Urinary Incontinence among Parkinson's Disease Patients in Alberta: Incidence and Risk Predictors

by

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Abstract

Background: Parkinson's disease (PD) is one of the most common neurological chronic diseases among older adults in Canada. More than 100,000 Canadians are diagnosed with PD with an annual incidence of 20 new cases (per 100,000 people). Urinary incontinence (UI) is one of the common non-motor symptoms of PD that significantly affect health-related quality of life. Approximately 55% of Canadians diagnosed with PD have reported UI, yet there is limited research that has examined UI in PD within the Canadian population context.

Objectives: We estimated the incidence rate and cumulative incidence of UI among PD patients aged ≥ 45 years within the first five years of their PD diagnosis in Alberta. We also investigated age, sex, and Charlson comorbidity index (CCI) score as predictive risk factors of developing UI in PD patients.

Methods: A retrospective cohort (2004 - 2014) of PD cases ≥ 45 years with incident UI was assembled using provincial health administrative databases (physician's claim, inpatient, ambulatory, and drug files) of Alberta. Incidence rate and cumulative incidence of UI among PD patients were estimated over the follow-up years and stratified by age and sex. Cox proportional hazard regression was used to evaluate the associated risk predictors of UI in PD.

Results: Among 9,540 PD patients aged 45 years or older in Alberta, a total of 1,253 UI incident cases were identified among them anytime between 2004 to 2014 study period. Within the study period (2004-2014), after following the PD patients for the first 5 years post PD diagnosis, a total of 1,159 incident UI cases were identified among them. Among these cases, 41.8% (21.7% male and 20.0% female) of UI cases belong to age group 75-84 years.

The crude incidence rate of UI in PD patients was 17.8 per 1,000 person-years and the observed highest incidence rate (37.1 per 1,000 person-years) belonged to the age group 75-84 years. The overall cumulative incidence of UI among all PD patients was 3.8% (95% CI 0.03-0.04) at the sixth month and 14.7% (95% CI 0.14-0.16) at the fifth year. PD patients with UI aged 75-84 years had the highest cumulative incidence (16.2%, 95% CI 0.15-0.18). The cumulative incidence of female patients was comparatively higher than male patients of all ages. At the fifth-year post PD diagnosis, the estimated cumulative incidence of males and females was 13.7% (95% CI 0.13-0.15) and 16.0% (95% CI 0.15-0.17), respectively. After an adjustment for age, the female-to-male standardized cumulative incidence also showed a significantly higher cumulative incidence of UI in females aged 75-84 years throughout the follow-up years.

Hazard ratios (HR) were estimated using age, sex, and CCI score predictor variables in the regression model. Age groups (45-54: reference, 55-64: multivariate-adjusted HR 1.74, 95% CI 1.23-2.45, 65-74: multivariate-adjusted HR 1.84, 95% CI 1.32-2.56, 75-84: multivariate-adjusted HR 2.08, 95% CI 1.50-2.87 and ≥85: multivariate-adjusted HR 1.66, 95% CI 1.17-2.34), sex (male: reference, female: multivariate-adjusted HR 1.24, 95% CI 1.04-1.39), and CCI score (multivariate-adjusted HR 1.04, 95% CI 1.01-1.06) were significantly associated with the development of UI within the first five years of diagnosis of PD. PD patients who belonged to the age group 74-84 years showed a two-fold increased risk of developing UI (multivariate-adjusted HR:2.08, 95% CI 1.50-2.87). The predicted risk of developing UI among PD patients was 1.2 times higher in females. For each 1-point increase in CCI score, there was a 4% greater risk of developing UI in PD individuals.

Conclusion: With the advancement of age, UI incidence among PD patients in Alberta increased, especially in patients aged 75-84 years, and was consistently higher in females.

However, further nationwide research is needed with a longer follow-up period to better understand the burden of UI in PD patients. We believe that our study will provide valuable information concerning the Canadian PD population diagnosed with UI and will influence future studies to address this important health topic.

Preface

This thesis is an original work by Shahela Akhand Laboni. No part of this thesis has been previously published.

Acknowledgments

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PD	Parkinson's disease
UI	Urinary incontinence
WHO	World Health Organization
HRQoL	Health-related quality of life
TCCF	The Canadian Incontinence Foundation
ICS	International Continence Society
OAB	Overactive bladder
PMC	Pontine micturition center
AH	Alberta Health
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canadian Modification
CCI	Charlson Comorbidity Index
CI	Confidence interval
HR	Hazard ratio

Chapter 1: Introduction

1.1 Overview

Parkinson's disease (PD) is the second most common chronic neurodegenerative movement disorder occurring in older populations aged 65 years or above.[1, 2] This chronic condition has a varying progression, and is incurable.[3] Approximately 1.4% of adults over the age of 55 worldwide have PD.[4]

In Canada, PD is one of the leading causes of disability among older individuals.[5, 6] The older population is expected to increase in Canada with a concurrent rise in the incidence of PD.[7] By 2031, it is estimated that about 15% of Canada's total population will be over the age of 65, and the incidence of PD will double between 2011 and 2031.[6] One national surveillance study published in 2013-2014 by the Public Health Agency of Canada (PHAC) reported the prevalence of PD among Canadians (over 40 years) was 0.4%, with a 55.1 per 100,000 population incidence rate.[6] This study was based on the Canadian Chronic Disease Surveillance System (CCDSS) data using two or more physician claims with a diagnosis code (ICD-9) of PD.[6] Other studies show a wide range of PD prevalence in Canada ranging from 69 to 252 per 100,000 people.[5, 8-10] With the increasing incidence of PD and the rising aged population, PD will be a significant health burden for both individuals and the health system in the coming years.

People who are diagnosed with PD typically have motor signs and symptoms, such as resting tremor, rigidity, bradykinesia, and impaired postural reflexes.[2] Non-motor symptoms, such as urinary incontinence, bowel dysfunction, postural hypotension, depression, and dementia are also commonly seen with PD.[11]

Urinary incontinence (UI) is one of the most common non-motor symptoms reported in patients with PD.[10, 12] UI is caused by loss of urinary bladder control, which leads to the involuntary passage of urine.[13] Currently, over 3.3 million people in Canada have UI regardless of PD status.[14] Anywhere from 27% to 70% of the people diagnosed with PD are expected to develop problems with their urinary function throughout the disease course.[15, 16] Approximately 2.8% of the total population of Alberta in 2014 was diagnosed with UI and were predominantly female.[17] Most Canadians diagnosed with UI (74.5%) reported a disturbance in their daily activities and social interactions.[17] Although UI significantly affects an individual's health-related quality of life (HRQoL), UI often goes undiagnosed and therefore remains untreated.[18-21] This could be due to several reasons, including a lack of knowledge of proper management and patients' reticence to report due to embarrassment.[22] According to the Canadian Incontinence Foundation (TCCF), half of the people diagnosed with UI do not know what incontinence means.[17] As well, about 84.3% of people experiencing the symptoms of UI feel uncomfortable talking about it.[14] Therefore, the primary focus of PD may remain limited to the diagnosis and treatment of motor symptoms with little attention toward urinary problems.

1.2 Statement of the Problem

UI can become a serious health concern for a person living with PD due to its adverse impact on health.[13] The health burden associated with UI can lead to disability and therefore significantly reduce the quality of life.[23-26] Some studies have suggested that UI in older PD patients might increase the likelihood of falls and fragility.[27, 28] Although the incidence and economic burden of PD and UI is increasing in the Canadian population, little evidence has been found reporting UI in PD patients.[6, 14, 29]

To determine UI occurrence in PD patients, researchers have mostly used survey data, questionnaires, clinical settings, and literature reviews.[4, 11, 30, 31] Only one Canadian study reported detrimental effects on HQRoL investigating PD adults with UI.[32] There are no studies using administrative health data that have categorized (age and sex) and measured the incidence of UI in Canadian PD population, including associated risk factors. Internationally, only one study has reported the cumulative incidence of overactive bladder (OAB) in PD patients using administrative health data of Taiwan.[30] Therefore, further research is needed to enumerate the actual burden of UI within the PD population.

To measure the burden of UI with PD, the incidence of UI among PD individuals based on provincial health data could be investigated. Examining UI in PD at a population level will allow identifying the burden of UI that may not otherwise be identified through surveys or clinical case series studies. Demographic characteristics and associated risk factors will also be helpful to understand the target population. Moreover, findings from this analysis may provide the basis for specific health care services to address UI with PD.

1.3 Aim and Objective

This thesis examines UI cases in the PD population using provincial (Alberta) administrative health data obtained from Alberta Health (AH) for the fiscal year 2004/2005-2013/2014. The overall aim of this study is to estimate the incidence rate, cumulative incidence, and risk predictors of UI among PD patients aged ≥45 years over the first five years post PD diagnosis.

The specific objectives are:

1. To estimate the incidence rate and cumulative incidence rate of UI among PD patients aged ≥45 years,
2. To estimate the incidence rate and cumulative incidence by sex and age groups,
3. To determine whether age, sex, and comorbidity are risk factors for the development of UI in PD.

1.4 Research Hypothesis and Question

For the estimation of incidence rate (per person-year) and cumulative incidence of UI in PD, we wanted to examine the crude rate and adjusted rates to identify potential risk groups. A prior hypothesis of this study was that age- and sex-adjusted incidence rates would show a significant increase, especially in high-risk groups like the elderly, indicating that age and sex are significant risk factors. We also hypothesized that poor comorbidity would increase the risk of developing UI in PD individuals. Therefore, two main research questions were formulated to check the hypotheses:

1) What are the crude as well as age- and sex-specific incidence rates of UI in patients with PD aged ≥45 years?
2) What are the possible risk factors for developing UI in patients with PD?

1.5 Significance

In response to the Neurological Health Charities Canada, the Public Health Agency of Canada, Health Canada, and Canadian Institute for Health Information that encouraged the

examination of the prevalence, incidence, impact, risk factors, and comorbidities of neurological chronic conditions, we will examine a common health condition (UI) in the PD population.[33] Findings from this work will be one of the first to report the cumulative incidence and risk factors of developing UI in Canadian adults diagnosed with PD.

The lack of evidence regarding UI occurrence in Canadian PD patients is an obstacle to an optimal management plan. Reporting the incidence of UI may put in context the burden of UI with the PD population. Furthermore, this study will identify the potential high-risk group of the PD population with UI. This may also facilitate dialogue between physicians and patients about UI with PD so that effective management can be implemented. Moreover, from a public health perspective, investigating this PD population with UI will have a significant implication on the magnitude of this non-motor chronic health issue among Canadians.

1.6 Thesis Outline

Along with this current chapter, this thesis consists of four additional chapters that include:

- A literature review of UI and PD, including causes, types, possible pathophysiological mechanisms, and treatment options,
- Methods of the analysis which include study design, case definition, and identification of UI cases from PD patient cohort,
- Presentation of the findings,
- A summary discussion of the overall study results in context to important public health perspectives, strengths, limitations, conclusions, and future recommendations.

Chapter 2: Literature Review

2.1 Background

Chronic diseases are now the greatest reason for early mortality and disability among the worldwide older population.[34, 35] Prevalence of chronic disease increases with age and over the next few decades, the overall population of older people is projected to rise.[36] According to the World Health Organization (WHO), the older population (above 60 years) will double by 2050.[37] In response to a global awareness report by WHO on chronic neurological disorders and public health challenges in the aging population, the Canadian Institute for Health Information (CIHI) released a report in 2007 supporting the connection between the increasing incidence of chronic neurological diseases such as PD and the aging population in Canada.[7, 36] As PD occurrence is most in people over 45, it is likely that a common non-motor symptom of PD, UI development is associated with older age groups.[38] Still, an estimate of the occurrence of UI has not been clearly established in older Canadian PD patients.

Most countries are facing major challenges to address the increasing demands of health care utilization, particularly for an aging population with chronic conditions.[34, 39] Chronic health conditions like PD and UI in the older population are also associated with increased healthcare costs.[40, 41] Over the last 30 years, the disease growth curve and financial burden for PD has risen.[42] Global estimations of PD numbers will continue to rise to 8.7 million by 2040 and will cost $50 billion annually for health care services. According to a report from Parkinson Canada, the total direct annual healthcare cost related to PD in Canada was $120,358,000 in 2011.[43] UI is also a substantial economic burden to the Canadian population, and approximately 2.98% of Canadians diagnosed with UI in 2014 had an associated healthcare cost of $2.3 billion.[14] Due to

the increasing aging population and the incidence of UI in PD, this financial burden will continue to rise in Canada.

Although several studies have addressed UI among PD patients in the Canadian population context, we could not find any that reported incidence rate and cumulative incidence using population-based administrative health data.[10, 32, 41, 44] By examining UI in PD at the population level, we will be able to estimate the incidence, which will provide specific evidence-based information for future studies. In addition, understanding the predicted risk factors may help determine future strategies for early detection and treatment of UI within PD.

