1.02	1.12	1.15	1.03	1.14	1.19
		(0.58-2.14)	(0.51-2.04)	(0.57 - 2.23)	(0.57-2.34)	(0.52-2.04)	(0.58-2.24)	(0.59-2.38)
	>2.99 to 10.99	1.25	1.15	0.90	0.89	1.10	0.91	0.99
		(0.65-2.39)	(0.58-2.31)	(0.46-1.79)	(0.53-1.83)	(0.55-2.20)	(0.46-1.81)	(0.47-2.07)
	>10.99	1.25	1.00	0.94	1.77	0.98	0.97	2.01
		(0.65-2.39)	(0.50-2.00)	(0.43-2.04)	(0.64-4.90)	(0.48-2.00)	(0.44-2.11)	(0.71-5.71)
Whole body	No occupational	1.08	1.27	1.29	1.61			
vibration dose	exposure	(0.66-1.76)	(0.74-2.18)	(0.74-2.23)	(0.95-2.74)			
(m ⁴ ·s ⁻⁸ ·work-years ^b)					p=0.08			
	>0 to 0.16	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
	>0.16 to 0.91	1.25	1.06	1.08	1.08	1.07	1.09	1.16
		(0.65-2.39)	(0.53 - 2.12)	(0.54-2.16)	(0.52-2.23)	(0.54-2.13)	(0.55-2.17)	(0.57 - 2.38)
	>0.91 to 4.16	0.64	0.51	0.67	1.07	0.50	0.68	1.17
		(0.33-1.23)	(0.25-1.02)	(0.33-1.36)	(0.50-2.27)	(0.25-1.02)	(0.33-1.37)	(0.54-2.52)
			p=0.06			p=0.06		
	>4.16	1.75	1.37	1.15	1.60	1.33	1.20	1.81
		(0.90 - 3.37)	(0.68 - 2.79)	(0.55 - 2.43)	(0.72 - 2.77)	(0.65 - 2.71)	(0.57 - 2.54)	(0.80 - 4.10)

^aMultivariate models adjusted for birth year, sex, smoking and previous head injury. ^bA work-year of exposure is 2000 working hours of exposure (as though exposure occurred for 8 hours for every day at work in a single year).



Figure 7. Participation flow chart showing the fates of 3,783 potential participants for a case control study of Parkinson's disease.

CHAPTER 5: REFLECTIONS AND FUTURE WORK

Overview

The intention of this chapter is to place the contributions of the thesis research in the context of current knowledge, to reflect on broader issues raised during this work, and to venture suggestions for future lines of inquiry. The "Scientific contributions" section briefly summarizes key findings of each chapter and how they relate to the current view of Parkinson's disease epidemiology and the health effects of whole body vibration. In the "Challenges and limitations: retrospective", I offer an analysis of two related issues that I took particular interest in during the course of this thesis research: data access impediments due to privacy protection policy and the interpretation and determinants of participation rates in case control studies. Lastly, in "Suggested future lines of research", I present several ideas for studies that could extend the contributions of each of the studies presented in the foregoing chapters.

Scientific contributions

Chapter 2 – Parkinson's disease case ascertainment

We found that a large and possibly increasing proportion of levodopa users do not have Parkinson's disease. Use of levodopa unrelated to Parkinson's was greatest among women and those under age 65. This finding means that studies relying on levodopa to trace (29) or define (169) Parkinson's disease cases could be less efficient or less accurate than records of physician diagnosis. This reduced efficiency likely affected our case control study, particularly the frequency matching of cases and controls on age and sex (because the potential cases who were excluded because they did not have Parkinson's disease were disproportionately younger and female). Furthermore, there may be long term population health implications of increased levodopa use for conditions other than Parkinson's disease (168).

Chapter 3 – Retrospective assessment of whole body vibration exposure

We developed a method for estimating occupational whole body vibration exposure from elements that can be assessed with self report. We found that occupational whole body vibration was relatively common, meaning that future studies should not have difficulty in locating sufficient numbers of exposed persons for the investigation of associations. Given the relative paucity of evidence on the long term health effects of occupational whole body vibration exposure, the method described in Chapter 3 could be applied to other case control and retrospective studies of chronic illnesses arising long after exposure.

