THE IMPACT OF OBSTRUCTIVE SLEEP APNEA ON OCCUPATIONAL INJURIES

by

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the dissertation entitled:

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Abstract

Background: Obstructive Sleep Apnea (OSA) is a common but under diagnosed respiratory disorder characterized by recurrent upper airway obstruction during sleep. OSA results in sleep fragmentation and hypoxemia and is associated with neurocognitive impairments.

OSA negatively affects vigilance and work performance, yet there is limited evidence on the relationship between OSA and the risk of occupational injuries (OI). It is hypothesized that individuals with OSA would have an increased risk of OI, and that OSA treatment may reduce this risk.

Dissertation Objectives:

1. Summarize the existing evidence on the relationship between OSA and OI (Chapter 1).
2. Evaluate the association between the presence and severity of OSA and the risk of OI, both before and after diagnosis (Chapters 2-4).
3. Evaluate the impact of Continuous Positive Airway Pressure (CPAP) treatment on the risk of OI (Chapter 5).

Methods: Patients referred to the UBC Sleep Disorders Clinic (SDC) for suspected OSA (2003-2011) were recruited to participate and diagnosed with OSA using polysomnography (PSG). Rates and risk of OI in the five years pre and post-PSG were calculated and compared by OSA status by linking to workers claims data. In addition, a matched sample of residents linked to claims data was drawn from the provincial health registry and compared to the OSA group. CPAP adherence data was collected from all OSA patients whose charts were available, and the impact of CPAP on the risk of OI was assessed using a pre/post treatment design.

Results: OSA was associated with an increased risk of OI for both retrospective and prospective follow-up periods; prospectively, OSA severity also increased OI risk. There was no difference between the rate of OI in patients with OSA compared to the matched comparison group. CPAP treatment was also not associated with a significant effect on the frequency of OI.

Conclusions: OSA is associated with an increased risk of OI among patients referred to the UBC SDC, but CPAP may not reduce this risk. Comparisons of OI rates among OSA patients with a general population sample did not indicate an increased risk, but this may have been hampered by methodological issues.

Lay Summary

Obstructive Sleep Apnea (OSA) is a common yet under diagnosed respiratory disorder characterized by upper airway obstruction during sleep. OSA results in daytime sleepiness and neurocognitive impairment and may increase the risk of occupational injuries (OI), a major problem worldwide resulting in almost a million injured workers daily.

Consenting patients referred to the UBC Sleep Disorders Clinic for suspected OSA were recruited to participate and diagnosed using polysomnography (PSG). OI were identified from workers' compensation claims data. We analyzed the rate of OI among patients with OSA compared to those without OSA in both a pre-PSG and post-PSG period. CPAP treatment data was collected from patient charts to determine adherence status.

The presence of OSA was associated with the occurrence of OI retrospectively. Prospectively, both the presence and severity of OSA were associated with the occurrence of OI. However, no relationship existed between CPAP adherence and the frequency of OI.

Preface

This dissertation comprises my research in the evaluation of the association between Obstructive Sleep Apnea (OSA) and the risk of Occupational Injury (OI) in a clinic-based cohort of patients presenting to the University of British Columbia (UBC) Sleep Disorders Clinic (SDC) for suspected OSA. I was responsible for the majority of data collection and cleaning, construction of the analytic database, data analyses, interpretation of results, and writing the manuscripts. Advice and support on data cleaning, the analytic approach, and the analysis was provided by Ms. Julie Park, Mr. Patrick Daniele, Dr. Najib Ayas, Dr. Mieke Koehoorn, and Dr. Nick Bansback. Ethics approval was provided by the Clinical Research Ethics Board of the University of British Columbia (certificate number H04-70366). All inferences, opinions, and conclusions drawn in this dissertation are those of the authors, and do not reflect the opinions or policies of the Data Steward(s). Data Extracts were provided by the British Columbia Ministry of Health and WorkSafeBC. Theses extracts are cited below in compliance with Population Data BC protocols.

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List of Abbreviations

AHI: Apnea Hypopnea Index

AOR: Adjusted Odds Ratio

BMI: Body Mass Index

CF-6: Wisconsin Brief Pain Questionnaire

CI: Confidence Interval

CPAP: Continuous Positive Airway Pressure

CVD: Cardiovascular Disease

EDS: Excessive Daytime Sleepiness

EEG: Electroencephalographic

EMG: Electromyographic

EOG: Electrooculographic

ECG: Electrocardiographic

ESS: Epworth Sleepiness Scale

EWPS: Endicott Work Productivity Scales

GEE: Generalized Estimating Equation

ICSD-2: international classification of sleep disorders

ILO: International Labour Organization

IQR: Interquartile Range

MSP: Medical Service Plan

MVC: Motor Vehicle Crash

N: Sample Size

OI: Occupational Injury/ Occupational Injuries

OR: Odds Ratio

ORP: Odds Ratio Product

ODI: Oxygen Desaturation Index

OSA: Obstructive Sleep Apnea

PSG: Polysomnography

RR: Relative Risk

UBC: University of British Columbia

UOR: Unadjusted Odds Ratio

SA02: Arterial oxygen saturation

SAS: Statistical Analysis System

SD: Standard Deviation

SDC: Sleep Disorders Clinic

SF-12: 12 Item Short Form Survey

SRE: Secure Research Environment

WHO: World Health Organization

WLQ: Work Limitations Questionnaire

-2Log (LR): Likelihood Ratio Test

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Dedication

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1 Introduction

1.1 Background

Obstructive sleep apnea (OSA) is the most common respiratory disorder. OSA is caused by the loss of upper airway dilating muscle activity during sleep that is superimposed on a narrow upper airway, resulting in recurrent nocturnal asphyxia[1]. These events result in both sleep fragmentation and hypoxemia that lead to poor quality sleep, excessive daytime sleepiness, reduced vigilance, injuries, neurocognitive dysfunction, decreased work productivity, and reduced quality of life[2]. Furthermore, patients with untreated OSA are at an increased risk of hypertension, stroke, heart failure and atrial fibrillation[3].

There are many predisposing risk factors for OSA including male gender, endocrine disorders, (e.g., hypothyroidism, acromegaly), use of muscle relaxants, smoking, fluid retention and increased age[4]. However, the strongest risk factor is obesity, particularly central obesity. Fat deposition narrows the upper airway and predisposes it to collapse. Furthermore, obesity reduces lung volume that also destabilize the upper airway by reducing the tethering effect of higher lung volume. The link between obesity and OSA are of particular concern given the increasing rates of obesity worldwide. The prevalence of OSA in obese adults (aged 30 to 69 years) ranges from 11 to 46% in women and 33 to 77% in men[3,5]. Weight gain is also a strong predictor of incident OSA[5,6].

The prevalence of OSA in the Western world is considered high and varies greatly depending on the diagnostic criteria that are used. OSA is diagnosed by sleep testing that usually consists of an attended, overnight sleep study, a polysomnogram (PSG) in a sleep laboratory or unattended, overnight, cardio-pulmonary monitoring in the patient's home. Disease severity is classified according to the apnea-hypopnea index, or AHI (the number of times the patient stops or decreases breathing per hour of sleep). By consensus, an AHI of <5 events/hour of sleep is considered normal, between 5-15 is considered mild, 15-30 is considered moderate, and $\geq$30 is considered severe disease[7].

In 1993, Young and colleagues reported a prevalence of 2% in middle-aged women and 4% in middle-aged men, where cases had both an apnea-hypopnea score of 5 or greater as well as daytime hypersomnolence[8,9]. Only two decades later, using models that predict OSA prevalence based on increases in obesity, Peppard and colleagues now estimate these percentages to be approximately 6% and 13% respectively for the same groups[5]. The National Commission on Sleep Disorders Research in the United States estimates that OSA affects 7 to 18 million Americans overall regardless of age group (~2-6% of the general population), among which 92% of females and 80% of males remain undiagnosed[10].

Continuous positive airway pressure (CPAP) therapy is considered first line treatment for moderate to severe OSA[11]. By establishing a positive transmural pressure in the pharynx during sleep, CPAP prevents the upper airway from collapsing. CPAP reduces severity of sleep fragmentation and improves nocturnal oxygenation, thereby improving daytime sleepiness, quality of life, and neurocognitive function[12]. One of the major impediments to CPAP effectiveness is adherence, which ranges from 50% to 75%[13]. It is well established that CPAP improves vigilance, and accumulating evidence suggest that CPAP improves a variety of other outcomes such as decreased rate of motor vehicle crashes (MVC) and cardiovascular events. Other therapies for OSA include dental appliances, weight loss, upper airway surgery, nasal valves, and upper airway electrical stimulation.

The broader societal and public health impacts of OSA are receiving increasing attention. For example, patients with OSA have a significantly increased risk of MVC[14-21], consume more healthcare resources, and have associated annual costs in the billions of dollars per year[22]. The associated costs include both direct and indirect health care-related costs[23]. Direct health care costs refer to those associated with OSA treatment and diagnosis itself in addition to the costs of medical conditions that arise as a result of OSA. The indirect health care costs derive mainly from loss of quality of life and premature death[24,25]. There is emerging evidence linking OSA to two important indirect health care costs:

work disability and work- related injuries. Below is a summary of the current state of knowledge in these two areas.

1.1.1 OSA and Work Disability

1.1.1.1 Absenteeism

Absenteeism commonly refers to the number of missed days or hours of work for employed people. However, the concept of absenteeism can be extended to cover work loss attributable to employment status changes, including the reduction in routine working time; job loss, which can lead to disability benefits; and early retirement. Observational studies, mainly from Scandinavia, have consistently shown that workers with OSA have increased work absences compared to controls[26,27]. These work absences and their accompanying financial burden are largely the result of comorbidities associated with OSA, including hypertension, vascular disease and depression. A recent study estimated that the total yearly cost of treating OSA in Australia was approximately (AUS)$657 million, (AUS)$409 million of which went to treating the aforementioned comorbidities[28]. Furthermore, a recent Danish study observed that when compared to age and gender matched controls, OSA patients have significantly higher unemployment rates, and those that are employed have a lower average annual income[24].

A recent Finnish study compared absenteeism between patients with OSA and controls, where absences were due to medically certified sicknesses (<9 days) or disability pension[25]. In this study, 957 patients with OSA taken from the national hospital discharge register (all admissions with a primary diagnosis of OSA) were compared to 4785 control subjects matched for age, gender, and illness. There was an increased risk of lost workdays in patients in the 5 years prior to their diagnosis compared to control subjects. Specifically, OSA was associated with a mean of 80.5 additional workdays lost in women and 30.0 workdays lost in men in the 5 years prior to diagnosis. The risk of lost workdays was

1.6 times greater in men (RR = 1.61, CI 1.24-2.09) and 1.8 times greater in women (RR= 1.80 95% CI = 1.43- 2.28) with OSA.

Similarly, Omachi and colleagues carried out a study in this field of research[28]. They investigated self-reported work disability, 4-week cumulative incidence of missed work days, work duty modifications, missed promotions, and changes in job duties, job schedule or job pay specifically attributed to sleep in 183 consecutive patients who were referred to their clinical center in California. Patients were tested for OSA using PSG and were grouped into one of four categories, based on the presence or absence of either OSA or excessive daytime sleepiness (EDS) or the presence or absence of both. They found that patients with both EDS (defined as an Epworth Sleepiness Scale (ESS) score > 10) and OSA (AHI > 5 events/ hr) had a markedly higher risk of both recent work disability (OR 13.7, CI 3.9-48) and long-term work duty modification (OR, 3.6; CI, 1.1 – 12) than patients with neither. When either OSA or EDS were absent, the relationship was much weaker. However, patients with OSA were still at greater odds than those without OSA in terms of recent work disability (OR 2.6; 95% CI 1.2-5.8). Overall, the research evidence supports an association between OSA and work disability outcomes.

1.1.1.2 OSA and Work Impairment

In addition to the evidence supporting an association between OSA and work absence, the presence of OSA also seems to contribute to decreased performance while at work; often referred to as presenteeism. This is not surprising given that OSA is associated with a myriad of adverse cognitive impairments including deficits in verbal functioning, problem solving, executive functions[29,30], and impaired memory, attention, vigilance and psychomotor skills[31,32]. Researchers from the United States recently demonstrated that the productivity losses associated with sleep disorders accounted for approximately two thirds of the total financial costs on society (all costs excluding those associated with lost disability adjusted life years)[33]. A recent review by Gugliemi and colleagues concluded that,

although more methodologically rigorous studies are needed, studies consistently found relationships between OSA and work limitations in patients (i.e., difficulties maintaining attention, learning new tasks, or performing monotonous tasks)[34].

Furthermore, EDS, a cardinal symptom of OSA, is strongly associated with work impairment in non-OSA populations[35]. The impairment in work productivity due to EDS is similar to that found with other chronic conditions such as diabetes, depression and arthritis[36,37]. For example, in a survey study, 1758 people with a self-reported physician diagnosis of OSA, depression, narcolepsy, multiple sclerosis, or shift work, were compared to a group of 1977 people without these conditions. The groups were assessed using the Work Productivity and Impairment Scale as well as several other surveys including the Cognitive Function Scale and the SF-36. The results indicated that EDS (considered present with any one of the following: a) ESS score > 10; b) self-reported physician diagnosis of hypersomnolence; or c) patients with self-reported problems of sleepiness who had a response of > 3 on a 5-point scale regarding symptom severity during the previous 4 weeks) in both groups was associated with highly significant impairments in health status, daily activities, and work productivity. In the first group, patients who had EDS reported lower mean scores on both the SF-12 (42.3 vs 45.5, $p<0.0001$) and the CF6 (68.8 vs 79.8, $p< 0.0001$) than patients without EDS. The same trend was seen in the second group where participants with EDS once again scored lower on both the SF-12 (47.7 vs 51.4, $p< 0.0001$) and on the CF6 (82.3 vs 89.5, $p< 0.0001$). Researchers concluded that EDS likely has a measurable negative impact on work productivity above that of the diseases studied[35].

Mulgrew and colleagues found a clear relationship between excessive sleepiness and decreased work productivity in a population referred for suspected sleep disordered breathing. They studied patients who underwent full PSG's and were then assessed using the Work Limitations Questionnaire (WLQ) and the ESS questionnaires[9]. Data was collected on 498 patients who had an average AHI of 21 events/hour. While there was no significant relationship between severity of OSA and overall work limitation, a

significant relationship was found among blue-collar workers with mild (AHI 5-15/hr) versus severe OSA (AHI>30/hr) in the domain of time management (limited 23.1% of the time versus 43.8 % of the time, p= 0.05) and mental/personnel interactions (17.9% versus 33.0%, p=0.05). There were also strong associations between subjective sleepiness and three of the four scales of work limitation.

Ulfberg and colleagues[38] studied a random sample of the general population (223 non-snorers and 62 snorers) and compared them to 351 patients (289 snorers, 62 patients with OSA) referred to a sleep disorders clinic for suspected OSA. Compared to control non-snoring subjects, patients with OSA (defined as patients with obstructive periodic breathing exceeding 45% of total sleep time in combination with an oxygen desaturation index (ODI) greater than 6) were significantly more likely to complain of difficulty doing their job because of tiredness/ sleepiness after adjusting for age and BMI (prevalence of 82% versus 8.1%, OR= 37). Furthermore, patients with OSA were significantly more likely to complain of large or very large difficulties in concentrating on new tasks (prevalence of 48 versus 0.9, OR- 7.5), learning new tasks (prevalence of 40% versus 2.7%, OR 9.1), and performing monotonous tasks (prevalence of 31% versus 5.8%, OR=20).

Nena and colleagues[39] also performed a study assessing work productivity in OSA patients. Work productivity was assessed using the Endicott Work Productivity Scales (EWPS), which was given to 115 polysomnographically confirmed OSA patients (AHI > 5/hr) of working age without comorbidities. Daytime sleepiness was measured using the ESS (where presence of EDS exists if ESS > 10). The mean EWPS scores were significantly higher in somnolent versus non-somnolent OSA patients (31.2 +- 16.2 versus 20.8 +- 11, respectively; p< 0.001).

Accattoli and colleagues investigated work performance amongst 331 OSA workers compared to 100 non–apneics and found that workers with OSA reported more impairment in work performance than non-apneics[40]. These impairments included difficulties with memory, vigilance, concentration, performing monotonous tasks, responsiveness and learning new tasks.

Several other studies have corroborated much of the evidence above showing OSA to be related to considerable problems at work, including difficulties staying awake[41], deficits in executive functioning, problem solving, verbal functioning[30], as well as issues with mood[10].

1.1.2 Occupational Injuries

OI are a major societal problem. In British Columbia alone, there were a total of 53,187 short-term disability, long-term disability, and fatal claims paid in 2012/13. The total cost of claims paid by the British Columbia workers compensation system in 2012/13 was $1,252,863,956[42]. In 2016, there were 5190 work-related fatalities in the United States, with a death rate of 3.6 per 100,000 workers per year[43]. Worldwide, OI are estimated to result in over 360,000 fatalities per year[44]. Additionally, more than 960,000 workers become injured daily because of OI[45]. The International Labour Organization (ILO) and the World Health Organization (WHO) have estimated that 5 to 7% of all fatalities in industrial countries are attributed to work-related illnesses and OI[46,47].

Injuries have traditionally been defined as physical damage to a person caused by an acute transfer of energy (mechanical, thermal, electrical, chemical or radiation energy) or by the sudden absence of heat or oxygen. In recent times, the definition has been broadened to include damage that results in psychological harm, maldevelopment, or deprivation[48]. There has been growing acknowledgement that an evidenced-based approach to the prevention and management of injuries should be adopted as it has been done in the case of other major global causes of disease[48].

Understanding injury mechanisms is an important part of this evidence-based approach and is of major interest in the investigation of the relationship between OI and OSA, as they help to guide researchers to look at those OI that may be related to sleepiness. Drawing upon the well-established body of literature on motor vehicle injuries, “an injury mechanism is a precise mechanistic description of the cause of a specific injury sustained in a particular crash”[49]. Dennis Shanahan goes on to describe

the importance of injury mechanisms in the book entitled Injury Research, where he explains that "Determining injury mechanisms in a series of crashes allow epidemiological researchers, vehicle manufacturers, and governmental agencies to quantify the prevalence of injuries and associated injury mechanisms for various crashes as well as provide objective data upon which to base mitigation priorities and strategies"[49]. Understanding injury mechanisms in the case of OI would be similarly valuable.

Despite increasing knowledge of the relationship between OI and injury risk, it has remained difficult to predict and thus prevent the occurrence of OI, in part because of the rarity of its incidence when studied within defined sample population. In order for an OI to occur, it is generally necessary that a combination of factors line up temporally. These factors include a period of inattentiveness, high cognitive demands and a significant impact of error (significant energy transfer)[50].

OSA can significantly impact several of these factors. The cognitive deficits associated with OSA, specifically affecting behavioral alertness and attentiveness, will make an injury more likely to occur[51]. There is also evidence that the effect of sleep loss and sleep restriction is greatest on highly nuanced skills like when dealing with "stressful, rapidly evolving, complex situations", as is often the case when injuries occur[51].

The suspected mechanism by which OSA decreases cognitive performance is through a combination of sleep fragmentation and hypoxemia. Evidence suggests attention and memory errors are likely related to sleep fragmentation, while executive function deficits are more likely related to hypoxemia[52].

Indeed, the neurocognitive impairments discussed above have been shown to lead to errors while driving and result in an increased risk of MVC, including a high rate of collisions in patients who drive as a part of their occupations[53]. Howard and colleagues found that in a large sample (n=2,342) of commercial vehicle drivers, drivers with OSA (diagnosed based on symptoms) had an increased rate of

self-reported MVC compared to controls (OR = 1.30). It is hypothesized based on the preceding evidence, that workers with OSA would have an increased risk of other occupational injuries[Error! Bookmark not defined.]

The vast majority of studies investigating the relationship between OSA and OI have shown a significant relationship[40,54-56]. However, many of these studies were suboptimal, using subjective criteria to diagnose OSA, OI, or both. Nevertheless, the consistency of the findings across studies indicates the likelihood of a relationship. Furthermore, in the context of consistent evidence of the relationship between MVC and OSA[55], a recent meta-analysis by Tregear and colleagues found a significant relationship between commercial vehicle incidents (a form of OI) and OSA[57]. They found the odds ratio of the association of MVC with OSA to range between 1.21 and 4.89.

Recent research by Garbarino and colleagues[58], who published a meta-analysis on the relationship between OI and OSA, found OSA patients had a 2-fold (OR: 2.18; 95% CI = 1.53-3.10) increase in the odds of OI. The authors of the meta-analysis indicated that injuries were often self-reported and studies were retrospective in nature with observation periods that were often long, therefore, leading to a potential recall bias. Studies that included only commercial vehicle drivers resulted in relationships with higher ORs than those including all forms of OI. Furthermore, studies with more rigorous methodologies had lower OR magnitudes than those with less rigorous methodologies.

Another meta-analysis performed by Uehli and colleagues[55] investigated the relationship between general sleep problems (defined as all sleep disorders described in the international classification of sleep disorders (ICSD-2)) and work injuries. They found that individuals with sleep problems had a 1.62 times higher relative risk of being injured at work compared to individuals without sleep problems. Focusing specifically on OSA, Table 1 summarizes some of the recent literature concerning the impact of OSA on OI; all five studies found significant associations between either diagnosed OSA or symptoms of OSA and OI.

Table 1 OSA and Work-Related Injuries
(Table published in Chest. 2015 May;147(5):1422-1428. doi: 10.1378/chest.14-1949. Review.)

Reference	Type of Study	Sample Studied	Main Result
Ulfberg et al.[56]	10-year retrospective comparison	Consecutive patients with sleep disordered breathing (n=704) vs. subjects drawn from a general population (n=540) Sleep disordered breathing diagnosed using nocturnal recording and oximetry	Risk of occupational injury was 2-fold higher in male heavy snorers and OSA patients and 3-fold higher in female heavy snorers and OSA patients compared to the general population
Lindberg et al.[54]	10-year follow-up	Working age men (30-64) who completed a mailed questionnaire (n=2,874)	Risk of occupational injury was increased in patients who reported EDS and snoring (AOR of 2.2; 95% CI = 1.3-3.8). Workers who had both EDS and snoring at baseline averaged 0.6 accidents per year compared to less than 0.1 in those workers who neither snored nor reported EDS at baseline
Accattoli et al.[40]	Retrospective comparison	Workers with OSA (n=331; 144 blue-collar and 187 white-collar) and referents without OSA (n=100; 50 blue-collar and 50 white-collar	Risk of occupational injury was greater in workers with OSA (27.2% vs. 20%) (p=0.013)
Spengler et al.[59]	Cross-sectional survey	Kentucky Farmers (n=1004), 6.7% of who reported symptoms of OSA	Risk of occupational injury was greater in farmers with OSA than farmers without OSA (19.4% vs. 10%) even after controlling for potential confounders (OR = 2.48, 95% CI = 1.13-5.41)
Heaton et al[60]	1-year retrospective cohort	Farmers from Kentucky and South Carolina (n=756)	Risk of occupational injury was greater in farmers who reported problems staying awake and breathing cessation while asleep (OR = 1.86, 95% CI = 1.04-3.35)

Legend: OSA= Obstructive Sleep Apnea, n = Sample Size, AOR = Adjusted Odds Ratio, EDS= Excessive Daytime Sleepiness, CI = Confidence Interval

Multiple studies reported rates of OI that were between 2 and 3 times higher in OSA patients than in controls[54,56,59]. The study by Ulfberg and colleagues[56] in Table 1, a 10-year retrospective study in Sweden, was particularly important because all patients were tested for OSA using simultaneous nocturnal recording and oximetry during a minimum of four hours of sleep. OSA was defined as patients with obstructive periodic breathing exceeding 45% of total sleep time in combination with an oxygen desaturation index (ODI) greater than 6. Injury rates for 704 patients suffering from sleep-disordered breathing were compared with the rates for an employed, age-matched random sample of

580 subjects drawn from the general population. The risk of being involved in an OI was about 2-fold greater among male heavy snorers and 50% greater among males suffering from OSA compared to the general population referents. For females, the risk was increased by at least 3-fold in heavy snorers and OSA patients compared to referents. Ulfberg and colleagues proposed reduced vigilance and attention due to sleep-disordered breathing as mechanisms for increased risks of occupational injuries.

Accattoli and colleagues[Error! Bookmark not defined.,40] demonstrated similar results in another retrospective study in 2008, investigating 100 referents workers without OSA (50 blue-collar and 50 white-collar) and 331 workers with self-reported OSA (144 blue-collar and 187 white-collar). Workers affected by OSA were involved in OI more often than those without OSA (27.2% vs. 20%). The average number of injuries per year in blue-collar workers with OSA was slightly higher than in the controls. In the white-collar workers the rate of OI was significantly higher ($p=0.013$) in OSA participants than in referents.

In a population-based study, Lindberg et al[54] studied 2874 men aged 30-64 years who answered questions on snoring and daytime sleepiness. Ten years later, respondents answered a follow-up questionnaire that included work related questions. Men who reported snoring and EDS at baseline were at increased odds of OI (AOR of 2.2; 95% CI = 1.3-3.8). In this study, OSA was not assessed directly.

Finally, Spengler and colleagues[59] and Heaton and colleagues[60] both studied the relationship between OI and OSA in groups of farmers in the southern United States. Both studies relied on self-reported survey data for both the presence of OSA symptoms and OI and both found increased rates of OI in farmers suffering from symptoms of OSA.