2.2 Urinary Incontinence

UI is a broad term that includes bladder dysfunction, voiding dysfunction, neurogenic overactive bladder, and neuropathic bladder.[29, 45] The International Continence Society (ICS) defines UI as "*a symptom of overactive or neurogenic bladder as the complaint of any involuntary loss of urine*."[46] It also can be described as bladder dysfunction that resembles the symptoms of UI, such as urgency and frequent urination.[47] The two main disorders featuring incontinence are overactive bladder (OAB) involving urge incontinence and sphincter incompetence involving stress incontinence.[16] Urgency is considered an indispensable indicator of OAB.[48] According to ICS, OAB is a clinical diagnosis of "*urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology*."[49, 50]

2.2.1 Epidemiology of Urinary Incontinence

Worldwide, about 200 million people are diagnosed with UI.[51] Its prevalence is variable across studies, most likely due to methodological differences. The majority of studies have used survey data or questionnaires to determine the prevalence of UI.[47, 48, 51-55] Population-based epidemiological studies reported a prevalence of UI ranging from 9.9% to 36.1% with a higher occurrence in women than men.[48, 56] The first large study of UI on the Canadian population reported an overall prevalence of 18.1% with female predominance.[57] One cohort study reported an overall prevalence of UI in male patients ranging from 3% to 11% with the prominent symptom of urge incontinence.[52] In women, it was estimated that 10% to 55% were affected by UI worldwide, with stress incontinence the most prevalent symptom.[51] Other studies investigating only female patients reported UI prevalence of 36.5% in Canada, 44% in France, 42% in the UK, 41% in Germany, 23% in Spain, and 42.2% in United Arab Emirates.[53-55] One population-based study, which was the first to use the 2002 ICS definitions to evaluate UI symptoms collected data from Canada, Germany, Italy, Sweden, and the UK, and reported an overall prevalence of UI at 11.8% with a similar rate in both males and females.[48]

2.2.2 Overview of the Micturition Reflex

Basic understanding of the physiological process of micturition reflex is necessary to understand the pathological changes related to UI. It is a complex method of neurotransmission that involves central and peripheral nervous systems and sympathetic and parasympathetic receptors.[58, 59] The micturition center located in sacral plexus receives the stimulus from the brain to process urination.[60] This process comprises two anatomical parts: urinary bladder and

urethra.[61] These parts have muscarinic, adrenergic alpha, adrenergic beta, and nicotinic receptors.[61]

Regulatory functions of the bladder (urine storage and voiding) require proper neural signaling through receptors from the micturition center of the brain.[62] Storage of urine is facilitated by the pontine micturition center (PMC). The voiding process is initiated and maintained by a part of the midbrain (periaqueductal gray matter) and PMC.[1, 62] After the formation of urine in the upper urinary tract, it is transported to the bladder. Voiding function involves the stretching of bladder muscles due to the presence of urine and stimulates receptors on the bladder wall to transmit a signal to the central nervous system (CNS).[63] In the returning neural signal, initiation of the bladder muscle and relaxation of urethral sphincter for urination occurs.[63]

2.2.3 Risk Factors for Urinary Incontinence

There is no specific age or time to develop the symptoms of UI; however, the risk of development is associated with the following prognostic or risk factors:

Age: Although UI is not a consequence of normal aging, vulnerability increases with age-related physiological changes in the presence of chronic health conditions. As aging causes physiological modification, the likelihood of developing symptoms of UI increases with age.[64] Earlier studies support UI developing with advancing age, usually after 45 years.[64-66] One cross-sectional study that examined the association between age and prevalence of UI found a significant association in males (OR: 5.3, 95% CI 2.26–12.62) compared to younger adults.[67] Another study found that the prevalence of UI increased significantly with age in females (RR:2.2, 95%CI 1.86–2.57).[68]

Sex: UI incidence is more common in women than men.[14, 64] Some contributors include pregnancy, multiple childbirths, and hormonal changes (menopause).[14] Labour causes multiple phases of contraction and relaxation of internal muscles, which may decrease the integrity of the bladder muscles.[68, 69] A decrease in estrogen during menopause may also weaken the pelvic muscle that supports the bladder.[70] A cross-sectional population survey reported an increased prevalence of UI with pregnancy (RR: 2.2, 95% CI 1.71–2.87), previous vaginal delivery (RR: 2.2, 95% CI 1.72–2.69), and the postpartum period (RR:2.6, 95% CI 2.22–2.97).[68] Another cross-sectional study found the risk of UI increased in multiparous women (RR: 3.3, 95% CI 2.4-4.4) compared to primiparous women (RR: 2.2, 95% CI 1.8-2.6).[70]

Pelvic surgery or trauma: Supporting bladder muscles in the pelvic area may become weak due to pelvic surgery or trauma associated with childbirth.[17] This may eventually increase the risk of developing UI. Using questionnaire data, Peyrat et al. reported an increased risk of UI after hysterectomy (RR:1.5, 95% 1.11–2.08) and caesarean delivery (RR:2.3, 95% CI 1.72–2.69).[68]

Health conditions: The chance of having UI increases with certain health conditions.[65] In chronic urinary tract infection or cystitis, chronic irritation and bladder inflammation may cause UI.[71] Ueda et al. reported a significant association of UI and cystitis in both male (OR:3.1, 95% CI 1.11–8.48) and female (OR: 1.9, 95% CI 1.46–2.63) adults.[67] Neurological conditions like PD, Alzheimer's disease, and multiple sclerosis can cause UI by interrupting both sympathetic and parasympathetic neural pathways of the micturition reflex.[65 72] A cohort study by Buchman and colleagues found a significant association of UI (HR: 1.07, 95% CI = 1.02, 1.12) with incident parkinsonism in older adults (average 78.3 years).[73] Patients diagnosed with cerebrovascular disease may also show symptoms of UI due to weakening or paralysis of the

bladder muscle.[58] One systematic review reported a significant risk of developing UI (pooled OR: 2.7 95% CI 1.3–5.5) in stroke patients.[72]

2.2.4 Types of Urinary Incontinence

There are several types of UI manifested with different clinical signs and symptoms. Among all types, stress incontinence is more common in women, while men are more at risk for urgency and overflow incontinence.[74]

According to the Canadian Continence Foundation (TCCF),[14] the most prevalent types of UI are:

I. **Stress incontinence**: This condition arises from leakage of urine due to exercise, sneezing, or cough. This is involuntary and the urge of urination is absent here.[4] The sphincter becomes hypotonic, which is related to pelvic muscle weakness and urethral abnormality. Approximately 35% of incontinence patients suffer from this symptom.[64]

II. **Urge incontinence**: UI is also denoted as OAB or bladder hyperactivity and is the sudden involuntary leakage of urine with the urgency of voiding sensation.[45] Neurological nerve abnormality, which leads to involuntary spontaneous bladder spasm, is the main predisposing factor.[45] Up to 70% of incontinent patients may have this symptom.[64]

III. **Functional incontinence**: This happens when the patient cannot reach the toilet to void in time and the dribbling of urine occurs. It is common in patients with physical disabilities and limited mobility. Nearly 25% of the total incontinent patient population may have this symptom.[64]

IV. **Overflow obstruction incontinence**: This condition arises from the inability to empty a full bladder and causes involuntary dribble post urination.[75] It accounts for about 15% of patients suffering from UI.[64]

V. **Mixed incontinence**: This is the most common type of UI.[65] It usually combines the symptoms of stress and urge incontinence. The bladder muscle remains hyperactive while sphincter tone is absent.[65]

VI. **Total incontinence**: This happens due to the absolute lack of control over the urinary bladder.[65] As a result, involuntary voiding and incessant leakage occur. Loss of complete function of the detrusor muscle or nerve may lead to this condition.[31] This is commonly seen in spinal cord injury, where the bladder loses the ability to contract and neural transmission between the spinal cord and the central nervous system is interrupted.[31]

2.2.5 Treatment of Urinary Incontinence

Depending on the type, underlying cause, and severity, treatment for UI can be managed by a variety of approaches. Usually, a combination of treatments is needed if any underlying condition is present.[25]

Common treatment options available for UI are:

- **Behavioural therapies**: This includes bladder training (delaying the urge to urinate), learning to urinate twice with a few-minute gap to empty the bladder completely, urinating in a scheduled manner (every 2 to 4 hours), and managing diet and fluid consumption to gain control of the bladder.[76]
- **Exercise**: Pelvic floor muscles are frequently contracted to improve bladder control by strengthening the muscles that regulate the urination process.[76]

- **Electrical stimulation**: Electrical stimulation of the pelvic floor muscles can be effective, especially for urge and stress incontinence.[77]
- **Medical devices**: Some medical devices (urethral inserts and pessaries) that help support the bladder are also suggested to prevent UI.[77]
- **Medications**: A wide range of drugs (anticholinergics, mirabegron, alpha-blockers, and topical estrogen cream) are used to treat UI depending on the types and underlying causes.[78-80] Anticholinergics and alpha-blockers improve symptoms by blocking cholinergic receptors of the bladder muscle and increasing bladder capacity.[54] Mirabegron is commonly used to treat OAB symptoms by targeting the beta-3 receptor pathway to relax the surrounding bladder muscles and increase the bladder's capacity to store urine.[53] Topical estrogen cream may increase bladder tissue integrity and help reduce the symptoms of UI.[80]
- **Interventional therapies**: When conservative treatment fails, interventional therapies (nerve stimulator, urethral implants, and Botox injections) may help decrease the symptoms of UI.[81]
- **Surgery**: To treat OAB, bladder neck augmentation is usually done.[82] To improve symptoms of stress incontinence bladder neck suspension, artificial urinary sphincter, and sling procedures are performed.[83, 84] Success rates vary for these procedures, as they depend on the severity of symptoms and the age of the patient.[85] Korman et al. reported a success rate of 51% to 90% for bladder neck suspension surgery.[82] In the case of uncomplicated UI, the success rate can vary from 84% to 96% with sling surgical procedure.[85]

2.3 Parkinson's Disease

PD is a chronic progressive neurodegenerative movement disorder.[86] It has been known since ancient times and was mentioned in the ancient Indian medical system.[87] It was first documented in Western medical literature in AD 175 as "shaking palsy" by a physician named Galen.[87] Later, it was described in detail by Dr. James Parkinson in 1817.[88] No known cause has been positively identified for PD.[86]

PD is generally known to affect older people. It is uncommon in people aged less than 45 years and has a higher incidence among men.[37, 89, 90] The early-onset PD occurs due to a loss of dopaminergic neurons and less common (3-10%) compared to late-onset.[91] The first presentation of symptoms in early-onset can be different from symptoms appearing in older patients and can lead to misdiagnosis. With early-onset, the patient may complain of dystonia rather than typical motor symptoms of PD.[92] The slower disease progression in younger people may also contribute to difficulty in diagnosis of early-onset of PD.[74, 92]

2.3.1 Overview of Disease Pathology

The pathology of PD is correlated with the loss of dopamine in the substantia nigra.[60, 62, 93-95] PD is categorized by the motor (resting tremor, rigidity, and postural instability) and non-motor (UI, bowel dysfunction, postural hypotension, depression, and dementia) symptoms. [86, 96-98] Clinically, symptoms occur when more than 50% of dopaminergic neurons are lost.[99] As there is no permanent cure for PD, the symptoms are managed with medications.[100]

PD is primarily diagnosed by principal motor symptoms and patients' responses toward antiparkinson medication.[101] It could take years to make a confirmed diagnosis by a neurologist

with an approximate overall 80.6% accuracy.[102] It is usually diagnosed by observing cardinal motor symptoms like shaking or resting tremor, muscle rigidity, and slowness of movement.[103] No definitive laboratory test exists for PD, which can make the diagnosis challenging.[104-106] Although PD is diagnosed with motor symptoms, patients may not develop all of those features.[103] Therefore, PD diagnosis depends on a physician's knowledge of neurological diseases and can be easily misdiagnosed.[107] Accuracy of identifying PD from initial assessment and movement disorders were 83.9% and 79.6%, respectively.[102] Failure to identify neurological manifestation by a physician often causes under-reporting.[107] Therefore, for accurate diagnosis, PD patients need to be examined by a specialist neurologist.[100]

2.3.2 Epidemiology of Parkinson's Disease

Heterogeneity of incidence and prevalence rates of PD exist worldwide. Using data from a large cohort, Driver et al. reported a crude incidence rate of 121 cases/100,000 person-years.[108] One US-based cross-sectional study reported a mean incidence rate with a wide range from 279 to 3,111 (per 100,000).[109] In addition to the US, some Europe-based studies examined the incidence of PD, with one reporting the overall incidence (84/100,000 person-years) among patients aged above 50 years.[110] Another population-based prospective cohort study reported an increase of PD with age, stating a range of 0.3/1,000 person-years for patient groups aged 55 to 65 years to 4.4/1,000 person-years for patients 85 or older.[111] The incidence rate was relatively lower in developing countries.[112] In India, the average reported incidence rate of PD was 5.71/100,000.[113]

There have also been discrepancies in age- and sex-related findings in studies that might have occurred due to the different patient or population settings. Age is considered an important

variable and it is widely accepted that the incidence of PD increases with age.[1, 75] Several studies suggested a predominance of PD in males with increased age.[109-111, 114, 115] The male-to-female incidence ratio was reported as ranging from 1.2:1 to 1.5:1.[116]

In one systematic review, the reported overall pooled worldwide prevalence of PD was 315/1,000,000 people.[117] Studies focused on the US population reported that approximately one million were diagnosed with PD.[114] The age of onset ranged from 55 to 65 years and 1% prevalence in the general population was found for PD patients over 65.[114] Another US-based cross-sectional study reported a mean prevalence of 1,588.43/100,000 in individuals aged 65 years and above.[109] The prevalence found in one Australian cross-sectional study was 362/100,000 in patients 50 years and older. The wide prevalence range might be attributable to case ascertainment strategies, regional variations, and risk factors that may affect survival after diagnosis.[114]