Chapter 4 – Association of whole body vibration and Parkinson's disease

We found that a previous history of occupational whole body vibration exposure was less likely among Parkinson's disease cases than control participants, but that the greatest intensity of exposure was associated with increased odds of Parkinson's disease, particularly when exposures were limited to those incurred more than 20 years prior to diagnosis. This study was the first (to our knowledge) to test the association between Parkinson's disease and whole body vibration exposure and our results therefore open a new avenue for etiological research, and could also bring research attention to other potential physical hazards that have been understudied with respect to Parkinson's disease (e.g. noise, cold and heat stresses).

Challenges and limitations: retrospective

The centrepiece of this thesis is the case control analysis of the relationship between whole body vibration and Parkinson's disease. It was directly affected by restrictions on data release motivated by privacy protection. Chapter 2 presented an analysis of different case ascertainment methods using secondary data sources rather than data from the case-control study, so it was not directly affected by the same impediments. However, data access restrictions meant I could not expect to conceive, initiate and complete the study in the timeline of a doctoral dissertation if direct access to an independent data extraction (for example, administrative records of prescriptions and physician billing/hospital discharge) was required. Below, I discuss the impact of privacy restrictions and the related issue of participation rates as they related to the conduct of the research reported in the central chapters of this thesis and to population-based case control studies in general.

Data access and privacy restrictions

Probably the most significant difficulty my thesis research encountered was obstruction by rules, regulations and laws ostensibly designed to protect personal privacy. The case control study of Parkinson's disease that I would eventually join was first funded by the Medical Research Council (which later became the Canadian Institutes of Health Research) in 1999. The experienced investigators on this study had derived the case ascertainment and control sampling plan based on previous experience using population-based data held by governmental bodies (such as the voters' list, or registrants of the provincial universal health insurer). As described in Chapters 1 and 4, Parkinson's disease cases were to be detected by their claims to the provincial prescription reimbursement program (administered by the Ministry of Health), which subsidized drug purchases. The controls were to come from the list of registrants in the provincial health insurance program (essentially universal, also held by the Ministry of Health). However, in 2000, the provincial government of British Columbia began to implement restrictions on the release of information to researchers intending to contact potential participants. This policy was eventually formally legislated in the Freedom of Information and Protection of Privacy Act (FOIPPA). British Columbia was unusual in having legislation that explicitly forbade any release of data for the purposes of contact (209), although other provinces in Canada have implemented similar policies non-legislatively. Because our study was already underway and funded, the onus was on the study investigators to negotiate a compromise that would be both acceptable to the data custodians (Ministry of Health) and methodologically defensible. This compromise was revisited several times during the course of the study, but involved a process by which potential participants were contacted first by clerical staff at the Ministry of Health to request permission to release their contact information to our research team, before they could be contacted directly by the research team to request participation in the study. These clerical staff had to find time for this work in addition to their regular work schedule (e.g. through overtime work, or in parallel with day to day work). As described by Iversen et al. (210), this type of compromise

can pose challenges because clerical staff cannot be expected to have the same commitment to study recruitment as researchers. In addition, it may not be possible for data custodian employees to be sufficiently knowledgeable about the proposed research to address the types of questions potential participants may ask. Even though the first contact stage was intended to request release of contact information rather than study participation, it is understandable that potential participants would not fully distinguish between these two types of requests.

When I joined in 2005, the study was at a turning point. Forwarded contacts from the Ministry of Health had slowed dramatically, but a revitalized effort to improve the process and complete recruitment was beginning. New to epidemiology and public health research, I received a "crash course" in data access and trends to increasing restriction. In addition to hearing a number of stories from local population health researchers, the published literature presented several examples of privacy related research impediments in many places throughout the world. In Australia, O'Grady et al. described a study of vaccination that could not proceed despite having research ethics board approval because data custodians refused to release contact information that would allow the researchers to invite participation (211). Researchers in the United Kingdom reported being unable to proceed with a study of health outcomes among veterans (210), despite meeting all legal requirements for information release. In the United States, McCarthy et al. found that requiring study specific consent for inclusion in a medical records based pharmaco-epidemiological study of drug side effects resulted in a low participation rate (19%), while the rate was 93% when no studyspecific consent was required (212). They also found that the increased expense associated with extensive follow up calls and mailings did not substantially increase the participation

rate (212). In Canada, Tu et al. recorded similar findings in their study of implementing consent in a stroke registry, because consent was obtained from fewer than half of possible participants, despite added expenses estimated at \$500 000 (213). But perhaps most worrying was their finding that those who did not consent to inclusion in the registry were systematically different from those who did offer consent: the resulting registry sample was biased, and this bias was related to stroke severity (213). This type of bias is of serious concern to all researchers, including epidemiologists. For example, in our analysis of potential effects of privacy impediments on research validity, I conducted simulations to estimate the effect of biases (including response biases) on the results of case control studies and found that even small biases can substantially distort study findings (209).