1.1.3 The Impact of CPAP Treatment on Work Productivity and Occupational Injuries

Given the body of evidence on the relationship between OSA and work performance/injuries, researchers have investigated the impact of OSA treatments on work-related outcomes. CPAP therapy is the main treatment for OSA and is known to significantly improve both objective and subjective sleepiness. Consistent with these results, the use of CPAP seems to improve work performance in patients with OSA.

Ulfberg and colleagues[61] evaluated 152 patients with substantial OSA (AHI > 20) who answered four questions concerning self-perceived work performance before and after CPAP use. After CPAP, patients were significantly less likely to report difficulty concentrating on new tasks, learning new tasks, and performing monotonous tasks ($p< 0.01$). Ulfberg and colleagues concluded, "given that OSA patients are motivated in using CPAP, the results indicate that CPAP treatment may be effective in improving subjective work performance."

Similar results were obtained from Mulgrew and colleagues[9], who looked at 33 OSA patients (AHI > 5) who were using CPAP. In this study, there were significant improvements in time management (limited 26% of the time vs. 9%; $p < 0{,}001$), mental interpersonal relationships (16% vs. 11%, $p< 0.009$) and work output dimensions of WLQ after CPAP-treated.

Scharf and colleagues[62] also investigated 316 patients in Ohio, where they saw CPAP use increase subjective work productivity (as measured on a 10-point scale) from 6.8 to 8.4 ($p< 0.001$).

While there exists a plausible hypothesis that CPAP could lead to reductions in OI, we did not find any publications to support this.

1.1.4 Conceptual Frameworks for Understanding the Causes of Injury

The studies conducted for this dissertation are a part of an evidence-based approach in the field of injury research, and aim to improve the understanding of the causes of injuries and help in the prevention and management of these injuries.

The epidemiologic triad is a conceptual model containing three factors: the host, the vector, and the environment[63]. This model formed the basis for understanding injury causation throughout this dissertation, and helped to place its research and results within the broader context of injury research as a whole. Originally, the use of the epidemiologic triad was only applied to the understanding of the pathological pathway of disease. The agent factor – which is carried by the vector – was originally thought of as the etiologic element that was necessary for the initiation of the pathological process of a disease[63]. In the late 1940's researchers first started to apply the triad to the understanding of injury mechanisms[64]. When the model was applied to injury research, the agent factor was most likely to be a physical agent such as mechanical force or heat as opposed to a biological or chemical agent.

The host in the triad refers to the organism (in our research the patient or subject) who is susceptible to the agent. There are intrinsic factors that influence an individual's exposure, susceptibility, or response to a causative agent. These factors include lifestyle, behaviours, and psychological characteristics. Age, BMI, gender, and alcohol use are all factors that influence a patient or subjects' susceptibility to injury as well as to the presence or severity of the disease (OSA in our research)[63].

The environmental factor encompasses all the extrinsic variables that may influence the occurrence of disease in a population, including the physical environment (climate, terrain), the biological environment (population density, fauna and flora), and the socio-economic environment (SES, policy, law, culture access to car, etc.)[63,64].

Both the host factor and the environment have always been thought to be amenable to change. When considering changing or intervening on the host factor, possibilities include behavioral change such as alcohol or drug use, psycho-social change such as occupation or education, or biological change such as age, gender, or genotype. While often a focal point of intervention, evidence suggests that intervention on the host is far less effective than intervention on the environment[63]. Targeting the socio-economic environment involves changing laws, regulations, and policy, as well as access to healthcare, and has proven to be one of the most effective targets of intervention[63,64].

The epidemiologic triad is at the core of the combination of two conceptual frameworks that formed the basis for understanding the mechanisms of injuries in this dissertation: Haddon's matrix and the Public Health Approach (PHA)[65-68].

Haddon's matrix consists of two axes. The first includes the elements of the epidemiological triad. He explains that in an injury such as a fall, the host and the vector are in fact one in the same. Conceptually this is the case for the majority of injuries studied in this dissertation[67].

Haddon further explained that in an injury, energy is the pathogen carried by the vector (in our studies the patient or subject). Energy can be positive or negative (i.e. a burn vs. frost bite), and both the physical and socio-cultural environment should be included in the injury model[65,66].

On the second axis, Haddon included three-time intervals: a) the pre-event, b) the event (i.e. the moment of energy transfer, and c) the post-event, which is the interval after energy transfer. The importance of this axis is that it conceptualizes an event as predictable within time, and, as such, amenable to study within populations, and to prevention[65,66]. Haddon's framework is particularly useful in that it is able to identify a systematic point of action, be it the vector, the host, or the environment. However, the framework lacks a systematic plan of action[65,66].

A second framework that contributed to the understanding of injury and injury mechanisms in this dissertation is supported by the Center for Disease Control in Atlanta and is called the Public Heath

Approach (PHA)[68]. The PHA contains a hierarchy of four levels which are scientifically intuitive. These four levels are surveillance, risk factor identification, intervention evaluation, and program intervention. This approach emphasizes that injury prevention should be addressed using scientific methodology, and injury control programs should be implemented on high priority injuries. The PHA also suggests that programs should be implemented only after the evaluation of interventions, and based on data and risk analysis which is part of evidence-based practice[67,68].

Unlike Haddon's matrix, the PHA lacks a systematic point of application, but does contain a systematic action plan. Given the strengths and limitations of each of the frameworks, both were used to guide our research and place our studies in context with respect to previous research in the field. When our individual studies are understood within the larger context represented by the two frameworks, taken together, we hope to achieve greater clarity as to: a) the potential limitations of individual studies; b) the ability of our studies to fill a recognized gap in the current literature. In this way we hope to minimize erroneous conclusions[67].

When investigating OI, it is crucial to understand the importance of the work environment and how it can play a significant role in the risk of injury. The work environment is made up of a combination of the social environment and the physical environment. Characteristics of the social and physical environment interact and can mutually reinforce outcomes leading to either increases or decreases in injuries. A factory work environment with dangerous equipment and limited safety training is an example of the physical and social environments interacting leading to the potential for an increased injury risk.

Additionally, the causes of a workplace injury can either be attributed to the individual or to the workplace system and environment. Our studies are interested in those injuries that are attributed to the individual, specifically those injuries that are related to OSA in the individual. However, given the interaction of the physical and social environments, certain work settings may alter the relationships

between individual factors and the risk of OI. As a result, it is important to ensure that in any investigation of the impact of OSA on the risk of OI, the work environment as a whole, both the physical and social environments, must be as similar as possible when comparing those with OSA to those without OSA.

1.1.5 Summary of Background Information

OSA is associated with increased absenteeism, OI, and decreased work performance. This evidence is well summarized by Teng and colleagues[16], who state, "The consequences of OSA pose a danger to public safety not only for workers but for those whom they serve".

While increasing research has strengthened the knowledge base in the aforementioned areas, several limitations of this research should be noted. In terms of evidence on work disability, many of the studies have been performed in Scandinavian countries where social security and other mechanisms may influence rates of absenteeism and limit the generalizability of the results of these studies to different contexts. Also, few studies have used validated questionnaires that measure the full spectrum of work disability outcomes, including costing their impact[69]. In terms of evidence on OI, many of the studies relied on subjective symptoms (e.g.: snoring and sleepiness) rather than objective criteria. Subjective assessments of sleepiness are not always reliable. In certain cases, under-reporting of symptoms among patients may be driven by economic gain, for example, among commercial motor vehicle operators[70].

While there appears to be promise for CPAP therapy in efforts to reduce work disability and OI[71], the lack of randomized control trials and large prospective epidemiological studies in this area leave a substantial gap in the literature. Given the degree to which OSA is underdiagnosed, the occupational health and economic productivity gains to be made if a population was more actively screened and treated for OSA could potentially be substantial.

1.2 Research Goals

The overall goal of this PhD research was to investigate the association between OSA characteristics and the risk of OI, and to investigate the potential impact of treatment on reducing injury risk.

OI were chosen over other work-related measures as the main outcome for this dissertation for a number of reasons. First, robust objective outcome data was available on OI in BC and could easily be linked to the recruited study sample. Objective data is more difficult to obtain on other work-related outcome measures, like work impairment, where the outcome is less discrete and measures of the outcome are often subjective.

Second, few robust studies to date have focused on the relationship between OSA and OI and as such, significant gaps remained in the literature, allowing for novel research in this area.

Last, as was demonstrated in the background section above, it is important to study OI both because of the cost to society related to the health of individuals and the financial burden that OI place on the healthcare system more generally. Research that can provide an evidence base for intervention can potentially save both lives and significant health care costs.

1.2.1 Gaps in the literature

The studies outlined in this dissertation were developed to help fill one or more gaps identified in the literature. Four main gaps were identified.

First, there was a lack of research focusing on the relationship between OSA severity and OI. While there was a dearth of studies on the relationship between OSA and OI in general, studies investigating OSA severity and the identification of high-risk groups were almost completely absent from the literature. The identification of a high-risk group is particularly important from a public health industry perspective, as it enables policy planners and health systems operators to design specific interventions and to allocate resources to the group or groups most in need of intervention.

Second, studies that investigated OI and OSA often lacked adequate sample sizes to achieve statistical power for investigating the relationship. Sanna and colleagues write, although studies investigating the relationship between OSA and OI showed significant results, these results "should be confirmed in larger series of subjects undergoing polysomnography"[21]. Additionally, the relative rarity of OI compared to conditions like OSA, means that large sample sizes are needed in order to adequately power a study investigating this relationship. Similarly, large sample sizes are needed in order to allow for the appropriate controlling of many potential confounding variables including, BMI, gender, industry, age, ethnicity, smoking status etc.

Third, few previous studies used objective measures to identify either the presence or severity of OSA in patients or the presence of OI in patients. The need for PSGs or comparable sleep measurement tools in order to accurately diagnose the presence and severity of OSA, mean that costs both in terms of time and resources needed to complete a large-scale investigation of OSA and OI are significant. Gugliemi and colleagues performed a systematic review on the relationship between OSA and OI and concluded that studies were needed that were "more methodologically rigorous"[34]. Many previous studies used either subjective measures of OI, including self-reported snoring or cessation of breathing or inadequate measurement techniques, that include simple oximetry or a combination of oximetry and demographic variables. Previous literature exploring this relationship also included studies using self-reported OI data rather than objective OI data obtained from a centralized data repository such as WorkSafeBC, the provincial workers' compensation system in the province of British Columbia. Objective measures of both OSA and OI are important in convincing policy makers that studies were done with academic rigor and that study results are sufficiently reliable and valid to act upon.

Finally, there was a lack of literature surrounding the impact of CPAP treatment in patients with OSA on the risk of OI. In our narrative review published in the journal CHEST, we concluded that "to our knowledge there has yet to be a study that has investigated the impact of CPAP on occupational

injuries"[73]. Mulgrew and colleagues also write "There are few studies that have investigated potential improvements in work-related outcomes after treatment of OSA"[9]. Furthermore, a randomized controlled study on the impact of CPAP treatment on OI in patients with OSA "would be ideal to objectively assess the effectiveness of CPAP treatment"[9].

Studies investigating the impact of CPAP on this relationship are important because they help health professionals and policy makers to understand whether or not any increased risk in OI found in patients with OSA can be mitigated with treatment. Furthermore, the use of CPAP therapy has been shown to improve work performance[9,70,71]. Given the degree to which OSA is underdiagnosed, the potential occupational health and economic productivity gains to be made if a population was more actively screened and treated for OSA could be substantial.

The four studies conducted for the purposes of completing this dissertation were designed to address the four gaps described above. First, the studies included used PSG to objectively identify OSA and its severity in patients. Second, the studies used workers' compensation claims from WorkSafeBC in order to objectively identify OI in patients. Third, the studies used both large sample sizes and in the case of Study 2, a large matched comparison group. This enabled researchers to control for important variables and also provided adequate power to enable the breakdown of results into AHI severity groups and the identification of a high-risk group. The final study used before and after CPAP treatment adherence data to explore the impact of CPAP therapy on the risk of OI.

1.3 Summary of Projects

1.3.1 Hypotheses

Three hypotheses below formed the basis for four research studies that were conducted for this dissertation. These hypotheses were based both on a combination of the background information

above, and the importance of addressing evidence needs and methodological issues pertaining to OSA and OI, as follows:

1. Patients with OSA will have an increased risk of OI when compared to individuals without OSA, both within a clinic-based cohort with sleep related problems and when compared to a matched group from the general worker population;
    a- Patients with OSA will have an increased risk of OI prior to presenting to the sleep clinic
    b- Patients with OSA will have an increased risk of OI after presenting to the sleep clinic
2. The odds of OI will increase with increased OSA severity; and
3. CPAP treatment will reduce the rate of OI in patients with OSA.

1.3.2 Overview of projects

The studies conducted for the purposes of completion of this dissertation relied on the creation of a database that was made up of extensive surveys collected from patients at the UBC SDC (Appendix A) and Clinical Data collected from the patients PSGs and Charts. The surveys that were collected included demographic information, information on the potential health related consequences of sleep disorders, and information on potential confounders of the relationship between OSA and OI. The PSG reports that were collected on all patients, included data on sleep fragmentation, desaturation and OSA severity (AHI). The data collected from the questionnaires and the PSGs were linked with the WorkSafeBC database with through Population Data BC. Following the linkages, the resulting larger database formed the basis for the analysis performed in all four studies. Finally, the sleep clinic charts of all patients that were recruited during the study period were retrieved and information was collected on their treatment and updated health status.

The first study conducted was a retrospective cohort study, investigating the association between OSA severity and the incidence of OI in patients visiting the UBC SDC (a clinic-based cohort) after

controlling for relevant confounders. The second study was a retrospective matched case-comparison study designed to investigate whether patients with diagnosed OSA are at an increased risk of OI compared with a matched comparison group (matched on industry, gender and age) created by Population Data BC. It was assumed that this comparison group would not have OSA. In both retrospective studies, a five-year time prior to OSA diagnosis was chosen as the study time frame. This five-year period before the PSG was important because the vast majority of patients with OSA would have had the sleep disorder for a significant amount of time prior to diagnosis. This time period provides an opportunity to study any risk OSA may have caused without the potential need to control for the effect of treatment. The third study was a prospective cohort study, investigating the association between OSA severity and the incidence of OI in patients visiting the UBC SDC. The first three studies were also designed to potentially allow for the identification of high-risk groups that could be the focus of subsequent prevention efforts. Moreover, each study was designed to build on the previous study by addressing some of the limitations identified in the earlier study or studies. Finally, the fourth study was designed to investigate whether CPAP treatment reduced the risk of OI in patients suffering from OSA.

1.3.3 Research Study Description

1.3.3.1 Research Study 1

The first retrospective cohort study was designed to quantify the relationship between OSA and OI and to determine if OSA severity is related to the risk of OI. Although diagnosed during the PSG, OSA was likely present in individuals for many years prior to diagnosis. As a result, if OSA does increase the risk of OI, it is important to investigate this retrospective period. Our goal was to expand the current state of knowledge in the field through the use of PSG to identify patients with OSA and by using large samples sizes (>1500 subjects) that enabled us to control for confounding variables and to potentially identify a high-risk group suitable for focused prevention efforts. This study was an internal

comparison of individuals presenting to the UBC SDC with diagnosed OSA compared to those who presented to the UBC SDC but did not have OSA.

1.3.3.2 Research Study 2

The second study was a retrospective case comparison study that was designed to determine whether patients with OSA suffer a higher prevalence of OI compared with a comparison group, matched on gender, industry and age group. Our goal was to use objective measures of both exposure and outcome, while obtaining adequate sample sizes to control for confounding variables in an attempt to show, with a high degree of rigor, that patients with OSA have a significantly higher rate of OI than their matched counterparts.

1.3.3.3 Research Study 3

The third study was a prospective cohort study designed to further quantify the relationship between OSA and risk of OI, as well as to determine if OSA severity was related to the risk of OI. The prospective methodology in Study 3 was necessary to eliminate the possibility that an OI (the outcome) was the cause of a patient's trip to the UBC SDC, or even potentially, the cause of his/her OSA. Our goal was to improve on several of the limitations identified while conducting Studies 1 and 2 through the use of a prospective follow-up period and to continue to expand the current state of knowledge in the field.

1.3.3.4 Research Study 4

The fourth and final study conducted was a prospective study aimed at determining whether the use of CPAP treatment therapy reduced the risk of OI associated with OSA. To assess whether therapy reduces these risks, the difference in the rate of injuries before and after CPAP in each patient

prescribed CPAP was determined. Further, the relationship between adherence with CPAP therapy and the difference in OI rate before and after therapy was assessed by stratifying the data into adherent (defined as mean CPAP use greater than four hours/night) versus nonadherent patients.

2 The Severity Obstructive Sleep Apnea and Frequency of Occupational Injury

2.1 Introduction

The first of four studies conducted for the purposes of this dissertation was designed to fill the first major gap identified in the literature. Despite OSA being both prevalent and potentially dangerous from a public health perspective, few studies had investigated its impact on OI and even fewer have looked at OSA severity to identify a high-risk group. Researchers have estimated the prevalence of OSA to be 6% in women and 13% in men in a middle-aged working population[5]. The National Commission on Sleep Disorders in the United States estimates that OSA affects 7 to 18 million Americans, among whom 92% of females and 80% of males remain undiagnosed[10]. Extrapolating to Canada and assuming similar rates, OSA could affect over 1,000,000 Canadians. Moreover, OIs are a major problem worldwide, resulting in an estimated 360,000 fatal injuries per year and more than 960,000 injuries daily [45].

Furthermore, OSA results in neurocognitive impairments, including memory deficits, inability to concentrate and decreased alertness[35]. Given the association between OSA and both an inability to concentrate and decreased alertness, it is reasonable to consider a link between OSA and OI, particularly those injuries that might be related to reduced vigilance.

The use of rigorous methods to measure OSA severity and ultimately identify a high-risk group is particularly important as it enables the design of specific interventions and the allocation of resources to the group or groups most at risk of injury and in need of intervention.

2.2 Research Questions/Hypotheses

The first research question for Study 1 tested the hypothesis that patients with diagnosed OSA have an increased risk of OI compared to patients who presented at the UBC SDC but who did not have diagnosed OSA. The second research question for Study 1 tested the hypothesis that increased OSA severity was associated with a higher risk of OI. Both questions were addressed retrospectively and used a five-year pre-PSG study period.

Two secondary research questions were explored in Study 1. First, the study investigated the relationship of the other study variables with the risk of OI in this sleep disorder related cohort, including: self-reported daytime sleepiness (ESS), type of industry, BMI, previous medical history, habits or life style factors (alcohol, caffeine, daily sleep duration), and prior claim history. Second, the study investigated whether diagnosed OSA was associated with a higher risk of vigilance related OIs (i.e. those resulting from falls, contact with objects, motor vehicle related injuries).

2.3 Design and Methods

2.3.1 Recruitment and Study Sample:

Consenting adults (18 years to 65 years old) referred to the UBC SDC for PSG for suspected sleep disordered breathing between January 2003 and July 2011 were asked to participate in our study. Only those patients who reported working more than 10 hours/week in the 24 months prior to the PSG at the time of the PSG were included.

Patients were excluded if they were referred to the UBC SDC for a PSG for the diagnoses of another sleep disorder (e.g. narcolepsy) known to cause EDS. These patients were removed from the pool of eligible participants by research assistants who reviewed the charts of patients prior to their PSG and used the physician notes to determine the rationale for the requested PSG. Patients who were referred for the PSG by Sleep Psychiatrists rather than Respirologists were also excluded from the

potential pool of study subjects. The removal of these patients was necessary because they were unlikely to have OSA, and rather, they were at the clinic because they were suspected of a non-respiratory sleep problem (e.g. severe insomnia, narcolepsy, restless leg syndrome) that could affect their likelihood of suffering an OI. Finally, patients experiencing a different serious medical condition that made them medically unstable, those who had a mental disability or dementia, those who had active psychiatric disease, or those were unable to provide informed consent because they could not speak English, were also excluded. These patients were all removed by research assistants based on patient chart information.

Given the broad spectrum of patients that visit the UBC SDC, a range of occupations and sleep related disorders were expected in Study 1, including those with severe OSA, profound sleepiness, and asymptomatic snorers without OSA.

2.3.1.1 Risks and Confidentiality

The surveys and procedures used in this study had minimal physical risks for patient participation. Some of the information obtained (e.g. occupational injuries) was sensitive. The use of the workers' compensation claims and health registry data, and the linkage to patient survey data, was done in accordance with Government of British Columbia policies for the use of health data for research purposes, including privacy-sensitive access and computer storage processes for researchers. This included: having a separate database with confidential identifying information separate from the main database where subjects are identified by code only. The database created with information gathered from patient PSG's and from the patient surveys was merged with claims and health registry data by a neutral third party, Population Data BC, adhering to privacy and security protocols, and removing personal identifiers replaced with study identifiers in the linked database provided to researchers. This linkage process ensures patient confidentiality through a number of methods including the removal of

personal identifiers, access to the data only through a secure remote login and the collection of a very limited amount of patient information (i.e. month and year of birth only).

Sleep specialists or the research coordinator explained the consent form (Appendix B) to eligible patients at the UBC SDC once the patients were scheduled for a sleep study. Potential subjects were given the consent form and asked to read and sign it prior to the sleep study, if they wished to participate. Subjects were also given a second copy of the consent form to take home and were told they could withdraw from the study and could have their data destroyed at any point in the process.

The confidential database (Questionnaires, PSG and Patient Chart data) was stored in a locked cabinet in an office at VGH. The main database had no identifying information, and was stored in a locked office at VGH. The computer was password protected. Data was not downloaded onto an unsecured computer or a portable laptop.

2.3.2 Data Collection

2.3.2.1 Questionnaires

All questionnaires (Appendix A) were self-completed in the UBC SDC. A technician reviewed the questionnaires to verify completion. The surveys were administered prior to subjects' sleep studies, and particularly concentrated on demographic variables in addition to events occurring in the two years prior to the sleep study. These variables and events included self-reported OI, occupational history, MVC, information on shift work, sleep habits, sleep symptoms (e.g. snoring, witnessed apnea), past medical history, medications (including stimulants and sedatives), health habits (e.g. smoking, alcohol, caffeine usage), and subjective daytime sleepiness (measured using the ESS). Subjective work productivity was assessed using a validated survey (Work Limitations Questionnaire). The surveys also included questions on type of industry worked, and a variable was created to define physical or manual labour related occupations (primary resources, manufacturing, construction or transportation and

warehousing industries) versus administrative, managerial or service-related occupations (e.g. financial services or sales/services industries). Body Mass Index (BMI) was calculated from height and weight measurements taken while patients were wearing light clothing.

2.3.2.2 Polysomnography

The main exposure of interest in Study 1 was the presence and severity of OSA. PSG is a standard procedure commonly used in clinical practice to diagnose and quantify the severity of OSA.**Error! Bookmark not defined.** Sleep and its various stages were documented using standard electroencephalographic (EEG), electrooculographic (EOG) and electromyographic (EMG) criteria. EEG was also recorded with electrodes applied at C3-A2 and C4-A1 (according to the International 10-20 system). EMG activity was recorded from the submental muscles and anterior tibialis muscles. Airflow was detected by recording of nasal pressure. Snoring was measured using a microphone that was attached to the middle of the respitrace band at the level of third intercostal space. The output of the microphone was fed into a sound meter (Model SL120, Pacer Industries, Toronto, Canada) that was calibrated in the range of 40 to 110 dB using a 1 KHz signal. A single ECG (modified V2) was monitored in order to detect cardiac arrhythmias. Arterial oxygen saturation (SaO2) was monitored continuously with a pulse oximeter (Model N-100, Nellcor Inc., Hayward, CA) attached to the index finger. Chest wall movement was monitored by a respiratory inductive plethysmograph (Respitrace, Ambulatory Monitoring Equipment, Ardsley, NY). The entire record was manually scored for sleep stage, and apnea type and duration. Respiratory events were scored using standard criteria[73]. Apnea was defined as cessation of airflow for >10 seconds and hypopnea were defined as a 30% decrease in thoracoabdominal (Respitrace sum) amplitude for >10 seconds or a decrement in airflow associated with arousal or a 3% desaturation. Severity of OSA was assessed in terms of the number of apneas or hypopneas per hour of sleep (apnea hypopnea index, AHI).

Patients were dichotomized as “yes” or “no” for diagnosed OSA, based on an AHI of 5 or more per hour. Among patients diagnosed with OSA, severity was also classified according to standard threshold values (AHI 5-15/hr for mild disease, 15-30 for moderate, ≥30/hr for severe).

2.3.2.3 Database

Sleep and questionnaire data collected from participating patients at the UBC SDC were stored in a Microsoft Excel Spreadsheet. The file was password protected and kept in a locked office. Only researchers and support personal directly involved in the study were allowed to access the database. To further maintain subject confidentiality, patients within the database had identifying information (name, personal health number) removed from the main dataset, and were identifiable by a code number only.