Few studies have investigated PD in Asian countries, but the prevalence is comparatively lower than in western countries.[116] Crude prevalence of PD (100,000 population) has been reported to vary from 100 to 250 in western countries and 15 to 657 (per 100,000 population) in developing countries.[116] One systematic review that included studies focused in various regions of the People's Republic of China reported the standardized prevalence of PD (79.5 to 193.3 per 100,000), which is comparable with data reported for Asian and European countries.[112] The annual age-adjusted prevalence of PD in India was 52.85/100,000 people.[113]

2.4 Epidemiology of Urinary Incontinence in Parkinson's Disease

The prevalence of UI has been documented among PD patients and ranges from 24% to 95%.[50, 118] The only Canadian prevalence rate of UI among PD adults reported by PHAC (2011-

2012) showed 55% of people with PD had UI.[5] Reported incidence and prevalence rates are extensively dispersed due to variations in the study population and methodology.[119] Several studies have shown patients, especially older ones, do not always express their concerns about UI, thinking of it as a common side effect of aging, which could be a reason for under-reported cases.[22, 47, 55, 120]

Age- and sex-specific statistics of UI in PD have also been investigated in several studies.[23, 48, 107] While some studies have reported an association between increasing age and UI in PD patients,[121, 122] others have reported the contrary.[13, 123] A cohort study by Ou et al. reported an increase in urinary symptoms with no relation to age with the progression of UI in PD (mean follow-up 1.8 years).[38]

Although sex-specific variation in the prevalence of UI exists among PD patients, it is inconclusive whether women with PD have a higher prevalence than men.[48, 107] While general UI occurrence is more common in female patients,[44, 120, 124] some studies reported a higher percentage of male PD patients with UI ranging from 50% to 54%.[88, 125] A cohort study that examined the relation of PD and UI reported an increased prevalence of urinary urgency in men with PD over the two-year follow-up period, but interestingly, it decreased in women.[126]

PD along with UI can have a serious health impact on HRQoL.[25, 127, 128] More than half of Canadians suffering from PD have reported poor health quality and their average Health Utility Index Mark 3 score was 0.51 (severe disability).[37] A study using the Canadian Community Health Survey (CCHS) has reported a statistically significant (-0.22, CI = -0.40 to -0.05) impact on HRQoL among PD patients with UI compared to other chronic conditions.[36]

Worldwide use of administrative health databases to evaluate the chronic disease has increased as it allows to address disease occurrence and progression in all residents for a long time.[129] To our knowledge, only one study has used administrative data to investigate OAB among PD patients.[30] This study reported a significant overall incidence rate (14.5/10,000 person-years) and cumulative incidence (0.65%) of OAB in PD patients at the fifth follow-up year since PD diagnosis.[30]

The relationship between UI and PD severity is unclear. Several studies have investigated the possible correlation of developing UI with the progression of PD disease severity.[71, 130, 131] While some studies reported a late presentation of UI,[130, 131] others have reported symptoms of UI within 5 years of PD diagnosis.[132-134] Uchiyama et al. found approximately 64% of PD patients presented with urinary symptoms within 23.6 months of PD diagnosis.[133] Another study using the questionnaire in 41 newly diagnosed PD patient cohorts reported UI symptoms after 2.7 years of PD diagnosis.[135] One small and three large cohort studies reported that UI is most likely to develop with the progression of PD symptoms.[13, 123, 136, 137] In contrast, several cohort studies did not find associations between developing UI and severity of PD symptoms.[122, 138, 139] This was most likely due to different population criteria and methods.[38, 126]

2.5 Clinical Background: Urinary Incontinence in Parkinson's Disease

Past research has stated some possible theories to establish the pathophysiological connection between PD and UI.[11, 13, 31] The most speculated theory was that non-motor symptoms of PD are associated with CNS degenerative changes in the frontal cortex, basal ganglia, thalamus, and anterior cingulate gyrus of the brain.[11] CNS involvement includes

decreased dopamine in the striatum of the basal ganglia, which is associated with the development of symptoms of UI.[11] Relative degeneration of the caudate of basal ganglia may also responsible for overactive bladder muscles.[140]

The weakening of pelvic floor muscles may also contribute to UI due to brain and spinal nervous system abnormality.[17] Abnormal neural signaling from these weak muscles to the CNS stimulates the micturition reflex even if the bladder is not full. These muscles are located at the floor pelvic bone and support the muscles of the urinary tract. Loss of coordinated pelvic muscle contraction influences bladder muscle activity.[141] Pelvic floor muscle strengthening and coordination provide support to the urethra to reduce hyperactivity of bladder.[77]

Other mechanisms of UI include more peripheral involvement, such as bladder sphincter abnormality and bladder muscle hyperreflexia and hypoactivity.[73, 142] Bonnet et al. reported that 36% to 90% of patients with PD manifested bladder muscle hyperreflexia with or without complete relaxation of sphincter during voiding.[143]

2.6 Symptomatic Features of Urinary Incontinence in Parkinson's Disease

The symptoms of UI in PD may vary.[140] The severity and nature of neurological damage, along with some coexisting factors, may play a role in symptom development. These symptoms could arise from both bladder storage and emptying problems; however, symptoms related to the storage problem, precisely OAB, are commonly seen in patients diagnosed with PD.[75] Urinary symptoms of PD patients can be categorized into two types:

I. Difficulty in holding urine

The most common urinary symptom presented by PD patients is OAB.[31] Over 60% of patients reported urgency as the main urinary complaint in PD.[59] This symptom is related to urinary bladder sphincter abnormality because of spontaneous bladder muscle rigidity that leads to urgency and hesitancy.

II. Difficulty in voiding urine

This symptom is manifested by bladder outflow disturbance, which includes hesitancy, weak stream or dribbling of urine, and urinary tract infection with the sensation of a full bladder.[140] The urinary bladder sphincter tends to close whenever an attempt is made to void due to neural signaling and the individual fails to empty the bladder.[140] One clinical study reported that approximately 5% of 21 PD patients showed bladder sphincter abnormality during the voiding phase.[144]

2.7 Possible Neurogenic Mechanisms of Urinary Incontinence in Parkinson's Disease

Based on past clinical and epidemiological studies, several well-established mechanisms have been identified:

- **Bladder muscle abnormality**

  Urinary bladder or detrusor muscle functional abnormality, usually overactivity, is considered the leading cause of UI in PD.[142] Neural degeneration in PD hampers the normal bladder muscle activity and causes UI. One clinical study found detrusor muscle overactivity in 75% of patients with PD.[145]

- **Urethral sphincter function abnormality**

Some studies have identified atypical sphincter function in PD patients.[146] The micturition reflex is controlled by both inhibitory and facilitatory dopamine receptors. Activation of these receptors influences the neural pathway of this micturition reflex and detrusor muscle of the bladder.[147] Loss of dopamine in the midbrain causes an interruption in the micturition reflex pathway and resultant high sphincter tone or spasm that inhibits the relaxation of sphincter during the time of micturition.[144, 147] This type of abnormality cause outflow type of UI. Detrusor-external sphincter bradykinesia (delayed relaxation) or pseudo-dyssynergia (involuntary urethral sphincter contraction) in PD patients could also be related to bradykinesia of the limbs.[75, 145] One clinical study reported that about 11% of 30 PD patients showed sphincter bradykinesia.[145] However, another clinical study by Sakakibara R et al. found no detrusor-external sphincter dyssynergia in UI patients with PD.[144]

- **Dopaminergic mechanisms on bladder muscle**

Lack of dopaminergic neurons in PD patients may lead to both stimulatory and inhibitory effects on the PMC.[140] The widely accepted theory is that basal ganglia directly inhibit receptors that initiate micturition reflex due to dopamine depletion and cause muscle hyperactivity.[99] This could then result in bladder muscle overactivity and create symptoms such as urgency.

- **Other coexisting health conditions**

Although limited work has examined the incidence of UI in PD patients and coexisting health conditions, conditions like advanced age, benign prostatic hypertrophy

(BPH), infection of the urinary tract (UTI), and diabetes could be responsible for UI in PD patients.[71, 148] Incomplete voiding due to BPH can lead to secondary infection like UTI. BPH and UTI are relatively common in older people.[71] Therefore, these conditions can coexist in men diagnosed with PD and influence the symptoms of UI.[71] Even after prostatectomy, the reported risk of UI in PD patients with normal urethral sphincter control was 4%, compared to 84% with poor sphincter control.[71] Following a clinical study, Becker et al. reported 8% of total PD patients were diagnosed with diabetes over the five-year follow-up period.[149]

- **Effect of antiparkinson medication on UI**

Although several studies have investigated the influence of antiparkinson medication like Levodopa on UI, its role in the treatment of UI is still unclear.[71, 137, 150, 151] This drug may increase neurogenic bladder muscle overactivity.[137] While Aranda et al. reported improvement of symptoms in 12 PD patients after administration of Levodopa,[151] contrast findings were also reported.[137, 150] Levodopa deteriorates bladder muscle hyperactivity in PD patients by affecting the urine storage process.[137] One clinical study reported an increase of detrusor muscle overactivity with concurrent improvement in motor symptoms after administration of Levodopa in 17 PD patients with known UI.[150]

2.8 Limitations and Challenges of Identification of Urinary Incontinence Cases in Parkinson's Disease Using Administrative Data

The use of administrative data in epidemiological studies to investigate UI in patients with PD is extremely limited. Past studies have mainly used survey data (national and clinical), telephone interviews, and questionnaires to report the epidemiology of UI in PD.[58, 73, 88, 97, 138] To date, several studies investigated age and sex as risk factors using the survey data,[13, 16, 48, 88, 152] while only one study used administrative data.[30] The methodological differences among these studies, along with the data source, may influence the variations in the age- and sex-specific incidence of UI in PD.

Studies have used multiple ICD codes to identify PD cases either using ICD-9 codes (3320 or 332.0 or 332) or ICD-10-CA code (G20).[10, 30, 153-155] This becomes also very challenging with a chronic disease like UI, which have several specific and non-specific ICD diagnostic codes (ICD-9: 596.5 or 625.6 or 788.3 or 788.4 or 788.6 and ICD-10-CA: N31 or N32 or N39 or R35).[30, 69, 156] Although studies used some similar ICD codes for UI case diagnosis, a certain degree of variation exists with the use of ICD codes for different study objectives. There also may be some variation with ICD diagnosis codes (PD and UI) depending on how the physician's record is interpreted and entered into databases by coders.

Health administrative databases routinely accumulate patients' data during a physician visit, hospitalization, and emergency visit.[157, 158] Primarily these databases were created to manage financial and billing purposes but have become a popular data source for

epidemiological studies.[30, 159, 160] However, studies examining PD and UI individually using administrative data have stated some limitations, especially with physician's claims-based data.[161-164] The incomplete nature of records and the possibility of coding errors are likely to affect study findings.[164] Further, if drug dispensing data is not available or used, it may also limit the accuracy of identifying cases.[163]

Chapter 3: Method

3.1 Study Population

Individuals residing in Alberta diagnosed with PD between April 1, 2004 and March 31, 2014 were included in this study. About 99% of the population is covered by Alberta Health Care Insurance Plan (AHCIP)[i] in Alberta. Individuals (approximately 1%) without AHCIP coverage were not included in this study.[165]

3.2 Study Design

A retrospective population-based cohort study design was used to identify UI cases among PD patients. At first, individuals aged ≥ 45 years diagnosed with PD from anytime between the fiscal years 2004/2005 to 2013/2014 were examined to identify UI cases. Then patients were followed to identify UI cases that occurred within the first five years of PD diagnosis. Although UI is a common non-motor feature in patients with PD, their early diagnosis has not been extensively studied. Older PD patients may seek early medical attention as UI may deteriorate their overall health condition.[166, 167] Using clinical data, Baig et al. reported that non-motor symptoms are common even at the early stage of PD, compared to control subjects.[132] Since a greater chance of death is predicted with a longer follow-up period in the older population, mortality adjustment was done to evaluate the actual estimate of UI occurrence in the PD population. Ethics approval for this study was obtained from the Health Research Ethics

[i] Publicly funded universal health care system and all residents of Alberta are eligible to receive fully covered medical services except for those covered by federal health insurance.

Board (HREB) of the University of Alberta.

3.3 Data Sources

The health data utilized in this project to collect complete health information of all individuals diagnosed with PD included the data sets listed in Table 3-1.