It does not appear that the public has the same intensity of concern about health researchers accessing their information as do data custodians, who can exert extensive restrictions beyond formal regulations (214). In our survey of opinion regarding contact by health researchers, we found that 85% of respondents indicated they would be willing to participate in health research at least sometimes, and that methods of contact were not equal with regard to acceptability (215). Specifically, 10% were not comfortable with contact by a university, compared to 12% if by a hospital, 26% if by government and 55% if by a private research firm (215). Although "public opinion" is not a definitive construct and is certainly a moving target, our findings and those of others (216) suggest that the public is at least receptive to the idea of releasing identifiable information to health researchers for studies that require contact.

Our research team has discussed the importance of research data access in the academic literature (209, 215, 217) and in news articles for professionals (218) and the public (219, 220). The privacy commissioner of British Columbia had apparently long attempted to warn legislators that prohibiting contact for the purposes of research was too extreme (220). An effort led by a group of senior British Columbia health researchers representing diverse research interests was eventually successful in effecting legislative change. On May 29, 2008, the British Columbia Legislative Assembly passed Bill 24 which comprised an e-Health Act and amendments to the Freedom of Information and Protection of Privacy Act. Sections of both acts now permit release of information to researchers for the purposes of contacting potential study participants, if obligations such as ethics review are met. While the formal legislative obstruction has been removed, it is not yet clear when and how information will be released in practice, because what legislation permits and what data custodians choose to allow can be inconsistent (214).

Our case control study suffered delays and cost increases as a result of privacy related impediments. But these impediments may also have affected our study sample. I described the calculation of our overall participation rate in Chapter 4, but, because the original sample was not available to our research team (even with respect to variables such as age and sex), we cannot test assumptions about the non-participating sample or attempt to examine the possibility that those who participated in our study were systematically different from those who did not participate.

Participation rates

We had difficulty calculating definitive participation rates for our case control study because we did not know the proportion of the initially extracted sample that were eligible to participate. This is always true when a large proportion of the non-participating sample cannot be contacted, because the eligibility of non-respondents is not known. We do not know what proportion of potential participants refused to allow the Ministry of Health release of their contact information to our study team, but previous studies suggest that active refusers comprise only a small fraction of the non-participating sample and that most non-participants are those who were never contacted (210, 213). In Chapter 4, we made the assumption that the proportion of eligible participants was the same in those who were not contacted. Although there is no clear consensus on how participation rates should be calculated and presented in scientific articles (217, 221), the greater the discrepancy between the number of people sampled and those who actually participants can influence study results (209, 221).

To put our observed participation rate of approximately 51% among cases and 32% among controls in context, we should consider potential influences of the study design and possible underlying cultural trends. Firstly, our case control study required contact with participants to obtain job history data. Other case control studies have examined variables that can be obtained from anonymized registers meaning that participants do not have to be directly recruited at all, resulting in very high participation rates (102). Given that contact with participants was necessary, the most problematic aspect of the study design with respect to

our eventual participation rate was the two stage consent process described above. Iversen et al. showed that government agents acting as recruitment proxies obtained substantially lower participation rates than researchers, which they speculated could be explained by the different personal and professional priorities of researchers as opposed to government administrators with respect to health research (210). A second explanation of the reduced success of government proxies could be that potential participants are more receptive to contact by researchers than by government (215). Contact by someone known to the participants, such as their treating physician (21), may make some individuals feel more comfortable to participate in research (10), but this would demand near universal participation on the part of general practice and specialist physicians to be truly population based.

