PAIN REPORTS AMONG A COMPLEX CHRONIC CARE POPULATION IN CANADA

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Abstract

The present dissertation examines pain reports among a complex chronic disease (CCD) population of adults from complex chronic care (CCC) facilities across Ontario, Canada. The literature review provides an overview of multimorbidity, complex chronic disease, acute and chronic pain, and the interactions between these constructs. The present dissertation comprises three studies that examine reports of pain among the CCD population, with each study drawing upon data from the Canadian Institute of Health Information (CIHI) Continuing Care Reporting System (CCRS) dataset, obtained through the Graduate Student Data Access Program (GSDAP). The first study investigates combinations of multimorbidity associated with pain. Specifically, pain prevalence, intensity and frequency are examined in relation to medical disease categories, as well as, combinations of two to five of the most prevalent multimorbid disease categories among this adult, CCD population. This study provides an overview of the types of disease combinations that are particularly problematic in regard to pain among this population. Results indicate that the top five most prevalent combinations of multimorbid disease patterns are endocrine/metabolic/nutrition, heart/circulation, musculoskeletal, neurological and psychiatric/mood. Building further upon these findings, Studies 2 and 3 examine pain reports from specific disease categories in the greater CCD population. Study 2 examines the phenomenon of hypertension-associated-hypoalgesia, investigating the difference in pain reports between Ontario CCC residents with and without hypertension. Optimal propensity matched groups were compared for differences on various pain report scales and results indicated that residents with hypertension experience less pain (hypoalgesia) than residents without hypertension. Study 3 investigates pain reports in another sub-group of the CCD population; specifically, those with missing limbs. Similar to Study 2, propensity matching was utilized to

create comparably matched groups of residents with and without missing limbs. Findings from this study are consistent with existing literature that individuals with amputations are more likely to report greater pain than those without. In both studies 2 and 3, females were more likely to report pain than males, consistent with extensive pain literature in this area.

All three studies benefit from the use of a reliable, comprehensive dataset that allows for the inclusion of multiple control variables and a large, diverse and generalizable sample size. A limitation permeating each study, however, is the pain reporting scale and vague disease descriptions. These strengths and limitations are addressed in detail throughout each study, as well as in the General Discussion of the dissertation. The contributions of each of the three studies presented in this dissertation allows for more information about the demographic, medical and pain experiences of this unique population, which in turn can be used in a clinical context to inform training for current and future health care providers, as well as in the policy context to guide intervention efforts. Future research that identifies the successful approaches to managing CCD and pain would be invaluable to delivering individualized, adaptive and patient-centered care for this growing population. This research is necessary for ensuring that this significant patient population is receiving the highest quality of care from multidisciplinary health care teams.

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Chapter 1: Introduction

Over the last decade, chronic health problems have been recognized as the leading health burden for those over the age of 65 years (Marengoni et al., 2011; McPhail, 2016). Life expectancy is increasing slowly, and more individuals are developing multiple chronic health problems (Oeppen & Vaupel, 2002). “Chronicity”, proposed by O’Halloran, Miller and Britt (2004) is a qualifier connoting disease lasting at least six months, having a documented pattern of recurrence or deterioration, as well as an impact on an individual’s quality of life. Chronic health problems include diseases and health complications that develop slowly over time, typically progressing in severity and intensity, and can rarely be cured (Ministry of Health and Long-Term Care, 2007). Management of chronic health conditions often becomes the primary care focus, but can be costly (McPhail, 2016) and have associated social (Noël, Frueh, Larme, & Pugh, 2005), functional (Rijken, Van Kerkhof, Dekker, & Schellevis, 2005) and mental health (Fortin et al., 2006; Kuluski et al., 2013) challenges. Chronic conditions include cancer, cardiovascular disease, arthritis, pain, asthma, chronic obstructive pulmonary disease (COPD) and chronic depression (Ministry of Health and Long-Term Care, 2007).

A growing number of Canadians live with chronic health conditions that can be classified as complex chronic disease (CCD). A CCD is a condition involving multiple morbidities (MM) and a combination of functional (Bayliss, Bayliss, Ware, & & Steiner, 2004; Rijken et al., 2005), social (Noël et al., 2005), vocational (Kuluski et al., 2014) and/or mental health challenges (Fortin et al., 2006). Although the disease combinations reported in multimorbidity (MM) are diverse, the most common diagnoses are diabetes, stroke, hypertension, cancer, arthritis, asthma, fractures, the presence of an artificial knee or hip, fatigue, multiple sclerosis, demyelinating diseases of the central nervous system, gonarthrosis, ataxia, COPD, renal failure, malignant

neoplasm of breast/prostate, depressive episodes and anxiety, and hypercholesterolemia (Kuluski et al., 2013; Pefoyo et al., 2015). The top five most prevalent combinations of MM disease patterns are endocrine/metabolic/nutrition, heart/circulation, musculoskeletal, neurological and psychiatric/mood (Ferguson, Svendrovski, & Katz, 2020). Individuals with CCD are both challenging and unique in that they require attention and assistance from multiple health and social service providers (Kuluski et al., 2013). This typically involves management of complex treatment regimens that include multiple appointments, numerous medications, regular monitoring and surveillance, and adherence to treatment recommendations and protocols (Mercer, Salisbury, & Fortin, 2014; Moffat, 2015; Onder et al., 2015).

A qualitative study by Kuluski et al. (2014) collected in-depth semi-structured one-on-one interviews with 116 patients at a complex rehabilitation and continuing care institution in Canada, in order to characterize the needs and experiences of this population. This mixed-methods study contained quantitative standardized measures as well as open-ended questions with interviews in efforts to capture biomedical, psychological and social aspects of a patient's particular needs within this type of setting. Of the 116 interviews, 95 patients conferred on health problems that had impacted their lives and elaborated on the ways in which their lives were changed. Thematic experiences and views emerged, denoting six primary areas of impact: autonomy; meaningful activities; structures of meaning; social fabric; mental health; and, finances (Kuluski et al., 2014). Consistent with similar previous research (Sells et al., 2009), there was a relationship between illness severity and the number of domains impacted by patients. Specifically, patients with a greater number of multimorbid illnesses/symptoms (e.g. pain, weakness, emotional distress, sensory challenges, etc.), typically described experiencing a greater loss among multiple domains (Kuluski et al., 2014). These findings highlight that

individuals with multimorbidity and a complex disease profile report a negative cascade of effects impacting multiple areas of life as a result of illnesses.

Low socioeconomic status, female sex, and older age have been associated with multimorbidity, in both longitudinal and cross-sectional studies. Among an older population, the prevalence and incidence rates are reported at 55% and 12-33%, respectively (Marengoni et al., 2011; Melis, Marengoni, Angleman, & Fratiglioni, 2014). In Ontario, specifically, CCD is most prevalent in elderly individuals and is often considered the "norm rather than the exception" (Statistics Canada, 2003). This results in poorer quality of life (Moffat, 2015; O'Halloran, 2004), as well as higher demand for primary healthcare services, hospital stays and intensive care treatments, associated with higher costs (Ryan, Wallace, O'Hara, & Smith, 2015; Chris Salisbury, 2012). The 2011 Commonwealth Fund Survey of Sicker Adults found that 96% of respondents with a chronic disease had access to regular medical attention (Health Council of Canada, 2011). Of these, the majority (95.1%) of adults ages 40 years and older from the provinces of Ontario, British Columbia, Alberta, Manitoba and Saskatchewan reported having access to a regular primary health care provider (Weaver et al., 2015). Generally, these results are promising for Canadians; however, those with complex chronic diseases typically require access to more comprehensive treatment protocols, longer adherence and management, multiple medical tests and assessments, thus requiring the involvement of numerous health professionals on a long-term basis, such as specific disease specialists, dieticians, pharmacists, geriatricians, social workers, psychiatrists/psychologists, occupational therapists, at home attendants, and nursing staff (Rudland & Macey, 2013).

Complicating this complex health profile further, many elderly Canadians also experience comorbid chronic pain. Chronic pain alone is a prevalent and often debilitating condition that has

significant negative effects on the individual and the health care system, as it has been associated with declines in activities of daily living, loss of employment, mental health problems, large medical system expenditures and poor self-rated health and health related quality of life (HRQoL) (Agborsangaya, Lau, Lahtinen, Cooke, & & Johnson, 2013; Mills, Torrance, & Smith, 2016). In fact, back and neck pain are independently the largest contributors to disability in high income countries, including Canada, ahead of stroke and heart disease related disability (Murray et al., 2015). Suicidality also doubles among chronic pain patients due to the emotional toll associated (Campbell, Darke, Bruno, & Degenhardt, 2015).

In line with this, Hogan et al. (2017) highlighted that Canadians with chronic pain have worse HRQoL than other chronic diseases. Using the Canadian Community Health Survey (CCHS) data and linked Ontario health care administrative data, the researchers completed a retrospective matched cohort study of health utilities in people with and without chronic pain (Hogan, 2017). A health utility is a self-reported global measure of HRQoL. The Health Utility Index Mark 3 (HUI3) used includes both the individual's current health state and the preference for that state. Employing propensity matching statistics, the researchers were able to generate a matched sample of 12,146 respondents with chronic pain and 12,146 without chronic pain. Prior to matching, females were more likely to report chronic pain, as well as those among lower socioeconomic backgrounds, which is consistent with previous research in the area of chronic pain (King et al., 2011; Kuluski et al., 2013; Poleshuck & Green, 2008; Willadsen et al., 2018). The HUI3 has possible values ranging from -0.36 to 1; with a value of 1 representing perfect health, zero being dead, and values less than zero indicate states worse than death (Feeny, Furlong, Boyle, & Torrance, 1995).

Among the matched sample, results showed that the group with chronic pain had a mean utility of 0.59 (95% CI 0.58-0.59), whereas those without chronic pain had a mean utility of 0.90 (95% CI 0.90-0.91). Broken down further, individuals with mild, moderate and severe pain had utilities of 0.72 (95% CI 0.71-0.73), 0.59 (95% CI 0.58-0.60), and 0.35 (95% CI 0.33-0.36), respectively. Further, when taking into consideration the impact of activity limitations associated with pain, individuals reporting no, some, a few, and most activity limitations had utilities scores of 0.83 (95% CI 0.82-0.83), 0.72 (95% CI 0.72-0.73, 0.59 (95% CI 0.58-0.60), and 0.35 (95% CI 0.33-0.36), respectively. In assessing similarly conducted research among other chronic diseases, the authors noted that only individuals with Alzheimer's disease reported a lower health utility of 0.58, than moderate chronic pain (Mittmann, Trakas, Risebrough, & Liu, 1999). Further to this point, quality of life for individuals with severe chronic pain was notably worse than any other chronic disease reported in the community-dwelling population, with a utility score 0.35 (Hogan, 2017).

Similar to Hogan et al. (2017), researchers in Australia evaluated a longitudinal cohort of 351 adult CCD patients attending an Australian community-based rehabilitation service at baseline, and 3, 6 and 12 months later, in order to identify factors that predict HRQoL (Tyack et al., 2016). The SF-36, preference-based health utility, and linear mixed-effects regression were used. In line with findings from Hogan et al. (2017), the impact of chronic disease on daily activities was the most frequent significant predictor of HRQoL outcomes among patients with CCD. Other significant predictors included the impact of chronic back pain or sciatica on daily activities, the number of comorbidities, general health functioning and psychological distress (Tyack et al., 2016).

In light of the lack of understanding of pain and disease complexity within an elderly, health complicated population, this dissertation seeks to provide increased knowledge of these areas and provide a comprehensive overview of the complexity of patients with complex chronic disease, specific illnesses and how these relate to pain. The three studies that comprise this dissertation examine pain in individuals with CCD admitted to Canadian complex care institutions. Specifically, study 1 examines the association between multimorbid disease patterns and pain outcomes; Study 2 investigates cardiovascular disease, specifically hypertension and pain outcomes examining the phenomenon of hypertension-associated hypoalgesia; and Study 3 evaluates musculoskeletal difficulties and pain, specifically among residents with missing limbs. The findings from these studies will be of particular interest to health care professionals, clinicians and residents, as well as researchers, policy makers and the public.

Chapter 2: Literature Review

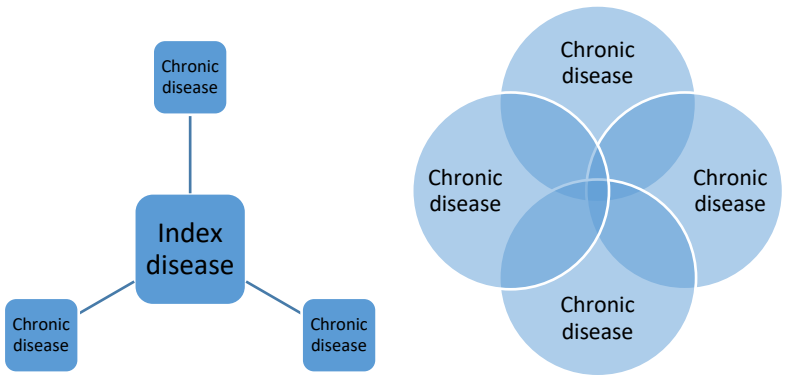
This chapter introduces the interrelated pillars of this doctoral research: complex chronic disease (CCD) and pain. Each pillar will be described separately; however, the interrelatedness of these concepts creates the basis for this research work.

Complex Chronic Disease (CCD)/Multimorbidity (MM)

Due to aging, increased longevity, and advancements in medical research, education and technologies, an increasing number of people are living longer with chronic illness (Busse, Blümel, Scheller-Kreinsen, & Zentner, 2010). In fact, many of these chronically ill individuals suffer live with CCD, also often referred to as multimorbidity (MM), meaning to the co-occurrence of two or more chronic conditions (Bower et al., 2011; Boyd & Fortin, 2010; Uijen & van de Lisdonk, 2008). CCD becomes more prevalent with age (Bower et al., 2011; Van Oostrom et al., 2012) and is associated with high mortality (Willadsen et al., 2018), lower

functional status (Williams & Egede, 2016), greater ambulatory health care requirements (Van Oostrom et al., 2012) and poorer health status (Williams & Egede, 2016).