Table 3-1 Administrative datasets accessed from Alberta Health[168]

	Datasets[ii]	Data Source	Key Variables of Interest
i)	Ambulatory Care	Emergency department and ambulatory service clinics	Most responsible diagnosis code, other health diagnosis codes, service episode start, and end date
ii)	Physician Claims	Fee for service claims submitted by physicians	Health diagnosis code, service event start, and end date
iii)	Inpatient	Patients discharge information from inpatient hospital stays	Most responsible diagnosis code, other health diagnosis codes, service episode start, and end date
iv)	Pharmaceutical Information Network (PIN)	Pharmacy dispensations from community pharmacies for all ages	Drug dispensed date, drug anatomical therapeutic chemical code (ATC)
v)	Alberta Blue Cross (ABC) claims	Pharmacy dispensations from community pharmacies those aged 65 and older	Anonymous person identification number, drug anatomical therapeutic chemical code (ATC)
vi)	Population Registry	Basic demographic information on health plan participants	Person birth month, person birth year, person gender code
vii)	Vital Statistics – Deaths	Death certificates	Date of death

[ii] Timeline (April 1, 2000 - March 31, 2014): ambulatory, physician's claim, inpatient, ABC, and population registry datasets
Timeline (April 1, 2008 - March 31, 2014): PIN dataset
Timeline (April 1, 2002 - March 31, 2014): vital statistics dataset

3.4 Study Measures

For this current study, we identified incident UI cases in PD patients linking the inpatient, ambulatory care, physician claim, and pharmaceutical information datasets through a unique lifetime identifier (personal anonymous health number that connects to patient detail).

This study investigated the epidemiology and risk factors associated with the development of UI in PD patients. To estimate UI cases among PD patients, data from physician claims, inpatient, ambulatory, Alberta Blue Cross (ABC), and pharmaceutical information network (PIN) were examined. Key demographic data characteristics were compared between the age groups using the t-test. To observe the actual risk of UI in PD, the PD population was adjusted for mortality using LIFETEST procedure.[75] The incidence of UI in PD patients using person-years and cumulative incidence using the cumulative incidence function (CIF) test were investigated by age and sex, including the change in rate over time.[169, 170] Association of the risk factors (age, sex, and comorbidity score) and the risk of developing UI in PD patients were investigated using univariate and multivariate Cox proportional hazard analysis.[171]

3.4.1 Parkinson's Disease: Case Definition

Identification of PD cases used the following case definitions: two physician claims within three years with an ICD-9 code (332.0) or one hospital record of ICD-10-CA code (G20). Cases were also identified if individuals used the following anti-parkinson medications across two consecutive one-year periods. Where only three-digit ICD-9 codes were available, a concurrent usage of PD medications was used to validate the diagnosis. These anti-parkinson medications were Sinemet, Selegiline, Levodopa, Carbidopa, and Azilect.[172] To avoid

misclassification, people who took medication less than one year were not considered as PD cases. The case definition for PD identification was adopted from published literature.[10]

After identifying PD cases, the cohort was restricted to only incident cases based on the first diagnosis date (index date). PD cases from the first two fiscal years were excluded to decrease the chance of identifying a prevalent case as an incident case.

3.4.2 Urinary Incontinence: Case Definition

Case definitions used to identify UI cases within the PD cohort (2004-2014) were one of several four-digit codes in physician claims (ICD-9) or one of several four-digit codes in hospital/ambulatory care codes (ICD-10-CA), one of several three-digit codes in physician claims (ICD-9), and a concurrent prescription for one of several medications used to treat UI.

Only a few studies have developed a working case definition of UI using ICD codes.[30, 69, 173, 174] In our study, appropriate and commonly used diagnostic ICD-9 and ICD-10-CA codes of UI were used for case definition (Table 3-2). To collaborate with published articles, case definitions, and algorithms were searched through multiple databases. Although some studies identified UI cases using administrative datasets, no specific case algorithm was described.[69, 161, 164, 174, 175]

UI case definitions were created based on all available ICD diagnosis codes in the administrative datasets. Physician claims (3 available diagnosis codes), ambulatory (10 available diagnosis codes), inpatient (25 available diagnosis codes), ABC, and PIN datasets were examined for UI diagnosis codes. Although ICD-10-CA provides more specific diagnosis codes, we used all relevant ICD codes of UI found in both formats (ICD-9 and ICD-10-CA) for case

definitions. All the ICD diagnostic codes of UI were applied in the case definition under each of the available diagnosis fields (primary and others) individually to identify UI cases.

The ambulatory and inpatient datasets consisted of full four-digit diagnostic codes, providing a more specific diagnosis than claim data. The physician claims data usually contains truncated three-digit ICD-9 codes, which may not have the specificity required to confirm a UI diagnosis. The use of a combination of datasets increases the ability to identify UI cases. To confirm UI cases from three-digit codes, we combined these three-digit physician claim records with a concurrent UI medication record (ABC and PIN datasets). ABC and PIN datasets were first combined and then ATC (the anatomical therapeutic chemical-classified medical drugs based on functions) drug codes for UI treatment (Table 3-2) were identified.[176] A combination of three-digit ICD-9 codes and medications (Emepronium, Flavoxate, Meladrazine, Oxybutynin, Terodiline, Propiverine, Tolterodine, Solifenacin, Trospium, Darifenacin, and Fesoterodine) was then matched to validate UI cases. Since the medications might have other indications, physician claim with concurrent drug dispensation was examined to confirm a UI case.

Table 3-2 Commonly used ICD diagnostic codes applied to find urinary incontinence cases in the relevant health administrative datasets

Datasets	ICD diagnostic and ATC drug codes	Study period (fiscal years)
1) Physician Claim	ICD-9 codes: 596, 596.5, 625, 625.6, 788, 788.3, 788.4, 788.6	2004/2005 - 2013/2014
2) Inpatient and Ambulatory	ICD-10-CA codes: R32, N32.81, N39.3, N39.41, N39.42, N39.43, N39.44, N39.45, N39.46, R35, R39.15, N39.49	2004/2005 - 2013/2014
3) Pharmaceutical Information Network (PIN)	ATC drug codes: G04BD01, G04BD02, G04BD03, G04BD04, G04BD05, G04BD06, G04BD07, G04BD08, G04BD09, G04BD10, G04BD11, G04BD12, G04BD13, G04BD1	2004/2005 - 2013/2014

3.4.3 Urinary Incontinence in Parkinson's Disease: Incident Case Cohort

An incident PD patient cohort aged ≥ 45 years was created linking physician claims, inpatient, ambulatory, and drug datasets through the unique identifier and UI cases were identified applying UI case definitions and algorithms within the cohort. To include demographic and mortality status, population, and vital registry datasets were also linked. Subsequently, a cohort of UI cases in PD patients from fiscal year 2002/2003 to 2013/2014 was created. To minimize the chance of identifying prevalent cases as incident cases, the first two fiscal years of the study period were not used to estimate the incidence. Therefore, UI cases were restricted to the first diagnosis to estimate incident UI cases anytime from fiscal year 2004/2005 to 2013/2014. Lastly, incident UI cases were identified within the first five years of a diagnosis of PD.

3.4.6 Charlson Comorbidity Index Score Calculation

To examine the total burden of disease in individuals with UI, comorbidity was measured using the Charlson Comorbidity Index Score (CCI) score. A CCI score is a weighted sum of certain disorders identified in administrative records.[177] Each of the comorbid conditions had weight and the sum of the weighted scores for each condition generates a single comorbidity score for each patient.[177] CCI estimates the prognosis related to chronic diseases depending on the adjusted risk of one-year mortality.[72] Therefore, comorbid conditions with higher mortality rates have a higher weight. We used the CCI scores of PD patients, which were calculated before their diagnosis based on the number and severity of the conditions. These scores were calculated from the hospital and claim datasets using ICD-9 codes and ICD-10-CA diagnostic codes. The algorithm of CCI scores was derived from a published report, which investigated measures of

data quality relevant to the linkage of Manitoba Cancer Registry data and other administrative health data.[71, 72, 177] The CCI scores range from 0 to 17 with higher scores indicating greater comorbidity, and 0 representing no relevant conditions.

3. 5 Statistical Analysis

3.5.1 Descriptive Statistics

Descriptive statistics were generated for PD cases with or without UI. The frequency of cases was stratified by age and sex. Age was stratified into five groups (45-54, 55-64, 65-74, 75-84, and ≥ 85 years), and sex was stratified as male and female. A comparison test, such as a t-test, was performed to determine any significant mean age differences between PD patients with or without UI. UI cases found within the first five years of PD diagnosis were also reported by age and sex. After mortality adjustment, UI cases were reported by the change in frequencies over the follow-up period using LIFETEST procedure. It is an estimation of the survivor function for a sample of survival data.[75] The frequency of UI cases was also reported with associated CCI scores. For the statistical significance, 95% confidence interval (CI) and p-value <.01 were considered significant.

3.5.2 Incidence Rate (Person-Year)

To observe the rate of actual UI event outcome in PD over total person-time-at-risk contributed to the study, the incidence rate (person-year) was estimated. Incidence rate using person-years provides the number of UI events per person-time. The rate is calculated using numerator (new cases) and denominator (total time experienced by population at risk).[169] Using person-years of follow-up period as the denominator, the overall incidence rate of UI among PD patients was calculated (2004 - 2014). The incidence rate (person-years) stratified by age and sex was also calculated. In this study, the incidence rate was reported as cases per 1,000 person-years.

3.5.3 Cumulative Incidence

Cumulative incidence of UI in PD cases was conducted using the CIF LIFETEST procedure. Statistically, CIF is the cumulative probability of an event across time.[170, 178] It is a non-parametric approach of calculating cumulative incidence.[146] The elderly who experience high-mortality death events may affect the study outcomes.[179, 180] CIF procedure accounts for death and allows to censor lost to follow-up patients.[181] Therefore, to outline the burden of UI incident cases in PD patients in the presence of competing risk, this seemed a suitable method. Considering the occurring event type (j) in the CIF test and time interval (0, t), the probability of experiencing the event can be expressed with the following equation:

$$F_j(t|X) = \Pr(T \leq t, \in= j|X)\, j = 1,2, \ldots, j \ (1)$$ [182]

The age- and sex-specific cumulative incidence of UI with PD patients were also estimated. Age and sex are considered important factors associated with UI and PD as these factors can affect the incidence. Cumulative incidence of males and females over five age groups (45-54, 55-64, 65-74, 75-84, and ≥ 85 years) were calculated. Cumulative incidence was reported with 95% confidence intervals (CI) and using p-values (p-value < 0.01). Statistical significant differences (p-value < 0.01) between groups were determined using Gray's test as it indicates a significant difference in the cumulative incidence in the presence of competing risk while using CIF LIFETEST procedure.[183]

3.5.4 Cox Proportional Hazard Regression

To examine the association between predictor variables (age, sex, and CCI score) and the risk of developing UI in PD, Cox proportional regression analysis was used.[184] Expressing

hazard function as $h(t)$, follow-up time as t, baseline hazard as h_0, predictors as $x_1, x_2,\ldots,x_i$ and coefficients as $b_1, b_2,\ldots,b_i$ the hazard regression model can be estimated and predicted with the following equation:

$$h(t) = h_0(t) * \exp\,(b_1x_1 + b_2x_2 + \cdots + b_ix_i)^{171}$$

The estimated regression coefficient $\exp(b_i)$ is a hazard ratio (HR). Therefore, an increase of b_i above 0, or equivalently a hazard ratio above 1 indicates the value of x_i th predictor (risk of increase event hazard). HR above 1 indicates a higher risk of developing UI in PD. In our study, the results from the Cox regression model were reported with HR including 95% CI.

All the data management and statistical analyses were performed using SAS 9.4 software (SAS Institute, NC, US).

Chapter 4: Results

4.1 Parkinson's Disease Patient Cohort: Overall Patient Profile

A total of 9,540 PD cases were identified among individuals in Alberta aged 45 years or older with or without UI during the fiscal year of 2004/2005 to 2013/2014. Differences in patient frequencies were reported based on age, and sex (Table 4-1).

Table 4-1 Parkinson's disease patient cohort by age and sex, Alberta (2004 - 2014)

Variable	Overall N (%)	Male N (%)	Female N (%)	95% CI	Male: Female Ratio
Age, years					
Total	9,540 (100.0)	5,392 (56.5)	4,148 (43.5)	10.79-11.10	1.3
45-54	581 (6.1)	316 (3.3)	265 (2.8)	2.61-2.93	1.2
55-64	1,443 (15.1)	859 (9.0)	584 (6.1)	2.74-2.95	1.5
65-74	2,458 (25.6)	1449 (15.2)	1009 (10.6)	2.77-2.93	1.4
75-84	3,511 (36.8)	2026 (21.2)	1485 (15.6)	2.75-2.89	1.4
≥ 85	1,547 (16.2)	742 (7.8)	805 (8.4)	2.89-3.10	0.9
Age, mean (±SD)	73.8 (±11.0)	73.3 (±10.6)	74.4 (±11.3)	10.79-11.10	

CI: Confidence interval.
SD: Standard deviation.

In the PD cohort, males represented 56.5% (N=5,392) of all concurrent patients. The overall male: female ratio was 1.3. As shown in Table 4-1, statistically significant age differences (95% CI) were observed between the groups of PD patients. The overall mean age of the PD patients regardless of UI status was 73.8 (±11.0) years. The majority (62.4%) of the PD patients were between 65 and 84 years of age while those aged ≥ 75 years represented 29% male and 24% female patients.