There also may be a time trend in the readiness of potential participants to comply when contacted by strangers. Semchuk et al. conducted a case control study of Parkinson's disease in Calgary (Canada) in late 1980s and reported a response rate of 88.4% for Parkinson's disease cases and 75.8% for controls (222). A more recent study in Washington state located cases through their group health insurer between 1992 and 2002 and reported that participation rates were 73% for cases and 66% for controls (80). It is notable that neither of these studies was subjected to the additional consent stage we were obliged to include. Because population based case control studies of Parkinson's disease are rare, it is difficult to attempt to establish a time trend in participation rates. There does seem to be a belief among epidemiologists that participation in epidemiologists in 1995 and found that most believed it

was more difficult then to obtain participation that it had been in the 1980s. In informal discussions with colleagues at home and at conferences where I have spoken about privacy impediments, many have advanced the hypothesis that an increase in the number of nuisance calls has exhausted the patience of potential research subjects meaning they are unlikely to respond to calls from researchers. Establishing whether there is indeed a trend to decreased participation rates in population based case control studies is an empirical question that could benefit from a meta-analysis.

Conducting a meta-analysis of participation rates reported in the peer-reviewed literature for population based case control studies of chronic disease would allow us to estimate the magnitude of a trend to decreased participation rates and generate hypotheses as to its underlying causes. However, a meta-analysis would face several challenges. First, and most importantly, there is a distinct lack of consistency in the methods of participation rate calculation and the reporting of these calculations (217, 221). In the absence of a reliably reported figure or the inclusion of raw participant count data, comparisons are difficult or impossible. A second challenge is that studies are not indexed by their design, so it will be difficult to generate search algorithms that can detect relevant studies. Finally, there is the difficulty of detecting the relevant date variables. We will be most interested in the dates during which recruitment occurred and publication dates do not correspond well with recruitment dates because studies often appear in the literature long after recruitment is completed (e.g. (73)).

The participation rate we observed in our case control study was certainly less than ideal, and may reflect both the impediments imposed by privacy restrictions and a decreasing patience with all forms of recruitment contact on the part of the general public. We have no particular reason to believe that our participation rate reflects a selection bias that would be differential between cases and controls and influence the results presented in Chapter 4, although we certainly cannot discount this possibility. Given that we could find no previous studies to have examined the relationship between Parkinson's disease and whole body vibration exposure, our results remain informative. The many sources of non-differential misclassification that likely impaired our ability to detect an association make it less likely that differential selection bias could explain the increased odds of Parkinson's disease we observed in those exposed to the greatest intensities of exposure long before Parkinson's diagnosis, while simultaneously explaining the inverse association with ever being exposed. However, the scientific process I followed is iterative and the knowledge gained must be considered as provisional. In order to continue and improve the work presented in Chapters 2, 3 and 4, several lines of future research are suggested below.

Suggested future lines of research

Parkinson's disease case ascertainment

The first and simplest follow up study to that presented in Chapter 2 would be to apply for an administrative data extract that would allow more direct testing of different case identification algorithms. For example, with detailed data for all physicians' billings with a Parkinson's disease diagnostic code (ICD-10: G20) over all available years (in British Columbia, since 1986), we could estimate the effect of restricting the Parkinson's case definition to neurologist billings only. A second effect to test would be the length of observation period in the case ascertainment algorithm, because physicians could record secondary reasons for treatment of prevalent cases as Parkinson's disease advances (e.g. bladder problems, or perhaps even impulse control disorders secondary to antiparkinsonian drug use). Because most population level case definitions of Parkinson's disease using administrative health data rely on records both of diagnosis and prescription of antiparkinsonian drugs (169, 170), we could apply to link physician billing and hospital discharge records to records of all filled prescriptions for any antiparkinsonian medication, and apply to have dosage information included so that we could estimate the potential for dosage and medication combinations to improve case ascertainment over records of drug use or diagnosis alone. Individual level data could include all diagnostic codes rather than requiring dichotomous case definitions as was the case for the secondary use reported in Chapter 2. If all diagnostic codes recorded for each antiparkinsonian drug recipient were extracted, a related study could examine the diagnostic codes recorded for non-Parkinson's users of antiparkinsonian medications to test hypotheses of why we found an increase in such users in Chapter 2. One challenge to this approach will be the lack of precision in billing codes to identify conditions such as restless legs syndrome (RLS). For example, currently we might expect treatment for RLS to be billed under G25.8: "Other specified extrapyramidal and movement disorders", which includes both RLS and "Stiff-man syndrome". However, a descriptive analysis of the diagnostic codes found among non-Parkinson's users of different

antiparkinsonian drugs would help to clarify hypotheses for future studies of dopaminergic prescription practices and pharmacoepidemiology.