2.3.2.4 Ascertainment of Occupational Injuries

The major outcome of interest was the occurrence of OI in the five-year period prior to PSG. This five-year period prior to PSG was important because it allowed for the retrospective investigation of individuals who likely had the same disease status as they did at the time of PSG, but who had not yet been treated. For all patients, OI were identified from workers’ compensation claims data. WorkSafeBC is the sole provider of workers’ compensation benefits in the Canadian province of British Columbia for almost all (93 to 94%) of the labour force. The only exclusions from workers’ compensation coverage are self-employed individuals who have not purchased personal optional protection coverage from WorkSafeBC, and other small segments of the labour force (e.g., athletes, domestic workers employed for less than 8 hours per week, military, federal police). Short-term (at least one day of work absence) and long-term disability (permanent impairment) claims, but not ‘medical only’ claims (serious enough to warrant medical attention but the worker is able to remain at

work), were included. This database contained and provided by WorkSafeBC was comprehensive from 1986 forward and included information about the date of injury, injury type, nature of injury incident, days of missed work, type of occupation and industry, and costs related to each OI. Population Data BC was provided with a list of participating study subjects from the UBC SDC and all the variables that researchers requested to be linked with the WorkSafeBC database. Population Data BC created new study IDs (for confidentiality), and provided the research team with a new database with original data linked to subjects' OI history. This linkage allowed for the calculation of the number and rate of injuries (number of injuries/person/year of work) in subjects.

A secondary outcome variable that was investigated was vigilance related OI. Vigilance related OI were injuries that were more likely to be related to reduced vigilance and were classified using previous literature on the mechanisms and causes of injury[51,74]. The vigilance related injuries included falls from elevation, falls on the same level, contact with heat, cold or electricity, commercial motor vehicle crashes, and injuries related to slipping or tripping. These types of injury were classified as vigilance related because we felt they would be more likely due to momentary lapses of attention or concentration. The rationale behind including a specific class for vigilance-related injuries is that these injuries were thought to be more likely associated with OSA and the neurocognitive impairments seen in patients with OSA. Researchers have confirmed the association between OSA and deficits in multiple cognitive domains including attention, vigilance, and executive function. Furthermore, sleep fragmentation is associated with longer reaction times[2, 29-32]. An understanding of the nature of the impairments associated with OSA was used to select the injuries that were most proximally related to vigilance.

Furthermore, a previous study investigating injuries associated with sleep problems eliminated all injuries associated with repetitive strain as the authors stated "repetitive strain injuries were not hypothesized to be related to sleep problems"[74]. We therefore removed these injuries from our

definition of vigilance-related injuries as well. Note that repetitive strain injuries were the most prevalent classification of injury in the database. Finally, MVCs were included in the definition of vigilance-related injuries because although these injuries could include passengers whose injuries would likely not be vigilance-related, the vast majority of the commercial MVCs would involve motor vehicles where the driver was the sole occupant of the vehicle and thus the category as a whole could be deemed to be likely associated with vigilance deficits.

Finally, there were several classifications of injuries that may have been associated with decreased vigilance and potentially OSA, but which were not included in the definition of vigilance-related injuries either because there was no current literature supporting a relationship (in contrast to MVCs and OSA) or because the proposed mechanism of the relationship was less obvious than it was for the included injuries.

2.4 Analysis

In Study 1, the relationship between the presence and severity of OSA and the incidence of OI was assessed for the retrospective period of five years before PSG. Descriptively, for continuous study variables with either skewed or extreme values, median and interquartile range values were reported. Group differences were tested using the Kruskal-Wallis test. For categorical variables, counts and percentages were reported, and group differences were tested using the Chi-square test.

Subjects were excluded from the analysis with a missing value for either AHI or gender. Subjects were also excluded if they worked fewer than 10 hours per week or had a missing value for industry group. Subjects were required to work at least 10 hours per week to be deemed at risk of an OI for the purposes of this study.

A total of 1848 subjects were initially considered for the analysis with linked UBC SDC and workers' compensation data. An OI that occurred more than 5 years prior to the PSG date or after the

PSG data was not included in the outcome definition; however, patients with an injury more than 5 years before their PSG date or after their PSG date were included in the analysis as a patient without the outcome of interest (i.e. an occupational injury during the retrospective follow-up period).

The number of OI in the 5 years prior to the PSG was determined for each patient. The crude rate of having an OI was calculated by dividing the number of injuries by the total number of subjects in either the OSA group or the non-OSA group and the time at risk for each subject (reported months of work). Since only a small portion of patients had multiple injuries, a binary definition for outcome, (i.e., any OI or no OI) was used. All patients included in the analysis had claims data going back 5 years prior to their PSG date (i.e. same exposure time period). Univariate analyses were performed on the relationship between other study variables and the risk of OI. These analyses were used to determine which variables were to be included in the final logistic regression analysis. Special attention was given to the variable ESS because the hypothesized mechanism by which OSA may lead to OI could be at least partially mediated by excessive daytime sleepiness and inattention. As a result, we investigated both its potential effects on OI in univariate analyses as well as the potential for an interaction between the variable OSA (yes/no) and ESS.

Logistic regression analysis was used to model the odds of OI between the OSA versus no OSA groups. The final model was adjusted for gender, BMI, alcohol use and industry group because these variables remained significant in the multivariable model.

In a sub-analysis, the OI outcome was further defined as at least one vigilance related injury (yes versus no). The vigilance related injuries were analyzed as a subset of all injuries and were compared both to those subjects who did not suffer any injury as well as to those who suffered a non-vigilance related injury. Given the three levels of outcomes in the sub-analysis (i.e. vigilance related injury, non-vigilance related injury and no injury), multinomial logistic regression was used to model the association between the odds of injury (vigilance injury, non-vigilance injury, no injury) and OSA. The

final model was adjusted for gender, BMI, alcohol use [Y/N], and industry (i.e. physical or manual labour related occupations [Y/N]) because these variables remained significant in the multivariable model.

In a secondary analysis, looking at the association between OSA severity and OI, severity was classified according to standard threshold values (AHI 0-5/hr for no disease, AHI 5-15/hr for mild disease, 15-30 for moderate, >30/hr for severe). Logistic regression analysis was used to model the odds of OI between the OSA severity groups.

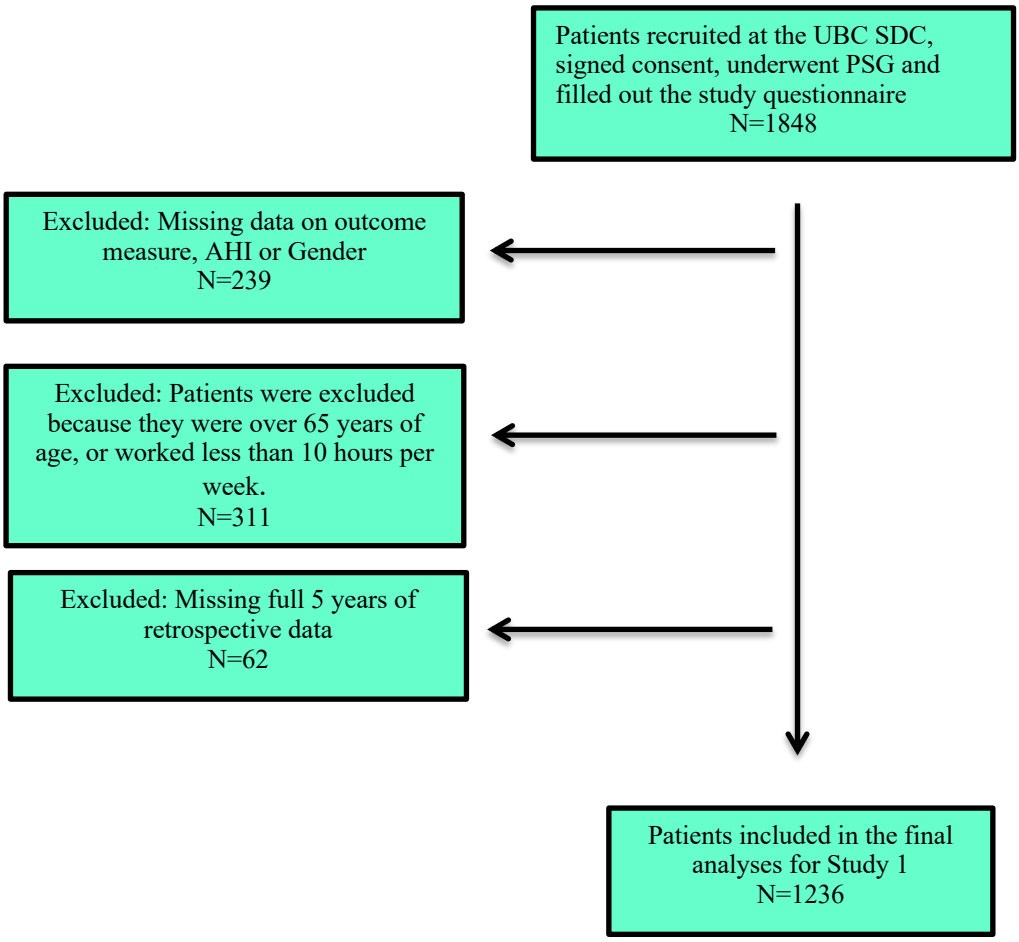
All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

2.5 Results

2.5.1 Baseline Numbers

A total of 1848 subjects were recruited at the UBC SDC to participate in Study 1. The final dataset used for the analysis included 1236 patients. A total of 239 patients were excluded because they were missing AHI or gender data or because they were missing data on the outcome measure. Only four patients could not be matched to the registry database. An additional 311 patients were excluded because they were over 65 years of age or because they reported working less than 10 hours per week in the two years prior to PSG. A total of 65 patients were excluded because they did not have the full 5 years of retrospective registry data prior to their PSG

Figure 1 Overall Description of Recruited UBC Sleep Disorders Clinic patients included in Study 1



The majority of the included subjects (70%) were male and the median age was 49 years (IQR= 40.55) (Table 2).

Table 2 Baseline characteristics by OSA status for the investigation of risk with OI in the five years prior to PSG

Variable	All (n=1236)	No OSA (n=242)	OSA (n=994)	P-value
Continuous Variables (Median/ IQR)				
Age (Yrs)	49 (40, 55)	44 (35, 53)	49 (42, 56)	<0.01
AHI (Events/Hr)	15 (7, 30)	2 (1, 4)	20 (12, 35)	<0.01
ESS (0-24)	10 (6, 14)	11 (7, 14)	10 (6, 14)	0.86
Hours worked per week	40 (37, 50)	40 (37, 50)	40 (37, 50)	0.67
BMI	30 (27, 35)	28 (25, 33)	31 (27, 35)	<0.01
Categorical Variables (Frequency/ Percentage)				
Gender (Female)	374 (30.3%)	93 (38.4%)	281 (28.3%)	0.01
Alcohol (Yes)	855 (69.2%)	182 (75.2%)	673 (67.8%)	0.03
Industry (physical or manual labour related occupations)	346 (28%)	61 (25.2%)	285 (28.7%)	0.28

The median AHI was 15 events per hours (IQR= 7,30), and 80% of the patients were defined as having OSA (AHI greater than or equal to 5 events per hour). Patients with and without OSA reported working a similar number of hours per week (40 hours per week; p=0.67) and reported a similar degree of daytime sleepiness according to the ESS (median score of 11 in the Non-OSA group vs. 10 in the OSA group; p= .86). Patients with OSA had significantly higher median BMI compared with patients without OSA (31 versus 28 kg/m2; p<0.01). Finally, patients with OSA were significantly less likely to drink alcohol at least once a month (67.8% versus 75.2%; p=0.03) and were slightly (though not significantly) more likely to work physical or manual labour occupations (28.7% versus 25.2%, p=0.28).

2.5.2 Occupational Injury Risk

Among the study sample, a total of 152 OI claims were identified for 111 patients (9% of the sample) in the five years prior to PSG. There were 59 vigilance related OI (39% of the total number of OI) and 93 non-vigilance related OI (61% of the total number of OI). Of the 111 patients with OI, 49 patients (44%) had at least one vigilance related injury, while 62 patients (56%) had non-vigilance related injuries.

In a univariate analysis, when ESS was used as the independent variable in the model, it was not found to be a significant predictor of OI (p= .70). Furthermore, when ESS, OSA (yes/no), and the interaction term ESS*OSA (yes/ no) were included in a model, the interaction term did not approach significance (p= 0.42). Given that ESS was non-significant with a relatively high p-value, we did not include it in the final logistic regression model.

Table 3 Comparison of the number of vigilance and non-vigilance related injuries by OSA status (yes/no) in the five years prior to PSG

Occupational Injuries	**All (n=1236)**	**No OSA (n=242)**	**OSA (n=994)**	**P-value**
Subjects with Injuries	111 (8.98%)	13 (5.37%)	98 (9.86%)	.03
Subjects with Vigilance Related Injuries	49 (3.96%)	4 (1.65%)	45 (4.53%)	.04
Subjects with Non-Vigilance Related Injuries	62 (5.02)	9 (3.72%)	53 (5.33%)	.30

The differences in results when comparing OI in subjects with and without OSA are reported in Table 3.

Almost ten percent (9.86%) of patients with OSA had an OI compared with 5.37% of those without OSA in the five-year period prior to their PSG. The unadjusted odds of OI associated with OSA using logistic regression was 1.93 (CI = 1.06-3.50, p= 0.03) (Table 4).

Table 4 Association between diagnosed OSA (yes/no) and OI outcome (yes/no in five years prior) using logistic regression among a sample of patients presenting to the UBC SDC

	Odds ratio for OI	**95% CI**	**P-value**
OSA (yes versus no) (Unadjusted)	1.93	(1.06, 3.50)	0.03
OSA (yes versus no) (Adjusted)*	1.76	(0.95, 3.26)	0.08

* adjusted for gender, BMI, alcohol use and Industry (physical or manual labour related occupations

In other words, prior to controlling for potential confounding variables, subjects with OSA compared to those without OSA had a two-fold increased odds of an OI in the five years prior to their PSG. The association between OSA and OI was attenuated but remained elevated in the multivariable model that controlled for the confounding effects of gender, BMI, alcohol use and industry (OR= 1.76, CI = 0.95-3.26, p= 0.08), although the 95% confidence interval (CI) around the point estimate included '1'.

The details of each of the two models (including parameter estimates, standard errors, Wald chi-squared values and p-values) referenced in Table 4, are provided below in Tables 5 and 6

Table 5 Unadjusted model estimates for logistic regression model of diagnosed OSA (yes/no) and OI outcome (yes/no in five years prior) among a sample of patients presenting to the UBC SDC

Maximum Likelihood Estimates	**Estimate**	**SE**	**Wald Chi-Square**	**P-Value**
Parameter				
Intercept	-2.87	0.29	101.24	<.01
OSA Yes/ No (reference)	0.66	0.30	4.66	0.03

Table 6 Adjusted model estimates for logistic regression model of diagnosed OSA (yes/no) and OI outcome (yes/no in five years prior) among a sample of patients presenting to the UBC SDC

Parameter	Estimate	SE	Wald Chi-Square	P-Value
Intercept	-3.68	0.59	38.42	<.01
OSA Yes/ No (reference)	0.56	0.32	3.18	0.08
Gender (Male/ Female (Reference))	0.32	0.29	1.26	0.26
BMI	0.01	0.01	0.64	0.42
Alcohol Use	-0.16	0.22	0.53	0.46
Industry (physical or manual labour related occupations)	1.63	0.22	54.72	<.01

In the sub-analysis, patients with OSA were also more likely to have a vigilance related injury (4.53%) than subjects without OSA (1.65%). In the unadjusted analysis, there was an almost three-fold increase in the odds of a vigilance related injury associated with OSA (OR= 2.88, CI = 1.02-8.08, p-value= 0.05) (Table 7).

Table 7 Association between diagnosed OSA (yes/no) and both vigilance related injuries (yes/no injury in five years prior to PSG) and non-vigilance related injuries (yes/no injury in five years prior to PSG) using multinomial logistic regression among a sample of patients presenting to the UBC SDC

Univariable	Odds ratio for OI	95% CI	P-value
Vigilance Related Injuries (yes versus no injury) (unadjusted)	2.88	(1.02, 8.08)	0.05
Non-Vigilance Related Injuries (yes vs no injury) (unadjusted)	1.51	(0.72, 3.10)	0.27
Vigilance Related Injuries (yes versus no injury) (Adjusted)	2.42	(0.85, 6.93)	0.10
Non-Vigilance Related Injuries (yes vs no injury) (Adjusted)	1.49	(0.71, 3.14)	0.30

* gender, BMI, alcohol use [Y/N], and industry (i.e. physical or manual labour related occupations [Y/N])

Again, this association was attenuated after adjusting for confounders (OR= 2.42, CI = 0.85-6.93, p-value= 0.10), and the 95 CI around the point estimate included '1'.

The details of each of the four models (including parameter estimates, standard errors, Wald chi-squared values and p-values) referenced in Table 7, are provided below in Tables 8, 9, 10 and 11.

Table 8 Unadjusted model estimates for logistic regression model of diagnosed OSA (yes/no) and vigilance related injuries (yes/no in five years prior) among a sample of patients presenting the UBC SDC

Maximum Likelihood Estimates	**Estimate**	**SE**	**Wald Chi-Square**	**P-Value**
Parameter				
Intercept	-4.05	0.50	64.42	<.01
OSA Yes/ No (reference)	1.06	0.53	4.02	0.05

Table 9 Adjusted model estimates for logistic regression model of diagnosed OSA (yes/no) and vigilance related injuries (yes/no in five years prior) among a sample of patients presenting the UBC SDC

Parameter	**Estimate**	**SE**	**Wald Chi-Square**	**P-Value**
Intercept	-5.76	0.86	45.32	<.01
OSA Yes/ No (reference)	0.88	0.54	2.73	0.10
Gender (Male/ Female (Reference))	0.2	0.39	0.33	0.57
BMI	0.04	0.02	5.49	0.02
Alcohol Use	-0.16	0.32	0.24	0.62
Industry (physical or manual labour related occupations)	1.52	0.32	22.75	<.01

Table 10 Unadjusted model estimates for logistic regression model of diagnosed OSA (yes/no) and non-vigilance related injuries (yes/no in five years prior) among a sample of patients presenting the UBC SDC

Maximum Likelihood Estimates	**Estimate**	**SE**	**Wald Chi-Square**	**P-Value**
Parameter				
Intercept	-3.24	0.34	90.71	<.01
OSA Yes/ No (reference)	0.41	0.37	1.24	0.27

Table 11 Adjusted model estimates for logistic regression model of diagnosed OSA (yes/no) and non-vigilance related injuries (yes/no in five years prior) among a sample of patients presenting to the UBC SDC

Parameter	**Estimate**	**SE**	**Wald Chi-Square**	**P-Value**
Intercept	-2.99	0.81	13.58	<.01
OSA Yes/ No (reference)	0.40	0.38	1.087	0.30
Gender (Male/ Female (Reference))	0.39	0.39	0.96	0.31
BMI	-0.03	0.02	1.22	0.27
Alcohol Use	-0.15	0.29	0.25	0.61
Industry (physical or manual labour related occupations)	1.74	0.29	35.77	<.01

In the secondary analysis, logistic regression analysis showed that there was no observed relationship between OI and OSA severity. In fact, there was no linear relationship between OSA group severity and OI and odds ratios were not significant (Table 12).

Table 12 Association between OSA severity group and OI (yes/no in five years prior to PSG) using logistic regression among a sample of patients presenting to the UBC SDC

Univariable	Odds ratio for OI	95% CI	P-value
Mild OSA vs No OSA	1.67	(0.94, 3.10)	0.05
Moderate OSA vs No OSA	1.69	(0.94, 3.15)	0.27
Severe OSA vs No OSA	1.69	(0.94, 3.16)	0.10

Patients with severe OSA were not significantly more likely to suffer an OI than patients with either moderate or mild OSA (OI in 2.27 % of subjects with severe OSA, OI in 2.83% of subjects with moderate OSA and OI in 2.83% of subjects with mild OSA).

2.6 Discussion

Based on our unadjusted analysis, patients with OSA had almost twice the odds of suffering an OI compared with those without OSA prior to PSG (p= 0.03). When the model was controlled for a number of potential confounders, patients with OSA still had 1.76 times the odds of suffering an OI compared to patients without OSA, although the association only trended to significance (p= 0.08). In the multinomial model, where vigilance related injuries were assessed, the results were similar. Patients with OSA were almost 2.5 times as likely to suffer a potentially vigilance related injury when compared with patients without OSA. This association, however, only trended towards significance (p-value= 0.10) in the adjusted model. There was no significant relationship between the severity of OSA and OI.

The attempt to identify a high-risk group using standardized groupings of OSA severity was unsuccessful. Patients with moderate or severe OSA were no more likely than those with mild OSA to

suffer an OI. The inability to observe the hypothesized association was likely due, at least in part, to a lack of power given the smaller numbers in each severity group among the subset of the study sample with diagnosed OSA.

Our findings are consistent with previous research showing increased rates of OI in patients with OSA as compared with subjects without OSA[53-56,72]. In addition, our use of objective measures of both OSA and OI in conjunction with a relatively large sample size, helps to validate previous literature analyzing the relationship between OSA and OI. Further, the observed associations were in reference to a patient sample presenting to a clinic with sleep problems but not diagnosed OSA, helping to highlight the direct impact of this condition. The consistency of our findings, indicating that vigilance related injuries are more strongly associated with OSA, adds to the body of literature in terms of plausibility. A recent meta-analysis performed by Uehli and colleagues[55] investigated the relationship between general sleep problems (defined as all sleep disorders described in the international classification of sleep disorders (ICSD-2)) and work injuries. They found that individuals with sleep problems had a 1.62 times higher relative risk of injury compared with individuals without sleep problems.

Focusing specifically on OSA, a study by Ulfberg and colleagues used objective criteria to identify both injuries and OSA[56]. In their study, all patients were tested for OSA using simultaneous nocturnal recording and oximetry. Injury rates for 704 patients with sleep-disordered breathing were compared with the rates for a random sample of 580 subjects drawn from the general population. The risk of an OI was about 50% greater among men with OSA compared with those without OSA. For women, the risk increased by at least 3-fold in OSA patients. Other studies found similar relationships[17, 20] despite not using objective criteria to identify both OSA and OI.

Our findings add to the body of evidence on the association between OSA and OI. First, in contrast to many of the previous studies, we used the gold standard for the diagnosis of OSA (inpatient PSG) as opposed to relying on sleep related symptoms or limited ambulatory testing[31]. Second, our

ascertainment of OI was validated through a claims database rather than self-reports (which would be susceptible to recall bias). Finally, our large sample size provided significant power in a study in which the outcome was relatively rare. The findings with respect to vigilance related injuries strengthen the argument regarding the specific effects of OSA on injury mechanisms. Specifically, that the neurocognitive impairments, including an inability to concentrate and decreased alertness[34], caused by the combination of sleep fragmentation and hypoxemia, lead to an increased risk of OI. Furthermore, the 5-year retrospective time period studied, provided an important opportunity to study patients who were objectively diagnosed with OSA, but who were until the time of the PSG, treatment-free.

2.6.1 Limitations

There were a number of study limitations that are important to acknowledge in the interpretation of the findings. A number of these limitations would likely have biased the study towards the null hypothesis, while others would likely have had the opposite effect. The overall effect of these limitations is impossible to determine; however, the acknowledgement of these limitations and the potential for improvement in future studies is crucial to the improvement of research in this field.

The risk of OI was assessed retrospectively from patients seen in a sleep disorders clinic, rather than from a population-based sample. This may introduce a form of selection bias in that work performance or injury may have been a factor contributing to referral. That is, patients may have been either referred to a sleep physician or approached their physician on their own volition because they had recently been involved in an OI. This may have biased the study because these individuals may have been more likely than the average individual with OSA to have recently suffered an OI. Selection bias occurs when individuals, groups or data are selected in a way that fail to make the sample representative of the population intended to be analyzed. In this case the bias is a combination of two sub-types of selection bias; referral bias and volunteer bias. The two types of bias are present because

patients could either be referred or volunteered to come to the UBC SDC based on characteristics that make them more likely to have been injured in the past. This type of bias would likely exaggerate the rate of OI in the sample overall, but within the sample of patients referred to the UBC SDC, any bias would likely have been non-differential, as both the OSA and the non OSA subjects would have been equally affected.

Conversely, in this retrospective study, patients with very severe injuries likely would not have presented to the UBC SDC as they would be more concerned with other more serious acute medical issues. Additionally, patients with fatal injuries were obviously not included in the study. The exclusion of individuals with both fatal and severe injuries from the study sample, if associated with OSA, would likely have underestimated the association between OSA and OI. This is another form of selection bias, referred to as non-response bias.

Another important limitation is that not all OI are reported or captured by the workers' compensation system, and the current measure of OI represents injuries requiring at least one day of work disability. It is important to note that several professions are excluded from the workers' compensation system database as was outlined in the methods. Again, underreporting of work-related injuries would have underestimated the observed associations, while the impact of the exclusion of some professions is unknown but should be noted. Again, this is a form of selection bias as the exclusion of certain professions results in a sample that is not 100% representative of the population intended to be analyzed.

The ability to investigate the association between OSA and OI may have also been diluted by a study sample that included patients referred to the clinic for non-respiratory sleep disorders (i.e. insomnia, narcolepsy, depression). These patients might have been included in the non-OSA comparison group, despite being at an increased risk for OI because they were suffering from another sleep disorder that also caused similar attention and vigilance issues, ultimately biasing the estimates

toward the null hypothesis. However, this is likely a minor concern since patients with predominately non-respiratory complaints are usually referred to Psychiatrists associated with our SDC rather than Respirologists. Patients recruited for this study were almost exclusively recruited from the pool of patients referred to the Respirologists, and were thus less likely to have been included in our database if they were suffering from insomnia, depression or narcolepsy. Further, even if the non-OSA group have an increased risk of OI, our study found a relative increased odds among those with OSA, strengthening the case for OSA as a strong predictor of OI. In order to improve on this study and eliminate this limitation, a matched population-based comparison group should be used in future studies. This group will both allow us to measure the rate of OI in the general population in a sample that is matched to our study sample; and, will eliminate the potential bias associated with using patients referred to a UBC SDC (and the potential increased risk of OI in this population) as a control for this study.