Table 4-2 Parkinson's disease patient characteristics with and without urinary incontinence, Alberta (2004 - 2014)

	PD patients without UI			PD patients with UI		
Variable	**Overall N (%)**	**Male N (%)**	**Female N (%)**	**Overall N (%)**	**Male N (%)**	**Female N (%)**
Age, years						
Total	8,287 (100.0)	4,735 (57.1)	3,552 (42.9)	1,253 (100.0)	657 (52.4)	596 (47.6)
45-54	535 (6.5)	294 (3.6)	241 (3.6)	46 (3.7)	22 (1.8)	24 (1.9)
55-64	1,260 (15.2)	763 (9.2)	497 (6.0)	183 (14.6)	96 (7.7)	87 (6.9)
65-74	2,121 (25.6)	1,268 (15.3)	853 (10.3)	337 (26.9)	181 (14.5)	156 (12.5)
75-84	2,998 (36.2)	1,754 (21.7)	1,244 (15.0)	513 (40.9)	272 (21.7)	241 (19.2)
≥ 85	1,373 (16.6)	656 (7.9)	717 (8.7)	174 (13.9)	86 (6.7)	88 (7.0)
Age, mean (±SD)	73.7 (±11.1)	73.2 (±10.7)	74.4 (±11.6)	74.1 (±9.8)	74.0 (±9.6)*	74.2 (±9.9)*

*P=0.796.
SD: Standard deviation.

4.1.2 Parkinson's Disease without Urinary Incontinence

A total of 8,287 (86.9%) PD patients (2004 - 2014) were not diagnosed with UI anytime during the study period since their PD diagnosis (Table 4-2). The average age of the PD patients without UI was 73.7 (±11.1) years. Among them, 57.1% were male, and 42.9% were female.

4.1.3 Parkinson's Disease with Urinary Incontinence

Within the study period (2004-2014), total 1,253 incident UI cases aged ≥ 45 years post PD diagnosis were identified in Alberta (Table 4-2). The overall mean follow-up period was 1.9 (±1.8) years from the first PD diagnostic date to that of the UI diagnosis.

As shown in Table 4-2, a greater number of male PD patients (52.4%) were diagnosed with UI compared to female patients (47.6%). The average age of UI cases was 74.2 (±9.8) years, and no significant variation was observed regardless of their sex (p-value= 0.796). Among the PD patients with UI, the highest percentage of male (21.7%) and female (19.2% of female) patients were from the 75- 84 years age group. This group of patients was diagnosed with UI over an average of a 1.6-year observation period following their PD diagnosis.

Overall, PD patients under 65 years comprised 18.3% of the incident UI cases (229/1,253). Those aged from 65 to ≥ 85 years contributed to 81.7% (1,024/1,253) of the total UI cases, while 13.9% (174/1,253) of them were ≥ 85 years.

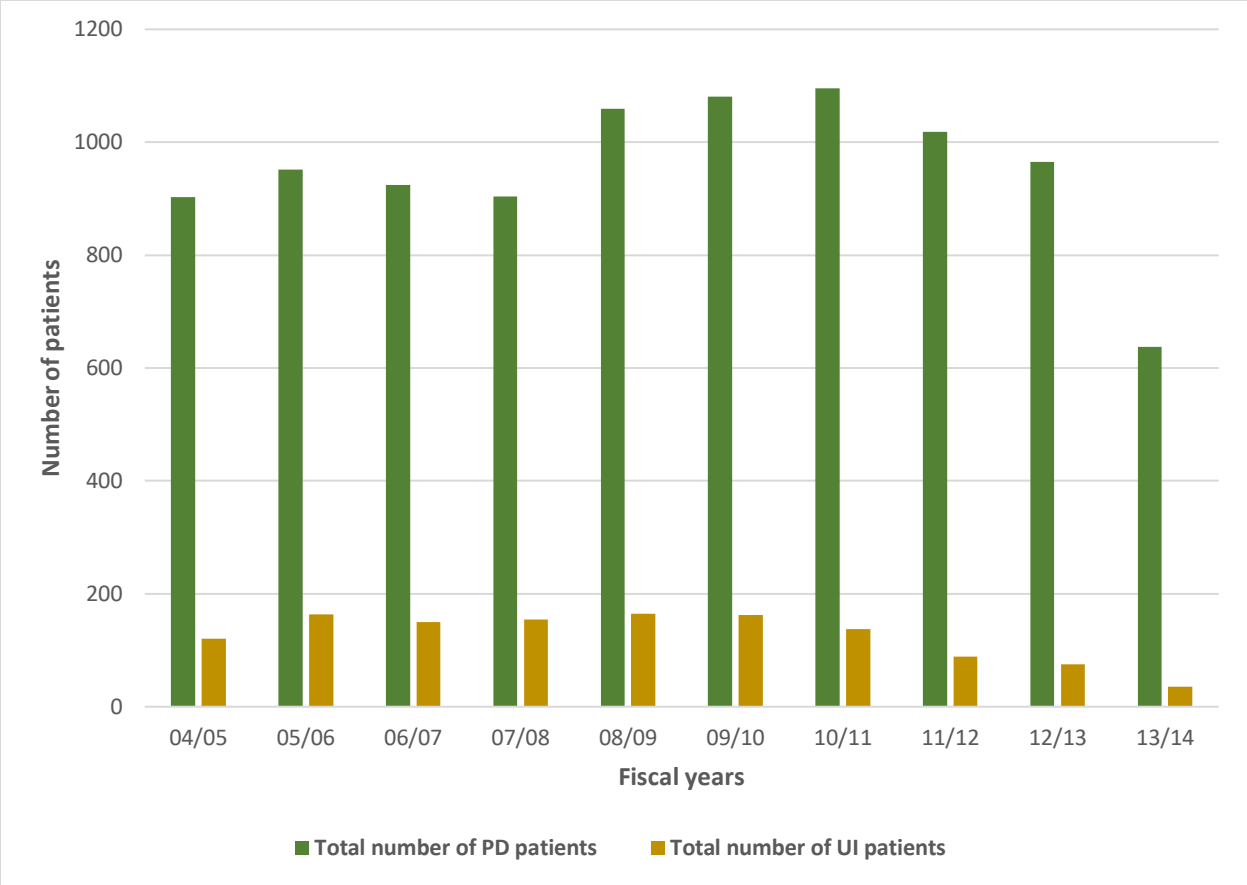

Figure 4-1 Number of urinary incontinence cases identified among Parkinson's disease patients by fiscal year, Alberta (2004 - 2014)

Most UI cases (N=327) among the PD patients were identified from the fiscal year 2008/2009 to 2009/2010 (Figure 4-1). The highest percentage, 13.2% (N=165) of the UI cases, was identified in the fiscal year of 2008/2009, during an average observation period of over 1.9 years following their PD diagnosis.

4.2 Urinary Incontinence within the First Five Years of Parkinson's Disease

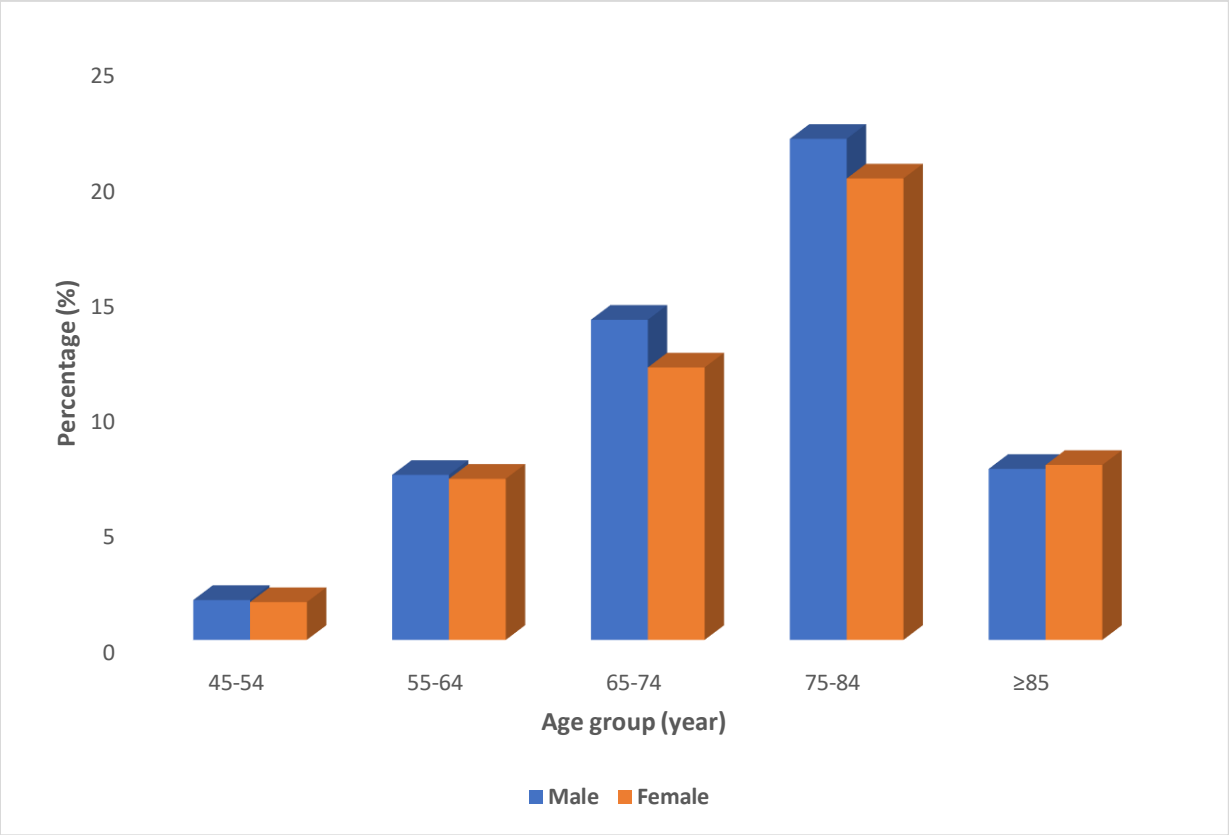

Figure 4-2 Distribution of urinary incontinence cases identified within the first five years of Parkinson's disease diagnosis by age and sex, Alberta (2004 - 2014)

A total of 1,159 incident UI cases aged ≥ 45 years was identified during the five years of follow-up post PD diagnosis (Figure 4-2). Among them, 51.9% were male and 48.1% females. Most UI cases (41.8%) belonged to the age group 75-84 years.

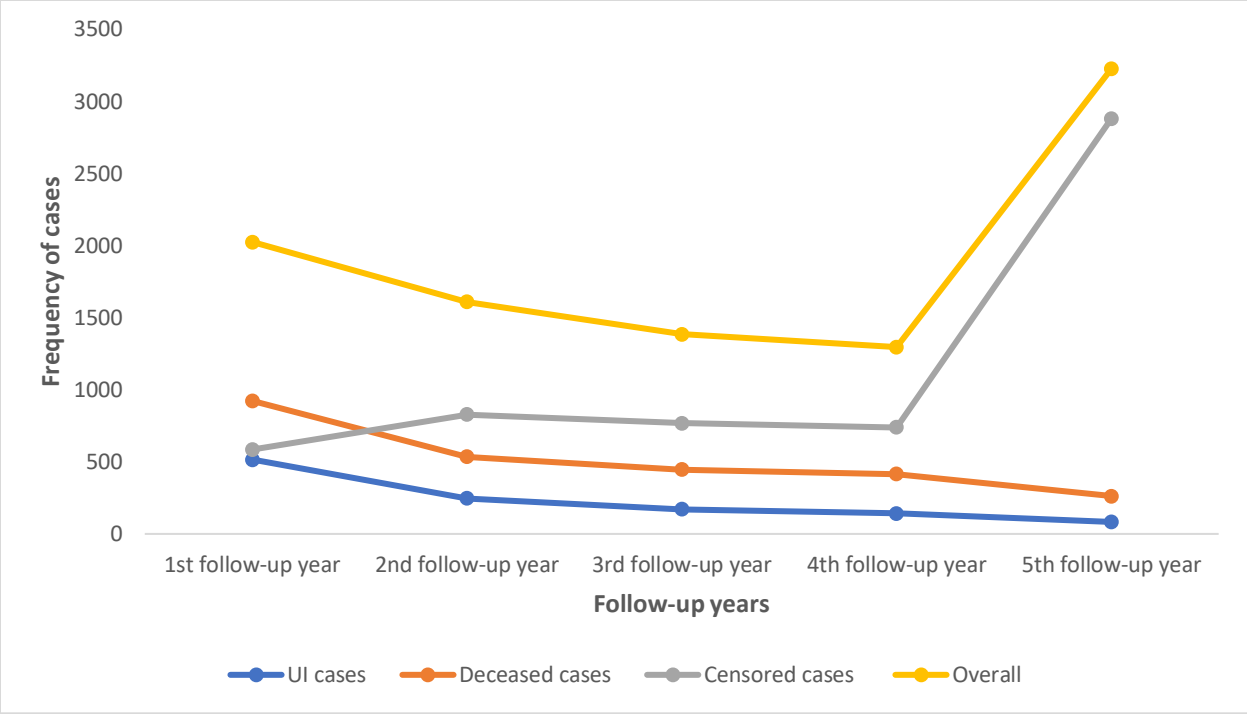

Figure 4-3 Number of urinary incontinence cases among Parkinson's disease patients identified over the follow-up years after mortality adjustment, Alberta (2004 - 2014)

As shown in Figure 4-3, after adjusting mortality, the maximum number of UI cases (N=516) was identified during the first follow-up year. The number of incident UI cases gradually decreased over the follow-up period, which might have occurred as a subsequent result of lost to follow-up or mortality during the follow-up years.