The construct of "comorbidity" was established in 1970 by Alvin Feinstein who coined the term to address the functional effects of comorbid conditions on the patient (Feinstein, 1970). The term was first defined as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" (Feinstein, 1970). Thus, the definition implies that the main interest is on a specific, individual index condition that is the primary focus. Multimorbidity or CCD, in contrast, is defined as any co-occurrence of 2 or more diseases in the same person (Batstra, Bos, & Neeleman, 2002).



Comorbidity vs. Multimorbidity

Figure 2.1. Conceptual diagrams showing the difference between how comorbidity and multimorbidity are defined. Adapted from Boyd and Fortin (Boyd & Fortin, 2010).

Operationalization and Measurement of Multimorbidity

Various operational definitions of chronic multimorbidity have been proposed; however, to date, there is no internationally accepted list of chronic diseases that define patients with multimorbidity (Almirall & Fortin, 2013; Stewart, Fortin, Britt, Harrison, & Maddocks, 2013).

There are, however, three major perspectives typically adopted. First, employing a numerical count (two or more) of concurrent diseases in the same individual. This definition is most commonly applied in epidemiological studies (Huntley, Johnson, Purdy, Valderas, & Salisbury, 2012). Second, researchers may use cumulative indices evaluating the number, as well as the severity, of concurrent diseases. In these cases, specific indices are typically used, including the Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987), the Cumulative Illness Rating Scale (CIRS) (Linn, Linn, & Gurel, 1968), and the Index of Co-Existent Diseases (ICED) (Greenfield, Apolone, McNeil, & Cleary, 1993). The use of these indices provides additional weighting information, as they include aspects of severity, disease type (e.g., Type II diabetes, stage 4 ovarian cancer), mortality outcomes, and/or likely resource utilization. These approaches are most appropriately used in clinical studies, where the focus is to identify patients at risk for poor health and treatment outcomes. Lastly, when examining trends of prevalence rates among patients with multiple health diseases, some authors have proposed a cumulative collection of concurrent diseases, their effects, as well as factors such as symptoms, cognitive, physical, and psychosocial problems (Huntley et al., 2012).

Research in this area has assessed the prevalence of multimorbidity by comparing different methods of measurement (Brilleman & Salisbury, 2013; Diederichs, Berger, & Bartels, 2011; Fortin et al., 2006; Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005; Harrison, Britt, Miller, & Henderson, 2014; Huntley et al., 2012). The following section will review the prevalence of CCD in clinical populations in greater detail.

Prevalence of CCD in Clinical Populations

A systematic review (Fortin et al., 2012) examined previously published prevalence estimates of MM in primary health care and general, community populations from more than ten

different countries including Canada, United States, United Kingdom, Netherlands and Australia. The review concluded that MM (defined by two diseases or more) ranged from less than 10% to as high as 70% in general population studies, stratified by age. Studies examining populations in these specific countries have highlighted similar results.

In a Canadian study, Broemeling et al. (2008) analyzed the 2005 Canadian Community Health Survey (CCHS Cycle 3.1) and found that MM was a common problem for more than one-half of adults over the age of 65 years, noting that respondents identified having at least two of seven diseases (arthritis, cancer, chronic obstructive pulmonary disease, diabetes, heart disease, high blood pressure and mood disorders). The study also highlighted that these individuals living with CCD used health care services more often than those without chronic disease and the frequency of service use increases as the number of chronic diseases increase (Broemeling, Watson, & Prebtani, 2008).

The 2010 National Health Survey in the United States found that of respondents over the age of 18 years, 26% reported at least two of ten chronic diseases (Ward & Schiller, 2013). Barber et al. (2010) found similar results in the United Kingdom, with MM (again defined as two or more chronic diseases) being prevalent in approximately one-third of adults over the age of 50 years. This study involved the use of a self-reported postal health survey and review of electronic medical records. MM was present among 36.2% and 32.3%, respectively (Barber, 2010).

A study conducted by Brett et al. (2013) estimated patterns and prevalence of MM across the entire age spectrum of patients attending two large metropolitan medical practices in Western Australia during a six-month period. Medical records were extracted for 7,247 patients (58.5% female) in 2008 and the Cumulative Rating Scale was utilized to categorize 42 conditions into 14

domains (musculoskeletal, psychiatric, respiratory, vascular, endocrine, eye/ear/nose/throat, genitourinary, lower gastrointestinal, hematological, upper gastrointestinal, neurological, cardiac, hepatic/pancreatic, and renal). Across all age groups, MM was reported in 52% of patients (2 or more medical domains), with a prevalence of 20.6% for patients younger than 25 years, 43.7% for those between 25 and 44 years, 75.5% aged 45 to 64 years, 87.5% aged 65 to 74 years and 91.7% for those 75 years and older. Using a more conservative definition of MM consisting of three versus two conditions, prevalence remained similar among the groups, particularly among the older age groups (92% for 75 years and older; 74.6% for 65-74 years; 56.1% for 45-64 years; 22.3% for 25-44 years; and 4.8% for less than 25 years). The severity of the disease domain also increased with age (Brett et al., 2013).

Although many studies have been conducted outside of Canada, the research indicates that there is reasonable agreement between prevalence estimates of chronic diseases derived from multiple data sources that access general and clinical populations, further emphasizing the demands of this growing population of patients.

Burden of CCD on the Canadian Health Care System

Not surprisingly, CCD is associated with significant costs to the Canadian Health Care System (Meana, Cho, & DesMeules, 2004), given its connection to more adverse health outcomes including more frequent and longer hospitalizations (Agborsangaya et al., 2013; Gijsen et al., 2001b; Pefoyo et al., 2015), reduced functional status (Ryan et al., 2015; Vogeli et al., 2007), polypharmacy (Boyd & Fortin, 2010), reduced quality of life (Agborsangaya et al., 2013; Boyd & Fortin, 2010), compromised care and patient safety (Vogeli et al., 2007), higher mortality (Gijsen et al., 2001b; Willadsen et al., 2018), and higher health care costs (Hartmann,

Hehner, Hemmrich, Körs, & Möhlmann, 2011; C. Salisbury, Johnson, Purdy, Valderas, & Montgomery, 2011; Vogeli et al., 2007).

According to the Canadian Community Health Survey (CCHS), almost 80% of Canadians living in the province of Ontario over the age of 45 years have a chronic disease and of those, approximately 70% suffer from two or more chronic conditions (CCHS, 2013). With an ageing population, the number of elderly patients with CCD will continue to increase (Alonso-Morán, Nuño-Solinis, Onder, & Tonnara, 2015). This translates to a potential increase in morbidity, mortality and economic cost for the health-care system. The estimated burden of chronic illness in Ontario amounts to just over 55% of the total direct and indirect health-care costs and is estimated to rise (Rapoport, Jacobs, Bell, & Klarenbach, 2004). Similarly, an American study conducted by Charlson et al., (2008) used electronic medical records to construct a model that identified the demographic and clinical features (e.g., sex, age, medication, and number of morbidities) predictive of total yearly costs to the healthcare system. Among data collected from almost 6,000 patients over a one-year period, health care costs were estimated be $2,655 per patient per year (Charlson et al., 2008). Further, the model highlighted that individuals with higher levels of CCD incurred exponentially higher total annual costs, ranging from $4,317 among patients with two comorbid diseases to $13,326 among those patients with seven or more morbidities (Charlson et al., 2008). A review by Alonso-Morán et al. (2015) also highlighted the negative impact of CCD on the health care system, finding that predictive risk models for negative health outcomes (e.g., cost, hospitalizations, readmissions) were most accurate when including disease counts (Alonso-Morán et al., 2015).

These studies further highlight the impact of CCD on repeated health care utilization. For CCD patients who are the most frequent users of health-care services, this translates to a

potential increase in morbidity, mortality and economic cost for the health-care system. Given the limited resources in health care, spending and the rising demand for services by an increasingly ageing population experiencing complex chronic disease, there is a need to find new models of delivering healthcare services to this population (Alonso-Morán et al., 2015).

Pain: Operationalization of Acute and Chronic Pain

Acute and chronic pain are highly prevalent conditions that affect wellbeing and quality of life (Voscopoulos & Lema, 2010). Two of the top three medical conditions for which people seek medical help involve pain as a primary symptom (osteoarthritis/joint disorders and back problems). Pain symptoms are present in up to 80% of visits to physicians, suggesting this is a prevalent concern for individuals and society (Voscopoulos & Lema, 2010). Although acute and chronic pain are different diagnoses and contribute to different experiences, the encumbrance of these conditions on the healthcare environment is drastic (Meana et al., 2004; Sessle, 2011). Pain-related conditions may affect an individual's ability to attend work, placing a burden on the employer to cover shifts and pay employees while they are out of the workplace. There are also financial and utilization concerns (e.g. overuse of the healthcare system) regarding pain outcomes (Guerriere, Choinière, et al., 2010; Guerriere, Zagorski, et al., 2010; Yu, Guerriere, & Coyte, 2015).

Acute pain serves as a warning system for the body, alerting of damage, injury, or inflammation (Sessle, 2011; Woolf, 2010). It is a healthy response to actual or potential tissue damage. Although acute pain can be cured in most situations, there are cases when acute pain develops into chronic pain (Katz & Seltzer, 2009; Meana et al., 2004; Sessle, 2011). There are various theories as to how and why this occurs. Melzack and Katz (2013) propose that pain is personal and subjective, largely influenced by cultural learning, situational meaning, attention

and psychological variables; rather than simply the stimulation of neural receptors. The authors present a neuromatrix theory which proposes pain to be a multidimensional experience influenced by multiple sources and experiences (Melzack & Katz, 2013). This is important to consider, given the multifaceted experiences of a CCD population with multiple morbidities that may contribute to the overall experience of pain.

The International Association for the Study of Pain defines pain as: “An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (Raja et al., 2020). Establishment of a unified system for classifying chronic pain has long been debated. Most commonly used worldwide is the *International Classification of Diseases (ICD)* of the World Health Organization (WHO), which serves as the preeminent tool for coding diagnoses and therapeutic measures with health care systems. Unfortunately, historically the ICD diagnoses have failed to capture the actual epidemiology of chronic pain and have not been categorized in a systematic way. This has created difficulties in the past with record keeping, health care billing and expenses, and creating access to specific diagnostic treatments (Fillingim et al., 2014; Hart et al., 2015; Rief et al., 2010). In response to this, the IASP and WHO established a Task Force for the Classification of Chronic Pain, with chronic pain defined as “pain that persists or recurs for more than 3 months” The IASP Task Force developed a more pragmatic classification for chronic pain, which has been included in the 11th revision of the *ICD*, which includes 7 of the most common clinically relevant disorders: 1) chronic primary pain, 2) chronic cancer pain, 3) chronic posttraumatic pain and postsurgical pain, 4) chronic neuropathic pain, 5) chronic headache and orofacial pain, 6) chronic visceral pain, and 7) chronic musculoskeletal pain (Scholz et al., 2019; Treede et al., 2019).

Research indicates that chronic pain affects between 19% and 29% of the Canadian population (Boulanger, Clark, Squire, Cui, & Horbay, 2007; Hogan, Taddio, Katz, Shah, & Krahn, 2016; Moulin, Clark, Speechley, & Morley-Forster, 2002; Schopflocher, Taenzer, & Jovey, 2011; Sessle, 2011). This is similar to the prevalence rates observed in other countries around the world, where chronic pain is estimated to affect ~20% of people (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Goldberg & McGee, 2011), accounting for 15% to 20% of physician visits. This number is even higher among women, in both Canada and worldwide (Meana et al., 2004). Meana and colleagues (2004) examined data from the Canadian Community Health Survey and found that 18% of women reported chronic pain, compared to 14% of men.

Sex and Pain

Sex-related differences in pain have been widely reported throughout the pain literature for decades. The expansive literature in this area clearly indicates that females, relative to males, demonstrate a consistently greater pain prevalence, are at greater risk for developing chronic pain disorders, exhibit greater pain sensitivity to noxious stimuli in laboratory testing, and generally have lower pain tolerances (Bartley & Fillingim, 2013; Fillingim, 2000; Fillingim, Edwards, & Powell, 2000; Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley Iii, 2009; Rosen, Ham, & Mogil, 2017). Epidemiological studies, across many geographical regions, indicate that prevalence rates of chronic pain are 6% higher among females than those of males (Fillingim et al., 2009; Mogil & Bailey, 2010).

This trend also has been observed in various types of studies that expose healthy participants to a controlled stimulus (e.g. cold pain, heat pain, and pressure pain) and are then evaluated for pain threshold and tolerances (Racine et al., 2012). Similar results have also been

found outside of controlled laboratory studies. Specifically, in a study of patients with osteoarthritis of the knee, females generally reported higher levels of pain than males with the same functional status (Elboim-Gabyzon, Rozen, & Laufer, 2012). Results from Gerdle and colleagues (2008) also found the population prevalence for several common chronic pain conditions, including fibromyalgia, headaches and migraines, temporomandibular disorders, interstitial cystitis and irritable bowel syndrome, were greater among females (Gerdle et al., 2008). Another retrospective study of the diagnosis-associated pain scores recorded in patients electronic medical records, showed that females had documented pain scores higher than males for multiple diagnoses, including infections, musculoskeletal, respiratory, circulatory and digestive illnesses (Ruau, Liu, Clark, Angst, & Butte, 2012).

A number of potential biological and psychosocial mechanisms have been theorized to underlie these sex differences in pain (Fillingim et al., 2009), including sex hormones, endogenous opioid function, genetic factors, and sex roles, pain coping, catastrophizing and self-efficacy. Biological factors such as the influence of sex hormones have been found to represent a significant source of pain-related variability, impacting males and females differently. There is some evidence to suggest that sex hormones play a role in sex-related cortical differences when processing pain stimuli (Bartley & Fillingim, 2013). Further, sex hormones have been theorized to impact the immune system, such that gonadal hormones (estrogen, progesterone, and testosterone) affect the immune system and affect pain signaling and chronic pain development and maintenance (Rosen et al., 2017).