As case ascertainment methods are refined by the analyses described above, these methods could be used to facilitate the establishment of a Parkinson's disease registry in Canada. In California, an effort to create a Parkinson's disease registry is currently in the pilot stages (223). This effort has involved legislation to mandate the reporting of Parkinson's disease cases detected by health care providers such as physicians and pharmacists. A similar approach was used in the creation of the Nebraska Parkinson's disease registry (31, 224). The population based records of physician treatment held by Canadian provincial health insurers could allow for automated recruitment into a Parkinson's disease registry, which would be highly cost efficient. Based on previous observations (160), we can reasonably hypothesize that it will be possible to establish a purely administrative based algorithm of sufficient sensitivity and specificity to allow an automated registry, and we could test this empirically. A pilot study could test the specificity of case definition algorithms refined in purely anonymized studies by conducting a contact-based study in which a subset of the identified cases are examined by a specialist to verify Parkinson's disease status. The immediacy of possible automation of case identification should also be tested, because newly diagnosed cases may not be well detected by this approach. However, given the insidious onset of Parkinson's disease (10), a delay of several months may not be of sufficient concern to offset the cost-efficiency and utility of an administrative data derived registry.

It is important to note that, whether this proposed Canadian registry employs direct clinician reporting or administrative data automation, it will not be practicable to request individual consent for inclusion in the registry (213) if data quality is to be preserved. Furthermore, if this registry is to facilitate research into the causes and treatment of Parkinson's disease, contact of registry members by researchers who have met reasonable requirements (such as research ethics approval and establishment of strict confidentiality protection protocols) must be allowed. A registry of Parkinson's disease cases would make epidemiological studies more efficient and cost-effective, which could encourage greater research interest.

Occupational whole body vibration exposure assessment

The primary goal of future work concerning occupational whole body vibration exposure assessment for epidemiological studies will be to reduce the non-differential misclassification inherent to the method described in Chapter 3. We might expect direct measurements of individual vibration exposures to be associated with less non-differential error. However, as discussed in Chapter 3, the requirement for a retrospective assessment makes contemporaneous measurements less relevant. Ideally, a validation study would conduct measurements on a representative sample of the entire population (not only the most highly exposed) and would have sufficiently long follow up to allow relevant comparison for the long period of recall we relied on for our exposure assessment. While such a study could be initiated, other approaches may be more practicable in the near term. One option is to examine study participants whose whole body vibration exposure measurements have previously been recorded. For example, researchers at the University of British Columbia

directly measured occupational whole body vibration exposures in approximately 50 heavy industry workers for a study of back injury risk factors between 2004 and 2006 (186, 225). A future study could attempt to follow up with these same workers several years after these measurements, administering the whole body vibration portion of the questionnaire used for our case control study. The method described in Chapter 3 could be applied to derive estimates of average daily vibration exposure dose (total dose divided by total number of working days) and then compared with the actual measurements and interview responses recorded by Trask et al. (225). Although the results of this comparison would be relevant to validity, a lack of correspondence could also result from the comparison of average exposures to single day measurements, because single day measurements may not be representative (144).

A second line of inquiry could involve more precisely characterizing determinants of whole body vibration exposure and testing retrospective assessment of these determinants. For example, the type and condition of surfaces over which vehicles travel is an important determinant of the whole body vibration exposure incurred (e.g.(114)). This variable would be of particular relevance to refining exposure estimates within single vehicle types that can be used on a number of different surfaces (e.g. pickup trucks used both on and off road). Other possibly relevant factors include the presence of head rests (200) and body weight at the time of exposure (124). Body weight is an example of a variable that could be incorporated in future retrospective assessments. Kovalchik studied recall and self report of body weight in US survey data and found that, despite a bias towards underreporting weight, the average inaccuracy even with long intervals between measurements and reports was

approximately 1.8 kg (226). A future study could examine the accuracy and precision of selfreports of the presence of head rests in vehicles and the road types or surfaces driven. Because retrospective assessments need not rely entirely on self report, a further line of inquiry could seek relevant determinants data in employment records. Modelling to identify determinants could use could use direct measurements of vibration transmission to the head (227), rather than seat accelerometer measurements (225), because acceleration transmitted to the head may be more relevant to the proposed mechanism of its effect on Parkinson's disease risk.