4.2.1 Charlson Comorbidity Index Score and Urinary Incontinence in Parkinson's Disease

Table 4-3 shows the frequency of UI cases in PD patients according to the CCI scores. Overall, 45.6% of the total UI cases had a CCI score of 0, indicating that they were relatively healthy individuals. Only 9.2% of the PD patients with UI had CCI scores of 6 or more. Male UI cases had higher CCI scores (6 or more) than females. Table 4-3 also shows the average ages of the UI cases were significantly associated with CCI scores. The highest observed average age associated with comorbidity scores of PD patients with UI was 77.3 (±8.5) years.

Table 4-3 Charlson comorbidity index score and the average age of Parkinson's disease patients with urinary incontinence, Alberta (2004 - 2014)

	Charlson comorbidity index score (CCI)			
UI cases, N (%)	**0**	**1-2**	**3-5**	**6 or more**
Male	267 (23.0%)	135 (11.7%)	136 (11.7%)	64 (5.5%)
Female	262 (22.6%)	145 (12.5%)	108 (9.3%)	42 (3.6%)
Overall	529 (45.6%)	280 (24.2%)	244 (21.1%)	106 (9.2%)
Age, mean (SD)	72.0 (±9.8)	75.7 (±9.9)	77.3 (±8.5)	76.9 (±8.5)

p-value=<.0001, age and CCI scores of UI patients are significantly associated.
SD: Standard deviation.

4.2.2 Incidence of Urinary Incontinence Among Parkinson's Disease Patients

A total of 9,540 PD patients aged ≥ 45 years in Alberta were followed to estimate the incidence of UI among them. The crude incidence rate of UI was 17.8 (per 1,000 person-years). The highest age-specific incidence rates were observed in those aged 75-84 years (Table 4-4).

Table 4-4 Incidence of urinary incontinence among Parkinson's disease by age and sex, Alberta (2004 - 2014)

Age, years	Overall			Male			Female		
	UI cases	Person-years	Incidence rate*	UI cases	Person-years	Incidence rate*	UI cases	Person-years	Incidence rate*
45-54	39	6925.3	5.6	20	4194.9	4.8	19	2730.4	7.0
55-64	164	10418.9	15.7	83	5588.6	14.9	81	4830.3	16.8
65-74	298	12149.8	24.5	161	6219.6	25.9	137	5930.2	23.1
75-84	484	13128.4	36.9	252	6867.8	36.7	232	6260.6	37.1
≥ 85	174	22314.6	7.8	86	11622.3	7.4	88	10692.3	8.2
Overall	1,159	64937.0	17.8	602	34493.2	17.5	557	30443.8	18.3

*Incidence rate, per 1,000 person-years.

Table 4-4 shows that the overall incidence rate was higher in females (18.3 per 1,000 person-years). Among the age groups, the incidence rate for females was comparatively higher than that for males aged ≥ 75 years. The highest incidence rate in males and females was 36.7 and 37.1 (per 1,000 person-years), respectively. Following age adjustment, a linear increase in the incidence rate was observed up to 84 years. The incidence rate decreased among the patients aged ≥ 85 years (7.4 and 8.2 cases per 1,000 person-years for males and females, respectively) compared to that for patients aged 75-85 years; this may be due to the smaller number of individuals and a high mortality rate in this group.

4.2.3 Cumulative Incidence of Urinary Incontinence Among Parkinson's Disease Patients by Fiscal Year

Cumulative incidence of UI was examined per fiscal year to explore the annual occurrence of UI events among PD patients. Where data was complete, the highest overall cumulative incidence of UI in PD patients (15.4%) was observed for the fiscal year 2007/2008 (Figure 4-4).

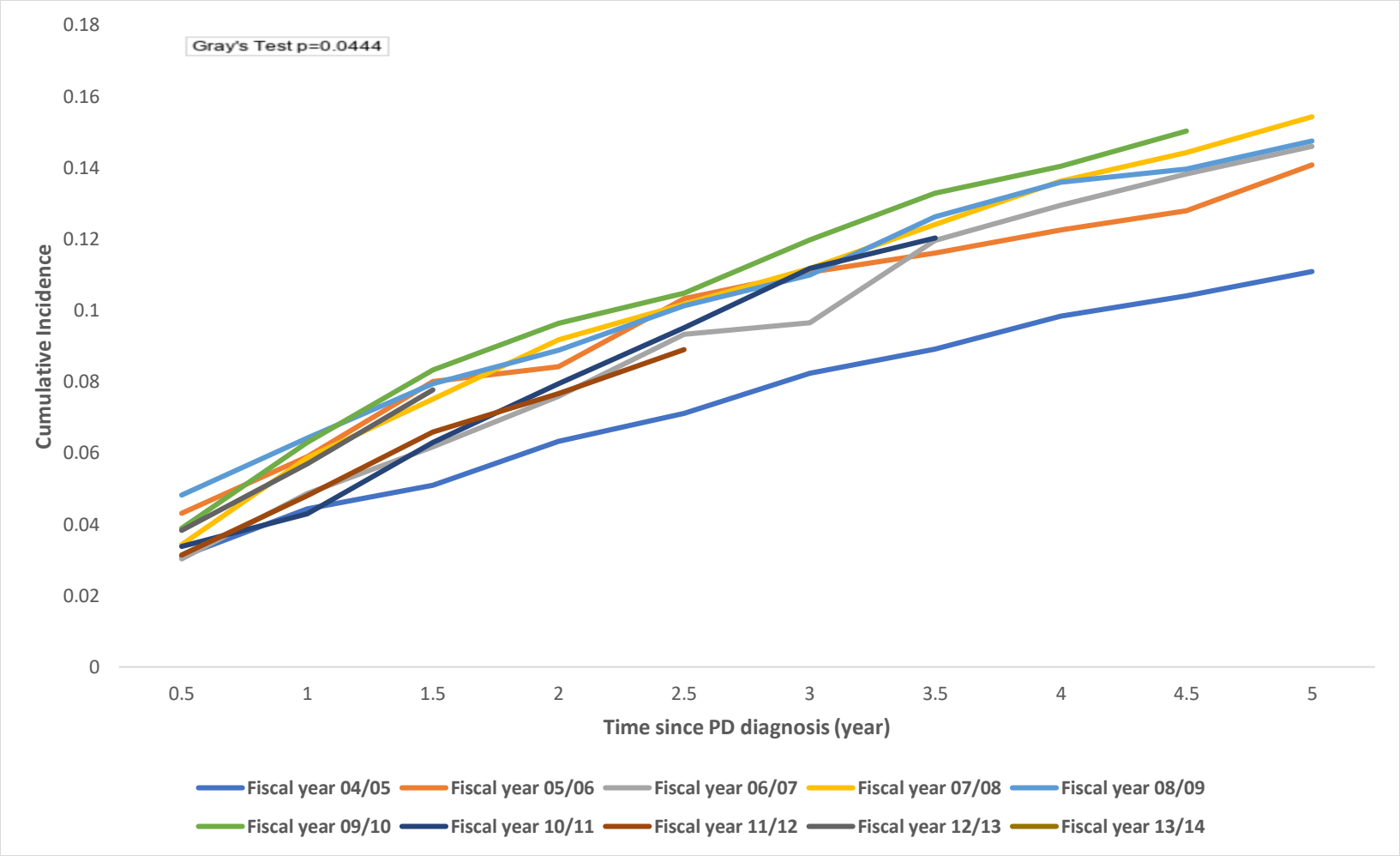

Figure 4-4 Cumulative incidence of urinary incontinence among Parkinson's disease patients by fiscal years, Alberta (2004 - 2014)

To compare the cumulative incidence curves over time, Gray's test was used to test for equality of cumulative incidence functions.[185, 186] With competing risks data, the CIF LIFETEST procedure estimates and compares the CIFs by using Gray's test.[187] In this study, a significant p-value of Gray's test indicated evidence to suggest differences in cumulative incidence curves over time. In figure 4-4, Gray's test showed a significant difference in the cumulative incidence for different fiscal years (p-value=0.044).

4.2.4 Cumulative Incidence: Crude, Age, and Sex-Specific Rates

The PD patients were followed for five years from their diagnosis date to estimate the crude cumulative incidence of UI (Figure 4-5).

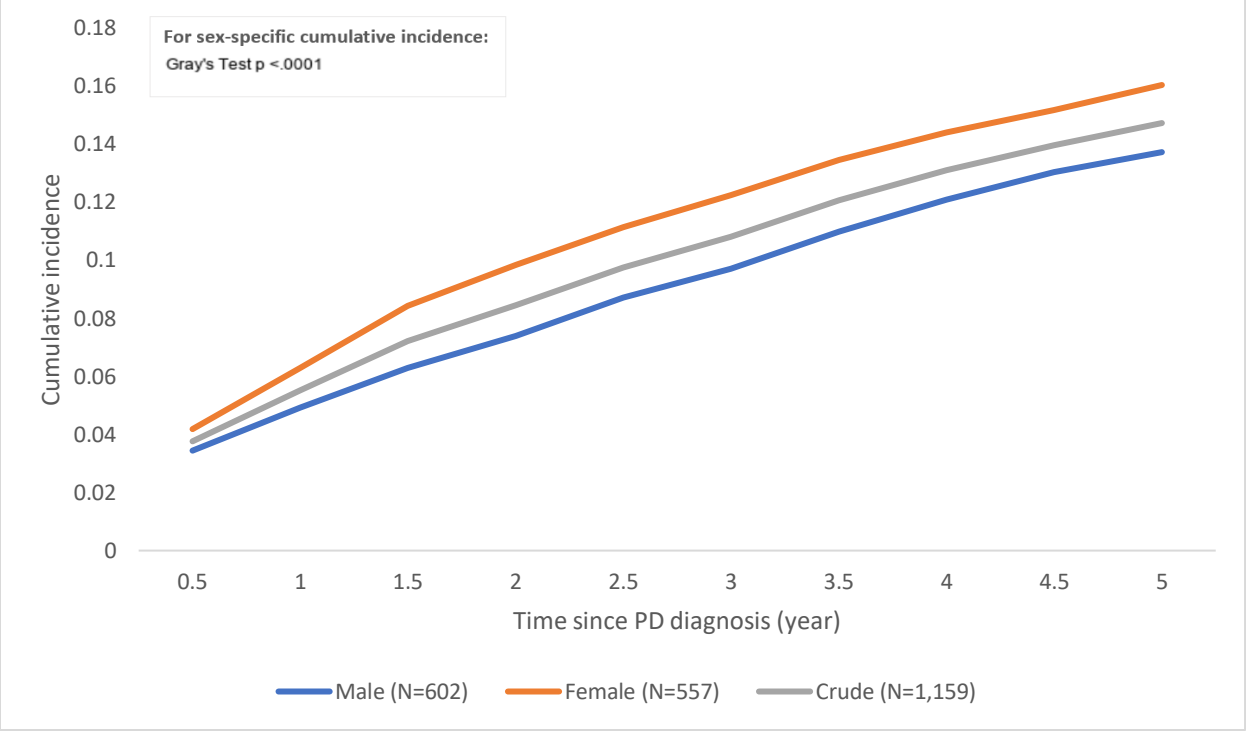

Figure 4-5 Crude and sex-specific cumulative incidence of urinary incontinence among Parkinson's disease patients, Alberta (2004 - 2014)

The crude cumulative incidence of UI in the PD patients at the sixth month from their PD diagnosis was 3.8% (95% CI 0.03-0.04). Overall, the five-year crude cumulative incidence of UI among all PD patients was 14.7% (95% CI 0.14-0.16).

Sex-specific cumulative incidence was also estimated. The cumulative incidence of UI was 3.4% (95% CI 0.03-0.04) for the male patients at sixth month following their PD diagnosis (Figure 4-5), whereas the five-year cumulative incidence of UI among male PD patients was 13.7% (95% CI 0.13-0.15). The female patients at sixth month had a cumulative incidence of 4.2% (95% CI 0.04-0.05). The five-year cumulative incidence of UI among all female PD patients showed comparatively higher cumulative incidence than men, which was 16.0% (95% CI 0.15-0.17). The male: female ratio was 1.1, with a significant difference between the male and female cumulative incidence of UI in PD patients (p-value < .01).