Research also suggests that the endogenous opioid system may be different in males and females, altering pain perception and response to opioid medications. Females may be more responsive to pain medications, with some studies reporting that females use less patient

controlled analgesia (PCA) than males (Bartley & Fillingim, 2013; Gear et al., 1996; Miaskowski & Levine). However, females also tend to experience more side effects related to analgesic use, which may impact the desire to self-administer opiates through PCA, or to request additional medications (Fillingim et al., 2009; Richardson & Holdcroft, 2009).

Studies of pain perception and responsiveness to pain medications are variable, but generally suggest that females have lower tolerance for pain stimuli than males, experience higher levels of pain than males with similar disease severity, and may respond better than males to certain opioid medications. These findings may be impacted by psychological factors such as anxiety, sex-role beliefs, pain coping strategies, pain-related expectations, mood, and familial and intergenerational influences (Fillingim et al., 2009).

Extensive research has pointed to the important role of psychological factors when explaining pain and physical disability. Specifically, pain catastrophizing, which is broadly defined as a tendency to focus excessively on pain and exaggerate its threat value (De Boer, Struys, & Versteegen, 2012; Vienneau, Clark, Lynch, & Sullivan, 1999), has been found to be related to pain outcomes (Burns et al., 2015; Kleiman, Clarke, & Katz, 2011) and as such, is often a target in psychological therapies for chronic pain (Eccleston, de C Williams, & Morley, 2009; Katz et al., 2015). More specifically, pain catastrophizing has been consistently associated with a wide range of health-related outcomes, including pain intensity, interference of pain with patients' life, physical disability, and mental well-being (Katz et al., 2015; Lu, Uysal, & Teo, 2011; Quartana, Campbell, & Edwards, 2009). Females have been found to engage in catastrophizing more often than males, and pain catastrophizing appears to mediate sex differences in pain responsivity (Forsythe, Thorn, Day, & Shelby, 2011). To a lesser degree, self-efficacy has also been found to be associated with higher levels of pain. Evidence has indicated

that males demonstrate greater self-efficacy which was subsequently related to lower cold pressor pain sensitivity (e.g. placing a hand in the cold pressor until too painful) (Jackson, 2007).

Among other psychosocial theories, social conditioning, primed sex roles, familial roles and culture-related variability in stereotypical beliefs about pain have been hypothesized to play a role in noted sex differences in pain (Edwards, Zeichner, Kuczmierczyk, & Boczkowski, 1985; Fillingim et al., 2000; Fowler, Rasinski, Geers, Helfer, & France, 2011). Early exposure to environmental stress, such as prior pain or histories of abuse, have also been theorized to contribute male and female differences in pain reports. For instance, Fillingim and colleagues (2005) observed an association between childhood abuse and decreased pain sensitivity, specifically among females only. Family history of pain has also been found to be associated with greater pain symptoms and pain sensitivity among females relative to males (Fillingim & Edwards, 2005; Fillingim et al., 2000).

Epidemiological and clinical studies convincingly demonstrate that sex differences in pain exist, such that females are at substantially greater risk for experiencing pain. The underlying mechanisms contributing to the disparity are uncertain; however, many biopsychosocial theories are well supported in the literature.

Pain and CCD

Management of CCD is of great significance in modern medicine (Ording & Sørensen, 2013) given the rapidly increasing aging population and the numerous adverse health conditions associated with CCD. These include the association with chronic pain, decline in functional status, poor quality of life and health outcomes, increased mortality and use of ambulatory, inpatient care services and healthcare resources (Gijsen et al., 2001b; Marengoni et al., 2011). Chronic pain is the most common outcome of complex disease states associated with CCD.

Notably, migraine, osteoarthritis, chronic gastritis, and chronic back pain are prodominent in multimorbid patients (Scherer et al., 2016). Many older adults suffer from both CCD and chronic pain (Butchart, Kerr, Heisler, Piette, & Krein, 2009), with an estimate one third of elderly CCD patients taking analgesics regularly or as needed (Freytag et al., 2014).

Additionally, it has been estimated that 60% of patients over the age of 65 years have significant pain associated with either diabetes or heart failure. CDD also confers the risk of developing anxiety and depressive symptoms, further contributing and excerbating chronic pain symptoms. Sharpe et al. (2017) highlight that patients with two or more physical illnesses with moderate to severe pain levels also suffer from clinical depression (Sharpe et al., 2017). Additionally, the number of pain sites among CCD patients has been implicated as an important marker of health-related quality of life (HRQoL). Specifically, as the number of pain sites increases, HRQoL significantly decreases among CCD patients. Lower HRQoL among a geriatric CCD population is further associated with cognitive decline, locomotor disability, poor lower extremity function, increased risk of disability, and the development of depressoin and anxiety (Lacey et al., 2014).

The interaction between chronic pain and CCD is not well understood. There is evidence, however, that management of CCD patients can become increasingly more challenging when patients also experience chronic pain, due to complications associated with medication dosing and interactions among mutiple diseases. The interaction of various diseases and pain can also become complicated and difficult to decipher (Gloth Iii, 2011). Additionally, the presence of chronic pain creates difficulties in performing essential self-management acitivities, both in terms of personal, daily acitivities and responsibilities associated with managing certain diseases (e.g. diabetes mellitus, hypertension) (Butchart et al., 2009; Rayner et al., 2016).

Burden of pain on the Canadian Health Care System

Chronic pain is associated with significant costs to society and the individual (Meana et al., 2004). It affects individual quality of life and as an economic burden on society. The literature regarding healthcare utilization and the impact of acute and chronic pain is highly relevant as healthcare delivery services must be available for this growing population. The increasing demand for chronic and acute pain care highlights the necessity for improvements within the Canadian healthcare system. In fact, the elderly population is expected to increase over the next 30 years, suggesting an increase in the number of people requiring healthcare services for chronic pain (Meana et al., 2004). There is an abundance of literature suggesting the Canadian healthcare system is burdened by the increasing number of chronic pain cases (Hogan et al., 2016; Lim, Jacobs, & Klarenbach, 2006; Rayner et al., 2016).

Healthcare utilization is high among those with chronic pain (Lim et al., 2006; Sessle, 2011). Lim et al. (2006) conducted a retrospective analysis of the utilization of healthcare treatments and services for 130,880 Canadians. Data was extracted from The Canadian Community Health Survey (CCHS), which is a cross-sectional survey designed to assess healthcare utilization and health status. Of the sample, 23,291 individuals were diagnosed with a chronic back disorder resulting in pain, whereas 4,158 individuals reported no health conditions. Researchers found those with a chronic back disorder were more likely to use provider services compared to those without a pain-related disorder. Those who were diagnosed with a chronic back disorder were also more likely to report a comorbid diagnosis of depression. This highlights the need for those with chronic pain to require more intense considerations to treat other diagnoses associated with pain. Overall, those with chronic back issues associated with pain

utilize Canadian healthcare services more often than those who do not have chronic pain (Lim et al., 2006).

Financial Stressors

There are notable financial costs associated with chronic pain. In Canada alone, the direct cost of chronic pain to the healthcare system is estimated to be over 6 billion dollars. Considering the associated indirect costs resulting from job loss and sick leave, are estimated to be over 37 billion dollars annually (Choinière et al., 2010; Phillips et al., 2009). In the United States, this number is expectedly significantly higher, estimated to be between 560 and 635 billion dollars annually (Gaskin & Richard, 2012).

Guerriere and colleagues (2010) examined results from the STOP-PAIN Project, which assessed the financial burden for chronic pain patients on waitlists for treatment. Researchers examined data for 370 patients who were randomly selected from the Canadian STOP-PAIN Project. Participants were required to complete a questionnaire that assessed their utilization of healthcare services financed by the government, private-pay, or third-party insurance companies. The survey also assessed for time costs, including how long caretakers or family members spent assisting them with health-related activities. Researchers found that the average monthly cost for healthcare was $3,112 (Guerriere, Choinière, et al., 2010).

Participants in the study were found to have visited family physicians the most, which were financed by the government, while the most utilized privately-financed services included massage therapist appointments (Guerriere, Choinière, et al., 2010). About 95% of total expenses dedicated to healthcare regarding chronic pain was privately financed, and some medications were paid for out of pocket (35%). This suggests that chronic pain patients utilize readily available services, such as visiting family physicians, while waiting for chronic-pain

specific treatments. This may put a strain on the healthcare system, as services are not being utilized for their intended purpose.

Sessle (2011) also examined the literature regarding Canadian healthcare costs for chronic pain. The individual costs of managing chronic pain, on average, were $1500 per month for Canadian residents. Notably, the cost of chronic pain is almost equivalent to those suffering from cardiovascular issues or cancer. Chronic pain management costs twice are as much as depression or other mental health concerns (Sessle, 2011).

More recently, Hogan el al. (2016) estimated the annual per-person incremental health care utilization and medical costs for patients in Ontario with chronic pain. Using electronic data from the CCHS between 2000 and 2011, the researchers used propensity matching to closely match individuals with chronic pain and individuals without chronic pain and used linked data to determine mean 1-year per-person costs and utilization and mean incremental cost for chronic pain. With 19,138 matched pairs (*M* age = 55 years, *SD* = 5.18 years; 61% female), the incremental cost in Canadian dollars was $1,742 per person (95% CI, $1,488-$2,020). This was 51% higher than the control group of individuals with no reported pain. Health care utilization was among the highest incremental cost ($514; 95% CI, $364-$683) (Hogan et al., 2016).

Research indicates pain also contributes to reduced productivity, increased absenteeism, and increased risk of unemployment (Blackmore et al., 2007; Phillips et al., 2009). For Canadians, absenteeism resulting from chronic pain may have detrimental effects on the workforce and an individual's sense of purpose and well-being. Munce et al. (2007) examined the correlation between chronic pain and absenteeism for Canadian individuals who completed the Canadian Community Health Survey (CCHS). Participants were 36,984 Canadian citizens who reported one chronic pain condition and who worked full time for at least 12 months.

Researchers found that about 40% of the sample reported a chronic pain condition and more than 3% of the sample was absent from their job within the past week. Notably, those reporting depression and a chronic pain condition were absent than work more often (8%) than those who did not report a dual diagnosis. Most importantly, there were significant correlations between absenteeism and chronic pain conditions, such as fibromyalgia, arthritis, back issues, and migraines. Individuals who were more likely to be absent were younger, had higher education, and a higher income compared to those who were less likely to be absent from work (Munce et al., 2007).

Similarly, Franche and colleagues (2011) examined factors associated with workplace absence among 11,762 female, Canadian nurses. Researchers examined the results from the Statistics Canada 2005 National Survey of the Work and Health of Nurses (NSWHN), which covered all 10 Canadian providences. Researchers found that 45% of the sample reported short-term absences and 19% reported prolonged work absences. Overall, pain and depression appeared to interfere with workplace attendance the most compared to other variables. The higher the pain rating, the longer the nurses were out of work. However, researchers discovered that support and respect from coworkers appeared to mediate absenteeism, suggesting those with higher support were better able to cope with depression and had a reduction of work absence (Franche et al., 2011). Pain-related work absences are a public health concern, as it has implications on society and Canada's economy.

Implications

Pain is both a global and nation-wide health problem with significant consequences for patients and the economic framework of healthcare systems. Chronic pain is associated with biological, social, psychological and neurological factors (Asmundson & Katz, 2009; Gatchel,

Peng, Peters, Fuchs, & Turk, 2007); subsequently requiring specific treatment strategies that simultaneously address these various factors. Typically, multidisciplinary approaches are encouraged. The International Association for the Study of Pain (IASP) proposes guidelines for the classification and standards of pain services (International Association for the Study of Pain, 2009). The ideal standard of treatment for chronic pain is through a "pain treatment facility", a term that encompasses the benefits of a team of multidisciplinary health care professionals (physicians, nurses, mental health professionals, and physical therapist), research, and educational and training opportunities, as well as specific modality treatment regimens (International Association for the Study of Pain, 1990). Unfortunately, in Canada, the available resources for this type of treatment appear to be limited.

Fashler et al. (2016) conducted a systematic review of multidisciplinary chronic pain treatment facilities in order to evaluate insight as to the availability and characteristics of facilities, caseloads and wait times. Results highlighted a notable inconsistency in the description and classification of pain facilities, as well as limited availability, large caseloads and long wait times. Most relevant, in Canada it has been reported, based on data from Peng et al. (2007), that there is only one pain facility for 258,000 people in Canada (Fashler et al., 2016). These results further support the need for appropriate treatment for chronic pain, given the rate of prevalence of chronic pain both globally and nationally.

In order to better understand the connection between CCD and chronic pain, and how to best consider the patients' multimorbidity spectrum in clinical pain treatment recommendations, further evidence is required to examine which disease combinations are most frequently related with the presence of pain. In line with this, the aim of the present dissertation is to further examine these areas among a population of CCD patients in Canada, with a focus on there main

areas: the association of mutilmorbid disease patterns and pain; hypertension and pain; and, post amputation/missing limbs and pain.

Chapter 3: Research Objectives

Extensive research has been conducted examining individual chronic diseases (Barker, 2004; Ben-Shlomo, Cooper & Kuh, 2016; Kuh, Ben-Shlomo & Ezra, 2004); however, fewer studies have examined multiple pathologies or general diseases, particularly including pain outcomes, highlighting the need to better understand the occurrence of multiple diseases and pain in more detail (Pavela & Latham, 2016; Vos, van den Akker, Boesten, Robertson, & Metsemakers, 2015; Wister et al., 2016). A better understanding of pain among CCD patients is necessary to develop interventions to prevent it and manage it when prevention is not possible, reduce its burden on patients as well as the health care system, and align health-care services more closely with the needs of patients. Currently, the cost of CCD is among the highest in the Canadian health care system, largely due to an inefficiency in aligning health care resources with the multiple demands of patients with multiple diseases (Charlson et al., 2008). Complicating the demands of this population is the high prevalence of pain among elderly patients with complex chronic disease profiles (Mills et al., 2016). As discussed earlier, acute and chronic pain are associated with significant costs to society and individuals (Meana et al., 2004). Sex-differences in pain have also been widely reported throughout the literature (Bartley & Fillingim, 2013). Given this information, the objectives of this dissertation are to evaluate the outcome of pain among specific populations of CCD patients in Ontario in order to provide further insight into the complexity of pain difficulties among CCD residents. We also explored sex differences in pain among this CCD population. In each study, the label of ‘sex’ refers to ‘male or female’, as defined by the CCRS dataset utilized in each study.