While the use of retrospective injuries before PSG allowed for the potential of several biases, it also eliminated the potential confounding effect of treatment. All patients were recruited at the time of their PSG and patients that had previously been on treatment for OSA were excluded from participation in the study. As a result, we were confident that patients in our study had not been treated for OSA in the 5 years prior to their PSG.

Another potential limitation is the possibility that both the presence and severity of OSA might have changed over the five years prior to the PSG. There are studies indicating that OSA severity tends to worsen significantly overtime, particularly with the combination of aging and weight gain[74-76]. Given the worsening of OSA over time, there is likely a group of people whose OSA status changed from no-OSA (AHI<5) to OSA (AHI≥5) in the 5 years prior to PSG. These people will have been included in the OSA group for the entirety of the analysis even though they did not technically have OSA for the entire 5-year pre-PSG study period. This misclassification bias would likely have biased

the study towards the null. This is a form of information bias referred to as misclassification bias, where subjects are incorrectly categorized with respect to their exposure status

Finally, many individuals with severe OSA will likely have either self-selected out of occupations where they may put themselves at harm of an OI or may have self-selected out of the workforce all together. Both of these issues would likely dampen the strength of the relationship between OSA and OI, making it more difficult to assess to overall impact of OSA in this field of study. Again, this is a form of selection bias in which patients are choosing to reduce their risk of exposure to OI prior to the analysis as a result of their disease status.

2.7 Conclusion

In Study 1, patients with OSA were more likely to suffer an OI in the five years prior to PSG than those without OSA, however after adjusting for potential confounders, the association between OSA and OI only trended toward significance ($p= 0.08$). The impact of OSA appears to be greater for vigilance related injuries. The attempt to identify a high-risk group using standardized groupings of OSA severity was unsuccessful.

2.7.1 Potential Impact and Future Directions

This study corroborates previous studies investigating the relationship between OSA and OI. Although the results need to be confirmed in additional studies, they are an important step in understanding the relationship between OSA and OI. Ultimately, the goal would be to improve prevention efforts by identifying those individuals at the highest risk of OSA and either treating them or removing them from high-risk jobs. To date there are no federal or provincial regulations requiring employees of any industries to be screened for OSA. Based on the results of this study and numerous

previous ones, both federal and provincial governments may want to reconsider this, focusing specifically on high-risk industries. Preventing OSA related OI could not only prevent injuries and reduce morbidity/morality and disability, but it also could result in an economic benefit for our healthcare and social security systems.

3 A Retrospective Matched Comparison Study: Obstructive Sleep Apnea and Occupational Injuries

3.1 Introduction

The second study that was performed for this dissertation was a retrospective matched comparison study. It was designed to address several limitations encountered in the first study, while continuing to fill several identified gaps in the literature. Study 1 found a significant association between OSA and OI in patients referred to the UBC SDC (though this was attenuated after adjustment for confounders). Additionally, the relationship was stronger when considering only those injuries that were more likely to be associated with vigilance.

Study 2 again investigated the relationship between OI and OSA; specifically hoping to verify and build on the first study's results through the use of a matched comparison group made up of individuals taken from the general population. The use of the population-based matched comparison group meant researchers no longer had to contend with the biases associated with a clinic-based cohort. Furthermore, unlike the first study, the bias associated with a control group that was referred to the UBC SDC because of reported sleep problems, but that was discovered not to have OSA, was eliminated. As discussed in Chapter 2, these individuals may have been more likely than the average person to suffer an OI, particularly one that was vigilance related, given that they were likely referred to the UBC SDC because of a sleep problem. The use of a population-based comparison group also improved the generalizability of the study.

As was the case in Study 1, Study 2 incorporated the same objective measures for the measurement of OSA and the measurement of OI, a large improvement on the majority of previous studies in the field. Furthermore, the use of a large matched comparison group considerably increased the study population and therefore allowed for the study of many more OI. The increase in outcome events contributed to an increase in power.

A matched comparison group was used to 'find' a similar population in the province of BC by requiring the matched population to be working in the same industry and of the same sex and age grouping. Both sex and age are known confounders of both OI and OSA, and industry is critical because OI are more likely to occur in certain industries (physical or manual labour related occupations) than others. It was assumed that these matched workers from the population would thus be similar to patients with OSA other than the absence of OSA.

3.2 Objectives

The main objectives of Study 2 were to: 1) test the hypothesis that patients diagnosed with OSA have an increased risk of OI compared to workers from the general working population without OSA matched by age, gender and industry type; and 2) test the hypothesis that the association between OSA and OI would be greater for vigilance related occupational injuries (e.g. those related to falls, contact with objects, motor vehicle related injuries).

3.3 Design and Methods

3.3.1 Recruitment and Study Sample:

The patient sample with diagnosed OSA was the same for Studies 1 and 2 (see section 2.3.1 for a description of the recruitment, inclusion/exclusion criteria, and the definition of diagnosed OSA).

Population Data BC assembled a comparison group for the study that was matched to the included OSA sample on age category (by 5 years), gender (man/woman), and industry type. Where possible, five comparison subjects were matched to each OSA subject. By design, subjects in the matched comparison group had not presented to the UBC SDC during the study period and were defined as not having diagnosed OSA. Information on the patients recruited from the UBC SDC was uploaded to a Secure Remote Environment (SRE) that was administered by Population Data BC. Population Data BC

personnel were then responsible for matching patients to comparison group subjects on the three criteria listed above and providing the data back to researchers (database of patients and matched counterparts) through the use of the SRE with all personal identifiers removed and replaced with an anonymous study identifier. It is important to note that the industry matching variable is only available for residents with employer paid health premiums and matching data was drawn from the health registry (an enumeration of the residents in the province for healthcare and updated with status changes). Patients were matched on industry in the health registry rather than occupation because specific occupation was not available. In order to be in the health registry, a person must either be a citizen or lawfully admitted to Canada for permanent residency. Additionally, they must make their home in BC and reside in BC for at least six months in a calendar year. Further, the requirement of having employer paid health premiums to be included in the matched comparison group limits the industries available for matching to those that are that are generally larger employers (e.g. health care, construction).

3.3.1.1 Risks and Confidentiality

Please see section 2.3.1.1 for Risks and Confidentiality associated with Study 2. The conditions governing data for the population-based comparison group were the same as for the patient group with OSA.

3.3.2 Techniques and Tools

3.3.2.1 Questionnaires

Please see section 2.3.2.1 for Questionnaires used in Study 2 as they are the same as Study 1.

3.3.2.2 Polysomnography

Please see section 2.3.2.2 for explanation of PSG used in Study 2 as they are the same as for Study 1.

3.3.2.3 Database

Please see section 2.3.2.3 for explanation of the Database used in Study 2 as they are the same as for Study 1.

3.3.2.4 Ascertainment of Occupational Injuries

Please see section 2.3.2.4 for explanation of the ascertainment OI used in Study 2 as they are the same as for Study 1. The date of OSA diagnosis in the patient group was used as the index for the matched population-based subjects in order to identify included OIs that occurred within the same five-year window as for their matched counterparts.

3.4 Analysis

To be included in the analysis, a subject or patient had to be at risk of OI for the majority of the time he/she contributed to the analysis. As a result, patients' and subjects' inclusion in the analysis was determined by residency in BC, which was based on Medical Service Plan (MSP) registry data. Annual intervals were created retrospectively for each patient using the PSG date. For each interval, a patient or matched comparison group subject had to be in the registry for a minimum of 75% of the year (274 days) to be considered a BC resident in that year. This criterion was used to ensure an equivalent at-risk period for OI among patients and matched counterparts. Patients and subjects who did not meet the residency requirement for any one of the five-year follow-up intervals were excluded

from analysis. Additionally, patients who lost all matched comparison group subjects due to the residency requirements were excluded.

The presence or absence of any OI in each interval was the primary outcome of interest (yes versus no) analyzed using logistic regression. When ignoring the matching scheme and the longitudinal nature of the data, the Chi-square test was used to compare the number of OI in patients versus comparison group subjects. Given that each individual could contribute up to five annual intervals to the analysis, the data was longitudinal in nature and any analysis done on the data had to include methods taking this into account. In order to take into consideration, the matching and the time-varying nature of the outcome (yes or no over five one-year follow-up periods), a strata variable was created in order to group a patient with his/her matched comparison group subjects. Next a 3-level hierarchical model was used. Level 1 in the model was used for the strata variable (grouping patients with their matched comparison groups subjects). Level 2 was the individual level, with subjects either being included as a case/patient or as a matched comparison group subject. Level 3 was the interval level with up to five yearly interval contributions per study subject. To account for the hierarchical scheme and the longitudinal nature of the data, generalized mixed effects models were constructed in SAS version 9.2 (SAS Institute, Cary, NC).

A second analysis using generalized mixed effects models was completed for OI that were considered vigilance related. The outcome of interest was any vigilance related OI in a given interval. Ignoring the matching scheme and the longitudinal nature of the data, Chi-square tests were performed to investigate differences between vigilance related injury rates in patients versus the population-based matched comparison subjects. Ideally, a multinomial model should have been created to capture vigilance related injuries, non-vigilance related injuries and the reference group, no injury. Unfortunately, the multinomial (GLM) model did not converge and a dichotomous outcome of vigilance related OI compared to no injury was used (i.e. excluding non-vigilance-related injuries). A

generalized mixed effects model was constructed to account for both the matching scheme and the longitudinal nature of the data for the investigation of the risk of a vigilance related injury (i.e. binary), in each of the five intervals.

Sensitivity analyses were performed to explore issues of selection bias. For these analyses, Population Data BC provided workers' compensation claim data to calculate the OI rate among patients presenting to the UBC SDC for suspected OSA during the clinic in-take period, but who did not meet the original inclusion definition for diagnosed OSA (i.e. an additional linkage of claim data was performed for those patients who were originally excluded). The OI rate was compared to that of the diagnosed OSA patient group and the matched population-based group.

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

3.5 Results

3.5.1 Baseline Numbers

There was a total of 872 OSA patients and 4,360 matched subjects included in the analyses for Study 2 (Figure 2). The majority of OSA patients (73.3%) were male and the median age was 49 years (IQR= 42, 55)(Table 13). Given the matched design, the non-OSA comparison subjects were also 73.0% male and with the same age distribution. The majority of patients and comparison subjects were workers in management, service or administration occupations (69.4%). The median AHI in patients with OSA was 20.4 events /per hour (IQR=11.7, 35.5). OSA patients for which additional clinical data was available from the UBC SDC had a median BMI of 30.6 kg/m^2, reported an average of 40 work hrs/week, and had a median Epworth Sleep Score (ESS) of 10.

Figure 2 Overall Description of Recruited UBC Sleep Disorders Clinic patients included in Study 2

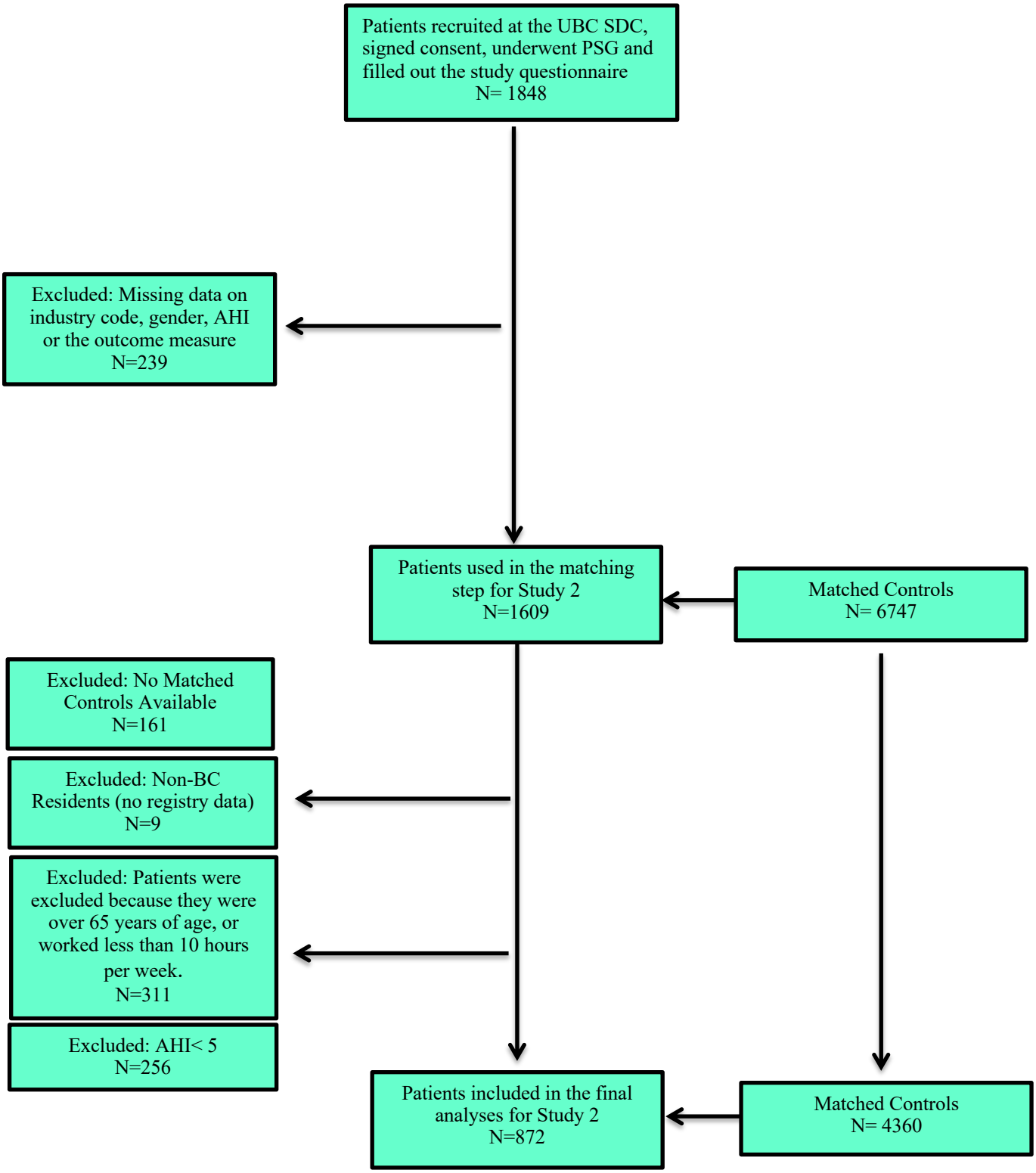


Table 13 Baseline characteristics of OSA patient group and matched population-based comparison group, 2003-2011

	OSA Patient Group	Comparison Group
Number of Subjects	872	4,360
Gender		
Male	639 (73.3%)	3,196 (73.3%)
Female	233 (26.7%)	1,164 (26.7%)
Age	49 years (IQR 42, 55)	49 years (IQR 42, 55)
Physical or Manual Labour Related Occupations [Y/N])	267 (30.9%)	1,347 (30.9%)
AHI (events/hour)[1]	20.4, (IQR 11.7, 35.5)	N/A
BMI[1]	30.6 (IQR 27.1, 35.1)	N/A
ESS[1]	10 (IQR= 6, 14)	N/A
Hours Worked Per Week[1]	40 (IQR= 37, 50)	N/A
Number and Percentage of Yearly Intervals with No injury	4030 (96.9%)	20504 (96.3%)
Number and Percentage of Yearly Intervals with Any Injury	128 (3.1%)	791 (3.7%)

[1]Only available for OSA patients as part of Sleep Laboratory in-take data

3.5.2 Occupational Injury Risk

A total of 4,030 person-years or annual intervals were available for longitudinal follow-up in the OSA patient group and 20,504 person-years or annual intervals for the matched comparison group. There were 128 OI captured during follow-up for 872 OSA patients (14 % of patients or 3.2 injuries per 100 person-years of follow-up) compared to 791 OI captured during follow-up for the 4,360 matched comparison subjects (18% of subjects or 3.9 injuries per 100 person-years).

The results of the Chi-squared test performed on the data shown at the end of Table 13 above (number and percentage of yearly intervals with injury/ no injury by OSA/comparison group status),

ignoring the matching and longitudinal nature of the data, show that subjects in the matched comparison group were more likely than patients to have an OI during the same follow-up period (p=0.04).

The results for the generalized mixed effects models assessing the odds of OI associated with OSA, adjusted for matching and confounding and taking into consideration the time-varying outcome, are summarized in Table 14. The details of each of the four models (including parameter estimates and CIs, standard errors and p-values) referenced in Table 14, are provided below in Tables 15, 16 ,17 and 18

Table 14 Generalized mixed effects models results comparing OI in OSA group vs. matched population-based comparison group without OSA for all OI and vigilance related injuries over five-year follow-up periods

Model Type	Odds ratio	95% CI	p-value
Crude Model for All Injuries	0.84	(0.68, 1.03)	0.08
Model for All Injuries Adjusted for Age and Gender	0.84	(0.68, 1.03)	0.08
Crude Model for Vigilance Related Injuries	1.00	(0.73, 1.37)	0.98
Model with Vigilance Related Injuries Adjusted for Age and Gender	1.01	(0.74, 1.37)	0.97

Table 15 Unadjusted generalized mixed effects model comparing OI in OSA group vs. matched population-based comparison group for all OI over five-year follow-up periods

Parameter	Estimate	95% CI	SE	P-Value
Intercept	-9.20	(-9.33- -9.08)	0.06	<.01
Patient / Matched Subject (reference)	-0.20	(-0.43-0.03)	0.12	0.08

Table 16 Adjusted generalized mixed effects model (for Age Group and Gender) comparing OI in OSA group vs. matched population-based comparison group for all OI

Parameter	Estimate	95% CI	SE	P-Value
Intercept	-9.20	(-9.54- -8.85)	0.18	<.01
Patient / Matched Subject (reference)	-0.21	(-0.44- -0.02)	0.12	0.08
Gender (Male/ Female (reference))	0.49	(0.28-0.70)	0.11	<.01
Age Category	-0.06	(-0.11- -0.01)	0.02	0.01

Table 17 Unadjusted generalized mixed effects model comparing OI in OSA group vs. matched population-based comparison group for vigilance related injuries

Parameter	Estimate	95% CI	SE	P-Value
Intercept	-10.31	(-9.33- -9.08)	0.12	<.01
Patient / Matched Subject (reference)	-0.01	(-0.43-0.03)	0.17	0.98

Table 18 Adjusted generalized mixed effects model (for Age Group and Gender) comparing OI in OSA group vs. matched population-based comparison group for vigilance related injuries

Parameter	Estimate	95% CI	SE	P-Value
Intercept	-10.92	(-11.45- -10.40)	0.27	<.01
Patient / Matched Subject (reference)	0.01	(-0.32- 0.33)	0.17	0.97
Gender (Male/ Female (reference))	0.67	(0.35-0.99)	0.16	<.01
Age Category	0.02	(-0.05- 0.08)	0.02	0.55

There was no evidence of a relationship between OSA and OI. Although the odds of OI were below '1' suggesting a protective effect of OSA, the 95% CI around these estimates included '1' for both the unadjusted (OR 0.84, 95% CI 0.68, 1.03) and adjusted models (OR 0.84 95% CI 0.68, 1.03).

Given the inclusion of '1' in the CIs and the distribution of the CIs for both the adjusted and unadjusted models, the results suggest that when looking at this clinic-based sample compared to a matched comparison group taken from the general population, there was no difference in injury rate prior to PSG date between the two groups.

In a secondary analysis looking specifically at vigilance related OI, the odds of OI were close to '1' and the 95% CIs included '1' in both the unadjusted model (OR 1.00, 95% CI 0.73-1.37, p= 0.99) and adjusted models (OR 1.006, 95% CI 0.77-1.37, p= 0.97) (Table 8). There was no evidence of a relationship between OSA and vigilance related OI in this study of patients with diagnosed OSA compared to population-based matched subjects without OSA.

In the supplementary sensitivity analysis to investigate potential selection bias, 204 patients who presented to the UBC SDC but who did not meet the criteria for diagnosed OSA had 18 OI among 15 patients during the five-year window leading up to their presentation to the clinic (7.4% of patients or 1.94 injuries per 100 person-years of follow-up). This compares to 149 OI in 108 subjects during the same five-year window for 1019 matched comparison subjects (10.6% of subjects or 3.02 injuries per 100 person-years). In other words, the rate of OI was more than 50% greater in the matched comparison group subjects compared to patients from the SDC who did not have OSA. Multivariable modeling could not be done for this supplementary analysis due to the low number of OI.

3.6 Discussion

Based on this retrospective analysis, patients with OSA had a similar rate of OI and vigilance related OI as compared to a matched comparison group taken from the general population. These results were confirmed in multivariable longitudinal models adjusted for matching and the potential confounding effects of age and gender.

The vast majority of studies investigating the relationship between OSA and OI have shown a significant relationship[54-56,77]. Many of these studies were suboptimal, using subjective criteria to diagnose OSA, OI, or both. However, the consistency of the findings across studies indicates the likelihood of a relationship.

A recent meta-analysis on the relationship between OI and OSA found OSA patients had a two-fold (OR: 2.18; 95% CI = 1.53-3.10) increase in the odds of OI[58]. The authors of the meta-analysis noted, however, that injuries were often self-reported and studies were retrospective, and that studies with more rigorous methodologies had lower OR magnitudes than those with less rigorous methodologies. These two factors, in part, help to explain the results obtained in the current study.

While multivariable modeling could not be performed for this supplementary sensitivity analysis due to the low number of OI, the finding that the comparison group subjects suffered 50% more OI than patients without OSA who presented to the UBC SDC, suggests the possibility of selection bias.

3.6.1 Limitations

While attempting to address the shortcomings of previous studies by using validated and or objective measures of OSA from a clinical sample and OI recorded in workers' compensation data, the current study is not without limitations. Some of these limitations may have contributed to the observed findings counter to the hypothesized effect of an association between OSA and increased OI.

Selection bias may be partly responsible for the findings of this study. This selection bias could have been caused by several factors. First, the injury claim rate in BC was approximately 2.40% per annual interval in the 5 years between 2011 and 2015[78]. This is compared to an injury rate of 2.56% per annual interval in the matched comparison group. The higher rate of injuries in the matched comparison group suggests that the controls may not accurately represent the general population. The industry coding in the health registry is only available for residents with employer paid health

premiums – these are generally larger employers (e.g. health care, construction), where injury rates can be higher for some occupational groups. This industry coding was necessary not only for the matching scheme, but also to ensure that these subjects were in fact workers and therefore at risk of an OI. Subjects from the general population whose employers do not pay their Medical Service Plan premiums as well as self-employed subjects would not be included in the matched comparison group. This factor would eliminate a large segment of the working population who would have otherwise been at risk of an OI. Additionally, a number of patients went unmatched and were not used in the analysis because the specific industry they worked in had no matched comparison group subjects available.

Additionally, while the matching scheme considers the industry that a patient or matched comparison group subject worked in, it does not consider the role or specific occupation that the person performed within the industry. Occupation might be a better predictor of injury risk and would thus have been the more effective variable to match on. In addition, patients who suffer from OSA may have been less likely to work high-risk jobs than their matched comparison group subjects working in the same industry, leading to a reduction in OI in OSA patients. Unfortunately, finding a sufficient number of matched comparison subjects was already difficult and matching on occupation rather than industry would have overly limited the available number of matched subjects.

Furthermore, patients who are referred to a sleep clinic might be at reduced risk of OI as compared with workers from the general population for several reasons. Specifically, patients who are symptomatically sleepy from OSA or other disorders may have self-selected out of either high-risk jobs/tasks or reduced their working hours. Additionally, those patients with the most severe OSA will likely have the most severe symptoms and may have been prevented from working altogether (and therefore may not have been included in the analysis as the highest risk group). Also, given the retrospective nature of our design, patients with an OI - especially if severe - may not be referred for sleep evaluation because other medical issues might have been more pressing for them.

It is also likely that a significant portion of the matched comparison group would be diagnosed with OSA if they were tested using PSG. As stated in the introduction, the majority of people with OSA remain undiagnosed and therefore would be misclassified as not having the disease in this study. This misclassification would have likely been differential, affecting the matched comparison group and not the patient's group. This misclassification would bias the results towards the null and may help to explain the results. Unfortunately, the trade-off that was made in order to obtain a large comparison group was that PSGs were not a viable option for the matched comparison subjects.

Further, given that the industry of patients in both the OSA group and the matched comparison was only recorded at one point in time (at the time of the PSG), it is certainly possible that many patients and matched comparison group subjects switched jobs and potentially industries over the course of the five-year study period. Although, workers employed in large industries such as health care, education or construction tend to stay within these industries over time (although they might change employers or even occupations within these industries). As such the misclassification at the level of industry is probably less than would occur using occupation at one point in time. However, it is plausible that workers may change jobs (and thereby industries) because of their OSA and/or OI status over the course of five years resulting in biases towards the null.

Lastly, there may be characteristics that are associated with presenting to a sleep clinic for a suspected sleep problem (i.e. being a part of clinic-based cohort) that make one less likely to suffer an OI. For example, patients who sought out a diagnosis for their sleep concerns may be more health conscious, and thus less likely to suffer an OI than patients who did not present to the sleep clinic. This is again a form of selection bias referred to as volunteer bias where an individual who voluntarily or actively seeks out care for a suspected health condition differs from those who do not in a manner that might affect their likelihood of being injured.