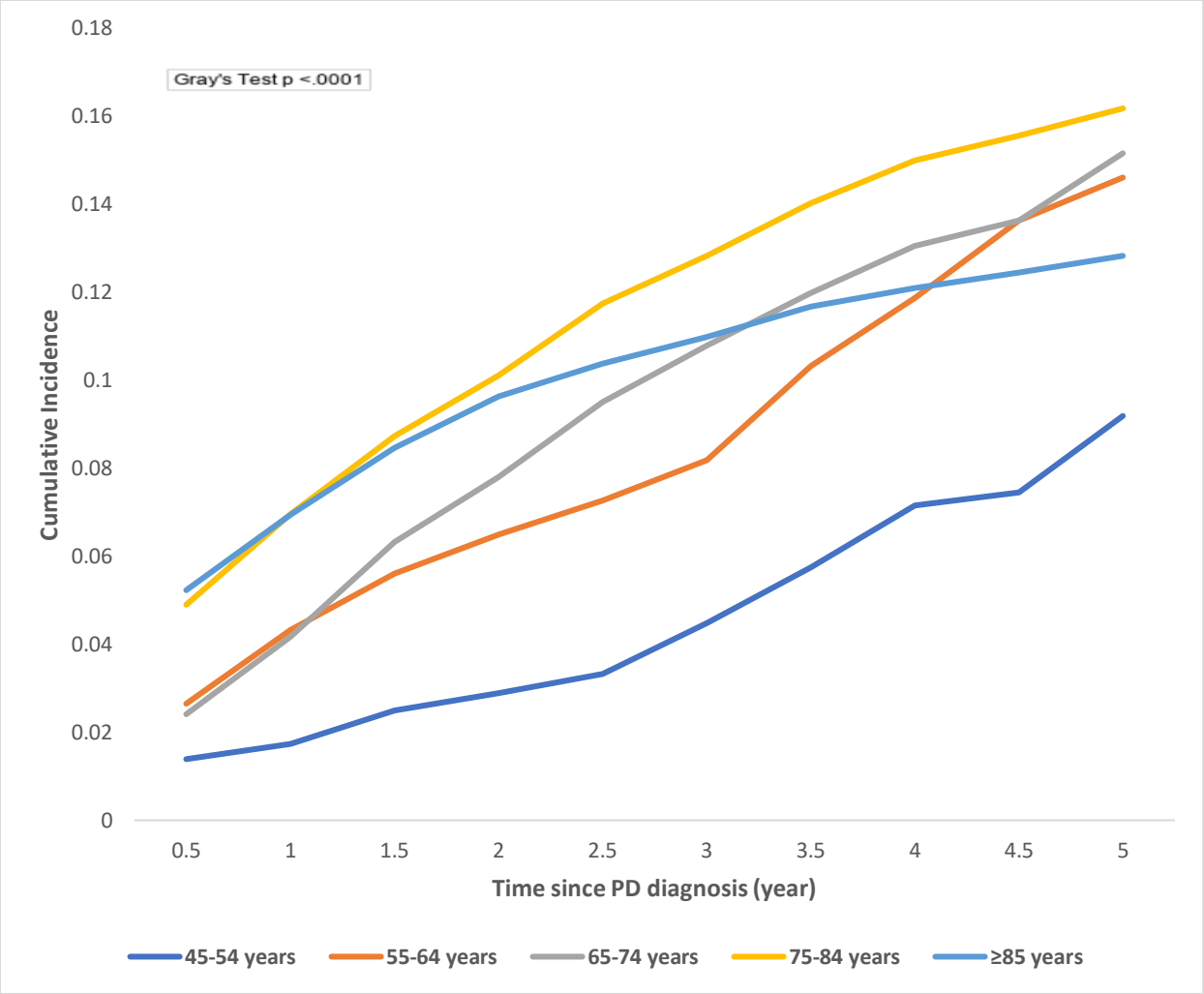

Figure 4-6 Age-specific cumulative incidence of urinary incontinence among Parkinson's disease patients, Alberta (2004 - 2014)

The cumulative incidence between the age groups of UI cases showed a significant difference (p-value < 0.01) (Figure 4-6). The highest five-year cumulative incidence (16.2%, 95% CI 0.15-0.18) was observed in the age group of 75-84 years, whereas the lowest cumulative incidence (9.2%, 95% CI 0.07-0.12) was observed in the age group of 45-54 years.

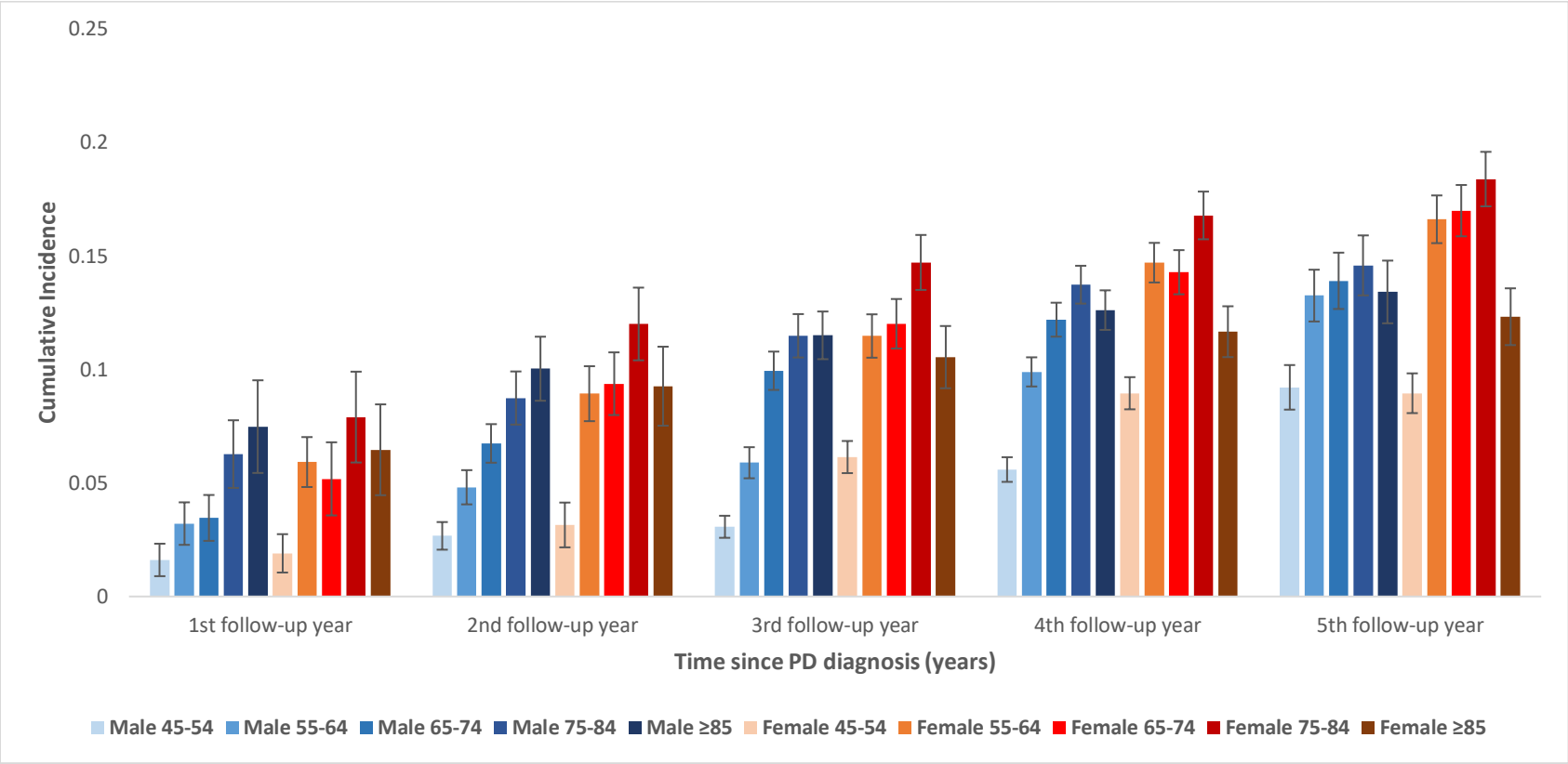

Figure 4-7 Age- and sex-specific cumulative incidence of urinary incontinence among Parkinson's disease patients, Alberta (2004 - 2014)

After an adjustment for age, the female-to-male standardized cumulative incidence was significantly different at all the time points (Figure 4-7). The cumulative incidence showed a non-linear increase in cumulative incidence with age. As shown in figure 4-7, the five-year cumulative incidence of UI for male patients aged over 45 years was 14.6% (95% CI 0.13-0.16) and for females 18.4% (95% CI 0.16-0.21). Female PD patients persistently showed a significantly higher cumulative incidence of UI as compared to males throughout the follow-up years.

The cumulative incidence of UI in PD patients aged between 75 and 84 years was comparatively higher than the other age groups (Figure 4-7). Our results revealed that the cumulative incidence of UI in the PD patients belonging to the age group of 45 to 54 years was 9.2% (95% CI 0.06-0.14), while patients belonging to the age group of 75 to 84 years had a higher cumulative incidence of 14.6% (95% CI 0.13-0.16) at the fifth follow-up year. Similar findings were also observed in female UI cases. The cumulative incidence of female patients belonging to the age group 45 to 54 years was 9% (95% CI 0.06-0.13), while patients belonging to the age group of 75 to 84 years had the higher cumulative incidence of 18.4% (95% CI 0.16-0.21) at the fifth follow-up year.

Overall, the effect of adjusting for age and the competing risk (mortality) on the cumulative incidence of UI in the PD patients was observed (Figure 4-7). The cumulative incidence curves of both males and females continually increased with the advancement in age and began to decay after age 85 years. This is probably due to the higher mortality rate and a lower number of patients aged 85 years and above.

4.2.5 Cox Proportional Hazard Model

We investigated the association between multiple risk factors (age, sex, and CCI score) and the development of UI among PD patients using the Cox proportional hazard model. Age, sex, and CCI scores were significantly associated with the development of UI in PD patients (Table 4-5).

Table 4-5 Cox proportional regression model analysis on variables affecting the development of urinary incontinence among Parkinson's disease patients, Alberta (2004 - 2014)

Variables	Hazard ratio (95% CI)	
	Unadjusted	Adjusted*
Age groups		
45-54	Reference	Reference
55-64	1.74 (1.23-2.45)	1.74 (1.23-2.45)
65-74	1.88 (1.35-2.61)	1.84 (1.32-2.56)
75-84	2.18 (1.57-3.00)	2.08 (1.50-2.87)
≥85	1.79 (1.26-2.52)	1.66 (1.17-2.34)
Sex		
Male	Reference	Reference
Female	1.22 (1.08-1.36)	1.24 (1.04-1.39)
Charlson comorbidity score	1.05 (1.02-1.06)	1.04 (1.01-1.06)

* Multivariate analysis including age group, sex, and Charlson comorbidity score

PD patients who belonged to the age group 75-84 years showed a two-fold increased risk of developing UI (multivariate-adjusted HR:2.08, 95% CI 1.50-2.87). Females were 1.2 times more likely to develop UI (multivariate-adjusted HR:1.24, 95% CI 1.04-1.39) within the first five years of diagnosis of PD. For each 1-point increase in CCI score, there was a 4% greater risk of developing UI (multivariate-adjusted HR:1.04, 95% CI 1.01-1.06) in PD patients.

Chapter 5: Discussion

5.1 Summary

This is the first Canadian retrospective cohort study that involves a large PD population to investigate the increased risk of UI among them. UI is one of the most prevalent non-motor symptoms that often develops in PD patients.[15, 108] Individuals with UI tend to reduce physical activities which significantly affects HRQoL.[25, 26] UI may contribute to specific geriatric health problems, such as falls and hip fractures, which are also more frequently reported in older PD patients with UI.[28, 188] With the growing worldwide prevalence of UI among PD patients,[23] its distribution in the Canadian populations was needed to be investigated.

In this provincial population, UI cases were identified by a case definition algorithm applied to linked administrative health databases (2004 - 2014) within the PD cohort. Over the study period (2004-2014), 13.1% of the total PD population aged 45 years and older were diagnosed with UI. Among the total UI patients, males (52.4%) were higher in number than females (47.6%) at a similar mean age of 74 years. Two clinical studies that investigated urinary dysfunction in PD, Campos-Sousa et al. (male 50.8%, female 49.2%) and Winge et al. (male 59.8% of male, 40.2% of female) reported male study population being higher in number similar to our study.[122, 189] However, our results showed no sex-specific difference in terms of mean age (p-value= 0.796). This finding is also consistent with one cross-sectional study done in Chinese PD patients with OAB.[190]

After following PD cases for the first five years since PD diagnosis, we found a total of 1,159 incident UI cases. Considering age as an important demographic factor, we found that most of them were (82.5%) were diagnosed with UI after age 65. This supports the increased risk

of being diagnosed with UI in PD with age found in earlier studies.[73, 121, 191-193] Furthermore, the highest number of UI cases (41.8%) were identified between the ages of 75-84 years which indicates this specific age group may play a significant role in developing UI among PD patients.

As our study involves older people, we adjusted for mortality to evaluate the actual cumulative incidence of UI in this PD population. The estimated crude incidence rate of UI in the PD patients aged 45 years and older was 17.8 per 1,000 person-years, and cumulative incidence was 14.7% at the fifth follow-up year. In comparison, with a study which used Taiwan's research health insurance database, the crude incidence rate of OAB (14.5 per 10,000 person-years) in PD patients was much lower over the five years follow-up than our findings.[30] They also reported a cumulative incidence of 0.65% at the fifth follow-up year.[30] The difference in incidence rates may be, in part, due to case selection and methodology. Taiwan's study used a single ICD-9 code for case selection while excluding non-specific urinary symptom code (ICD-9 code 788.X),[30] whereas we included all the relevant ICD codes (ICD-9 and ICD-10-CA) of UI. Moreover, we included drug dispensing data to increase the accuracy of administrative data in the identification of UI cases.