Objective one: Examine the association between multimorbid disease patterns and pain outcomes among a complex chronic care population

Disease multimorbidity and pain is a complex, yet common, problem for the aging population, and a significant burden on the health care systems around the world. Despite this, disease comorbidity and the association with pain in a complex chronic care population is not well understood. This study will examine the most prevalent disease combinations in patients with CCC and their associations with pain. We hypothesize that the increase in multimorbidity will result in greater pain prevalence. Descriptive and chi square statistics will be used to summarize and compare the sample characteristics. Binary logistic regression analyses will be used to examine the association between multimorbid disease categories and pain outcomes. The findings from this study will help identify common comorbid disease patterns related to pain in an institutionalized, complex chronic care population. This information contributes to both the pain and multimorbidity literature, and is invaluable for creating care plans to meet the demands of a challenging population.

Objective Two: Evaluation of the association between hypertension and pain among a CCD population

Hypertension is a predominant chronic condition among adults in Canada and is associated with a high rate of multimorbidity (Sarkar et al., 2015). Also, the research examining the interesting relationship between pain and blood pressure (i.e., hypertensive hypoalgesia) is well documented (France, 1999; Olsen et al., 2013; Saccò et al., 2013). However, there is less attention in the literature to the outcomes of pain for CCD patients with hypertension. Further, there is currently a lack of research about the association of reduced pain sensitivity (hypoalgesia) and hypertension (Olsen et al., 2013; Saccò et al., 2013), in a population of

patients with CCD. The objective of this research to close that gap and examine the relationship between hypertension and hypoalgesia, specifically as it relates to pain outcomes in a CCD population. We hypothesize that residents with hypertension will report pain less frequently and at a lower intensity than those without hypertension. Descriptive analysis and binary and multinomial logistic regressions will be utilized in order to evaluate the association between hypertension and pain among a CCD population. The results from this study will contribute to the growing body of hypoalgesia research, as well as provide information that may better inform the understanding of disease combinations and subsequent treatment of this specific population.

Objective three: Evaluation of pain associated with having a missing limb among a CCD population

There are several gaps in the literature regarding difficulties faced by patients with CCD. As discussed in the above sections, most CCD patients also experience chronic pain, impacting a number of individualistic and societal facets. Pain can manifest in a number of ways; one of which is associated with having a missing limb, whether via amputation, congenital absence, or traumatic injury. Amputation of a limb is frequently accompanied by severe painful sensations in the missing limb (phantom limb pain, PLP), and/ or the residual limb (RLP), also known as 'stump pain.' Concurrent chronic pain problems may also be associated with post-amputation pain (e.g., back pain, or pain in the contralateral limb) (Larbig et al., 2019). Phantom limb pain (PLP) and residual limb pain (RLP) remain a significant problem following limb amputation.

There is a large literature examining the phenomena of post-amputation phantom limb pain and residual limb pain; unfortunately, the CCD population has been overlooked in this area, despite the high prevalence of individuals with amputated limbs among these patients. Given the noted prevalence of pain in the phantom limb/stump pain research, reported chronic pain among

CCD population, and the large number of residents qualified as having a missing limb within the CCD data, the main objective of this research study is to examine pain outcomes among a population of CCD patients identified has having “missing limbs”, while taking into consideration the multiple morbidities of these residents. We hypothesize that those residents with missing limbs will report pain more frequently and in greater intensity than those residents without missing limbs. Descriptive analysis and binary and multinomial logistic regressions will be utilized to assess this association. The results of this research will contribute to the understanding of pain among specific populations of CCD patients, while also providing a discussion of phantom limb and stump pain in relation to CCD.

Chapter 4: General Methodology

MDS Dataset: CIHI Facility-Based Continuing Care Reporting System (CCRS)

The use of structured electronic records can provide valuable, point-of-care data to inform academic research and clinical practice (Manca, 2015). Within epidemiological research, the use of standardized, data can be particularly advantageous to capture important health information among a sample of the target population of interest. The Canadian Institute for Health Information (CIHI) collects, stores, and analyzes real-world clinical information using a survey format from a large population of patients from across the country. This data is particularly useful for clinical, research and policy purposes. Primary data collection through surveys allows researchers to capture specific populations and variables of interest. Information included in these surveys may not be readily available through medical charts (e.g., socioeconomic characteristics, demographic factors, treatment activity). The benefits of utilizing a secondary, electronic source of longitudinal data arguably outweighs the limitations, particularly for the use of research as it eliminates many of the challenges associated with

primary data collection such as the time and resources that are required to hire research personnel and recruit a sufficient number of participants (Belletti, Zacker, & Mullins, 2010).

All studies included as part of this dissertation use data from CIHI Facility-Based Continuing Care Reporting System (CCRS), which captures information on individuals admitted to publicly-funded hospital facilities for complex chronic care in Canada (Continuing Care Reporting System, 2013-2014). Upon entry to a complex chronic care (CCC) facility, residents are administered a standardized assessment protocol, the Resident Assessment Instrument - Minimum Data Set/Full Assessment (RAI-MDS/FA 2.0 Canadian Version), within 14 days of admission. If the resident remains in the facility for longer than 92 days, quarterly assessments are conducted. These assessments are typically completed by the treating nurse or physician and include resident self-reports and information from medical files.

The assessment tool utilized upon admission is the Minimum Data Set (MDS 2.0), an internationally validated clinical assessment instrument (Fries, Simon, Morris, Flodstrom, & Bookstein, 2001; Hartmaier et al., 1995; Hawes et al., 1995; Lawton et al., 1998; Mor, 1995; Snowden et al., 1999). The MDS.20 collects a wide array of information, including basic demographic characteristics, diagnostic profiles, medication usage and treatment participation, and outcomes.

The assessment results become part of the Continuing Care Reporting System (CCRS), which was created to be a resource for standardized clinical and administrative information on continuing care in Canada. The dataset includes information on the clinical and functional status of continuing care residents. Given the richness of the information collected as part of these intake assessments, the Facility-Based Continuing Care Reporting System provides valuable demographic, clinical and resource utilization data which is critical to providing a framework for

better understanding the clinical needs of this highly specific population of chronically ill Canadians (Canada, 2004).

Data acquisition

The dataset used in the studies comprising this dissertation was acquired through the CIHI Graduate Student Data Access Program (GSDAP), which allows graduate students conducting research in the areas of Health Services, Health Spending, and Health Human Resources, no cost access to data through various databases and clinical registries (CIHI, 2019). In accordance with the GSDAP data request requirements, requested data was used to fulfill graduate requirements (in this case, a PhD dissertation), and the research project was approved by the York University Research Ethics Board and Faculty of Graduate Studies. Data requests were subsequently completed and signed by the primary investigator and her supervisor and submitted and approved by CIHI's GSDAP.

Methodological Considerations of the Data

The Ontario Ministry of Health and Long-Term Care (MoHLTC) provides complex chronic care through designated chronic care beds, both in free-standing CCC facilities and in designated units within acute care hospitals (Joint Initiative of the Ontario Hospital Association and the Government of Ontario, 2005). The majority of residents admitted to CCC facilities receive the standard MDS assessment; however, there are some occasions when a resident may not have completed the assessment and therefore, data are missing. This occurs when residents in the CCRS have remained in the facility for fewer than 14 days, during which time an assessment is not mandatory (although typically conducted).

Description of the Data Population and Data Cleaning

The original dataset obtained via CIHI's GDSAP included 610,500 observations of 254,382 residents, between 1996 and 2006, Canada-wise. The data was then sorted by subject ID and assessment date, with each assessment ranked by date for residents hospitalized more than once. After completing descriptive analysis on the dataset, errors in age accuracy were discovered. Given that CCC facilities typically service older adults, those residents whose age was recorded to be below the age of 18 years were removed from the dataset. Similarly, residents over the age of 101 years were considered to be inaccurately recorded given the unlikely nature of reaching such an age with multiple health problems. Therefore, residents older than 101 years were also removed from the dataset. The removal of patients less than 18 years and greater than 101 years resulted in the removal of n = 652 patients, or 0.257% of the original sample. The final resident count in the dataset is N=253,730, between the ages of 18 and 101 years (M age = 76.9 years). Multiple other variables, including treatment facility and resident code were also examined for accuracy and appropriately labeled.

Information within this dataset has been collected for a period of approximately 20 years, ranging from 1996-07-01 until 2016-04-30. It was determined that the most relevant information to include would be the most recent 10 years of data information (2006-2016), given the advancements in medical technologies and treatments over the past 20 years. It was also decided to use data only from Ontario, given the majority of the Continuing Care Reporting System information was collected from this province (98%). With these exclusions, the overall sample size was N=139,920 CCC residents. Table 4.1 describes the sample used in this dissertation.

Table 4.1. Demographic information for initial assessments for residents included in the CCRS dataset between 2006-2016 in Ontario, n = 139,920

Characteristic	***N* (%) or Mean ± SD [Range]**
Age (years)	77.32 ± 12.67 [18 – 101]
Sex	
Female	79,416 (57%)
Male	60,137 (43%)
Marital status	
Never married	13,266 (10%)
Married	56,264 (40%)
Widowed	49,769 (36%)
Separated	3,084 (2%)
Divorced	7,548 (5%)
Unknown	9,642 (7%)
Number of different medications	11.85 ± 5.35 [0 – 99]
Used analgesic medications	107,433 (77%)
Disease category	
Endocrine/metabolic/nutritional	53,701 (39%)
Heart/circulation	101,696 (73%)
Musculoskeletal	61,963 (44%)
Neurological	64,195 (46%)
Psychiatric/mood	33,799 (24%)
Pulmonary	26,884 (19%)
Sensory	18,095 (13%)
Cancer	40,850 (29%)
Gastrointestinal	26,219 (19%)
Total number of disease categories	
0	2,820 (2%)
1	15,965 (11%)
2	31,585 (23%)
3	38,781 (28%)
4	29,072 (21%)
5+	21,350 (15%)
Count of number of disease categories	3.06 ± 1.43 [0 – 9]
Count of number of diseases	4.17 ± 2.28 [0 – 33]

Dissertation Studies

The current dissertation follows a 3-study model. The studies included in this dissertation are cross-sectional, cohort studies using data from the CCRS dataset provided through CIHI. The data includes information for residents of Ontario CCC facilities, admitted between 2006 and

2016. As described previously, residents are administered the MDS 2.0 Full Assessment at various points during hospital stay. In order to ensure consistency between patients, only initial assessments were included in the evaluations for this dissertation. All studies use disease count as a measure of CCD. Analysis appropriate to each study is then described and conducted.

Data Analysis

Propensity Score Matching

The studies in this dissertation use data from the CCRS dataset. This dataset is a comprehensive collection of numerous variables and sample population. A full, detailed list of the dataset variables can be found in Appendix A. As such, statistical strategies were required for managing the complexity of the data. Given the number of variables included in the dataset, it was important to control for confounding which can occur when baseline covariates that predict the outcome under investigation are related to the outcome of interest, as well as variables that are associated with the exposure variable (Skelly, Dettori, & Brodt, 2012). A method of controlling for this and avoiding potential bias, is the use of propensity score matching estimators (Rosenbaum & Rubin, 1983). This strategy is widely used in evaluation research to estimate average treatment effects by matching scores. The propensity score allows for the design and analysis of an observational (nonrandomized) study to mimic some of the particular characteristics of a randomized controlled trial (Austin, 2008). It allows for matching on scores that form matched sets of treated/control or untreated/experimental subjects who share a similar value of the propensity score (Day, 2015; Staffa & Zurakowski, 2018; Steiner & Cook, 2013).

The most common implementation of propensity score matching is one-to-one or pair matching, also known as “optimal matching”, in which pairs of treated and untreated participants are formed and matched “perfectly” on the variables selected for matching (Hansen & Klopfer,

2006). Once a matched sample has been formed, the "treatment" effect can be estimated by directly comparing outcomes between treated and untreated participants in the matched sample. Following this, the analysis of a propensity score matched sample can mimic that of a randomized controlled trial (RCT) by directly comparing outcomes between the two groups within the matched sample. A secondary option is to employ "fuzzy matching", which is utilized to make propensity scores of two groups similar. With such scores, an experimental and a control group that have similar, albeit not identical, propensities can be created for comparison (Kim & Baek, 2016). A third option is "nearest neighbor matching" (also known as "greedy matching"), which involves selecting the closest eligible control unit to be paired with the treated unit. Thus, each pairing occurs without reference or consideration to how it is being paired, ultimately not allowing for optimization of the criterion (Thoemmes & Kim, 2011; Zakrison, Austin, & McCredie, 2018). The benefits of using an optimal propensity score matching strategy, aside from creating a similar design to the gold standard RCT design, include: providing a way to summarize covariate information about sample selection into a scalar value; adjusting for difference via study design; and, eliminating selection bias. A potential limitation, however, is in the selection of variables for matching, such that if any crucial variables have been omitted or overlooked, then the groups may remain unbalanced and the results may then be biased (Austin, Mamdani, Stukel, Anderson & Tu, 2005). There is also debate within the statistical literature about the agreement between observational studies using propensity scores and RCTs; specifically, whether the use of this technique truly captures the benefits of an RCT. A study by Dahabreh et al. (2012) aimed to systematically compare propensity score methods and RCTs for therapeutic interventions, finding that observational studies with propensity score methods produced treatment effect estimates greater than those found within the RCTs (Dahabreh,

Sheldrick, Paulus, Chung, Varvarigou, Jafri, et al., 2012). More recently, Forbes and Dahabreh (2020), examined six systematic reviews matching RCTs and observational studies with propensity score methods, again finding statistically significant disagreements between study findings. In studies 2 and 3 as part of this dissertation, samples have been matched 1:1 using propensity scores on the clinically relevant variables, of age (Marengoni et al., 2011), sex (Fillingim et al., 2009), marital status (August, 2010), disease count (Sells et al., 2009) and assessment year (Hogan et al., 2017).