A second limitation resulted from the fact that not all OI are reported or captured by the workers' compensation system, and the current measure of OI represents injuries requiring at least one day of work disability. Therefore, it is possible that a significant number of minor OI were not included in this analysis. Exclusions from workers' compensation coverage include those self-employed individuals who have not purchased personal optional protection coverage from WorkSafeBC, and minor segments of the labor force (e.g. athletes, domestic workers employed for less than 8 hours per week, military, federal police). In the current study, underreporting may be differential by exposure status because individuals with sleep problems leading up to a diagnosis may be reticent to report an injury. This would be the case especially if the injury related to vigilance, as the individuals may have feared losing their jobs if their sleep issues were perceived as affecting to their ability to perform those jobs safely.

Third, many potential confounding variables were not included in the analysis because the data was not available for our matched group. The potential confounding variables include, but are not limited to, data on shift working, sedative medications, BMI, alcohol use, smoking status and prior heart disease.

3.7 Conclusion

In Study 2, patients with OSA were no more likely to suffer an OI in the five years prior to PSG than their matched population-based comparison subjects. The impact of OSA was no greater for vigilance related injuries. Although it is certainly possible that OSA may not be associated with a risk of OI, these results would be contrary to the results of both our retrospective (Chapter 2) and prospective analyses (Chapter 4). The relatively high rate of OI in the matched controls of patients without OSA (i.e., 50% greater) suggests the potential for selection bias. Selection bias that may have resulted from a number of factors including the nature of a clinic-based cohort, undiagnosed OSA in the matched comparison group, or patients with severe OSA self-selecting out of high-risk jobs, likely

impacted the results of the study by preventing the necessary comparison required to adequately address the hypothesis put forth at the beginning of this chapter.

3.7.1 Potential Impact and Future Directions

Future research with prospective methodologies, larger sample sizes, and objective measures of OSA should be conducted in order to eliminate some of the potential methodological biases present in the current study. Specifically, future studies should address both the potential biases associated with clinic-based sampling, as well as studies that try to reconcile the potential misclassification biases associated with a matched population-based comparison group that likely contains a significant number of subjects that have OSA. The results of this study are important in that they can guide future research in the field of OSA and its potential harms in the workplace through a better understanding of the strengths and potential weaknesses of different methodological approaches to the question

4 The Severity of Obstructive Sleep Apnea and Frequency of Occupational Injury: A Prospective Analysis

4.1 Introduction

The third study that was performed for this dissertation was a prospective analysis investigating the association between the severity of OSA and the frequency of OI. It was designed to address several limitations from Studies 1 and 2, while also investigating OI during a different risk window. Study 1 found an association between OSA and OI that trended toward significance in patients referred to the UBC SDC. Study 2 attempted to replicate findings from Study 1 with the use of a comparison group of subjects taken from the general population versus an internal clinic comparison group without OSA. Study 3 also investigates the relationship between OI and OSA, but focuses on the period following diagnosis of OSA. The prospective methodology is an improvement on the first two studies because the exposure (diagnosed OSA using PSG) preceded the outcome (OI). OSA diagnosis typically represents the culmination of a period of chronic symptoms (i.e. not an acute onset or condition) that would be associated with an increased risk of OI prior to diagnosis. This is similar to the investigation in the retrospective period but does assume that symptoms are present before diagnosis that confer risk. In the prospective analyses, the OI being investigated could not have been the cause or impetus for the subjects' exposure or visit to the sleep clinic. Finally, in Studies 1 and 2, it is possible that at the time of retrospective OI, patients either did not have OSA or had less severe OSA than at the time of their PSG. In Study 3, OSA was diagnosed prior to the OI and thus misclassification according to disease status and severity is reduced.

As has already been argued in the Introduction, few studies with rigorous methodologies have addressed the question of the relationship between OSA severity and OI. The combination of objective criteria used to diagnose both OSA and OI, together with the prospective nature of the study make

Study 3 important in terms of its contribution to the scientific evidence base for the association between OSA and OI.

4.2 Objectives

The main objective of Study 3 was to test the hypothesis that OSA severity would be associated with an increased risk of OI during a prospective five-year follow-up period post diagnosis.

4.3 Design and Methods

4.3.1 Recruitment and Study Sample:

Please see section 2.3.1 for recruitment of the study sample used in Study 3 as it was the same as for Study 1.

Subjects were excluded from the analysis if data was missing for either AHI or gender. Subjects were also excluded if they worked fewer than 10 hours per week or had a missing value for the variable industry type to indicate the subject's occupational details. Subjects were required to report working at least 10 hours per week, in the two years prior to PSG in order to be deemed at risk of an OI for the purposes of this study. Registry data was used to ensure patients were registered for the majority of each year during follow-up over the prospective five years.

4.3.1.1 Risks and Confidentiality

Please see section 2.3.1.1 for Risks and Confidentiality associated with Study 3 as they were the same as for Study 1.

4.3.2 Techniques and Tools

4.3.2.1 Questionnaires

Please see section 2.3.2.1 for Questionnaires used in Study 3 as they were the same as used in Study 1.

4.3.2.2 Polysomnography and Definition of OSA Severity

Please see section 2.3.2.2 for explanation of PSG used in Study 3 as they were the same as in Studies 1 and 2.

OSA severity was quantified as it was in the two previous studies using the variable AHI. OSA severity was used both as a continuous variable and was also broken down in to the standard clinical groups: no OSA (AHI = 0-5), mild OSA (AHI = 5-15), moderate OSA (AHI=15-30), severe OSA (AHI$\geq$30).

4.3.2.3 Database

Please see section 2.3.2.3 for explanation of the database used in Study 3 as it was the same as in Study 1.

4.3.2.4 Ascertainment of Occupational Injuries

The outcome of interest was the occurrence of OI in the five-year period following PSG. Ascertainment of OI was obtained as it was in Studies 1 and 2 as described in sections 2.3.2.4 and 3.3.2.4, only this time injuries in the 5-year period following the patients' PSG were obtained. As a reminder, only short-term injuries, long term injuries and fatal injuries were considered ("medical care only" claims were excluded with no information on the injury date or nature/type of injury). Fatal injuries were available in this prospective analysis where they were not in the retrospective analysis

because if a person had had a fatal injury in the period before their PSG, they would not have been available for the PSG.

A dataset containing both the questionnaire results and the PSG data was merged to the WorkSafeBC database by Population Data BC to identify claims that occurred within the five years following the PSG. If a subject had an injury more than 5 years after their PSG date and/or before their PSG date only, they contributed to the analysis but as a patient without an injury. Since only a small portion of patients had multiple injuries, a binary definition, (i.e., any OI or no OI during the five-year follow-up) was used.

4.4 Analysis

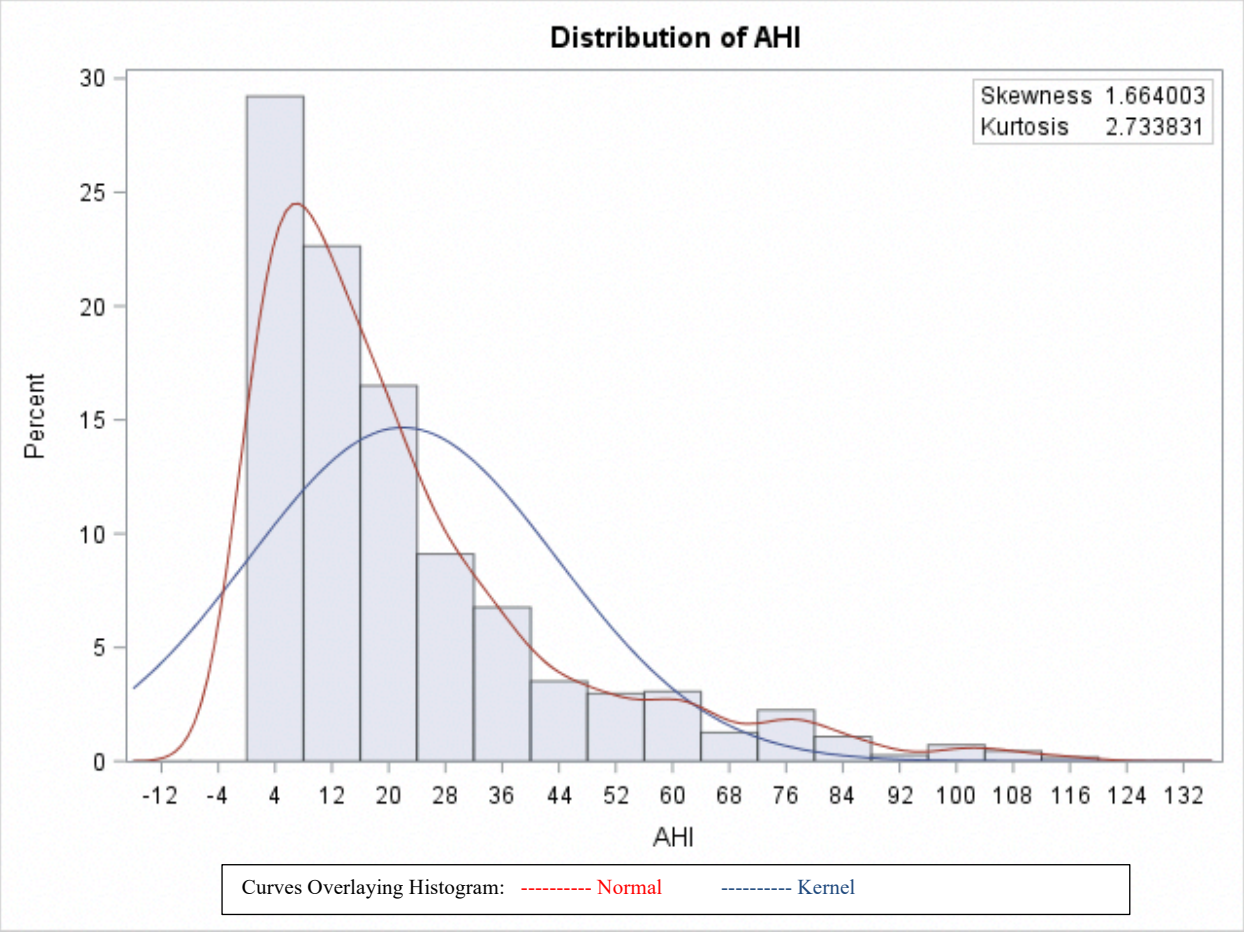
In Study 3, the relationship between the severity of OSA and the incidence of OI was assessed prospectively. Descriptively, for continuous variables with either skewed or extreme values, median and interquartile range values were reported. For categorical variables, counts and percentages were reported. As was the case in Study 1, special attention was given to the variable ESS, because of the hypothesized mechanism by which OSA may lead to OI, and the role excessive daytime sleepiness may play in this mechanism. A univariate analysis was conducted with ESS as the sole predictor of OI to investigate the relationship between ESS and the risk of OI in this prospective cohort. The number of patients with an OI in each of the OSA severity groups was modeled using Kaplan-Meier survival curves. These curves allow the reader to visually compare the number of patients with an OI over time and also show the loss to follow-up. An event or failure in the survival curves was the time at which the patient suffered an OI or suffered their first OI in the case of patients who suffered multiple OI. A Chi-squared trend analysis or Cochran-Armitage test for trend was conducted on the number of patients with an OI in each OSA severity group, in order to determine if there was a trend showing an increasing number of patients with an OI by OSA severity group. The Chi-Square test for trend is used

in the analysis of categorical data when the aim is to investigate the presence of an association between a variable with two categories (i.e. OI) and an ordinal variable (i.e.: OSA severity group). It modifies the normal Chi-Squared test to consider the ordinal nature of the data. A significant result suggests that the slope of the trend line is non-zero

Unfortunately, there were not enough events (OI) to fit the Cox-proportional hazards model and thus we were unable to control for several key variables using survival analysis.

Given a combination of factors, including relatively equal exposure time (only 68 people or 6.1% of the cohort was lost to follow-up and the loss to follow-up was relatively even across OSA severity groups), relatively rare outcome events, and a moderate sample size, logistic regression was selected as the appropriate model for this analysis. Logistic regression analysis was used to model the odds of OI first by OSA group and then by OSA severity (measured as the log [AHI+1]). Log (AHI +1) was used because AHI is often skewed with the majority of patients having an AHI between 1 and 30 and a small number of patients having an AHI in the hundreds. Figure 1 below shows the skewness of the distribution of AHI in this prospective analysis with a histogram of the distribution of AHI. The final models were adjusted for gender, BMI, alcohol use, and industry group. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Figure 3 Histogram showing the distribution of AHI of patients referred to the UBC SDC 2003-2011 for analysis of patients in the five years post-diagnosis



4.5 Results

4.5.1 Baseline Numbers

A total of 1848 subjects were recruited and provided survey and PSG data. The final dataset used for the analysis included 1109 patients. A total of 347 patients were excluded because they were missing data on gender, AHI or the outcome measure. Of these 347 patients, five were excluded because they could not be linked with the registry database and a further seven were excluded because they had no prospective follow-up data. Finally, a further 392 patients were excluded because they reported working less than 10 hours/week in the two years prior to PSG or because they were over 65 years of

age at the time of their PSG (Figure 3). The majority of subjects (70%) were male and the mean age was 47.1 years (Table 19).

Figure 4 Overall Description of Recruited UBC Sleep Disorders Clinic patients included in Study 3

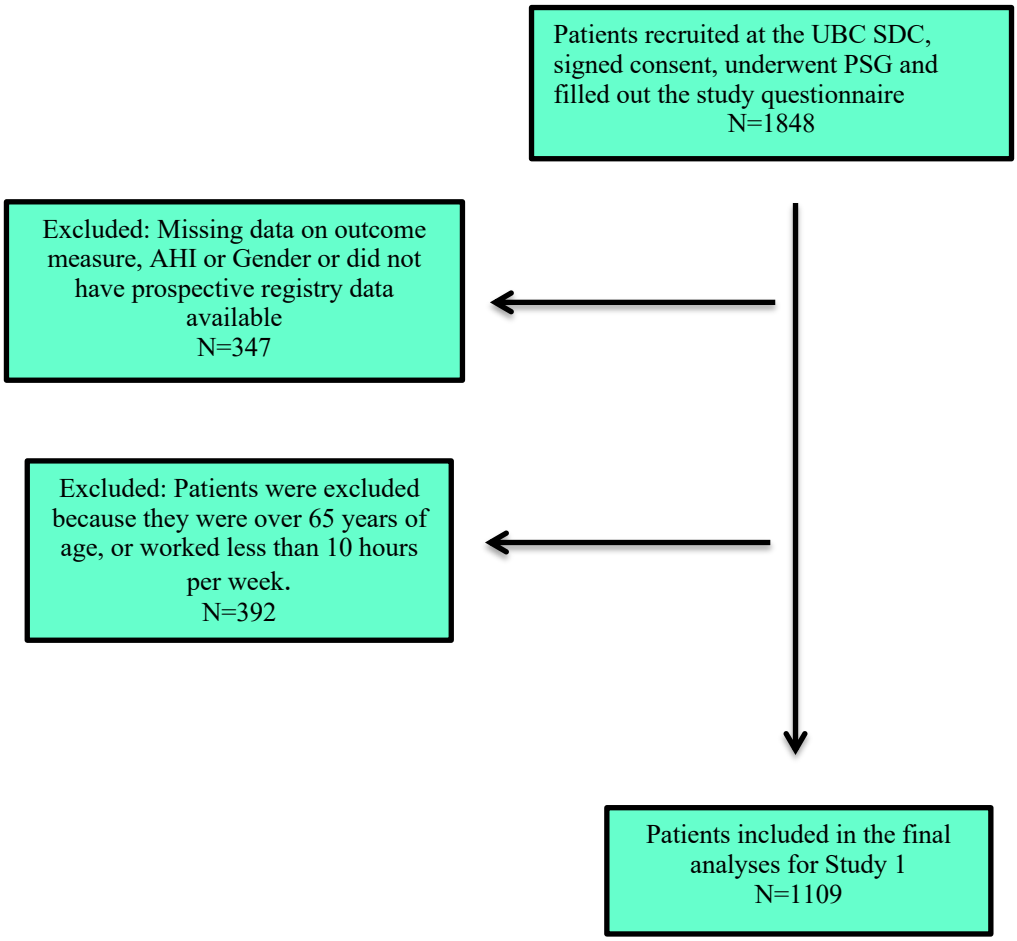


Table 19 Baseline characteristics of patients referred to the UBC SDC 2003-2011 for analysis of patients in the five years post-diagnosis

	All (N=1109)	NO OSA (N=223)	Mild OSA (N=326)	Moderate OSA (N=292)	Severe OSA (N=268)
Continuous Variables	Median/IQR				
AHI (Events/Hour)	15.30 (6.5-29.4)	2.10 (0.90-3.80)	9.60 (7.30-12.30)	21.05 (17.85-24.90)	48.30 (36.4-64.70)
Age (years)	48 (40-55)	44 (35-53)	48.5 (41-55)	49.0 (43-55)	50.0 (43-56)
BMI	30.10 (26.59-34.72)	27.74 (26.02-34.26)	29.34 (26.02-34.26)	30.47 (27.15-34.61)	32.86 (28.73-36.93
ESS*	10 (6-14)	10 (6-14)	9 (6-15)	10 (5-14)	11 (7-15)
Hour Worked Per/Week	40 (36-50)	40 (36-50)	40 (36-50)	40 (38-50)	40 (36-50)
Categorical Variables	Frequency and Percent				
Gender	Male= 787 (70.24%) Female= 322 (29.76%)	Male= 138 (61.88%) Female= 85 (38.12%)	Male= 204 (62.58%) Female= 122 (37.45%)	Male= 214 (72.29%) Female= 78 (26.71%)	Male= 223 (83.21%) Female= 45 (16.79%)
Physical or Manual Labour Related Occupations	Yes= 322 (29.04%) No= 787 (70.96%)	Yes= 57 (25.56%) No= 166 (74.44%)	Yes= 77 (23.62%) No= 249 (76.38%)	Yes= 96 (32.88%) No= 196 (67.12%)	Yes= 92 (34.33%) No= 176 (65.67%)

**ESS scores range from 0-24*

The median AHI was 15 events per hour (IQR= 6, 29), the median BMI was 30 (IQR=27, 35), and the median ESS was 10 (IQR= 6-14). Patients reported working a median of 40 hours per week and 29% of patients worked Physical or Manual Labour Related Occupations.

A total of 79 patients (7.03% of the cohort) had an OI in the 5 years after their PSG and therefore 92.97 % of subjects remained OI free in the five years post-PSG.

In the univariate analysis ESS was not associated with the risk of OI (p=.54).

4.5.2 Survival Curves

Table 20 shows the frequency of OI by OSA group severity status.

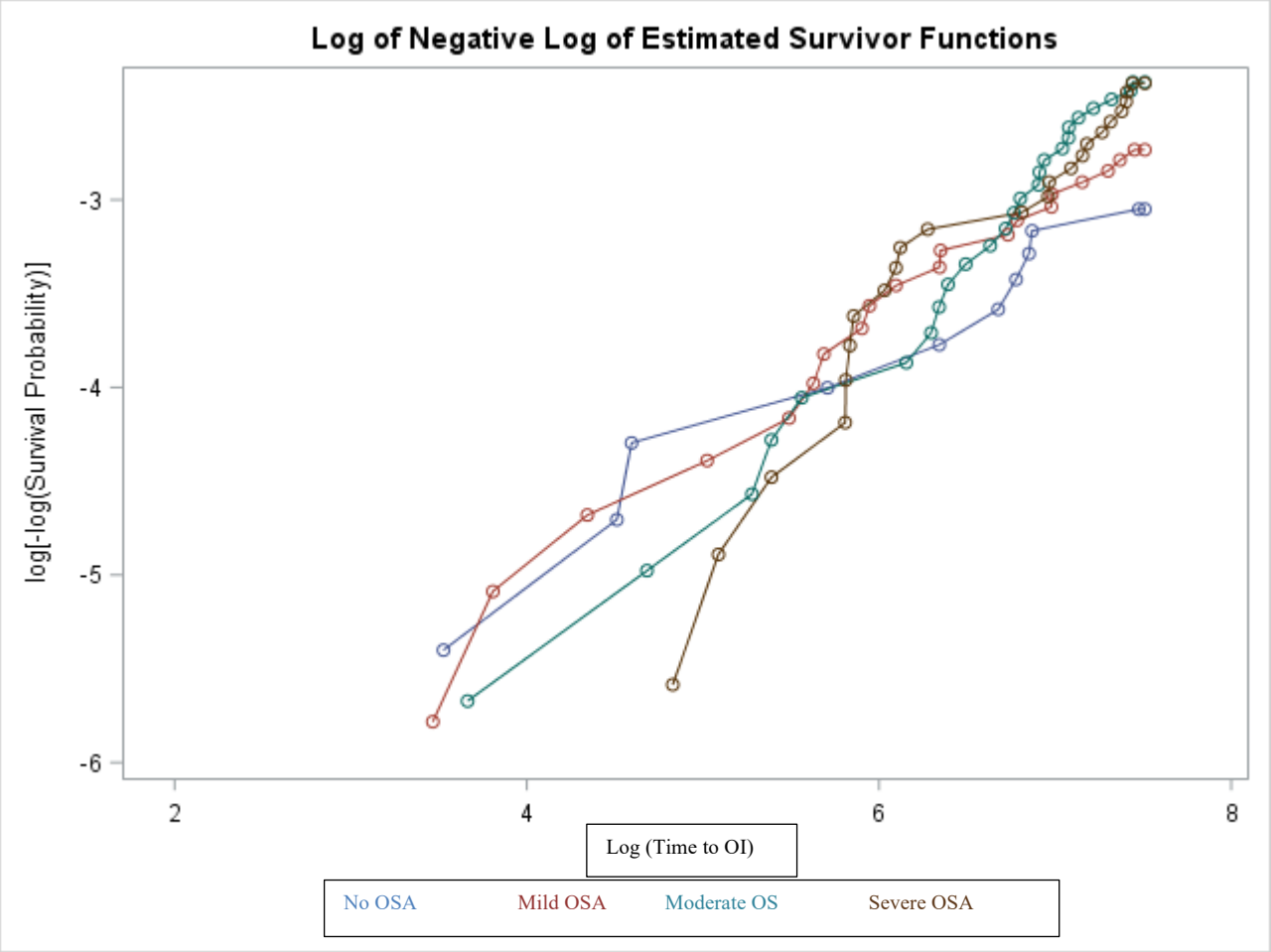
Table 20 OSA severity group by number of patients with an OI, OI frequency and odds of OI in five years post-diagnosis

OSA Severity	No OSA	Mild OSA	Moderate OSA	Severe OSA
Number of Subjects	222	325	291	268
# of Patients with an OI	10	20	25	23
% of Patients with an OI	4.50%	6.15%	8.59%	8.58%
Odds Ratio (Confidence Intervals) *	N/A	1.39 (0.65-3.16)	1.99 (0.96-4.44)	2.00 (0.96-4.49)

Patients with more severe OSA had OI more frequently than patients without OSA. Only 10 out of the 225 patients (4.5%) without OSA had an OI. Amongst those with mild OSA, 20 of 325 patients had an OI (6.1%). This compared to 25 out of 291 patients (8.6%) in the moderate OSA group and 23 of the 268 patients (8.6%) in the severe group.

The log of the negative log of the estimated survivor functions are plotted in Figure 2.

Figure 5 Log of the negative log of estimated survivor functions for the occurrence of OI by OSA severity group in the five years post-diagnosis



As can be seen in Table 21, the survival curves and results of the tests for homogeneity were not significant at the $p < .05$ level.

Table 21 Kaplan-Meier results: Tests for homogeneity of survival curves for the occurrence of OI by OSA severity group in the five years post-diagnosis

Test Performed	**No OSA**	**Mild OSA**	**Moderate OSA**	**Severe OSA**
Rank Statistic				
Log-rank	-5.7075	-3.0344	4.6160	4.1258
Wilcoxon	-5783	-2961	4642	4102
Test of Equality over Strata	**Chi-Square**		**Degrees of Freedom**	**P-Value**
Log-Rank	4.42		3	0.22
Wilcoxon	4.14		3	0.25
-2Log(LR)	4.67		3	0.20

When it came to the test of equality over the four strata, the results for the Log-Rank test were not significant at 0.22. Similarly, the results of the Wilcoxon test and the -2Log(LR) test were also not significant at 0.25 and 0.20 respectively. Unfortunately, due to the small number of events, modeling using the Cox-proportional hazards model was not feasible.

4.5.3 Chi-squared Test for Trend

A Chi squared trend analysis showed a significant trend in the relationship between the number of OI by AHI severity group (Cochran-Armitage Trend Test P-value= .042). Patients with moderate and severe OSA had approximately two times the odds of suffering an OI compared to the patients with no OSA.

4.5.4 Logistic Regression

In the first set of logistic regression models, log (AHI +1) was used as the independent variable and OI was the dependant variable in the unadjusted regression analysis. As can be seen in Table 22, the continuous measure of OSA severity was a significant predictor of OI frequency when it was the only independent variable in the unadjusted logistic regression model.