Vibration and the etiology of Parkinson's disease

As the ability to locate and recruit Parkinson's disease cases improves, and whole body vibration exposure assessment is refined, a number of lines of inquiry are suggested. Firstly, we must seek replication of our findings in case control and cohort studies of Parkinson's disease. A methodological strength of cohort studies is the ability to study the effects of exposures that were assessed before disease status is known, reducing or eliminating the potential for recall bias to influence exposure reports. Including assessments of occupational vibration exposure in a future or ongoing cohort study would also allow investigation of other long term health effects of whole body vibration exposure. However, this approach would require a large study cohort due to the rarity of Parkinson's disease and possibly decades of follow up, both to allow cases of Parkinson's disease to accrue, and because we noted that the most relevant vibration exposures occurred 20 years or more before diagnosis. Meanwhile, the method presented in Chapter 3 for retrospectively assessing whole body vibration exposure could be applied to case control studies. If new studies were methodologically similar to the one we report in Chapters 3 and 4, we could attempt a pooled analysis to increase statistical power to detect associations, particularly the increased odds of Parkinson's disease observed for those with the greatest intensity of exposure when including only exposures incurred 20 years or more before diagnosis.

An important research direction to inform future epidemiological analyses would be to attempt to characterize and test associations with other sources of vibration exposure in addition to occupational whole body vibration. Hand-arm vibration occurs in the use of certain tools and can also be transmitted to the head (227), although it is typically less efficiently transmitted than whole body vibration (105). A future analysis could test for associations between Parkinson's disease and the presence and duration of exposure to occupational hand-arm vibration. Because the frequency of vibration of hand-arm vibrating tools may be particularly important in determining transmission to the head (227), the effect of both the vibration frequency and acceleration of hand-vibrating tools could be estimated. Although the variance in non-occupational whole body vibration exposures is less than in occupational exposures (128), the ability to detect an association with Parkinson's disease could also be improved with rigorous estimates of non-occupational exposures.

Characterizing non-occupational exposures could also address the question of whether those sensitive to vibration deliberately avoid exposure in a way that could help explain our finding that ever experiencing occupational whole body vibration exposure was inversely associated with Parkinson's disease.

As discussed in Chapter 4, a promising strategy is the development of means of detecting intermediate responses that may relate to future disease risk. Inflammation and oxidative stress are implicated in the mechanism of Parkinson's disease (228). Use of anti-inflammatory medications has been associated with reduced risk of Parkinson's disease (61) although these results are inconclusive (229, 230). De Vera et al. found a lower risk of Parkinson's disease among gout patients than in control subjects without gout (170), which they hypothesized could be due to the antioxidant properties of uric acid. Chen et al. measured the association between biomarkers of inflammation in a small sample of 84 cases of Parkinson's disease and 165 controls (231). They found that high concentration of interleukin-6 was associated with Parkinson's disease and no significant associations with the other biomarkers examined (231). However, the follow up period of this study was relatively short (average interval between plasma sampling and disease diagnosis was 4.3 years). It is possible that, as larger studies are conducted and longer intervals between biomarker sampling and disease ascertainment are examined, that further biomarkers of Parkinson's disease risk will be identified. Of particular interest are biomarkers of neuroinflammation (207) and the potential for advances in neuroimaging to identify Parkinson's disease initiation much earlier than current methods allow (232). As techniques for identifying early markers of possible disease initiation improve, studies of occupational whole body vibration could experimentally test the effect of vibration exposure on these intermediate outcomes.

Pursuing the research directions suggested by the work of this thesis will advance the goal of preventing future cases of Parkinson's disease.

Key conclusions:

- The previous literature on Parkinson's disease and the paucity of literature on possible neurological effects of whole body vibration provide a rationale for hypothesizing a relationship, which can be tested with an epidemiological case control study.
- The use of antiparkinsonian drugs such as levodopa may not efficiently detect Parkinson's disease cases because they may be increasingly used for other purposes.
- Self report of vibrating equipment use and the peer-reviewed measurement literature on the intensity of vibration exhibited by equipment types can be combined to generate quantitative metrics of previous occupational exposure for epidemiological studies.
- Low intensities of occupational whole body vibration exposure appear to be inversely associated with Parkinson's disease, while high intensities may increase risk.
- Future studies of this relationship are required, and the quality and efficiency of these studies will be improved if impediments to study recruitment are reduced.