Covariates

As mentioned, studies 2 and 3 employed the statistical procedure of propensity matching. Given it was impossible to consider all relevant variables in creating matched groups, additional covariates were considered in regression analysis. These covariates were selected based on previous findings from the pain literature and thought to be important to control for in order to avoid confounding. The specific variables included were: Depression rating scale (DRS) scores (Sharpe et al., 2017), Activities of Daily Living (ADL) scores (Agborsangaya et al., 2013), Index of Social Engagement (ISE) scores (Kuluski et al., 2014), number of medications taken (Gloth Iii, 2011), days taking analgesics, (Freytag et al., 2014), and hospital visits (Ryan et al., 2012).

Disease Count

As discussed earlier in this dissertation, there is no internationally accepted list of chronic diseases that define CCD (Almirall & Fortin, 2013; Stewart et al., 2013). As such, there are a variety of approaches taken in the research to accommodate for this and define CCD. Typically, the approach is determined by the purpose of the research and the nature of the data (Huntley et al., 2012). There are three widely accepted approaches for assessing CCD. First, employing a numerical count (two or more) of concurrent diseases in the same individual. This definition is

most commonly applied in epidemiological studies. Second, researchers may use cumulative indices evaluating the number, as well as the severity, of concurrent diseases. In these cases, specific indices are typically used, including the Charlson Comorbidity Index (Charlson et al., 1987), the Cumulative Illness Rating Scale (CIRS) (Linn et al., 1968), and the Index of Co-Existent Diseases (ICED) (Greenfield et al., 1993). The use of these indices provides additional weighting information, as they include aspects of severity, disease type (e.g. Type II diabetes, stage 4 ovarian cancer), mortality outcomes, and/or likely resource utilization (Huntley et al., 2012).

The current research used a numerical count of concurrent diseases in the same individual to assess CCD. As noted, this is the most common approach in epidemiological research. Further, given the nature of the dataset and the information available, it was the most suitable. Although the Charlson Comorbidity Index (Charlson et al., 1987) would have been an ideal choice, the dataset did not provide enough thorough information pertaining to disease status to fit the index method. The count method has been accepted as an alternative to using formal indices (Harrison et al., 2014; Huntley et al., 2012).

Table 4.2. Disease Categories and Medical Diagnoses listed in the CCRS RAI/MDS/FA 2.0, n = 139,573, Ontario CCC residents, 2006-2016

Disease Categories	**Medical Diagnosis**	***N*=139,573**
Endocrine/Metabolic/Nutritional	Diabetes mellitus	39,920
	Hyperthyroidism	1,542
	Hypothyroidism	18,178
Heart/Circulation	Arteriosclerotic heart disease (ASHD)	15,928
	Cardiac dysthymia	22,574
	Congestive Heart Failure	18,153
	Deep Vein Thrombosis	4,093
	Hypertension	77,323
	Hypotension	3,479
	Peripheral Vascular Disease	9,721
	Other Cardiovascular Disease	33,658

Musculoskeletal	Arthritis	36,950
	Hip Fracture	17,003
	Missing Limb	2,961
	Osteoporosis	22,083
	Pathological Bone Fracture	3,778
Neurological	Amyotrophic Lateral Sclerosis	441
	Alzheimer's Disease	6,817
	Aphasia	6,891
	Cerebral Palsy	424
	Cerebrovascular accident	25,259
	Dementia not Alzheimer's Disease	25,041
	Hemiplegia Hemiparesis	10,696
	Huntington's Chorea	147
	Multiple Sclerosis	1,165
	Paraplegia	1,352
	Parkinson's Disease	5,572
	Quadriplegia	863
	Seizure Disorder	6,093
	Transient Ischemic Attack	5,343
	Traumatic Brain Injury	2,046
Psychiatric/Mood	Anxiety Disorder	11,135
	Depression	26,195
	Manic Depressive	1,744
	Schizophrenia	1,673
Pulmonary	Asthma	6,022
	Emphysema	22,826
Sensory	Cataracts	8,748
	Diabetic Retinopathy	1,249
	Glaucoma	5,987
	Macular Degeneration	4,366
Cancer	Cancer (type unspecified)	40,850
Gastrointestinal	Gastrointestinal Disease	26,219

Pain Outcomes

The CCRS MDS Full Assessment 2.0 tool provides information in the dataset on pain which was assessed using two ordinal rating scales with descriptors (scoring) as follows:

Pain frequency: no pain (0), pain less than daily (1), pain daily (2); and,

Pain Intensity: mild pain (1), moderate pain (2), times when pain is horrible or excruciating (3).

As per the MDS/FA assessment tool, 'pain' is qualified as pain occurring in the last 7 days. Therefore, throughout the following studies, we were unable to ascertain the duration of resident's pain. For the purposes of this dissertation, three pain scales were created from these two variables, and were used as statistical outcome measures. For the purposes of the following research, these outcomes are to be considered in a statistical manner, rather than implying causal effects.

The pain scales are as follows:

1. Dichotomous pain (P-Y/N). A two-level scale indicating the presence (Yes (Y)) or absence (No (N)) of pain created by combining the options from the CCRS RAI-MDS/FA 2.0 pain frequency items ('no pain' option) and pain intensity items (mild pain, moderate pain, times when pain is horrible or excruciating).
2. Pain intensity (PI-4). A four-level scale created by combining pain frequency (pain less than daily, pain daily) and pain intensity (mild pain, moderate pain, times when pain is horrible or excruciating).
3. Pain intensity and pain frequency combined (PIPF-7). A more detailed seven-level scale created by combining pain frequency (pain less than daily, pain daily) and pain intensity (mild pain, moderate pain, times when pain is horrible or excruciating).

Table 4.3. Frequencies of residents reporting various levels of pain on the three pain measures used in the present dissertation, n = 139,920, Ontario CCC residents, 2006-2016

Pain measure	*N* (%)
*P-Y/N	
0 No pain	38,254 (27%)
1 Pain (mild, moderate, times when pain is horrible or excruciating	101,319 (73%)
**PI-4	
0 No pain	38,254 (27%)
1 Mild pain	31,109 (22%)
2 Moderate pain	58,537 (42%)
3 Times when pain is horrible or excruciating	11,673 (9%)
***PIPF-7	
0 No pain	38,254 (27%)
1 Mild pain < daily	22,168 (16%)
2 Mild pain daily	8,941 (6%)
3 Moderate pain < daily	18,931 (14%)
4 Moderate pain daily	39,606 (28%)
5 Times when pain is horrible or excruciating < daily	10,735 (8%)
6 Times when pain is horrible or excruciating daily	938 (1%)

*P-Y/N, dichotomous no/yes pain scale; **PI-4, 4-point pain intensity scale; ***7-point combined pain intensity and pain frequency scale

Dissertation Studies

The following three chapters include the studies that comprise this dissertation. The first study, in Chapter 5, provides an overview of the complicated disease profile the CCD population experiences. Specifically, the study examines the most prevalent disease combinations and their association with pain. Various combinations of prevalent diseases are examined in relation to residents' pain reports and results are discussed in the context of future research and clinical implications for this specific population. The remaining two studies, in Chapters 6 and 7, examine the impact of a specific disease within the CCD population and the relation to pain reports. The study in Chapter 6 explores a newly researched phenomenon of hypertension-associated-hypoalgesia by comparing pain reports between CCC residents with and without hypertension.

Sex differences are also examined. The results contribute to the growing body of literature in this area and further support the hypothesis that hypertension may be related to lower pain tolerances. Chapter 7 presents a study that again examines pain reports among a specific disease population of CCC residents that have missing limbs. Similar methodology to Study 2 is applied and pain reports are compared between those residents with missing limbs and those without missing limbs. Again, sex differences are also explored. The results from all three studies inform the greater body of pain and CCD literature by providing important information about the demographic, medical and pain experiences of this unique population.

Chapter 5: Study 1 - Association between Multimorbid Disease Patterns and Pain Outcomes among a Complex Chronic Care Population in Canada

Disclosure Notes

The current study has been published, under the Creative Commons Attribution – Non Commercial (unported, v3.0) License, in the Journal of Pain Research (13; 3045-3057), November 20, 2020. The full article can be found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685348/

Some data from this dataset was also presented as a poster at the 2017 Canadian Psychological Association conference.

Abstract

Purpose: Disease multimorbidity and pain is a complex, yet common, problem for the aging population, and a significant burden on the health care systems around the world. Despite this, disease comorbidity and the association with pain in a complex chronic care population is not

well understood. This study examined the most prevalent disease combinations and their association with pain.

Methods: The study initially included 139,920 residents, aged 18-101 years, admitted to publicly-funded hospital facilities for complex chronic care in Canada between the years 2006-2016. Data was acquired through the Canadian Institute for Health Information (CIHI) Facility-Based Continuing Care Reporting System (CCRS). Descriptive and chi square statistics were used to summarize and compare the sample characteristics. Binary logistic regression analyses were used to examine the association between multimorbid disease categories and pain outcomes.

Results: The sample consisted of 139,573 residents (57% female), mostly older (mean age = 77.3 years), married (40%), or widowed (36%). Residents took an average of 11.9 medications and 77% were using analgesic medications. On average, residents had diagnoses from 3.06 disease categories (*SD* = 1.43). Heart/circulation diseases were the most prevalent among the sample (73%), with neurological second (46%) and musculoskeletal third (44%). Overall, 73% of residents reported pain, with 43% reporting moderate pain severity. Residents with multiple disease categories were more likely to report the presence of pain (OR = 1.08, 95% CI: 1.07 – 1.08, $p < .001$), with each additional disease category associated with an 8% increase in the odds of reporting pain.

Discussion/Conclusion: The findings from this study help identify common comorbid disease patterns related to pain in an institutionalized, complex chronic care population. This information contributes to both the pain and multimorbidity literature, and is invaluable for creating care plans to meet the demands of a challenging population.

Introduction

As life expectancy increases with every passing decade, more and more individuals are developing multiple chronic health problems (Oeppen & Vaupel, 2002). A growing number of Canadians live with chronic health conditions that can be classified as complex chronic disease (CCD). A CCD is a condition involving multiple morbidities (MM) and a combination of functional (Bayliss et al., 2004; Rijiken, van Kerkhof, Dekker, & Schellevis, 2005), social (Noël et al., 2005), vocational (Kuluski et al., 2014) and/or mental health challenges (Fortin et al., 2006). Although the disease combinations that comprise multimorbidity are diverse, the most common diagnoses are diabetes, stroke, hypertension, cancer, arthritis, asthma, fractures, the presence of an artificial knee or hip, fatigue, multiple sclerosis, demyelinating diseases of the central nervous system, gonarthrosis, ataxia, COPD, renal failure, malignant neoplasm of breast/prostate, depressive episodes and anxiety, and hypercholesterolemia (Kuluski et al., 2013; Pefoyo et al., 2015).

Managing the demands of the CCD population and their multiple health needs can be difficult and problematic for primary health care providers and the residents themselves (Piette & Kerr, 2006). Primary, acute health care services and facilities are generally unequipped to handle the health demands of the CCD population (Busse et al., 2010). In fact, the CCD population utilizes considerable province- and country-wide health care resources, and represents one of the heaviest users of the Canadian health care system as a whole (Hartmann et al., 2011; Maaten, Kephart, Kirkland, & Andreou, 2008; C. Salisbury et al., 2011; Vogeli et al., 2007).

Complicating this complex health profile further, many individuals experience chronic pain in association with multiple other medical and health problems (Scherer et al., 2016; Wolff, Starfield, & Anderson, 2002). Chronic pain alone is a prevalent and often debilitating condition that has significant negative effects on the individual and the health care system, as it has been

associated with declines in activities of daily living, loss of employment, mental health problems, large medical system expenditures and poor self-rated health and health-related quality of life (HRQoL) (Agborsangaya et al., 2013; Mills et al., 2016). Alarmingly, suicidality also doubles among chronic pain residents due to the associated emotional toll (Campbell et al., 2015).

Despite the complexities associated with pain and multimorbidity, very little is known about this population, particularly as it relates to trends in disease comorbidity, progression, pain, disability, and treatment management (Kuluski et al., 2013). In light of this overlapping information and the lack of understanding of pain and disease complexity within an elderly, health complicated population, the current study seeks investigate relevant combinations of multimorbidity, specifically the most prevalent combinations associated with pain outcomes within a CCD population.

Objectives

This study investigates relevant combinations of multimorbidity associated with pain. Pain prevalence, intensity and frequency are examined in relation medical disease categories, as well as, combinations of two to five of the most prevalent multimorbid disease categories among this adult, CCD population. The study has several specific aims. Using a Canadian CCD database of institutionalized complex chronic disease residents with multimorbid conditions we will:

1) Examine and compare demographic, medication usage and pain variables of the CCD population, and identify the top five most frequent single disease category and most frequent multimorbid two, three, four and five disease categories;

2) Examine the association of specific disease categories with pain prevalence;

3) Examine the association of the number of disease categories with pain prevalence;

4) Identify and compare the most prevalent disease categories and the most prevalent multimorbid combinations of two, three, four and five disease categories and the association with pain prevalence.

Methodology

Data source.