Table 22 Logistic regression parameter estimates modelling the univariable association between OSA severity (Log (AHI+1)) and OI in the five years post-diagnosis

Analysis of Maximum Likelihood Estimates **Parameter**	**Df**	**Estimate for OI (any vs no)**	**OR for OI**	**95% CI**	**SE**	**Wald Chi-Square**	**P-Value**
Intercept	1	-3.21	N/A	N/A	0.36	80.11	<.01
Log (AHI+1)	1	0.23	1.26	1.00-1.59	0.12	3.73	0.05

The p-value for a one unit increase in the severity of OSA (one unit increase in the log (AHI +1) was .05 with an odds ratio of 1.26 (95% CI= 1.00-1.59), meaning that for every increase in one unit of the log (AHI+1) the odds of occupational injury increased by 26%.

In the multivariate model (see Table 23) that was adjusted for age, gender, BMI, and Physical or Manual Labour Related Occupations work (Y/N), log (AHI+1) remained a significant predictor of the frequency of OI (p= 0.04). ESS was excluded from the multivariate models because ESS was not associated with the risk of OI in a univariate model.

Table 23 Logistic regression parameter estimates modelling the multivariable association between (OSA Severity (Log (AHI+1) and OI in the five years post-diagnosis

Analysis of Maximum Likelihood Estimates **Parameter**	**Df**	**Estimate**	**OR**	**95% CI**	**SE**	**Wald Chi-Square**	**P-Value**
Intercept	1	-1.33	N/A	N/A	0.94	1.98	0.16
Gender (Male vs. Female (Reference)	1	0.04	1.08	(0.58-1.96)	0.16	0.07	0.80
Age	1	-0.02	0.98	(0.96-1.01)	0.01	1.87	0.17
BMI	1	-0.02	0.98	(0.94-1.02)	0.02	1.14	0.20
Log (AHI+1)	1	0.27	1.32	(1.02-1.73)	0.13	3.95	0.04
Worked Per Week	1	-0.01	0.99	(0.97-1.00)	0.01	1.28	0.26
Physical or Manual Labour Related Occupations Hour	1	0.41	2.28	(1.37-3.78)	0.13	10.19	0.01

The odds ratio estimate for log (AHI+1) in the adjusted model was 1.32 (95% CI= 1.02-1.73), meaning that for every increase in one unit of the log (AHI+1) there was an increase in the odds of OI by 32%.

In the second set of logistic regression models, AHI severity group was used as the independent variable and OI (yes to any versus none in the five-year follow-up period) was the dependant variable. As can be seen in Table 24, AHI severity as a categorical measure was not significantly associated with the odds of OI in the five-year prospective follow-up period in the unadjusted logistic regression model. The p-value for AHI group was .21. While the p-value was not significant, the odds of an OI in the moderate and severe OSA groups was twice that of the odds of OI in the No OSA group.

Table 24 Logistic regression parameter estimates modelling the univariate association between OSA severity group and OI in the five years post-diagnosis

Analysis of Maximum Likelihood Estimates **Parameter**	**Df**	**Estimate**	**OR**	**95% CI**	**SE**	**Wald Chi-Square**	**P-Value**
Intercept	1	-2.63	N/A	N/A	0.12	444.04	<0.01
Group (Mild OSA vs. No OSA)	1	-0.10	1.39	(0.65-3.16)	0.21	0.23	0.63
Group (Moderate OSA vs. No OSA)	1	0.26	1.99	(0.96-4.44)	0.19	1.83	0.18
Group (Severe OSA vs. No OSA)	1	0.26	2.00	(0.96-4.49)	0.20	1.78	0.18

In the multivariate model (see Table 25) that was adjusted for age, gender, BMI and Physical or Manual Labour Related Occupations, AHI severity group remained a non-significant variable for the odds of OI during the five-year follow-up period (p= 0.15), and the odds of an OI in the moderate and severe OSA groups remained was twice that of the odds of OI in the No OSA group.

Table 25 Logistic regression parameter estimates modelling the multivariable association between OSA severity group and OI in the five years post-diagnosis

Parameter	Analysis of Maximum Likelihood Estimates					Odds Ratio Estimates and Profile-Likelihood Confidence Intervals	
	Df	Estimate	SE	Wald Chi-Square	P-Value	OR	95% CI
Intercept	1	-0.69	0.99	0.48	0.49	N/A	N/A
Gender (Male vs. Female (Reference)	1	0.02	0.15	0.02	0.89	1.04	(0.56-1.88)
Age	1	-0.02	0.01	2.06	0.15	0.98	(0.96-1.01)
BMI	1	-0.03	0.02	0.90	0.34	0.98	(0.94-1.02)
Group (Mild OSA vs. No OSA)	1	-0.03	0.21	0.02	0.89	1.70	(0.76-4.09)
Group (Moderate OSA vs. No OSA)	1	0.32	0.21	2.63	0.10	2.42	(1.11-5.74)
Group (Severe OSA vs. No OSA)	1	0.20	0.22	1.45	0.23	2.29	(1.01-5.65)
Physical or Manual Labour Related Occupations Hour	1	0.41	0.13	9.86	0.01	2.25	(1.35-3.74)
Hours Worked Per Week	1	0.01	0.01	1.32	0.25	0.99	(0.97-1.00)

4.6 Discussion

Log (AHI+1) was a significant predictor of the frequency of OI (p=.05) and became a stronger and more significant predictor of OI (p=.04) when the model was controlled for a number of potential confounders. Additionally, when OSA was broken down in to severity groups, patients with moderate

and severe OSA had approximately twice the odds of suffering an OI compared to the patients with no OSA (in the unadjusted analysis). Further, the Chi-squared trend test which showed a significant ordinal trend in the relationship between OSA severity group and OI (Cochran-Armitage Trend Test P-value= .042). However, when OSA severity group was used as an independent predictor of OI in both the unadjusted and adjusted analyses, the association between OSA severity group and OI was not significant (p= .15).

Our findings are generally consistent with previous research showing increased rates of OI in patients with OSA [53-56,72,77]. Our results should be interpreted with caution given both the relationship between log (AHI +1) and OI and the results from the Chi-square trend test showed only a borderline effect with p-values close to .05, and these findings should thus be verified in other studies."

With this said, our findings add to the body of evidence on the association between OSA and OI. The prospective methodology of Study 3 addresses two main concerns from Study 1. First, it ensured that the exposure (the diagnosis of OSA at the PSG) came before the outcome (the OI). This may have been an issue in Study 1 where work performance or injury may have been a factor contributing to referral. Patients may have been either referred to a sleep physician or approached their physician on their own volition because they had recently been involved in an OI. Secondly, it eliminates the possibility that the outcome caused the exposure (OI caused the OSA) by ensuring an accurate diagnosis of OSA at the time of PSG, prior to the time at risk.

4.6.1 Limitations

There were a number of study limitations that are important to acknowledge in the interpretation of the findings.

First, while the use of retrospective injuries in Study 1 allowed for the possibility of several biases to potentially limit the validity of the results, it also eliminated the potential confounding effect of treatment. All patients in Study 1 were recruited at the time of their PSG and patients that had previously been on treatment for OSA were excluded from participation in the study. As a result, we were confident that patients in our study had not been treated for OSA in the 5 years prior to their PSG. In Study 3, a significant number of patients on the prospective sample may have been treated and evidence suggests that patients with more severe OSA were more likely to have been treated. As a result, treatment would likely push results towards the null hypothesis. While this study limitation must be acknowledged, the fact that patients with more severe OSA (according to the logistic regression model with log (AHI+1) as a continuous independent variable) were at a higher risk of OI than those with less severe OSA despite the potential effect of treatment, adds to the strength of relationship between OSA and OI. In the next chapter, Study 4 will attempt to quantify the effect of treatment and will give the reader a better understanding of how to interpret the results from this study.

Second, there is a possibility that both the presence and severity of OSA might have changed over the five years following the PSG. There are studies indicating that OSA severity tends to worsen significantly over time, particularly combined with aging and weight gain[74-76]. Given the worsening of OSA over time, there is likely a group of people whose OSA status changed from no OSA (AHI<5) to OSA (AHI>5) in the 5 years after PSG. These people will have been included in the no OSA group for the entirety of the analysis even though they did not technically belong to that group for the entire 5-year post-PSG study period. This misclassification bias would likely have biased the study towards the null.

Third, patients who are referred to a sleep clinic might be at reduced risk of OI for several reasons. Patients who are symptomatically sleepy from OSA or other disorders may have self-selected out of either high-risk jobs/tasks or reduced their working hours and therefore reduced their overall risk of OI

as a result of OSA. Additionally, those patients with the most severe OSA will likely have the most severe symptoms and may have been prevented from working altogether (and therefore may not have been included in the analysis). These issues would bias the study toward the null, dampening the strength of our final estimates.

Fourth, not all OI are reported or captured by the workers' compensation system, and the current measure of OI represents injuries requiring at least one day of work disability. It is important to note that several professions are excluded from the workers' compensation system database as was outlined in the methods, but this would only be a concern if differential by OSA status.

Fifth, similarly to Studies 1 and 2, the association between OSA and OI may have been diluted because patients that were included in the study may have been referred to the clinic for non-respiratory sleep disorders (i.e. insomnia, narcolepsy, depression). These patients might have been at an increased risk for OI because they were suffering from a different sleep disorder that also causes similar attention and vigilance issues. These patients would have been in the no OSA group and might have biased the estimates toward the null hypothesis. However, patients recruited for this study were almost exclusively recruited from the pool of patients referred to the Respirologists and were thus less likely to have been included in our database if they were suffering from insomnia, depression or narcolepsy. This would have likely rendered this limitation a minor concern.

4.7 Conclusion

In Study 3, when the log (AHI+1) was used to model OSA severity as a continuous variable, a significant relationship was observed between OSA severity and OI. We were unable to replicate this finding when OSA severity group was used as the independent variable in our logistic regression models. With this said, patients with moderate and severe OSA had approximately twice the odds of

suffering an OI compared to the patients with no OSA, and the Chi-square trend test indicated a significant relationship between OSA severity and the risk of OI. These significant results were found despite the potentially confounding effect of treatment, which likely would have biased the results towards the null-hypothesis. Overall, the results from this study support the hypothesis of an association between OSA and OI.

4.7.1 Potential Impact and Future Directions

This study corroborates previous studies investigating the relationship between OSA and OI. The finding of a significant relationship between OSA and the occurrence of OI, corroborate the results from Study 1, and provide further support for the idea that selection bias may have hindered the ability to demonstrate the true relationship between OSA and OI in Study 2. In order to validate these findings future studies need to control for the potential effect of treatment on the risk of OI in this population. Additionally, the use of an appropriate control group, comprised of individuals from the general population that would allow for accurate OI risk comparisons would be an important next step in research in this field.

5 The Impact of Continuous Positive Airway Pressure Treatment (CPAP) on the Frequency of Occupational Injuries in Subjects with Obstructive Sleep Apnea: A Before and After Analysis

5.1 Introduction

The fourth study that was performed for this dissertation was an observational study designed to examine the effect of treatment. It was designed to investigate the impact of CPAP treatment on the frequency of OI in subjects with OSA. The study was the first study to attempt to quantify the impact of CPAP on OI in patients with OSA and was therefore designed to fill a major evidence need identified in the literature. Additionally, this study helps to address one of the limitations of the prospective study discussed in Chapter 4 - the potential impact of treatment on the prospective cohort that was studied. As with all observational treatment studies, it is crucial to identify and measure all important potential confounding variables, and to identify measures for controlling for these variables.

As was discussed in the Introduction, CPAP (continuous positive airway pressure) therapy is considered first-line treatment for moderate-to-severe OSA[11]. By establishing a positive transmural pressure in the pharynx during sleep, CPAP prevents the upper airway from collapsing. CPAP reduces the severity of sleep fragmentation and improves nocturnal oxygenation, thereby improving daytime sleepiness, quality of life, vigilance and neurocognitive function [12.] Consistent with these results, the use of CPAP seems to improve work performance in patients with OSA[9,61,62]. However, one of the major impediments to CPAP effectiveness is adherence (ranging from 50 to 75 %)[13]

While there exists a plausible hypothesis that CPAP could lead to reductions in OI, to date, there have been no published investigations using rigorous research methods to support this thesis.

As was the case in Studies 1, 2 and 3, this study incorporated the same objective measures of OSA and of OI. At the time of data collection, measurements of CPAP treatment and adherence for the

current study were abstracted by clinicians from a combination of subjective and objective information and data in the patient charts at the UBC SDC.

5.2 Objectives

The main objective of Study 4 was to test the hypothesis that patients with diagnosed OSA who were adherent to CPAP treatment would have a decreased rate of OI compared to patients who were prescribed CPAP but were non-adherent.

5.3 Design and Methods

5.3.1 Recruitment and Study Sample

Please see section 2.3.1 for a description of the Recruitment and Study Sample for Patients from the UBC SDC for Study 4.

The only change from the Recruitment and Study Sample as used in Studies 1 and 3 was that patients were followed for 5 years starting 30 days after their PSG date rather than just 5 years after their PSG. This five-year period was again chosen because it was short enough that the degree of OSA that a patient had was unlikely to change significantly and was long enough to capture a reasonable number of OI to power the study. The 30 additional days were selected because patients generally do not start CPAP until 30 days after their PSG.

In order to conduct the analysis for this study, the same decisions that were made in previous studies were used to determine patient eligibility. To be included in the analysis, a patient had to be at risk of OI for the majority of the time he/she contributed to the analysis. As a result, patients' inclusion in the analysis was determined BC residency, which was based on MSP registry data. Annual intervals were created both retrospectively and prospectively for each patient using the PSG date. For each interval, a patient had to be in the registry for a minimum of 75% of the year (274 days) to be

considered a BC resident in that year. This criterion is a commonly used to ensure a consistent period of risk for OI. Those patients who were not BC residents for any of the 5 yearly intervals after their sleep study were excluded from analysis.

In this study, the treatment group was all those patients who were diagnosed with OSA (AHI$\geq$ 5), who were prescribed CPAP and who were then adherent to CPAP. The reference group for Study 4 were those patients who were diagnosed with OSA who were prescribed CPAP and who were subsequently non-adherent to CPAP. To be eligible for the reference group, a patient had to be prescribed CPAP, but the patient did not have to obtain the machine. The reference group is made up of a combination of patients who obtained the CPAP machine but who were unable to comply with CPAP, in addition to patients who either did not bother to obtain a machine, or to return for a follow-up appointment after being prescribed CPAP.

Study 4 also investigated the number of OI prior to PSG compared to the number of OI post-PSG by CPAP adherence status. For this portion of the analysis, all patients had to have equal follow-up time both retrospectively and prospectively. Patients were thus only included in this portion of the analysis if they fulfilled the BC registry resident requirements for both the five years preceding and following PSG.

5.3.1.1 Risks and Confidentiality

Risks and Confidentiality associated with Study 4 were the same as for Studies 1, 2 and 3. Please see section 2.3.1.1.

5.3.2 Techniques and Tools

5.3.2.1 Questionnaires

The questionnaires used in Study 4 were the same as for Studies 1,2 and 3. Please see section 2.3.2.1.

5.3.2.2 Polysomnography

The explanation of PSG used in Study 4 was the same as for Studies 1,2 and 3. Please see section 2.3.2.2.

5.3.2.3 Database

The explanation of the database used in Study 4 was the same as for Studies 1, 2 and 3. Please see section 2.3.2.3.

5.3.2.4 CPAP Adherence

CPAP adherence was determined by reviewing patient charts from the UBC SDC for the included study sample. A group of sleep researchers that included myself, a fellow PhD Candidate (Dr. Bernardo Peres), and a Master's student (Morvarid Mehrtash), who worked with our research team, reviewed all available charts and reviewed both the objective and subjective (descriptive) data within the patient charts in order to fill out a CPAP adherence spreadsheet. CPAP adherence was defined according to the recognized standard of at least four-hours/night for at least 70% of nights[80]. Where objective data was available, it was used in concert with the subjective or descriptive data provided by both the physicians and the patients in order to determine adherence.

Objective data was available if patients used certain private CPAP providers who placed computer chips in the patient's CPAP devices. These computer chips recorded the patient's total minutes of adherence broken down by night. The data from the chips was then sent by the CPAP providers to the UBC SDC and was included in the patient charts.

Subjective data, was any information garnered from consultations between the sleep doctor (Respirologist) and the patient in follow-up appointments following the prescription of CPAP.

If only subjective data was available, it was used on its own. Two experts then reviewed the spreadsheet to determine whether or not patients were adherent with the therapy. Discrepancies were resolved by consensus – re-reading of the discrepant information on the chart. Ascertainment of adherence was done blinded with respect to the occurrence of OI. A Kappa statistic was calculated to determine the reliability between the two scorers. The kappa statistic was 0.99, indicating a high rate of inter-rater reliability.

An attempt was also made to contact patients two years following their PSG with a follow-up phone questionnaire in order to gather more accurate CPAP adherence data. Unfortunately, less than 50% of the cohort could be re-contacted despite many attempts to reach each subject.

For this analysis, patients were categorized as adherent group or non-adherent for CPAP. The non-adherent group of patients was made up of a combination of people who clearly reported that they were not using the machine or were unable to adhere to CPAP (as above), plus a group of people who failed to return for a follow-up consultation and were assumed to have never obtained or used a machine.

5.3.2.5 Ascertainment of Occupational Injuries

The explanation of the ascertainment OI used in Study 4 was the same as for Study 3. Please see section 4.3.2.5.

5.4 Analysis

The presence or absence of an OI in each interval was the primary outcome of interest. Multiple injuries within an annual interval were counted only once (yes to any versus none during the annual period with follow-up censored at the first period with an OI). Given that each patient could contribute up to five annual intervals to the prospective analysis, the data was longitudinal in nature and any analysis done on the data had to include methods taking this into account.

Calculations were performed to ensure there would be a large enough sample size to accurately power the study. For this calculation, we assumed an OI rate of 8 % (reasonable given the OI rate in the OSA group in the prospective analysis in Study 3). Additionally, we assumed 40% of the total recruited cohort would be treated (based on prior knowledge of the UBC SDC population). Given these assumptions, in order to power a study at .80 with the alpha (p-value) set at .05, we would need a sample size of 554 patients.

Descriptively for continuous variables with either skewed or extreme values, median and interquartile range values were reported for the descriptive analyses. For categorical variables, counts and percentages were reported, and group differences were tested using the Chi-square test.

As was the case in Studies 1 and 3, special attention was given to the variable ESS, because of the hypothesized mechanism by which OSA may lead to OI, and the role excessive daytime sleepiness may play in this mechanism. ESS was measured only once at the time of the PSG, as it was in the three previous studies. A bivariable analysis was conducted with ESS as the sole predictor of OI to investigate the relationship between ESS and the risk of OI in this prospective cohort.

The first analysis that was conducted was a survival analysis exploring the association between CPAP adherence and OI. Initially, survival analysis was chosen because of the unequal follow-up times of subjects (a combination of censoring due to OI, as well as issues of attrition). Patients were lost to follow-up, either due to their residency status, or because they died in the follow-up period)). The explanatory or predictor variable in the survival analysis was CPAP adherence (yes or no, based on the standardized definition of adherence described above and determined from patient chart data of follow-up appointments with the sleep doctor usually within the first few months following PSG). Kaplan-Meier curves were created for each CPAP group, providing both visual and numerical indicators of whether or not the OI frequency was likely different between groups. Log-rank and Wilcoxon statistics were used to test for homogeneity between survival curves. Unfortunately, there were not enough

events (OI) to fit the Cox-proportional hazards model and, therefore we were unable to control for several key variables in the survival analysis.

The Kaplan-Meier curves did, however, indicate that rates of loss to follow-up were quite low and did not differ between groups. As a result, the use of logistic regression was deemed to be a viable option that would allow for the controlling of several key potential confounding variables, including gender, OSA severity, BMI, and physical or manual labour related occupations. Logistic regression was then performed, first with adherence group as the sole predictor and OI (yes, no during any one-year follow-up period, over the five-year follow-up period post PSG) as the outcome variable, and subsequently with the aforementioned potential confounders included in the regression model.

A third analysis was also conducted using a combination of retrospective and prospective data (i.e., OI before and after PSG). This third analysis used Mcnemar's test within each of the two adherence groups. The OI frequency in subjects in the five years post-PSG was compared to the OI frequency in the same subjects in the five years prior to PSG. Given subjects were compared to themselves, there was no need to control for confounding variables, and the overall power of the analysis was greatly increased. Mcnemar's test does, however, require equal time at risk before and after PSG. As a result, all subjects who did not contribute to the full five years both before and after the PSG date were removed from the third analysis.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

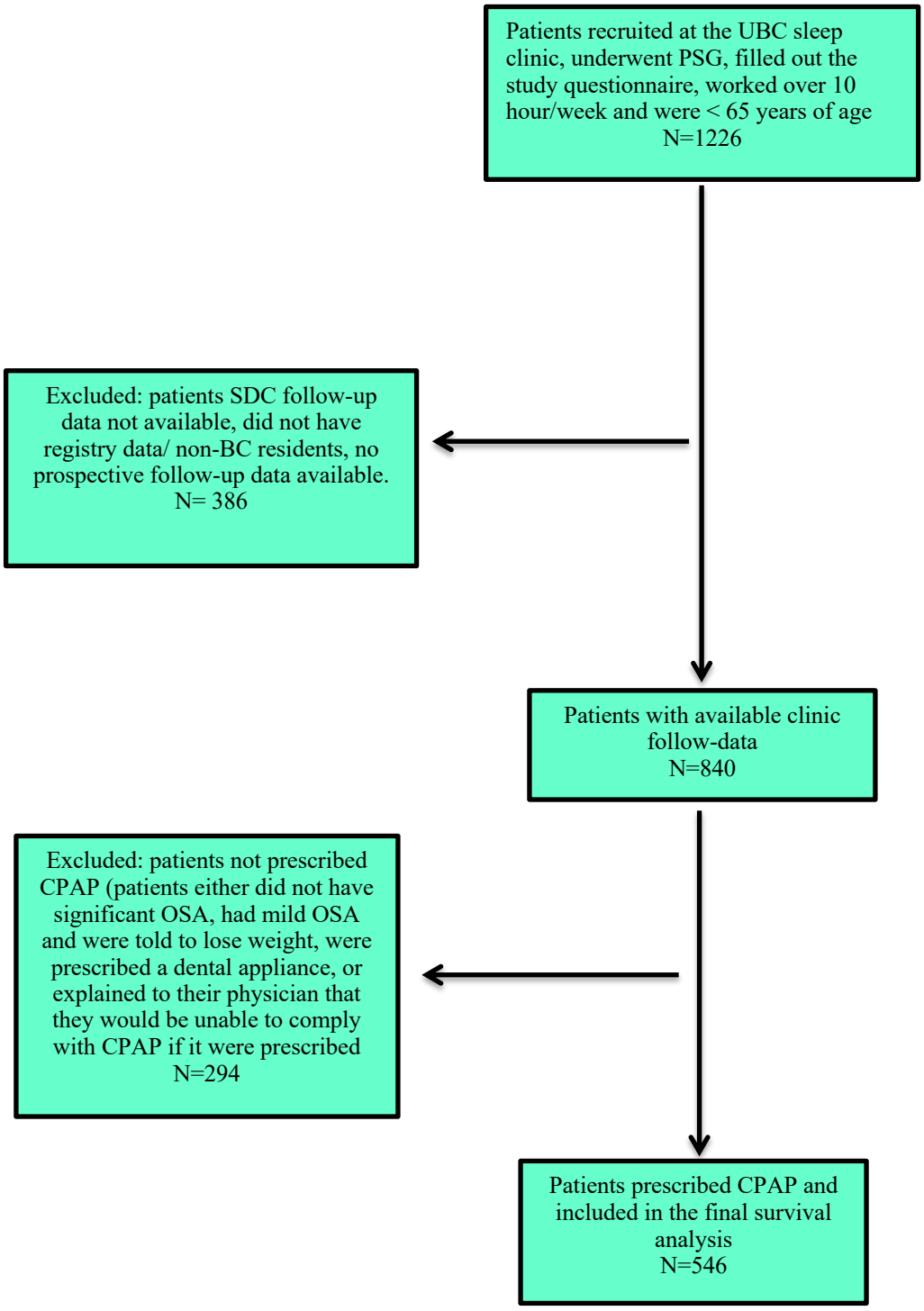
5.5 Results

5.5.1 Baseline Characteristics

As can be seen in Figure 3 below, a total of 1226 patients were recruited at the SDC, underwent a PSG and filled out the study questionnaire, were under 65 years of age at the time of the PSG, and worked at least 10 hours per week in the two years before their PSG. Only 840 patients had follow-up

data available through their UBC SDC charts. An additional 294 patients were excluded from the analysis because they were not prescribed CPAP. These patients were not prescribed CPAP either because they did not have significant OSA, had mild OSA and were told to lose weight, were prescribed a dental appliance, or explained to their physician that they would be unable to comply with CPAP if it were prescribed. As a result, 546 patients who were prescribed CPAP were used in the survival analysis.

Figure 6 Overall Description of Recruited UBC Sleep Disorders Clinic patients included in Study 4 on the association between CPAP adherence and the occurrence of OI



The final cohort used for the analysis was comprised of 546 patients categorized according to their CPAP status of adherent and non-adherent. As can be seen in Table 26, the majority of patients (73.7%) were male and the median age was 50 years (IQR= 43, 56). The majority of patients did not work physical or manual labour related occupations (71.3%). The median AHI in patients was 22.4 events /per hour (IQR=13.0, 41.4). Patients had a median BMI of 31.2 kg/m^2, reported a median of 40.0 work hours per week, and had a median Epworth Sleep Score (ESS) of 11.