Our results showed a comparatively higher five-year cumulative incidence of UI in females (16.0% vs. 13.7%) than males which is reflective of what is reported in the other studies.[73, 124, 194] Within the age groups, the highest age-standardized cumulative incidence (16.2%) was seen in the 75 to 84 age group, and the lowest cumulative incidence (9.2%) belonged to the age group 45-54 years. This suggests that younger adults were less likely to have UI than their older counterparts within the first five years after PD diagnosis. After an adjustment for age, the female-to-male standardized cumulative incidence (18.4% vs. 14.6%) was higher in patients aged between 75 and 84 years. However, after 85 years, the cumulative incidence started

to decline. This finding was consistent with one study reported by Ou et al. that the occurrence of UI may not increase as PD progresses.[38] In this current study, the total number of UI cases in PD patients aged 85 years and older (N=174) was lower than other age groups (65-74: N=298 and 75-84: N=484). This lower rate may be related to other reasons such as it becomes difficult for older patients to attend physician visits while dealing with chronic health conditions. With increasing age, the intricacy in disease diagnosis, and the possibility of underdiagnosis also appear. Along with the other possible causes, high mortality associated with very elderly people could be responsible for the declination.

This study also evaluated the association of the risk of developing UI among PD patients and some potential risk predictors. Our study showed a significant association of age, sex, and CCI score with the development of UI within the first five years of diagnosis of PD. The risk of developing UI in PD was two times more likely in people aged 75-84 years compared to the younger age group. Our results also revealed that a female PD patient (1.2 times) was more likely to develop UI than a male patient. Another interesting finding was the association of UI with increasing CCI scores. More than half of UI cases (54.4%) had CCI score 1 or more and showed an increased risk (4%) of developing UI in PD for each 1-point increase. There was also a significant relationship between age and CCI scores of UI patients (p-value=<.0001). The average age of patients who had CCI scores 3 or more was comparatively higher than patients with lower CCI scores. These significant correlations agree with the findings of the studies reported by Lin et al. and Buchman et al. that age, sex, and comorbidity are associated with the development of UI in PD patients.[27, 30]

5.2 Strength

The strengths of this study included the use of provincial health administrative datasets, linking multiple datasets to extract the UI cases among PD patients and mortality adjustment. Incident UI cases were detected combining multiple health administrative datasets of Alberta. As the datasets contain information of most residents (99%) of Alberta, the result of this study can be reasonably generalizable without sampling bias with comparable administrative databases. Non-specific or unclear UI diagnostic codes were confirmed linking drug files, which increases the accuracy of the finding of the results.[195] Another strength was that our estimated incidence rates were adjusted for mortality. Otherwise, the risk would be overestimated as our sample population included elderly PD patients.[179, 180, 182]

5.3 Limitation

Our study had some limitations, including no single ICD code for UI, and the possibility of selection bias. As UI does not have any single specific ICD diagnostic code, the incident UI cases were selected based on several diagnostic codes, which may cause misdiagnosis or bias to some extent. There is also a chance of selection bias due to the presence of false positive or false negative cases as we only identified those cases presented to physicians. Any typing error while inserting ICD codes in administrative databases could also be responsible for this selection bias. Older patients are often reluctant or feel embarrassed to discuss their symptoms thinking UI is a normal part of their aging process.[165] Therefore, there was a possibility of losing UI cases those need to be medically managed and can underestimate the true incidence of UI with PD.

5.4 Conclusion

The identification of UI in the early stage of PD could influence the overall management and improve HRQoL. This study has illustrated the significant occurrence of UI in older PD patients in Alberta. We were able to demonstrate the crude and adjusted incidence rates of UI in PD. The risk for developing UI in PD female patients was higher than male patients, and the risk was persistent in age distribution as well with the highest risk related to age group 75-84 years. Although the burden of UI is equally high, especially in PD patients aged 65 years and above, many government and private agencies are still giving far greater attention to only motor symptoms of PD.[196, 197] The significant findings of this study will have an impact on the future approach of other epidemiological studies to investigate more as we showed the overall probability of developing UI over a stated period in PD patients. Distribution and cumulative incidence pattern of this study based on sex and age groups will also influence overall health care management and policy direction as the most vulnerable groups were identified and reported through this current study.

5.5 Recommendations

Considering the magnitude of the burden, UI in PD patients needs to be further explored. Like the other western countries, Canada is also facing significant challenges in organizing the funding and provision of care to respond to the increasing demands of patients with these chronic conditions. By 2031, the total annual health care costs will double for people diagnosed with both UI and PD.[33] Therefore, this is the prime time to explore the financial burden side related to the future cost.

Based on the findings from our analysis, further research should focus on a longer follow-up from PD diagnosis and include data from all provinces to obtain a national incidence of UI in the PD population. Case validation of ICD diagnostic codes for UI should be investigated given that no universal algorithm exists. Additional studies are needed to identify UI among the residents who were not under health coverage or do not present UI concerns to physicians. Clinical or population-based surveys may help capture milder cases or people not within the healthcare system.

Although several clinical studies have suggested that the pathology of neurodegeneration related to developing UI symptoms may start years earlier, the diagnosis event of UI in PD patients varies.[198-200] While there was a disparity in the findings, few studies acknowledged the occurrence of UI among PD patients within five follow-up years of their diagnosis.[134, 135, 189] The underlying neurological disease stage of PD might be an important contributing factor to the UI development rather than disease duration. Therefore, further research is needed to clarify the association of disease severity and duration with the development of UI in PD. With the successful implications of these recommendations, future studies will provide a better understanding of UI epidemiology among the PD population of Canada.

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Appendices

Appendix A: Dataset Groundwork

All the datasets were obtained from Alberta Health (AH). Data sharing agreements were needed to access these data between the custodians of all data and AH. To keep the patients' identity anonymous in these administrative datasets, an algorithm was used by AH to scramble the unique lifetime identifiers with the ability to link through all the datasets.[iii] Once AH received the data, the analytics branch performed the integration of the datasets by linking the patients with generic unique identifiers before sending the datasets to the study team. Datasets used in this study contained information regarding socio-demographic, physician billings, pharmaceutical billing, emergency visits, hospital admissions, vital statistics, etc. from 2004/2005 to 2013/2014 fiscal years.

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Appendix B: Tables

Table 1: Algorithm of Identifying Urinary Incontinence in Parkinson Disease

Case definition algorithms	Study period
1) 1 physician claim (ICD-9 code 596.5, 625.6, 788.3, 788.4, 788.6) OR 1 inpatient hospitalization (ICD-10-CA code R32, N32.81, N39.3, N39.41, N39.42, N39.43, N39.44, N39.45, N39.46, R35, R39.15, N39.49) OR 1 emergency visit (ICD-10-CA code R32, N32.81, N39.3, N39.41, N39.42, N39.43, N39.44, N39.45, N39.46, R35, R39.15, N39.49)	Followed from PD index date anytime between fiscal years 2004/2005–2013/2014
2) 1 physician claim (ICD-9 code 596, 625, 788) AND 1 prescribed medication includes ATC codes: (G04BD01, G04BD02, G04BD03, G04BD04, G04BD05, G04BD06, G04BD07, G04BD08, G04BD09, G04BD10, G04BD11, G04BD12, G04BD13, G04BD1) for treating UI	Followed from PD index date anytime between fiscal years 2004/2005–2013/2014

Table 2: Total Number of Urinary Incontinence Diagnoses among Parkinson's Disease Patients by Fiscal Year, Alberta (2004-2014)

Follow-up years	PD cases (N=9,540)	PD cases with UI (N=1,253)
04/05	903	121
05/06	952	164
06/07	924	150
07/08	904	154
08/09	1,059	165
09/10	1,081	162
10/11	1,096	138
11/12	1,018	89
12/13	965	75
13/14	638	35

Table 3: Distribution of urinary incontinence cases identified within the first five years of Parkinson's disease diagnosis by age and sex, Alberta (2004 - 2014)

Age groups (year)	Male (%)	Female (%)
45-54	1.73	1.64
55-64	7.16	6.99
65-74	13.89	11.82
75-84	21.74	20.02
≥85	7.42	7.59

Table 4: Number of Urinary Incontinence cases among Parkinson's Disease Patients Developed Over the Follow-up Years After Mortality Adjustment, Alberta (2004-2014)

Time since PD diagnosis	Overall (N)	UI cases (N)	Deceased cases (N)	Censored cases (N)
1st follow-up year	2,024	516	923	585
2nd follow-up year	1,609	247	534	828
3rd follow-up year	1,386	172	447	767
4th follow-up year	1,296	141	416	739
5th follow-up year	3,225	83	263	2,879

Table 5: Cumulative Incidence of Urinary Incontinence among Parkinson's Disease Patients by Fiscal Years, Alberta (2004-2014)

Time point (year)	Fiscal year 04/05	Fiscal year 05/06	Fiscal year 06/07	Fiscal year 07/08	Fiscal year 08/09	Fiscal year 09/10	Fiscal year 10/11	Fiscal year 11/12	Fiscal year 12/13	Fiscal year 13/14
0.5	0.0310	0.0431	0.0303	0.0343	0.0482	0.0389	0.0338	0.0314	0.0383	0.0495
1	0.0443	0.0589	0.0487	0.0586	0.0642	0.0629	0.0429	0.0481	0.0570	
1.5	0.0510	0.0800	0.0617	0.0752	0.0794	0.0833	0.0630	0.0659	0.0777	
2	0.0633	0.0842	0.0759	0.0918	0.0889	0.0964	0.0795	0.0767		
2.5	0.0711	0.1033	0.0933	0.1018	0.1013	0.1048	0.0952	0.0890		
3	0.0824	0.1107	0.0966	0.1118	0.1099	0.1197	0.1118			
3.5	0.0892	0.1161	0.1196	0.1241	0.1262	0.1329	0.1203			
4	0.0983	0.1225	0.1294	0.1363	0.1359	0.1404				
4.5	0.1040	0.1279	0.1382	0.1442	0.1397	0.1503				
5	0.1109	0.14080	0.1460	0.1543	0.1475					

Table 6: Crude and Sex-specific Cumulative Incidence of Urinary Incontinence among Parkinson's Disease Patients, Alberta (2004-2014)

Time after PD diagnosis (year)	Overall (N=1,159)	Male (N=602)	Female (N=557)
0.5	0.0376	0.0344	0.0418
1	0.0552	0.0492	0.0629
1.5	0.0722	0.0629	0.0843
2	0.0845	0.0739	0.0982
2.5	0.0975	0.0870	0.1112
3	0.1079	0.0969	0.1222
3.5	0.1205	0.1098	0.1345
4	0.1308	0.1208	0.1438
4.5	0.1395	0.1303	0.1516
5	0.1471	0.1371	0.1602

Table 7: Age-specific Cumulative Incidence of Urinary Incontinence among Parkinson's Disease Patients, Alberta (2004-2014)

Time after PD diagnosis (year)	Age groups				
	45-54 years	55-64 years	65-74 years	75-84 years	≥85 years
0.5	0.0139	0.0265	0.0241	0.0490	0.0523
1	0.0174	0.0432	0.0417	0.0696	0.0695
1.5	0.0249	0.0561	0.0632	0.0874	0.0847
2	0.0289	0.0650	0.0781	0.1011	0.0963
2.5	0.0332	0.0727	0.0951	0.1175	0.1038
3	0.0448	0.0819	0.1079	0.1283	0.1099
3.5	0.0575	0.1032	0.1199	0.1403	0.1167
4	0.0716	0.1187	0.1305	0.1500	0.1210
4.5	0.0745	0.1363	0.1363	0.1556	0.1245
5	0.0919	0.1461	0.1516	0.1618	0.1283

Table 8: Age and Sex-specific Cumulative Incidence of Urinary Incontinence among Parkinson's Disease Patients including 95% Confidence Intervals, Alberta (2004-2014)

Sex	Age groups	Time since PD diagnosis				
		1st follow-up year	2nd follow-up year	3rd follow-up year	4th follow-up year	5th follow-up year
Male	45-54	0.02 (.01-.03)	0.03 (.01-.05)	0.03 (.02-.06)	0.06 (.03-.09)	0.09 (.06-.14)
	55-64	0.03 (.02-.05)	0.05 (.03-.06)	0.06 (.04-.08)	0.10 (.08-.12)	0.13 (.10-.16)
	65-74	0.03 (.03-.05)	0.07 (.05-.08)	0.10 (.08-.12)	0.12 (.10-.14)	0.14 (.11-.16)
	75-84	0.06 (.05-.07)	0.09 (.08-.10)	0.11 (.10-.13)	0.14 (.12-.15)	0.15 (.13-.16)
	≥85	0.07 (.06-.10)	0.10 (.08-.12)	0.12 (.09-.14)	0.13 (.10-.15)	0.13 (.11-.16)
Female	45-54	0.02 (.01-.04)	0.03 (.01-.06)	0.06 (.03-.10)	0.09 (.06-.13)	0.09 (.06-.13)
	55-64	0.06 (.04-.08)	0.09 (.07-.11)	0.11 (.09-.14)	0.15 (.12-.12)	0.17 (.13-.20)
	65-74	0.05 (.04-.07)	0.09 (.08-.11)	0.12 (.10-.14)	0.14 (.12-.17)	0.17 (.14-.20)
	75-84	0.08 (.07-.09)	0.12 (.10-.13)	0.15 (.13-.17)	0.17 (.15-.19)	0.18 (.16-.21)
	≥85	0.06 (.05-.08)	0.09 (.07-.11)	0.11 (.08-.13)	0.12 (.09-.14)	0.12 (.10-.15)