This study used data from the Canadian Institute for Health Information (CIHI) Facility-Based Continuing Care Reporting System (CCRS), which captures information on individuals admitted to publicly-funded hospital facilities for complex chronic care in Canada (Continuing Care Reporting System, 2013-2014) between the years 2006-2016. Upon entry to a complex chronic care (CCC) facility, residents are administered a standardized assessment protocol, the Resident Assessment Instrument - Minimum Data Set/Full Assessment (RAI-RAI/MDS/FA 2.0 Canadian Version), within 14 days of admission. If the resident remains in the facility for longer than 92 days, quarterly assessments are conducted. These assessments are typically completed by the treating nurse or physician and include resident self-reports and information from medical files.

The RAI/MDS/FA 2.0 is an internationally validated clinical assessment instrument (Fries et al., 2001; Hartmaier et al., 1995; Hawes et al., 1995; Lawton et al., 1998; Mor, 1995; Snowden et al., 1999). This standard tool collects a wide array of information, including basic demographic characteristics, diagnostic profiles, medication usage and treatment participation, and outcomes, as well as categorizes diseases.

Disease categories/multimorbidity.

The disease categories explored in this study were taken directly from RAI/MDS/FA 2.0. Table 5.1 provides a description of the disease categories and specific diseases found in the

RAI/MDS/FA 2.0. Regarding the definition of multimorbidity, there is no internationally accepted list or system for classifying disease states/diagnoses (Almirall & Fortin, 2013; Stewart et al., 2013). The most widely accepted approach for assessing multimorbidity within epidemiological research is to use a numerical count (two or more) of concurrent diseases in the same individual (Huntley et al., 2012). Consistent with this literature, the current study utilized this method of assessment to quantify disease counts among all subjects and multimorbidity was defined as having 2 or more diagnoses.

Table 5.1. Disease Categories and Medical Diagnoses listed in the CCRS RAI/MDS/FA 2.0, n = 139,920, Ontario CCC residents, 2006-2016

Disease Categories	**Medical Diagnosis**	***N*=139,920**
Endocrine/Metabolic/Nutritional	Diabetes mellitus	39,920
	Hyperthyroidism	1,542
	Hypothyroidism	18,178
Heart/Circulation	Arteriosclerotic heart disease (ASHD)	15,928
	Cardiac dysthymia	22,574
	Congestive Heart Failure	18,153
	Deep Vein Thrombosis	4,093
	Hypertension	77,323
	Hypotension	3,479
	Peripheral Vascular Disease	9,721
	Other Cardiovascular Disease	33,658
Musculoskeletal	Arthritis	36,950
	Hip Fracture	17,003
	Missing Limb	2,961
	Osteoporosis	22,083
	Pathological Bone Fracture	3,778
Neurological	Amyotrophic Lateral Sclerosis	441
	Alzheimer's Disease	6,817
	Aphasia	6,891
	Cerebral Palsy	424
	Cerebrovascular accident	25,259
	Dementia not Alzheimer's Disease	25,041
	Hemiplegia Hemiparesis	10,696
	Huntington's Chorea	147
	Multiple Sclerosis	1,165

	Paraplegia	1,352
	Parkinson's Disease	5,572
	Quadriplegia	863
	Seizure Disorder	6,093
	Transient Ischemic Attack	5,343
	Traumatic Brain Injury	2,046
Psychiatric/Mood	Anxiety Disorder	11,135
	Depression	26,195
	Manic Depressive	1,744
	Schizophrenia	1,673
Pulmonary	Asthma	6,022
	Emphysema	22,826
Sensory	Cataracts	8,748
	Diabetic Retinopathy	1,249
	Glaucoma	5,987
	Macular Degeneration	4,366
Cancer	Cancer (type unspecified)	40,850
Gastrointestinal	Gastrointestinal Disease	26,219

Pain measures. The CCRS RAI/MDS/FA 2.0 measures pain using two descriptive scales:

1) Frequency: no pain (0), pain less than daily (1), pain daily (2); and,
2) Intensity: mild pain (1), moderate pain (2), times when pain is horrible or excruciating (3).

For the present study, three measures of pain were created by combining various items from the above two existing CCRS RAI-MDS/FA 2.0 scales:

1) P-Y/N: Pain prevalence dichotomous measure: no pain (0); pain (1) (mild, moderate, severe);
2) PI-4: 4-point pain intensity scale (PI-4): no pain (0), mild pain (1), moderate pain (2), severe pain (3);

3) PIPF-7: 7-point combined pain intensity and pain frequency scale (PIPF-7): no pain (0); mild pain less than daily (1); mild pain daily (2); moderate pain less than daily (3); moderate pain daily (4); severe pain less than daily (5); severe pain daily (6).

Data Analysis

All data used in this study is derived from the initial assessment of all residents, aged 18–101 years, from Ontario's CCC facilities between the years 2006 – 2016, reported in the CIHI CCRS dataset.

Objective 1. Descriptive statistics were used to summarize the characteristics of the sample. Frequencies and proportions were used for categorical variables, and mean, standard deviation, and range for numerical variables. A Chi-square test was used to compare demographic variables of sex, marital status and analgesic use, and binary logistic regression for age and other medication usage.

Objective 2. As noted above, the CCRS RAI/MDS/FA 2.0 resident's medical diagnoses are classified into nine disease categories (refer to Table 1). With respect to evaluating the association of pain prevalence (P-Y/N) with specific disease categories, a binary logistic regression model was used. The regression analysis was modelled two times: first, using predictive demographic variables (sex, age, marital status) and medication use (use of analgesics, number of medications used in the last 7 days); and second, controlling demographics, medication use and disease categories.

Objective 3. The association of the number of disease categories and multimorbid combinations on pain prevalence were assessed using binary regression analysis. Again, the analyses were modelled two times, similar to objective two.

Objective 4. We explored the reported pain prevalence of the top five single disease categories and the most prevalent multimorbid combinations of two to five disease categories. The decision to not exceed five multimorbid combinations was intentional, as to encapsulate the majority of the population. The population of residents diagnosed with more than five disease categories significantly decreases as the number of categories increases. On average, residents have diagnoses within three different disease categories (M = 3.06; SD = 1.43); therefore, by examining combinations of five, we were able to include the majority of the sample. In order to compare pain variables between disease categories, frequencies for PI-4 and PIPF-7 ratings were obtained for each disease category and subsequent Chi-Square analysis were performed. Descriptive statistics were used to calculate the proportion of pain ratings for each combination of disease categories and ranked according to the top five categories with the highest proportion of pain reported.

All inferential statistical analyses were performed using IBM SPSS software version 26 (Armonk, NY, USA). P-values < 0.05 are reported as statistically significant. Odds ratios and corresponding 95% confidence intervals are reported for regression models.

Results

Objective 1: Examine and compare demographic and pain variables of the CCD population

All medical diagnoses were classified into one of the nine disease categories (Table 5.1). Demographic variables, number of diseases, medical characteristics, and pain measures are shown in Table 5.2. The sample consisted of 139,573 residents (57% female), mostly older (mean age = 77.32 years), married (40%), or widowed (36%). Residents took an average of 11.9 medications. More than 3/4 (77%) were using analgesic medications. The vast majority of residents were classified as having heart/circulation conditions (73%), followed by neurological

conditions (46%) and musculoskeletal disorders (44%). On average, residents have diagnoses from 3.06 disease categories (*SD* = 1.43). 15% of residents have medical diagnoses from five or more diagnostic categories.

Table 5.3 highlights the frequencies of reported pain levels (P-Y/N; PI-4; PIPF-7), regardless of the resident's medical diagnosis or disease category. Overall, 73% of residents report pain (P-Y/N), and more specifically, the majority of residents report moderate intensity pain (43%; PI-4), and 8% report severe intensity pain (PI-4; 9% on PIFI-7).

Table 5.4 identified the five most prevalent multimorbid combinations of one, two, three, four and five disease groups. Cancer was identified as the most prevalent individual disease category (3.64%).

Table 5.2. Descriptive characteristics of the sample, n = 139,573, Ontario CCC residents, 2006-2016

Characteristic	***N* (%) or Mean ± SD [Range]**
Age	77.32 ± 12.67 [18 – 101]
Sex	
Female	79416 (57%)
Male	60137 (43%)
Marital status	
Never married	13266 (10%)
Married	56264 (40%)
Widowed	49769 (36%)
Separated	3084 (2%)
Divorced	7548 (5%)
Unknown	9642 (7%)
Number of different medications	11.85 ± 5.35 [0 – 99]
Used analgesic medications	107433 (77%)
Disease category	
Endocrine/metabolic/nutritional	53701 (39%)
Heart/circulation	101696 (73%)
Musculoskeletal	61963 (44%)
Neurological	64195 (46%)
Psychiatric/mood	33799 (24%)
Pulmonary	26884 (19%)
Sensory	18095 (13%)
Cancer	40850 (29%)
Gastrointestinal	26219 (19%)

Total number of disease categories	
0	2820 (2%)
1	15965 (11%)
2	31585 (23%)
3	38781 (28%)
4	29072 (21%)
5+	21350 (15%)
Count of number of disease categories	3.06 ± 1.43 [0 – 9]
Count of number of diseases	4.17 ± 2.28 [0 – 33]

Table 5.3. Frequencies of residents reporting various levels of pain on the three pain measures used in the present study, n = 139,573, Ontario CCC residents, 2006-2016

Pain measure	***N* (%)**
*P-Y/N	
0 No pain	38,254 (27%)
1 Pain (mild, moderate, severe)	101,319 (73%)
**PI-4	
0 No pain	38,254 (27%)
1 Mild pain	31,109 (22%)
2 Moderate pain	58,537 (42%)
3 Severe pain	11,673 (9%)
***PIPF-7	
0 No pain	38,254 (27%)
1 Mild pain < daily	22,168 (16%)
2 Mild pain daily	8,941 (6%)
3 Moderate pain < daily	18,931 (14%)
4 Moderate pain daily	39,606 (28%)
5 Severe pain < daily	10,735 (8%)
6 Severe pain daily	938 (1%)

*P-Y/N, dichotomous no/yes pain scale; **PI-4, 4-point pain intensity scale; ***7-point combined pain intensity and pain frequency scale

All variables (sex, marital status, age, number of different medications used in the last 7 days, and use of analgesic medication) show statistically significant association with the dichotomous pain variable (P-Y/N) (Table 5.4). The proportion of female residents reporting pain (76%) was significantly greater than males (68%). The proportion of separated (75%) and divorced (74%) residents was significantly higher than never married residents (71%). Older

residents were less likely to have mild/moderate/severe pain (about 0.8% less likely to report pain for each year of age) than younger residents. Residents using more medications had higher odds of reporting pain (about 8.5% for each additional medication). The use of analgesic medications is the single most significant predictor of pain. Of residents who used analgesic medications, 86% reported pain compared to only 28% among residents who did not use analgesic medications.

Table 5.4. Examining and comparing demographic and medical covariates, n = 139,573, Ontario CCC residents, 2006-2016

Covariates	*N* (%) with no pain	*N* (%) with mild / moderate / severe pain	Odds ratio (95% CI)	Chi-square test results or p-value from binary logistic regression
Sex				$X^2(1) = 1174$,
Female	18938 (24%)	60478 (76%)		$p < .001$
Male	19309 (32%)	40828 (68%)		
Marital status				$X^2(4) = 80.60$,
Never married	3829 (29%)	9437 (71%)		$p < .001$
Married	16002 (28%)	40262 (72%)		
Widowed	13285 (27%)	2326 (75%)		
Separated	758 (25%)	5618 (74%)		
Divorced	1930 (26%)			
Age, years			0.992 (0.991 – 0.993)	$p < .001$
Number of different medications used in the last 7 days			1.085 (1.082 – 1.088)	$p < .001$
Use of analgesic medications				$X^2(1) = 41750$,
No	23144 (72%)	8996 (28%)		$p < .001$
Yes	15110 (14%)	92323 (86%)		

Table 5.5. The five most prevalent combinations of one, two, three, four and five disease categories, respectively. N = 139,573, Ontario CCC residents, 2006-2016

Rank	One disease category	Two disease categories	Three disease categories	Four disease categories	Five disease categories
1	Cancer 5074 (3.64%)	Heart/circulation+ Neurological 5981 (4.29%)	Endocrine/metabolic/nutritional+Heart/circulation +Neurological 4498 (3.22%)	Endocrine/metabolic/nutritional+Heart/circulation+Musculoskeletal+Neurological 2910 (2.08%)	Endocrine/metabolic/nutritional+Heart/circulation+Musculoskeletal+Neurological+Psychiatric/mood 1024 (0.73%)
2	Neurological 3458 (2.48%)	Heart/circulation+ Musculoskeletal 4533 (3.25%)	Heart/circulation+Musculoskeletal+Neurological 4211 (3.02%)	Heart/circulation+Musculoskeletal+Neurological+Psychiatric/mood 1422 (1.02%)	Endocrine/metabolic/nutritional+Heart/circulation+Musculoskeletal+Neurological+Gastrointestinal 673 (0.48%)
3	Heart/circulation 3404 (2.44%)	Endocrine/metabolic/nutritional+Heart/circulation 3241 (2.32%)	Endocrine/metabolic/nutritional+Heart/circulation +Musculoskeletal 3661 (2.62%)	Endocrine/metabolic/nutritional+Heart/circulation+Neurological+Psychiatric/mood 1302 (0.93%)	Endocrine/metabolic/nutritional+Heart/circulation+Musculoskeletal+Neurological+Sensory 655 (0.47%)
4	Musculoskeletal 1858 (1.33%)	Heart/circulation+ Cancer 2780 (1.99%)	Endocrine/metabolic/nutritional+Heart/circulation +Cancer 1903 (1.36%)	Endocrine/metabolic/nutritional+Heart/circulation+Neurological+Cancer 1023 (0.73%)	Endocrine/metabolic/nutritional+Heart/circulation+Musculoskeletal+Neurological+Pulmonary 580 (0.42%)
5	Endocrine/metabolic/nutritional 761 (0.55%)	Musculoskeletal+ Neurological 1501 (1.08%)	Heart/circulation+Neurological+Psychiatric/mood 1645 (1.18%)	Endocrine/metabolic/nutritional+Heart/circulation+Musculoskeletal+Psychiatric/mood 1004 (0.72%)	Endocrine/metabolic/nutritional+Heart/circulation+Musculoskeletal+Neurological+Cancer 486 (0.35%)

Objective 2: Examine the association between specific disease categories (1-9 categories) and pain prevalence

Binary logistic regression models showed a significant association between most disease categories and the dichotomous P-Y/N pain variable, when controlling for demographic variables (sex, age, marital status) and medications (number of medications used in the last 7 days and use of analgesics). Pain was reported more often among residents with cancer (OR = 1.48; 95% CI: 1.43 – 1.53; p <.001), musculoskeletal (OR = 1.32, 95% CI: 1.28 – 1.37; p <.001), gastrointestinal diseases (OR = 1.11; 95% CI: 1.07 – 1.16; p <.001) and psychiatric/mood (OR = 1.07; 95% CI: 1.03 – 1.11; p <.001), compared to residents without those conditions. In contrast, residents with neurological or sensory conditions had significantly lower pain prevalence (OR = 0.67; 95% CI: 0.65 – 0.69; p <.001; OR = 0.85; 95% CI: 0.81 – 0.88; p <.001, respectively). Given the strong ORs for medication usage, we completed a third, post-hoc model, in order to explore the association between specific disease categories and pain (P-Y/N) when excluding the use of medication (Table 6).