Table 26 Baseline characteristics of patients by CPAP adherence group status, 2003-2011

	All	CPAP Adherent	CPAP Non-adherent	P-Value
Number of Subjects	546	279	267	-
Gender				
Male	401 (73.7%)	209 (74.9%)	192 (71.9%)	0.44
Female	145 (26.6%)	70 (25.1%)	75 (28.1%)	
Age	50 (IQR 43, 56)	50 (IQR 43, 56)	50 (IQR 43, 55)	0.86
Physical or Manual Labour Related Occupations	157 (28.7%)	72 (25.8%)	85 (31.8%)	0.12
AHI (events/hour)	22.4, (IQR 13.0, 41.4)	27.0, (IQR 16.9, 48.4)	18.8, (IQR 11.3, 34.7)	<0.01
BMI	31.2 (IQR 27.5, 36.4)	32.2 (IQR 28.0, 36.7)	30.4 (IQR 27.2, 36.1)	0.20
ESS[1]	11 (IQR= 7, 15)	11 (IQR= 8, 15)	11 (IQR= 7, 15)	0.21
Hours Worked Per Week[1]	40 (IQR= 36, 50)	40 (IQR= 37, 50)	40 (IQR= 36, 50)	0.17

Patients who were adherent to CPAP had a similar BMI and worked a similar number of hours per week as the non-adherent patients. Furthermore, the distribution of gender and physical or manual

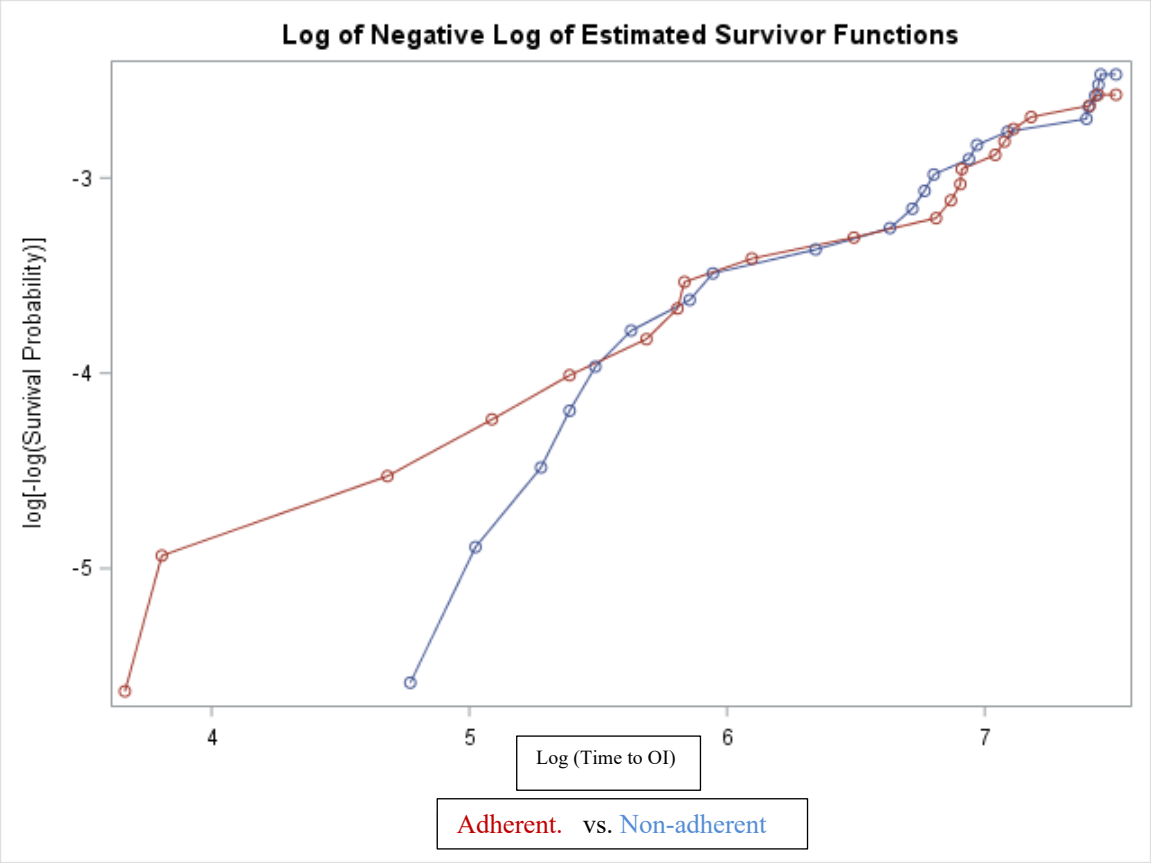
labour related occupations were similar between groups. Importantly, the adherent group a significantly higher AHI than the non-adherent group (median AHI of 27.0 vs. 18.8, p<.001). A univariate analysis revealed that ESS was not associated with the risk of OI in this cohort (p= 0.89).

5.5.2 Survival Curves

There were 279 patients in the CPAP adherent group, compared to 267 patients in the CPAP non-adherent group. Rates of OI were similar in both groups. In the adherent group, 20 (7.17%) patients had an OI in the five years after their PSG date, while in the non-adherent group, 21 (7.87%) patients had an OI in the five years after their PSG date.

Kaplan-Meier Curves were produced for time to OI by CPAP adherence status and the life-test procedure was conducted to test for the homogeneity of the survival curves. The log of the negative log of the estimated survivor functions are plotted in Figure 4.

Figure 7 Log of the negative log of estimated survivor functions for the occurrence of OI by CPAP adherence status in the five years post-diagnosis



As can be seen in Table 27, the survival curves and results of the tests for homogeneity were not significant. When it came to the test of equality over the two strata, the results for the Log-Rank test were not significant at 0.76. Similarly, the results of the Wilcoxon test and the -2Log(LR) test were also not significant at 0.78 and 0.76 respectively. Unfortunately, due to the small number of events, modeling using the Cox-proportional hazards model was not feasible.

Table 27 Kaplan-Meier Results: Tests for homogeneity of survival curves for the occurrence of OI by CPAP adherence status in the five years post-diagnosis

Test Performed	**Adherent**	**Non-Adherent**	
Rank Statistic			
Log-rank	-.98	.98	
Wilcoxon	-465	465	
Test of Equality over Strata	**Chi-Square**	**Degrees of Freedom**	**P-Value**
Log-Rank	0.09	1	0.76
Wilcoxon	0.08	1	0.78
-2Log(LR)	0.09	1	0.76

5.5.3 Logistic Regression

The low rate of loss to follow-up (only 23 out of 546 or 4.2% of patients who did not have an OI did not complete the full five-year follow-up), allowed for the use of logistic regression.

In the subsequent multivariate logistic regression analysis that was completed, the dependant variable was OI (Yes/No) and the independent variables that were used in the model included gender, physical or manual labour related occupations, AHI, BMI and adherence status. The results from the model can be seen in (Table 28). CPAP adherence status was not associated with the likelihood of patients suffering OI in the 5-years following PSG.

Table 28 Logistic regression parameter estimates modelling the association between adherence and OI in the five years post-diagnosis

Analysis of Maximum Likelihood Estimates **Parameter**	**Df**	**Estimate**	**OR**	**95% CI**	**SE**	**Wald Chi-Square**	**P-Value**
Intercept	1	-2.48	N/A	N/A	1.58	2.46	0.12
Adherence	1	0.52	2.86	(0.93-12.48)	0.32	2.69	0.10
Gender (Female = Reference)	1	0.07	0.88	(0.31-2.70)	0.27	0.06	0.81
Age	1	-0.01	0.99	(0.94-1.04)	0.02	0.23	0.63
BMI	1	0.01	1.00	(0.94-1.07)	0.03	0.02	0.89
AHI	1	-0.01	1.00	(0.98-1.01)	0.01	0.17	0.68
Physical or Manual Labour Related Occupations	1	-0.18	0.70	(0.27-1.94)	0.25	0.53	0.47

5.5.5 A Before and After Analysis

In a third analysis, Mcnemar's test was used to compare the frequency of OI in patients in the five years prior to PSG to the frequency of OI in the 5 years post-PSG by adherence status. Due to the requirement of equal follow-up times, the total number of patients analyzed in this third analysis was reduced to 489 (these patients contributed the full five years of follow-up both before and after the PSG).

The resulting two groups contained 250 adherent patients and 239 non-adherent patients. In the 250 adherent patients, 211 (84.0%) had no OI either before or after their PSG; 19 (7.6%) patients had an OI before, but not after the PSG; 15 (6.0%) had no OI before, but an OI after the PSG; and 5 (2.0%) had an OI both before and after the PSG. The results for the Chi-square test for the adherent group was equal to 0.47 with 1 degree of freedom and a p-value of 0.49, indicating there was no statistical difference in the likelihood of having an OI post-PSG compared to pre-PSG in patients who adhered to CPAP.

In 239 non-adherent patients, 205 (85.8%) had no OI either before or after the PSG; 19 (7.9%) patients had an OI before, but not after the PSG; 14 (5.9%) had no OI before, but an OI after the PSG; and 1 (0.4%) had an OI both before and after the PSG. The result for the Chi-square test for the non-adherent group was equal to .76 with 1 degree of freedom and the p-value was 0.38. These results indicate that there was no statistical difference in the likelihood of having an OI post-PSG compared to pre-PSG in parents who did not adhere to CPAP.

The frequency of OI before PSG was similar to the frequency of OI after PSG in both the adherent and non-adherent groups. Given the negative results in this before after analysis in both groups, and the fact that the two groups (adherent and non-adherent) were not comparable as evidenced by significant differences in OSA severity (27.7 events per hour vs. 18.8 events per hour), I felt that a 'difference in differences' analysis (i.e., comparing the change in pre-post OI frequency by adherence status) was not appropriate nor informative.

5.6 Discussion

In our cohort there was no relationship between CPAP adherence status and the occurrence of OI. There were no statistically significant differences between survival curves according to any of the three parameters that were used. The results of the logistic regression model (Table 19) confirmed these findings.

When Mcnemar's test was performed, the results indicated that both adherent patients and non-adherent patients were similarly likely to suffer an injury before the PSG as compared to after the PSG, again suggesting no significant impact of CPAP adherence. It is, however, important to note that the adherent group of patients had significantly more severe OSA when compared to the non-adherent group, potentially limiting the validity of the attempted comparison.

This is the first study to assess the potential impact of CPAP on OI (with the exception of studies focusing specifically on commercial vehicle drivers)[79-81].

The evidence supporting the deleterious effects of OSA on neurocognitive function, specifically on both vigilance and psychomotor function, provide the basis for the hypothesis that OSA would increase the rate of OI in patients suffering from the disease[82-84]. Similarly, evidence showing improvements in these two modalities following treatment with CPAP support the hypothesis that the increases in risk of OI associated with OSA would be reduced or eliminated by the use of CPAP[85-88]. This is the first study to date to attempt to prove this hypothesis separate from studies focusing specifically on commercial MVC. The results of the survival analysis, the logistic regression analysis, and the difference in differences analysis all indicate that in our cohort, CPAP did not reduce OI among workers with OSA.

5.6.1 Limitations

Our study is important because of the novel research question, the large sample size compared to previous studies investigating OSA and OI, and the objective measurement of both OSA and OI. We acknowledge that there are a number of limitations to our study. Many of these limitations have persisted across all 4 studies in this dissertation. These persistent limitations include the fact, not all OI are reported or captured by the workers' compensation system, and that the current measure of OI represents injuries requiring at least one day of work disability. Additionally, the presence and severity of OSA might have changed over the five years after the PSG, resulting in the misclassification of patients by OSA status.

There were also several limitations that were unique to Study 4. Notably, the majority of the CPAP adherence data was based on subjective reports, because most of the CPAP machines used at the time the data was collected did not have chips to measure objective adherence. Furthermore, CPAP adherence data was only collected at one time period, usually 2-3 months after the PSG. Therefore,

although past research has shown early adherence to CPAP is one of the best predictors of long-term adherence[89], it is conceivable that patients were adherent to CPAP in the first 3 months and then stopped using the device later on. The reverse is also possible, meaning that patients could have had trouble with adherence early in their treatment and then become more adherent in the months following their follow-up consultations. Both sets of circumstances could have resulted in a misclassification of patients into the incorrect adherence groups. This was a form of information bias in that subjects may have been incorrectly classified with respect to their exposure status.

Moreover, robust CPAP data was only available for a subset of the original recruited cohort. As a result, both the sample size and the number of events (OI) were small, thereby, making it difficult to see differences in OI occurrence by CPAP adherence status, if they were in fact present.

Lastly, the adherent group of patients had significantly more severe disease than the non-adherent group of patients. While this finding is not uncommon in CPAP studies, it does limit the comparability of the two groups and as a result the conclusions we can draw about the potential effectiveness of CPAP. Also, although the standardized definition of adherence was used (4 hours per night on 70% of nights)[80]; this definition is arbitrary and other thresholds of CPAP use (e.g. 6 hrs per night) might be necessary to reduce OI risk. In addition, we relied heavily on subjective reporting of CPAP adherence data that are not as accurate as objective measures." In general, patients tend to overestimate their adherence (social desirability bias) diluting the ability to detect an effect if one exists.

5.7 Conclusion

In Study 4, patients who were adherent to CPAP with OSA were no less likely to suffer an OI in the five years after their PSG than patients who were non-adherent to CPAP. Three different analyses were performed for Study 4; a survival analysis, a logistic regression analysis, and an analysis to test the rate of OI in subjects before and after their PSGs by adherence status. All failed to reject the null

hypothesis. The results suggest that CPAP may have a limited impact in the prevention of OI in patients with OSA.

5.7.1 Potential Impact and Future Directions

The results of this study are important because they address a previously unaddressed question; what is the impact of CPAP on the frequency of OI in patients with OSA? Although we did not find an impact of CPAP on OI, more work needs to be done in the area. Our study relied mostly on subjective adherence, and future research that uses objective criteria to define treatment adherence is necessary.

Given the proven efficacy of CPAP in improving sleepiness and quality of life [11-13], a randomized control trial of OSA patients in the workplace may be unethical. A randomized controlled trial of a fatigue risk management program in which OSA case finding was a component, could, however, be potentially justified as sites rather than patients would be randomized. Future larger prospective observational studies that could enable matching adherent and nonadherent patients (e.g. propensity score matching) and recording objective adherence through CPAP device downloads would significantly improve on the current study. Specifically, it would allow us to confirm that any differences observed between the adherent and non-adherent group in terms of the frequency of OI would be due to CPAP and not to initial differences in the comparability of the two groups.

Also, it would be interesting to know whether CPAP initiation in the context of a more comprehensive fatigue risk management system (which would also include more intense education and other interventions) might have been more effective.

6 Discussion

6.1 Summary of Results

This section of the discussion will focus on briefly summarizing the results from chapters 2-5 of this dissertation. This dissertation represents the most comprehensive set of studies to date investigating the association between OSA and the risk of OI. Additionally, the fourth and final study on CPAP treatment is the first study to investigate the impact of CPAP on the rate of OI in patients with OSA.

Chapter 2 focused on the first study that was conducted for this PhD - a study investigating the relationship between the presence and severity of OSA and the incidence of OI in a retrospective analysis of patients referred to the UBC SDC. In the unadjusted analysis, patients with OSA were almost twice as likely to suffer an OI compared with those without OSA (p= 0.03). When the model was controlled for a number of potential confounders, patients with OSA were still 1.76 times more likely to suffer an OI than patients without OSA, however the relationship only trended toward significance. In the multinomial model, where vigilance related injuries were assessed, patients with OSA were almost 2.5 times as likely to suffer a potentially vigilance related injury when compared to patients without OSA. However, again this association only trended towards significance (p-value= 0.10) in the adjusted model. The attempt to identify a high-risk group using standardized groupings of OSA severity was unsuccessful.

In Chapter 3, a second study - a retrospective matched comparison study - was conducted. The second study again investigated the relationship between OI and OSA, by comparing the same UBC SDC population investigated in Study 1 to a matched comparison group made up of individuals taken from the general population. In the second study patients with OSA had a similar rate of OI and vigilance-related OI compared to a matched comparison group taken from the general population.

There was no evidence of an association between OSA and OI or vigilance-related OI, nor of severity of OSA and OI in multivariate longitudinal models adjusted for matching and the potential confounding effects of age and gender. Of note, this study had results contrary to both our retrospective and prospective analyses (Studies 1 and 3).

Chapter 4 focused on the third study conducted for this dissertation. Study 3 was aimed at prospectively investigating the same questions as Study 1; the relationship between the presence and severity of OSA and the incidence of OI. In the unadjusted analysis, log (AHI+1) was significantly associated with the frequency of OI (p= 0.05). When the model was controlled for a number of potential confounders, log (AHI+1) remained significant (p= .04). When we used OSA severity group instead of the continuous measure of OSA, the results could not be replicated. OSA severity group was not a significant predictor of the frequency of OI in either unadjusted (p= 0.21) or adjusted models p=0.15). With this said, the Chi-square trend test indicated that OSA severity group was associated with OI risk and patients with moderate and severe OSA had twice the odds of suffering an OI than those without OSA.

In Chapter 5, the fourth and final study conducted for this PhD was designed to investigate the impact of CPAP treatment on the frequency of OI in subjects with OSA. In the first part of the analysis for Study 4, Kaplan-Meier survival curves indicated that there were no statistically significant differences between the adherent and non-adherent groups according to the -2Log(LR) (p= 0.76). In the second part of the analysis, logistic regression modelling indicated that adherence status was not a significant predictor of the outcome variable, the frequency of OI. In a third analysis, Mcnemars' test for paired samples indicated that both the adherent patients and non-adherent patients were similarly likely to suffer an injury before the PSG as compared to after the PSG.

Finally, in a second step of the third analysis, in order to determine the difference in differences, a logistic regression model estimated by the GEE (generalized estimating equation) algorithm indicated a

null finding and an inability to show a difference between the change in frequency of OI from before to after PSG when the adherent group of patients was compared to the non-adherent group of patients.

The association between self-reported daytime sleepiness (ESS) and the risk of OI was analyzed in Studies 1,3 and 4. In all three studies there was no significant association between ESS and the risk of OI in univariate analyses (p-values were in were .70, .54 and .89 respectively). The lack of a relationship between ESS and the frequency of OI was somewhat surprising as sleepiness would be a reasonable proposed mediator of increased OI risk in the setting of OSA. There are a few potential explanations of this lack of association. Patients that contributed data to the analyses in Studies 1,3 and 4 were referred to the UBC SDC for suspected OSA and as a result were generally sleepier than patients from the general population (median ESS in all three studies was 10, a score which is considered the threshold between "higher normal daytime sleepiness" and "mild excessive daytime sleepiness"). This may have diluted the impact of sleepiness as there was not enough variability in this measure in the study sample to be able to detect differences and results might have been different in an unselected worker population. Of note, in previous literature, ESS is not a significant predictor of MVCs in OSA populations[90], which would be consistent with our results. Though speculative, this may be due to conscious limitation of dangerous activities in patients who perceive themselves as sleepy."

Taken together, several key findings stand out from the collection of studies that were conducted:

1. OSA appears to be associated with an increased rate of OI.
2. The association between OSA severity and OI were more equivocal. That is, our retrospective Study 1 failed to show a significant relationship between OSA severity group and the occurrence of OI, but in the prospective Study 3, OSA severity (log (AHI+1) and (Chi-squared for trend)) was associated with risk of OI. Patients with moderate to severe OSA had almost twice the odds of suffering an OI compared to patients without OSA.

3. Study 4 indicated that CPAP adherence was not associated with a reduction in reducing rates of OI.

6.2 Implication of the findings

The conceptual frameworks discussed in the introductory chapter enable us to better understand our results within the broader context of the field of injury research. The results taken as a whole increase our understanding of the relationship between sleep, specifically OSA, and injury mechanisms. The results help to fill several gaps identified in the literature, while also indicating a need for further research in the field.

All four of the studies conducted for this dissertation explored the host factor (the patients or subject) in the epidemiologic triad. The four studies explored the interplay between injury and disease, an understudied element of injury research[63]. More specifically, the research presented in this dissertation attempted to show how the disease, OSA, increases the vulnerability of the host to the agent, energy transfer, through a combination of hypoxemia and sleep fragmentation. From a temporal perspective, our four research studies cover the entirety of Haddon's time axis through their use of both retrospective and prospective methodologies, as well as pre and post-injury data[65,66].

The importance of the temporal element of this research cannot be overstated. Study 1 was able to show how patients with diagnosed OSA were more susceptible to injury in the pre-diagnosis period. Later, Study 3 indicated that that this susceptibility persisted in the five-years after diagnosis. Lastly, Study 4 was an investigation into whether or not treatment was able to reduce this vulnerability.

The PHA model further helps to place our research in context, by requiring us to place the research within the systematic plan of action that it sets forth. As our background research from Chapter 1 indicated, prior surveillance research already indicated both the negative societal impacts and high prevalence of both OSA and OI[37,44,45,47,48]. Research gaps identified in Chapter 1 indicated a need for

risk factor identification - the exploration of the relationship between OSA and OI. Results from both Study 1, the retrospective internal comparison study, and Study 3, the prospective internal comparison study, helped to corroborate previous research identifying OSA as a risk factor for OI[54-58, 72]. The rigour of Studies 1 and 3, with their use of objective measures of both predictor and outcome, strengthened the rigour of the findings.

Study 2, the retrospective matched comparison study, attempted to improve on Study 1 with methods intending to make the results externally valid and generalizable. Unfortunately, a number of biases prevented the ability to accurately compare our study sample to the general population and the results that were obtained were contrary to the majority of previous literature[54-58, 72]. These biases will be discussed in detail below.

Study 4 proceeded to the intervention evaluation level of the PHA model, attempting to intervene on the risk factor identified in Studies 1 and 3. Ultimately, the results indicate that the intervention was ineffective in reducing the effects of OSA on OI. Previous research suggests these results may be unsurprising[91]. The most comprehensive study to date, a multi-center, randomized, double blinded, sham controlled trial on the effectiveness of CPAP, found that while CPAP was effective in mitigating some of the symptoms and comorbidities associated with OSA (i.e.: sleepiness in severe disease, and attention and psychomotor function in moderate disease), it was ineffective in combatting the neurocognition deficits caused by OSA that are likely one of the primary drivers of the relationship between OSA and OI[92].

Study 4 represents an attempt to mitigate an identified problem through an intervention on the host. As was mentioned in the introduction, the host has historically been a difficult target for intervention. Injury researchers have found more success intervening on the environmental factor. In the case of our research this could mean interventions on the socio-cultural environment, such as the

implementation of laws or regulations that could, for example, limit the ability of patients with OSA to performs high-risk jobs.

From a policy prospective, the variability in the results seen in Studies 1, 2 and 3 with regard to both the association between OSA and the risk of OI and the relationship between the severity of OSA and OI, limit the ability to call for broad policy or regulatory change (i.e. calling for screening for OSA in all high-risk industries). Nevertheless, based on the findings, it would not be unreasonable to consider regulations in British Columbia, requiring physicians to report OSA diagnoses obtained from PSGs at the sleep clinics to employers, particularly in high-risk industries. Precedence for this type of reporting already exists in Ontario, where physicians are required to reports a diagnosis of OSA to the Ministry of Transport, where licences may be revoked pending proven and adequate treatment of OSA.

Additionally, improved patient education provided by both sleep physicians as well as a larger scale education campaign on the part of WorkSafeBC about the potential additional occupational risks seen in patients with OSA appears appropriate given the consistency of findings in the field. This could be incorporated into a comprehensive fatigue risk management program. Large scale education campaigns have been successful in the past with respect to alerting the public to the harms of driving while under the influence of alcohol and reducing the overall cost of drinking and driving to society. Similar campaigns could go a long way to educating the public as to the causes and consequences of OSA, particularly in the occupational context.

6.2.1 Strengths and Weaknesses

The research conducted for this dissertation had major strengths and weakness. Studies 1, 2, 3, and 4 were all strengthened by their use of objective measures to identify both OSA and OI and their relatively large sample sizes. The results of Study 1 were further strengthened by success in

demonstrating a relationship between OSA and vigilance related OI (despite the association only trending toward significant in the adjusted logistic regression model), thereby helping to prove part of the mechanism by which OSA makes people more susceptible to OI. Studies 1 and 3 also had a high degree of internal validity because of the comparison of a clinic-based cohort with OSA to a similar clinic-based cohort without OSA. The combination of Studies 1 and 3 were important in demonstrating that the risk associated with OSA in the context of OI is potentially important in both the pre- and post-diagnosis time periods. Study 4 demonstrated that this risk likely persists even when OSA patients are treated with CPAP. Finally, Study 4 was also important because it was the first study to assess the potential impact of CPAP on OI (with the exception of studies focusing specifically on commercial vehicle drivers)[64].

Despite the overall strength of our research, the external validity of Studies 1 and 3 was lacking because of the limited ability to generalize the results from this clinic-based population to the general population. As Study 2 attempted to address these concerns of generalizability, a series of other methodological problems arose. Most importantly, a differential selections bias was present in that a significant number of the subjects in comparison group were likely disease positive (had OSA), resulting in misclassification bias. Misclassification bias also may have impacted the patient group throughout all four studies, as patients with diagnosed OSA at the time of the PSG may have been disease negative at some point in the five-year retrospective period prior to the PSG.