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APPENDIX 1 – RELEVANT ITEMS OF CASE CONTROL QUESTIONNAIRE

Job History

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Vibrating Equipment [See list 1 of the Interview Guide.] [Add sheet if necessary.]	What body part was exposed? 1 = hand/arm 2 = feet/legs 3 = head 4 = whole body	What operations were you performing when you used this equipment? [List 3 of the interview guide. Start with most frequent.]	Did you typically use this equip- ment every week?	If no, how many wks per yr did you typ- ically use this equip- ment?	You worked at this job hrs per wk. How many of those hrs were you using or exposed to this equipment?	In what month and year did this exposure start?	In what month and year did this exposure end?
 If "other": 		"Other":	1. Yes 2. No 9. DK 4. Rfs	(weeks)	 (hours)	(mm/yy)	Current [] (mm/yy)
 If "other": 		└────└───└──└──└──└──└──└──└──└──└──└──	1. Yes 2. No 9. DK 4. Rfs	(weeks)	_ . (hours)	(mm/yy)	Current [] (mm/yy)
_ If "other":		'' <i>"Other":</i>	1. Yes 2. No 9. DK 4. Rfs	_ (weeks)	_ . (hours)	(mm/yy)	Current [] [[(mm/yy)
 If "other":		"Other":	1. Yes 2. No 9. DK	_ (weeks)	_ . (hours)	(mm/yy)	Current
 If "other":		"Other":	1. Yes 2. No 9. DK	(weeks)	_ . (hours)	(mm/yy)	Current
 If "other":		"Other":	1. Yes 2. No 9. DK 4. Rfs	(weeks)	_ . (hours)	(mm/yy)	Current
 If "other":		"Other":	1. Yes 2. No 9. DK 4. Rfs	(weeks)	[] [] (hours)	(mm/yy)	Current

1A: Whole-Body Vibrating Equipment

Off-road and Earth-moving

Equipment

- Blast-hole drills
- Bulldozers
- Caterpillars
- Combines
- Continuous miners
- Draglines
- Drill rigs
- Excavators
- Forest machines
- Forklifts
- Graders
- Harvesters
- Loaders
- Mining and quarrying equipment, nec
- Open mine excavators
- Straddle carrier trucks
- Tanks
- Tractors

Road Vehicles

- Buses
- Cars
- Dump trucks
- Light trucks

Road Vehicles (con't)

- Motorcycles
- Semi-trailer trucks
- Vans
- Other Road Vehicles (Specify): ______

Vehicles, not listed elsewhere

- Helicopters
- High-speed marine craft
- Planes
- Railways
- Subways
- Trams
- Tug boats
- Snowmobiles
- Motorized dirt bikes
- Other Vehicles (Specify): ______

Whole-body Vibrating Equipment, not listed elsewhere

- Concrete levelling vibro-tables
- Concrete vibro-thickeners
- Cranes with end-span cab
- Cranes with mid-span cab
- Stamping sheet iron
- Weaving, reeling

LIST 3: Work Operations

To help us understand your exposure, please choose from the list below **up to 10 descriptions** that **best fit the operation**(s) you were performing **when you were exposed** to each piece of equipment from List 1 or each chemical from List 2.

- Annealing
- Assembling
- Blasting
- Blowing with
 compressed air
- Brazing
- Brushing
- Burning
- Carving
- Casting
- Cleaning
- Crushing
- Cutting
- Developing photographs, films, or x-rays
- Digging --
- Dipping
- Drilling
- Dripping
- Driving
- Dry-cleaning
- Dusting
- Electroplating
- Embalming
- Filling
- Finishing
- Fixing
- Foaming
- Fueling/Refueling
- Fumigating

- Fusing
- Gluing/Bonding
- Grinding
- Hammering
- Handling
- Handling packaged
 chemicals
- Heating
- Inspecting
- Installing
- Insulating
- Lubricating
- Machining
- Mixing
- Molding
- Moving closed containers
 - Moving packaged chemicals
 - Mowing
- Mowing
- Operating
- Packaging
- Painting, by brush or roller
- Painting, dip
- Painting, spray
- Picking
- Polishing
- Pouring
- Pumping
- Puttying
- Refueling/fueling

- RivettingRolling
- Konnig
 Samplin
- Sampling
- Sanding
- Sawing
- Screening
- Sculpting
- Sewing
- Slicing
- Smelting
- Soldering
- Spraying
- Staining
- Stirring
- Stripping
- Sweeping
- Thinning
- Transferring
- Using
- Vacuuming
- Washing
- Weighing
- Welding, MIG/TIG
- Welding, plasma arc
- Welding, standard arc
- Welding/burning/ cutting, oxyacetylene
- Wiping
- Working near chemical or vibrating equipment, but no direct contact