Table 5.6. Binary logistic regression with pain (yes/no) being the dependent variable for individual disease categories, n = 139,573, Ontario CCC residents, 2006-2016

Predictor	**Model 1***		**Model 2****		**Model 3*****	
	Odds ratio (95% CI)	***p***	**Odds ratio (95% CI)**	***p***	**Odds ratio (95% CI)**	***p***
Sex						
Male (reference)						
Female	1.38 (1.33 – 1.42)	<.001	1.32 (1.27 – 1.46)	<.001	1.42 (1.38 – 1.46)	<.001
Marital status						
Never married (reference)						
Married	1.06 (1.00 – 1.11)	< .001	1.07 (1.01 – 1.12)	0.17	1.18 (1.13 – 1.23)	<.001
Widowed	1.07 (1.01 – 1.13)	< .001	1.07 (1.01 – 1.13)	0.28	1.18 (1.12 – 1.24)	<.001
Separated	1.19 (1.07 – 1.32)	< .001	1.18 (1.06 – 1.32)	.003	1.24 (1.13 – 1.36)	<.001
Divorced	1.07 (0.99 – 1.15)	.013	1.05 (0.97 – 1.13)	.267	1.13 (1.06 – 1.21)	<.001
Age	0.99 (0.99 – 0.99)	<.001	0.99 (0.99 – 0.99)	<.001	0.99 (0.99 – 0.99)	<.001
Number of different medications used in the last 7 days	1.04 (1.04 – 1.04)	<.001	1.04 (1.04 – 1.04)	< .001		
Use of analgesic medications	14.24 (13.80 – 14.70)	<.001	13.00 (12.60 – 13.42)	< .001		
Endocrine/metabolic/ nutritional			0.92 (0.90 – 0.95)	< .001	1.00 (0.97 – 1.02)	.714
Heart/circulation			0.91 (0.87 – 0.94)	< .001	1.02 (0.99 – 1.05)	.295
Musculoskeletal			1.32 (1.28 – 1.37)	< .001	1.69 (1.65 –1.74)	<.001
Neurological			0.67 (0.65 – 0.69)	< .001	0.59 (0.57 – 0.60)	<.001
Psychiatric/mood			1.07 (1.03 – 1.11)	< .001	1.17 (1.14 – 1.21)	<.001
Pulmonary			0.93 (0.89 – 0.96)	< .001	1.03 (1.00 – 1.06)	.090
Sensory			0.85 (0.81 – 0.88)	< .001	0.92 (0.88 – 0.95)	<.001
Cancer			1.48 (1.43 – 1.53)	<.001	1.77 (1.72 – 1.83)	<.001
Gastrointestinal			1.11 (1.07 – 1.16)	<.001	1.16 (1.12 – 1.20)	<.001

*Model 1: demographic and medical variables **Model 2: demographic, medical variables, and number of disease categories (continuous) ***Model 3: Post-hoc analysis, using demographic and number of disease categories (continuous)

Objective 3: Examine the association of the number of disease categories with pain prevalence

We also examined the association between the number of disease categories (continuous, see Table 5.8, and categorical, see Table 5.9) and pain variables. Both the continuous and categorical disease category variables were assessed using binary regression, modelled in three blocks. Model 1 controlled for all demographics and medication usage, finding that female residents with multiple disease categories reported pain (P-Y/N) significantly more often than males (OR = 1.38, 95% CI: 1.33 – 1.42, p <.001). Age was also significant. The use of analgesic medication was found to be significant, indicating that residents who report pain are 14 times more likely to be taking analgesics (OR = 14.24; 95% CI: 13.80 – 14.70, p <.001).

In model 2, we additionally included the number of disease categories (for both continuous and categorical) and found a significant association between the number of disease categories and the P-Y/N variable (OR = 0.99, 95% CI: 0.98 – 1.00, p = 0.049). Sex, age and medication usage all remained significant. Given the finding that the use of medication and analgesics were found to have strong ORs, we ran a third model post-hoc analysis and excluded the use of medications and analgesics.

The post-hoc model 3 included demographic variables and number of disease categories only. Findings indicate that residents with multiple disease categories (continuous) were more likely to report the presence of pain (P-Y/N; OR = 1.08, 95% CI: 1.07 – 1.08, p < .001), with each additional disease category associated with an 8% increase in the odds of reporting pain, further suggesting the role of medication in managing pain. Categorically, the likelihood of reporting pain increased with multimorbidity, with five or more disease categories being the most highly associated with pain (OR = 1.71, 95% CI: 1.56 – 1.87, p <.001). See Tables 5.7 and 5.8.

Table 5.7. Binary logistic regression using P-Y/N (pain: yes/no) as the dependent variable for the number of disease categories, n = 139,573, Ontario CCC residents, 2006-2016

Predictor	**Model 1***		**Model 2****		**Model 3****	
	Odds ratio (95% CI)	***p***	**Odds ratio (95% CI)**	***p***	**Odds ratio (95% CI)**	***p***
Sex						
Male (reference)						
Female	1.38 (1.33 – 1.42)	<.001	1.38 (1.33 – 1.42)	<.001	1.53 (1.50 – 1.58)	<.001
Age, years	0.99 (0.99 – 0.99)	<.001	0.99 (0.99 – 0.99)	<.001	0.99 (0.99 – 0.99)	<.001
Marital status						
Never married (reference)				.035		<.001
Married	1.06 (1.00 – 1.11)	.040	1.06 (1.00 – 1.11)	.026	1.12 (1.11 – 1.21)	<.001
Widowed	1.07 (1.00 – 1.13)	.030	1.07 (1.01 – 1.13)	.002	1.18 (1.13 – 1.24)	<.001
Separated	1.19 (1.06 – 1.32)	.002	1.19 (1.07 – 1.32)	.089	1.26 (1.15 – 1.38)	<.001
Divorced	1.07 (0.99 – 1.15)	.098	1.07 (0.99 – 1.15)		1.17 (1.10 – 1.25)	
Number of different medications used in the last 7 days	1.04 (1.04 – 1.04)	<.001	1.04 (1.04 – 1.04)	<.001		
Use of analgesic medications	14.24 (13.80 – 14.70)	<.001	14.24 (13.80 – 14.70)	<.001		
Number of disease categories (continuous variable)			0.99 (0.98 – 1.00)	.049	1.08 (1.07 – 1.09)	<.001

*Model 1: demographic and medical variables **Model 2: demographic, medical variables, and number of disease categories (continuous) ***Model 3: post-hoc analysis, using demographic and number of disease categories (continuous)

Table 5.8. Binary logistic regression with pain (yes/no) being the dependent variable for multimorbid disease categories (0-5+), n = 139,573, Ontario CCC residents, 2006-2016

Predictor	**Model 1***		**Model 2****		**Model 3*****	
	Odds ratio (95% CI)	***p***	**Odds ratio (95% CI)**	***p***	**Odds ratio (95% CI)**	***p***
Sex						
Male (reference)						
Female	1.38 (1.33 – 1.42)	<.001	1.38 (1.33 – 1.42)	<.001	1.53 (1.49 – 1.58)	<.001
Age, years	0.99 (0.99 – 0.99)	<.001	0.99 (0.99 – 0.99)	<.001	0.99 (0.99 – 0.99)	<.001
Marital status						
Never married (reference)						
Married	1.06 (1.00 – 1.11)	.040	1.06 (1.01 – 1.12)	.032	1.16 (1.11 – 1.21)	<.001
Widowed	1.07 (1.01 – 1.13)	.030	1.07 (1.01 – 1.13)	.024	1.18 (1.13 – 1.24)	<.001
Separated	1.19 (1.07 – 1.32)	.002	1.19 (1.07 – 1.33)	.002	1.26 (1.15 – 1.38)	<.001
Divorced	1.07 (0.99 – 1.15)	.098	1.07 (0.99 – 1.16)	.084	1.17 (1.10 – 1.25)	<.001
Number of different medications used in the last 7 days	1.04 (1.04 – 1.04)	<.001	1.04 (1.04 – 1.04)	<.001		
Use of analgesic medications	14.24 (13.80 – 14.70)	<.001	14.23 (13.79 – 14.68)	<.001		
Number of disease categories						
0 (reference)						
1			1.19 (1.06 – 1.33)	.002	1.32 (1.21 – 1.45)	<.001
2			1.05 (0.95 – 1.17)	.336	1.25 (1.15 – 1.37)	<.001
3			1.05 (0.94 – 1.17)	.374	1.37 (1.25 – 1.49)	<.001
4			1.02 (0.92 – 1.14)	.699	1.45 (1.33 – 1.59)	<.001
5+			1.07 (0.96 – 1.20)	.234	1.71 (1.56 – 1.87)	<.001

*Model 1: demographic and medical variables **Model 2: demographic, medical variables, and number of disease categories (categorical) ***Model 3: post-hoc analysis, using demographic and number of disease categories (categorical)

Objective 4: Identify and compare the most common five combinations of one, two, three, four and five multimorbid disease categories and the association with pain prevalence

The top five combinations of one, two, three, four and five disease categories with the highest proportion of patients reporting pain P-Y/N shown in Table 5.9 and Figure 5.2. Of all the top combinations of diagnoses, the data show clearly that the residents with a cancer diagnosis were found to have the highest pain prevalence (86%) followed by residents within the musculoskeletal diagnosis category (82%). The most common combination of two disease categories with reported pain was psychiatric/mood and cancer. The remaining three, four and five disease categories with residents reporting pain were as follows: musculoskeletal + pulmonary + cancer; musculoskeletal + psychiatric/mood + sensory + cancer; endocrine/metabolic/nutrition + musculoskeletal + psychiatric/mood + pulmonary + sensory. Chi-square tests to compare the proportion of residents endorsing the various levels of PI-4 pain for various disease categories, show statistically significant differences between 9 disease groups in terms of their distribution of 4-point pain levels, $X^2(24) = 1992$, $p < .001$. The cancer group has the highest proportion of patients with severe (18%) and moderate (51%) pain levels. Musculoskeletal and gastrointestinal disease groups have the second largest proportion of moderate and severe pain (48% + 9% and 45% + 13% respectively). The neurological group has the lowest proportion of severe (4%) and moderate (26%) pain patients (Figure 5.1).

When evaluating pain using the more detailed PIPF-7 scale, the Chi-square test shows statistically significant differences between 9 disease groups in terms of distribution of 7-point pain levels, $X^2(48) = 2150$, $p < .001$. Again, the cancer group still has the highest proportion of patients with pain level 4 (moderate pain daily; 37%) and level 5 (severe pain less than daily; 17%).