Moreover, selection bias may have also differentially affected the patient group in all four studies in that patients at the highest risk of OSA may have self-selected out of the work force or chosen to work lower risk jobs, differentially affecting the likelihood that a patient group subject would suffer an injury. While the matching scheme in Study 2 was designed to control for industry, it did not consider the role or specific occupation the person performed within the industry and, as a result, a patient may have worked a less risky occupation within an industry than his/her matched control.

A limitation of Study 4 was that objective CPAP data was far less available at that time compared to today. As a result, much of the data collected for Study 4 was subjective in nature and therefore less reliable than it might have been if the study were conducted today. Furthermore, CPAP adherence was only measured at one time, limiting the reliability of the adherence data.

6.3 Future Directions

The findings from the four studies discussed in this dissertation represent significant progress in the investigation of the impact of OSA and its primary treatment on the risk of OI. The results from Studies 1 and 3 should make researchers more confident of the presence of a relationship between OSA and OI. Furthermore, researchers now have a first look at the impact of CPAP treatment on the rate of OI in patients with OSA. That said, the results from these studies are not conclusive and should not be seen as endpoints in research. Rather, they should be used to guide further research in the field.

The identification of a high-risk group was one of the main objectives of this dissertation as it would allow for the identification of the group most in need of intervention. Recent research suggests that AHI may not be the best way to identify this high-risk group because alternative measures of OSA severity may be more likely associated with the symptoms and comorbidities that lead to OI[93].

The Odds Ratio Product (ORP) is a newly developed measure of sleep quality that may be either an effective alternative to AHI or could be used in concert with AHI in identifying the high-risk group. The ORP provides a continuous estimate of sleep depth from the electroencephalogram (EEG)[94]. It uses power spectrum measurement of the EEG determined in 3-second epochs to determine the likelihood of arousal or awakening occurring in the next 30-second epoch. ORP may provide an added dimension in the evaluation of patient's sleep quality. The authors note, “this additional information may help explain symptoms that might not be explained by the conventional sleep report”[94]. As a

result, it may be useful to use ORP in future research that attempts to identify a high-risk group when exploring the relationship between OSA and OI.

Future research on the relationship between OSA and OI can take advantage of both the strengths and weaknesses of the four studies presented here to better understand the relationship between sleep and OI:

1. The results presented in this dissertation suggest the need for studies using different types of sampling. The limitations of a clinic-based cohort have been well documented in this dissertation and future studies should also include population or worker-based cohorts. Population-based cohorts would allow for generalizations to be made to a much larger population. Unfortunately, the cost of using objective measures to diagnose OSA in large population-based cohorts remain prohibitively high in most contexts. That said, ambulatory methods of OSA diagnosis are cheaper, more reliable, and more readily available than ever before.
2. Similarly, the results from Study 2 suggest a strong requirement for research with appropriate controls groups. Additionally, just as objective measures of OSA diagnosis were necessary in the development of the disease positive group, they also should be used in the investigation of the control group to either confirm or refute the presence of OSA, in order to prevent the misclassification bias that hampered Study 2.
3. There is a need for further prospective investigations in a multitude of jurisdictions. Such studies would help to verify the results of our studies and would confirm that the association between OSA and OI exists in other regions and contexts. While the internal validity of Study 3 was a strength, the lack of generalizability was a recognized weakness. Future studies in

different contexts would involve different insurers and different populations - two variables that may affect study results.

4. Future studies with large sample sizes are required. Large sample sizes would mean more events (OI) and an increased ability to stratify patients into groups of OSA severity. This would allow researchers to potentially identify a high-risk group. In the studies conducted for this dissertation, the number of events within each severity group were small enough that differences between groups may have been statistically undetectable even if they existed.
5. Studies are required to advance the understanding of the impact of CPAP treatment on OI risk. These studies should improve on the methodology of Study 4 in a number of ways. First, they should use objective adherence data that is now readily available and which would greatly enhance the validity of future CPAP studies. Secondly, a randomized control trial would be preferable in the investigations of the impact of CPAP on the risk of OI and would provide more reliable evidence to either confirm or reject the findings of our preliminary study. Finally, studies investigating the impact of CPAP on OI should use larger sample sizes because they would increase the likelihood of identifying the true relationship being investigated and would allow for stratification both by OSA severity and by the degree of CPAP compliance.

6.4 Conclusion

Overall, our research demonstrates that OSA is likely important and its presence should be considered in the occupational setting. Retrospectively, patients with OSA were twice as likely to suffer an OI than patients without OSA and were even more likely to suffer a vigilance-related injury in our clinic-based sample (although these associations only trended toward significance). Prospectively both the presence and severity of OSA was associated with the risk of OI. In our study,

CPAP adherence was not effective in reducing the risk of OI in this cohort; however, we believe the impact of OSA therapy on OI risk needs further work especially in the context of a more comprehensive fatigue risk management program. Nevertheless, given these results, intervening on the socio-environmental factors as opposed to on the host may be a more effective way forward. Preventing patients with severe OSA, especially in the presence of objective sleepiness, from performing certain high-risk jobs through government or industry regulation may be considered in the future. Research should also focus on clarifying the link between OSA severity and OI, so that future prevention efforts can be focused on those with the highest risk.

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Appendices

Appendix A: Questionnaire Given to all Consented Participants at the UBC Sleep Disorders Clinic

Please See Following Page for Appendix A

ID Number ☐☐☐☐☐ Today's Date ☐☐ / ☐☐ / ☐☐ MM/DD/YY

Vancouver Coastal Health Authority

North Shore/Coast Garibaldi, Vancouver & Richmond

DEMOGRAPHICS:

1. What is your date of birth: ☐☐ / ☐☐ / ☐☐☐☐ MM/DD/YYYY

2. What is your gender:

   ☐ Male ☐ Female

3. What is your current Marital status:

   ☐ never married
   ☐ married
   ☐ separated but not divorced
   ☐ divorced
   ☐ widowed/widower

4. Does another person regularly share your bed/sleep with you? :

   ☐ Yes ☐ No

5. What is the highest level of education you have completed?

   ☐ Less than high school diploma
   ☐ High school diploma
   ☐ College or University degree
   ☐ Masters or above

SLEEP HABITS:

6. After you have turned out the lights to fall asleep, how long does it usually take you to fall asleep?

   ☐ 0-15 minutes
   ☐ 16-30 minutes
   ☐ 31-60 minutes
   ☐ 61-120 minutes
   ☐ more than 2 hours

7. On average, how many hours of sleep do you get per night on weekdays?

   ☐ ≤5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10+ hours

   On weekends?

   ☐ ≤5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10+ hours

8. On average, how many hours do you spend napping during the daytime on weekdays?

   ☐ None or nearly none ☐ 1-2 ☐ 3-4 ☐ 5-6 ☐ 7+ hours

   On weekends?

   ☐ None or nearly none ☐ 1-2 ☐ 3-4 ☐ 5-6 ☐ 7+ hours

9. Over the last 24 months, which of the following, if any, did you have to do to keep from falling asleep at work? Choose all that apply.

- ☐ I don't have any problems staying awake at work
- ☐ chew gum or candy
- ☐ eat
- ☐ smoke
- ☐ chew tobacco
- ☐ drink coffee
- ☐ drink other caffeinated beverages
- ☐ listen to radio/music
- ☐ moves around/keep physically active
- ☐ other (please describe)

SLEEP-RELATED SYMPTOMS:

10. Do you have difficulty falling or staying asleep?

- ☐ never
- ☐ rarely (less than one night per week)
- ☐ sometimes (1-2 nights/week)
- ☐ frequently (3-4 nights/week)
- ☐ almost always (5-7 nights/week)

11. On average, how many days/nights during the last month have you snored or been told you snored?

- ☐ never
- ☐ rarely (less than once per week)
- ☐ sometimes (1-2/week)
- ☐ frequently (3-4/week)
- ☐ almost always (5-7/week)
- ☐ not sure

12. When falling asleep, how often do you have "restless legs" (a feeling of crawling, aching, or inability to keep legs still)?

- ☐ never
- ☐ rarely (less than one night per week)
- ☐ sometimes (1-2 nights/week)
- ☐ frequently (3-4 nights/week)
- ☐ almost always (5-7 nights/week)

13. In the last 24 months, have you found that you awaken and briefly cannot move your entire body (i.e. felt paralyzed as opposed to feeling very tired)?

- ☐ Yes
- ☐ No

14. In the last 24 months, have you seen or heard things that don't exist upon waking up or falling asleep?

- ☐ Yes
- ☐ No

15. In the last 24 months, have you had sudden muscular weakness (e.g. buckling of your knees) associated with emotion (e.g. while laughing or after hearing a joke)?

- ☐ Yes
- ☐ No

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DAYTIME ACTIVITY

16. In the last 30 days, how likely are you to doze off or fall asleep in the following situations (in contrast to feeling just tired)? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you

	HIGH CHANCE	MODERATE CHANCE	SLIGHT CHANCE	NO CHANCE
a. Sitting and reading	☐	☐	☐	☐
b. Watching TV	☐	☐	☐	☐
c. Sitting inactive in a public place (e.g. theater, Church)	☐	☐	☐	☐
d. As a passenger in a car for an hour without a break	☐	☐	☐	☐
e. Lying down to rest in the afternoon when circumstances permit.	☐	☐	☐	☐
f. Sitting and talking to someone.	☐	☐	☐	☐
g. Sitting quietly after lunch without alcohol.	☐	☐	☐	☐
h. In a car while stopped for a few minutes in traffic.	☐	☐	☐	☐

HEALTH HABITS:

17. Do you currently smoke cigarettes?

☐ Yes ⇨ If Yes, How many per day? ☐ 1-4 ☐ 5-14 ☐ 15-24 ☐ 25-34 ☐ 35-44 ☐ 45+

☐ No

How many years? ☐☐

18. Please fill in your average use of the following beverages during the past year.

	never or less than once per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6-10 per day	11-20 per day	more than 20 day
a. Cola or other carbonated beverage with caffeine, e.g. Coke, Pepsi, Mountain Dew (consider the serving size as 1 glass, bottle, or can)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
b. Tea or iced tea with caffeine (1 cup or glass), not herbal teas	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
c. Coffee with caffeine (1 cup)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
d. Beer (1glass, bottle, or can)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
e. Wine (4 oz glass)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
f. Liquor, e.g. vodka, gin, etc. (1 drink or shot)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

OCCUPATIONAL:

19. Which of the following best describes your current occupational status?

- ☐ employee
- ☐ self-employed
- ☐ disabled
- ☐ retired
- ☐ unemployed but looking for work
- ☐ unpaid work at home
- ☐ full-time student

20. In total over the last 24 months, approximately how many months did you work? ☐☐

21. On average, over the last 24 months, during weeks that you worked, approximately how many hours did you work per week?

☐☐☐

22. What was your predominant occupation over the last 24 months (describe)?

_____

23. Please also mark the ONE description that best characterized your occupation over the last 24 months:

Primary Resources:

- ☐ Agriculture
- ☐ Fishing
- ☐ Forestry
- ☐ Oil and Gas or Mineral Resources

Manufacturing:

- ☐ Food and Beverage Products
- ☐ Metal and Non-Metallic Mineral Products
- ☐ Other Products:
- ☐ Petroleum, Coal, Rubber, Plastic, and Chemical Products
- ☐ Wood and Paper Products

Construction:

- ☐ General construction
- ☐ Heavy Construction (e.g bridges, overpasses)
- ☐ Road Construction or Maintenance

Transportation and Warehousing:

- ☐ Warehousing
- ☐ Transportation and Related Services

Trade:

- ☐ Retail
- ☐ Wholesale

☐ **Working for the Federal Government**

☐ **Military Service**

☐ **Public Administration excluding working for the federal government (e.g. law enforcement, working for the local government)**

Service Sector:

- ☐ Accommodation, Food, and Leisure Services
- ☐ Business Services (e.g. accounting, law office)
- ☐ Education
- ☐ Other Services
- ☐ Healthcare and Social Assistance
- ☐ Professional, Scientific, and Technical Services
- ☐ Utilities

Other:

☐ Please describe:_____

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24. As a percentage, how many of each of the following shifts did you work over the last 24 months (total should equal 100%)

Day shift (e.g. 8am -5 pm)		%
Evening shift (e.g. 3 pm-11pm)		%
Nightshift (e.g. 11 pm to 7 am)		%

25. Given the hours you work, how much on average would someone employed in a field like yours earn in a year?

- ☐ $0-20 000
- ☐ 21,000 -40,000
- ☐ 41,000-60,000
- ☐ 61,000-80,000
- ☐ 81,000-100,000
- ☐ >100, 000

26. Over the last 24 months, did you suffer an occupational injury?

☐ Yes ☐ No

If YES, please answer the following cluster of questions.
If NO, please skip to question 27.

	0	1	2	3	4+
a. If so, how many injuries did you have?	☐	☐	☐	☐	☐
b. How many of these, if any, were reported to the Workers Compensation Board ?	☐	☐	☐	☐	☐
c. In how many of these, if any, do you think sleepiness or fatigue **in you** contributed?	☐	☐	☐	☐	☐
d. In how many of these, if any, was an emergency room visit required?	☐	☐	☐	☐	☐

e. Please take a moment and tell us a few words about each incident

27. Over the last 24 months, did you cause an occupational injury to someone else (do not include accidents described in the above question)?

☐ Yes ☐ No

If YES, please answer the following cluster of questions.
If NO, please skip to question 28.

	0	1	2	3	4+
a. How many injuries did you cause?	☐	☐	☐	☐	☐
b. How many of these, if any, were reported to the Workers Compensation Board ?	☐	☐	☐	☐	☐
c. In how many of these, if any, do you think sleepiness or fatigue **in you** contributed?	☐	☐	☐	☐	☐
d. In how many of these, if any, was an emergency room visit required?	☐	☐	☐	☐	☐

e. Please take a moment and tell us a few words about each incident

MEDICAL HISTORY:

28. What is your height? ☐ Feet ☐☐ Inches OR ☐☐☐ cm

29. What is your current weight (to the nearest pound)? ☐☐☐ Pounds OR ☐☐☐ kg

30. When was your weight last measured? Within the last ☐☐ Months

31. What is your neck circumference (e.g. shirt size) to the nearest inch?

☐ ≤11 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17 ☐ 18 ☐ 19 ☐ 20 ☐ 21 ☐ 22 ☐ 22+

☐ not sure

32. Check the sentence that best describes your situation

☐ I have remained about the same weight (i.e. within 5 pounds) over the last 24 months.

☐ I have gained 5 or more pounds in the last 24 months

Approximately how many pounds did you gain?

☐ 5-10 ☐ 11-15 ☐ 16-20 ☐ 21-25 ☐ >25

☐ I have lost 5 or more pounds in the last 24 months

Approximately how many pounds did you lose?

☐ 5-10 ☐ 11-15 ☐ 16-20 ☐ 21-25 ☐ >25

☐ I am not sure if I have gained or lost weight as I never weigh myself

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33. Has a **physician diagnosed** you with any of the following disorders (check all that apply)?

Psychiatric:

- ☐ A major mood disorder (e.g. depression)
- ☐ A major anxiety disorder (e.g. panic disorder)

Sleep Disorders:

- ☐ Narcolepsy
- ☐ Restless legs syndrome
- ☐ Periodic Limb Movements

Respiratory:

- ☐ Asthma
- ☐ Emphysema
- ☐ Chronic Bronchitis

Cardiovascular:

- ☐ Hypertension
- ☐ Myocardial infarction (heart attack)
- ☐ Cardiac arrythmias (irregular heartbeat)
- ☐ Angina
- ☐ Congestive heart failure

Endocrine:

- ☐ Diabetes
- ☐ Hypothyroidism (low thyroid level)
- ☐ Polycystic ovarian disease

Neurology:

- ☐ Stroke
- ☐ TIA
- ☐ Seizure

34. Have you been previously diagnosed with obstructive sleep apnea by a physician?

☐ Yes ☐ No

If YES, please answer the following questions.
If NO, please advance to question 35.

a. Was this diagnosis based on a full sleep study in which you slept in the sleep laboratory overnight?

☐ Yes ☐ No

b. Was this diagnosis based on a home oximetry study (i.e. where you wore a probe on your finger overnight)?

☐ Yes ☐ No

c. If you answered NO to the above two questions, please describe how your physician made the diagnosis

_____

d. What treatment are you currently using for obstructive sleep apnea?

- ☐ none
- ☐ Positive airway pressure (e.g. CPAP, BIPAP, smart CPAP)
- ☐ dental appliance
- ☐ other (please describe)

35. Have you had surgery specifically to treat your sleep apnea or snoring?

- ☐ Yes ⇨ If YES, please answer the following question: What kind(s) of surgery did you have? (Mark all that apply)
- ☐ No

  - ☐ sinus surgery
  - ☐ laser surgery of the palate/throat
  - ☐ somnoplasty (radiofrequency ablation) of the tongue
  - ☐ formal uvulopalatopharyngoplasty (UPPP) under general anesthesia in the operating room
  - ☐ other. Please describe:

Over the last 24 months, on average, how often did you take:

Any type of the following to get to or stay asleep? (i.e. sleeping aids)

36. Prescription medication:

- ☐ never
- ☐ very rarely (less than once per month)
- ☐ rarely (less than one night per week but more than once per month)
- ☐ sometimes (1-2 nights or days/week)
- ☐ frequently (3-4 nights or days/week)
- ☐ almost always (5-7 nights or days/week)

Name of medication:

37. Non-prescription medication

- ☐ never
- ☐ very rarely (less than once per month)
- ☐ rarely (less than one night per week but more than once per month)
- ☐ sometimes (1-2 nights or days/week)
- ☐ frequently (3-4 nights or days/week)
- ☐ almost always (5-7 nights or days/week)

Name of medication:

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38. Herbal or health food medication

- ☐ never
- ☐ very rarely (less than once per month)
- ☐ rarely (less than one night per week but more than once per month)
- ☐ sometimes (1-2 nights or days/week)
- ☐ frequently (3-4 nights or days/week)
- ☐ almost always (5-7 nights or days/week)

Name of medication: | | | | | | | | | | | | | | | | |

Over the last 24 months, on average how often did you take:

Any type of the following to stay awake? (i.e. stimulants)

39. Prescription medication: (eg. Modafinil, Ritalin)

- ☐ never
- ☐ very rarely (less than once per month)
- ☐ rarely (less than one night per week but more than once per month)
- ☐ sometimes (1-2 nights or days/week)
- ☐ frequently (3-4 nights or days/week)
- ☐ almost always (5-7 nights or days/week)

Name of medication: | | | | | | | | | | | | | | | | |

40. Non-prescription medication (eg. caffeine pills)

- ☐ never
- ☐ very rarely (less than once per month)
- ☐ rarely (less than one night per week but more than once per month)
- ☐ sometimes (1-2 nights or days/week)
- ☐ frequently (3-4 nights or days/week)
- ☐ almost always (5-7 nights or days/week)

Name of medication: | | | | | | | | | | | | | | | | |

Over the last 24 months, on average how often did you take:

Any of the following medications (for any reason)

41. Anti-histamines

- ☐ never
- ☐ very rarely (less than once per month)
- ☐ rarely (less than one night per week but more than once per month)
- ☐ sometimes (1-2 nights or days/week)
- ☐ frequently (3-4 nights or days/week)
- ☐ almost always (5-7 nights or days/week)

42. Antidepressant

- ☐ never
- ☐ very rarely (less than once per month)
- ☐ rarely (less than one night per week but more than once per month)
- ☐ sometimes (1-2 nights or days/week)
- ☐ frequently (3-4 nights or days/week)
- ☐ almost always (5-7 nights or days/week)

43. Other medications: (please list)

_____ _____

_____ _____

_____ _____

Driving Questions:

44. On average over the last 24 months, how many kilometers did you drive per week? ☐☐☐ kilometers

45. Over the last 24 months, did you have any motor vehicle accidents or crashes in which you were driving ?

☐ Yes ☐ No

If YES, please answer the following cluster of questions.
If NO, please skip to question 47.

	0	1	2	3	4	5+
a. How many crashes did you have over the last 24 months?	☐	☐	☐	☐	☐	☐
b. In how many of these, if any, was a police report filed?	☐	☐	☐	☐	☐	☐
c. In how many of these, if any, do you think sleepiness or fatigue in you contributed?	☐	☐	☐	☐	☐	☐
d. In how many of these, if any, was total property damage greater than $1000?	☐	☐	☐	☐	☐	☐
e. In how many of these, if any, were any vehicles involved towed away?	☐	☐	☐	☐	☐	☐
f. In how many of these, if any, were emergency room visits required by anyone?	☐	☐	☐	☐	☐	☐
g. In how many of these, if any, were fatalities involved?	☐	☐	☐	☐	☐	☐

46. Over the last 24 months, did you have any near miss motor vehicle accidents or crashes in which you were driving? (i.e. narrowly avoided property damage or bodily harm)

☐ Yes ☐ No

If so, how many did you have, on average, over this time period?

- ☐ <1 per month
- ☐ 1-4 per month
- ☐ 1-2 times per week
- ☐ 3-5 times per week
- ☐ more than 5 times per week but not everyday
- ☐ everyday or almost everyday

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MOOD QUESTIONS:

Over the last two weeks, how often have you been bothered by any of the following problems?

	Not at all	several days	more than half the days	nearly every day
47. Little interest or pleasure in doing things?	☐	☐	☐	☐
48. Feeling down, depressed, or hopeless?	☐	☐	☐	☐
49. Trouble falling/staying asleep, sleeping too much?	☐	☐	☐	☐
50. Feeling tired or having little energy?	☐	☐	☐	☐
51. Poor appetite or overeating?	☐	☐	☐	☐
52. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down?	☐	☐	☐	☐
53. Trouble concentrating on things, such as reading the newspaper or watching TV	☐	☐	☐	☐
54. Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around more than usual.	☐	☐	☐	☐
55. Thoughts that you would be better off dead or of hurting yourself in some way.	☐	☐	☐	☐

56. If you have checked off any problem on these questions (47-55), how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- ☐ Not difficult at all
- ☐ somewhat difficult
- ☐ very difficult
- ☐ extremely difficult

57. **Women Only:** What is your menopausal status:

- ☐ Premenopausal
  - If premenopausal: Are your periods
    - ☐ regular
    - ☐ irregular
- ☐ Post menopausal (i.e. complete absence of periods)
  - If post menopausal, how long ago did your periods completely stop? ☐☐ Years ago
- ☐ Peri-menopausal

Thank you very much for completing the survey. Your information is very important to us and we really appreciate your time and consideration.

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Appendix B: Consent form for Participation in the Dissertation Research Studies

Consent Form

THE UNIVERSITY OF BRITISH COLUMBIA
RESPIRATORY MEDICINE

Consent Form

Title of Project: Work-related Accidents in Patients with Sleep-Disordered Breathing

Principal Investigator: Najib Ayas MD, MPH. Department of Medicine, Respiratory Division,

Contact Number: (604) 875-5311.

Co-Investigator(s): John Fleetham (875-5653), Jeremy Road (875-4473), Frank Ryan (875-4241), Pearce Wilcox (689-9329), all in the Dept. Of Medicine, Respiratory Division.

Purpose:

We would like permission to enroll you as a participant in a research study. You have been asked to participate because your physician has sent you for an overnight sleep assessment to rule out Obstructive Sleep Apnea (OSA). The purpose of the study is to assess whether OSA leads to worse quality of life, motor vehicle crashes, work-related accidents, and other adverse health effects. Furthermore, we also want to see if patients improve with therapy. We hope to accomplish this by administering a series of questionnaires.

You may refuse to answer any questions on the surveys. If you choose not to continue with the study after or during any one part, you are under no obligation to do so.

Study Procedures:

If you agree to participate in the research, you will be asked to complete several questionnaires on the night of your overnight sleep assessment. These surveys include information about your occupation, driving, sleep habits, general health, cardiovascular health, and chronic pain. These should require about 25 minutes to complete. You will also be contacted for a follow up telephone survey approximately 24 months after your sleep study is completed. This should take about 15 minutes.

We may also link your data with other research databases in the province. This may include linkage with the Workers Compensation Board database, Insurance Corporation of British Columbia, Medical Services Plan, Pharmacare, PharmaNet, and the Mental Health database. This will be for research purposes only, and you will not be identified individually. The database will be developed in accordance with Ministry of Health policies for the use of health

data for research purposes, including privacy-sensitive access and computer storage processes for researchers.

We may also compare your data to randomly selected anonymous individuals (i.e. control subjects) from one or more of these provincial databases.

Confidentiality

We will take precautions to ensure that your information is kept confidential. All documents will be identified only by code number and kept in a locked filing cabinet. Subjects will not be identified by name in any reports of the completed study. All identifying information will be kept separate from the main database in a locked cabinet, with only the Principal Investigator having access to the data. We will keep your data for a total of 20 years. In the future, we may perform further analysis of the data in terms of assessing quality of life, accidents, and other health effects of sleep disorders.

Remuneration/Compensation:

There will be no remuneration for the study.

Contact for information about the study:

If you have any questions or desire further information with respect to this study, you may contact Dr. Najib Ayas or one of his associates at (604) 875-5133.

Contact for information about the rights of research subjects:

If you have any concerns about your treatment or rights as a research subject, you may contact the Research Subject Information Line in the UBC Office of Research Services at 604-822-8598.

Consent:

Your participation in this study is entirely voluntary and you may refuse to participate or withdraw from the study at any time without jeopardy to your medical care.

Your signature below indicates that you have received a copy of this consent form for your own records. You do not waive any of your legal rights by signing this consent form.

Your signature indicates that you consent to participate in this study.

_____

Subject Signature Date

_____

Signature of a Witness Date

Print Name: _____