Table 5.9. The top five combinations of one, two, three, four and five disease categories with highest proportion of residents within each disease category or combination reporting pain, respectively. N = 139,573, Ontario CCC residents, 2006-2016

Rank	One disease category % with pain	Two disease categories % with pain	Three disease categories % with pain	Four disease categories % with pain	Five disease categories % with pain
1	Cancer 87%	Psychiatric/mood + Cancer 89%	Musculoskeletal + Pulmonary + Cancer 90%	Musculoskeletal + Psychiatric/mood + Sensory + Cancer 96%	Endocrine/metabolic/nutritional + Musculoskeletal + Psychiatric/mood + Pulmonary + Sensory 100%
2	Musculoskeletal 82%	Cancer + Gastrointestinal 87%	Musculoskeletal + Psychiatric/mood + Gastrointestinal 89%	Endocrine / metabolic / nutritional + Psychiatric/mood + Cancer + Gastrointestinal 95%	Endocrine/metabolic/nutritional + Musculoskeletal + Psychiatric/mood + Sensory + Gastrointestinal 100%
3	Gastrointestinal 76%	Musculoskeletal + Cancer 87%	Pulmonary + Cancer + Gastrointestinal 89%	Endocrine / metabolic / nutritional + Musculoskeletal + Pulmonary + Gastrointestinal 95%	Endocrine/metabolic/nutritional + Psychiatric/mood + Sensory + Cancer + Gastrointestinal 100%
4	Psychiatric/mood 72%	Pulmonary + Cancer 85%	Musculoskeletal + Psychiatric/mood + Cancer 89%	Musculoskeletal + Psychiatric/mood + Pulmonary + Cancer 95%	Musculoskeletal + Pulmonary + Sensory + Cancer + Gastrointestinal 100%
5	Endocrine / metabolic / nutritional 70%	Musculoskeletal + Psychiatric/mood 85%	Endocrine/metabolic/nutritional + Psychiatric/mood + Cancer 88%	Endocrine / metabolic / nutritional + Psychiatric/mood + Pulmonary + Gastrointestinal 94%	Neurological + Pulmonary + Sensory + Cancer + Gastrointestinal 100%

Figure 5.1. PI-4 pain severity ratings by individual single disease category

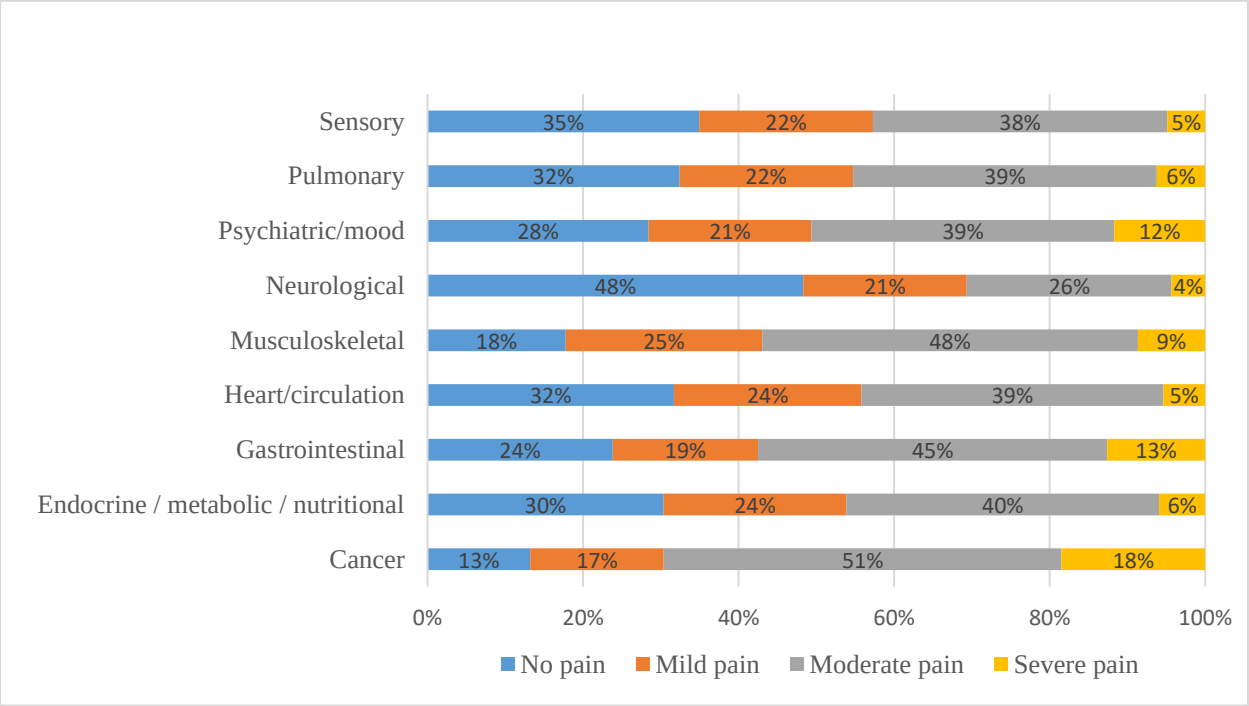
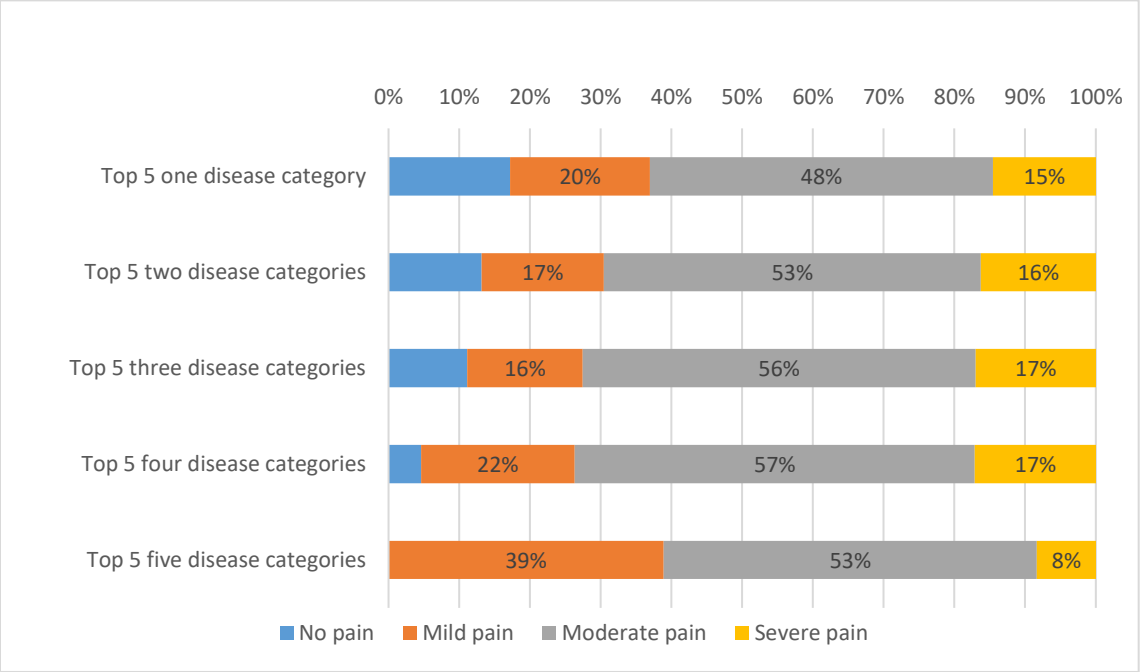


Figure 5.2. PI-4 pain severity ratings for the top five disease combinations with residents reporting pain.



Discussion

We examined the prevalence of different multimorbidity combinations and the associated pain levels in a province-wide cross-sectional study of Ontario-based residents with complex chronic disease (CCD) (*n*=139,573). CCD involves multimorbidities (MM), in this study defined as 2 or more diseases in a single person. The prevalence of MM has been found to vary from 3.5% to 98.5% (Fortin, Stewart, Poitras, Almirall, & Maddocks, 2012; Violan et al., 2014), depending on age, sex and setting, with higher prevalence among older populations and higher rates in women. Our findings indicated an average of 3.06 diseases per resident. With respect to overall pain findings, the presence pain (i.e., non-zero pain prevalence) was reported by 73% of the entire sample, and was significantly higher for females than males with a similar disease

profile. Population-based studies indicate higher prevalence of general chronic pain among women, as well as several specific chronic pain conditions (Fillingim, 2017b). These results are consistent with widely-reported sex differences in the clinical pain literature (Catuneanu, Paylor, Winship, Colbourne, & Kerr, 2019; Mapplebeck, Beggs, & Salter, 2016; Sorge & Totsch, 2017) and the CCD literature (Marengoni et al., 2011; Melis et al., 2014). Age was also significantly associated with pain.

In examining the prevalence of disease categories, we found that heart/circulation diseases were the most prevalent among the sample (73%), with neurological second (46%) and musculoskeletal third (44%). Consistent with previous research on pain and MM (e.g. (Butchart et al., 2009; Gijsen et al., 2001a; Marengoni et al., 2011; Scherer et al., 2016; Sharpe et al., 2017), our overall findings indicate that the greater the number of disease categories, the more likely the resident is to report the presence of pain. In fact, results showed that with each additional disease category, there was an 8% increase in the odds of residents reporting pain. Pain intensity also increased with multimorbidity of disease categories.

Although pain is common among CCC residents, little is known about the implications or role of pain and analgesic treatment among this population (Butchart et al., 2009). Our study initially controlled for the use of analgesic medication, as well as the number of other medications a patient was taking. We found that the use of medication, particularly analgesic medication, was the strongest predictor of pain, with residents taking analgesic medication to be 14 times more likely to report pain. Given these findings, we subsequently conducted a post-hoc analysis excluding the use of medication. When excluding medication usage, the number of disease categories was significantly associated with pain prevalence.

Residents with musculoskeletal, psychiatric, cancer and gastrointestinal diseases showed higher pain prevalence than those without these diseases. Residents with cancer were found to have the highest pain prevalence (87%), with musculoskeletal diseases next (82%). Individually and combined, both these disease categories are well documented in the published pain literature as diseases highly associated with pain (Blyth & Noguchi, 2017; Murray et al., 2015; van den Beuken-Van, Hochstenbach, Joosten, Tjan-Heijnen, & Janssen, 2016).

Multimorbidity of disease categories was also found to increase the prevalence and intensity of reported pain. Figure 5.1 clearly shows that as number of MM conditions increase from one to five, the proportion of residents reporting mild pain decreases to zero among residents with 5 MM conditions. Several factors are known to contribute to pain intensity and frequency; most notably, depression and anxiety (see (IsHak et al., 2018) for a recent review), musculoskeletal problems (Blyth, Briggs, Schneider, Hoy, & March, 2019; Blyth & Noguchi, 2017), and cardiovascular diseases (Fayaz, Ayis, Panesar, Langford, & Donaldson, 2016); unfortunately, the interaction between chronic pain and CCD is not well understood. There is evidence, however, that management of CCD patients can become increasingly more challenging when patients also experience chronic pain, due to complications associated with medication dosing and interactions among mutiple diseases. The interaction of various diseases and pain can also become complicated and difficult to decipher (Gloth Iii, 2011). The current study sought to further explore these assocations and provide further information for research and patient care.

Limitations and Strengths

We examined multiple disease combinations by clustering and analyzing disease categories, while controlling for important demographic variables and medication usage. Despite

this, residual confounding factors cannot be ruled out, particularly because we were unable to incorporate specific information about the disease profiles, such as disease progression, severity and treatment. Similarly, we were also unable to include information specific to pain factors, including pain site, cause and duration. Similar to other studies in pain research, pain was obtained by self-report. There also remains room for additional subjectivity among patient responses or clinician interpretation when completing surveys, such as the RAI/MDS/FA 2.0 utilized in this study. Similarly, surveys may not truly capture the level of morbidity in a population, as many symptoms, conditions or diseases a patient may have are not brought to the attention of the clinician completing the survey or the clinical records. This is an inherent limitation of using cross-sectional data, given our inability to determine whether pain was present before or after disease onset. Unfortunately, this restricts our ability to establish causal inferences about the relationship between multimorbidity and pain.

The benefits, however, of utilizing secondary, standardized, electronic sources of longitudinal data arguably outweigh the limitations; particularly in epidemiological research. Many of the challenges associated with primary data collection are avoided, including time and resources that are required to hire research personnel and recruit sufficient number of participants (Belletti et al., 2010). A strength of our study is the large, province-wide sample of CCD residents in Ontario between the ages of 18 and 101 years, further contributing to the generalizability of the study. The large sample size also makes it possible to not only explore the impact of specific diseases, but also combinations of disease categories.

The data utilized is of high quality, given the use of standardized electronic records through the CIHI Facility-Based Continuing Care Reporting System, which captures information

on residents admitted to publicly funded hospital facilities for complex chronic care in Canada. The RAI/MDS/FA 2.0 utilized in this validated tool, further contributing to the quality of the data (Fries et al., 2001). The primary argument for the use of binary logistic regression analyses to assess the associations between multimorbid disease categories and pain variables was to avoid confounding effects with ORs that are more directly comparable across the different diagnosis categories.

Implications

Individuals with CCD are both challenging and unique in that they require attention and assistance from multiple health and social service providers (Kuluski et al., 2013). This typically involves management of complex treatment regimens that include multiple appointments, numerous medications, regular monitoring and surveillance, and adherence to treatment recommendations and protocols (Mercer et al., 2014; Onder et al., 2015). Pain is often associated with multiple medical conditions (Wolff et al., 2002) and can further add to the complexity of this population; yet, very little is known about multimorbid disease profiles and pain among this population (Butchart et al., 2009).

The findings from this study are a step toward identifying multimorbid disease categories that are related to pain experience in a CCD population and have several implications for research and health care. Within the research realm, information pertaining to the relationship between various multimorbid disease categories provides beneficial information to consider when understanding the patterns of multimorbidity their relationship to pain variables among a complex care population. Given the complexity of this population, additional information about disease patterns and their relationship to pain is invaluable for organizing health care and

creating care plans to meet the demands of an already challenging population. With information about the association between pain and multimorbidity, extra awareness can be given to the multimorbid diagnoses that may require further resources and attention. Future research would be useful for more closely examining disease severity and progression as it related to the development from acute to chronic pain within the CCD population.

Chapter 6: Study 2 - Hypertensive Hypoalgesia among a Complex Chronic Disease Population

Disclosure Notes

The current study has been submitted for publication and is currently under review for the Journal of Clinical Medicine, as of May 2021. An abstract of the study was also accepted as a poster presentation at the May 2020 Annual Meeting of the Canadian Pain Society, but cancelled due to COVID-19, and published in abstract form in the Canadian Journal of Pain (Ferguson, Slepian, & Katz, 2020). The study was also accepted for a poster presentation at the 2020 World Congress on Pain sponsored by the International Association Study of Pain but the meeting was cancelled due to COVID-19.

Abstract

Introduction: Hypertension-associated hypoalgesia, also known as decreased pain sensitivity in individuals with high blood pressure has been documented in small-scale studies but has yet to be examined in a large Canadian database of complex care residents.

Methods: The Continuing Care Reporting System database was used, containing health information on residents of Canadian complex chronic care facilities (Ontario only) who were

assessed using the Resident Assessment Instrument Minimum Data Set, V2.0. Hypertension was reported among 77,323 residents (55.5%, total N=139,920). Propensity score matching, with a 1:1 ratio, was used to identify a control record without hypertension for each case. McNemar's test was used to evaluate dichotomous pain variables and Wilcoxon Signed Ranks test for ordinal pain levels (4-level; no pain, mild, moderate, severe). Multinomial logistic regression was used to quantify the effects of hypertension and sex on 4-level ordinal pain variables, controlling for potential confounders.

Results: The matched dataset included n=40,799 cases with and n=40,799 without hypertension, with 57% female and 43% male. Results showed a significantly lower proportion of hypertension residents with pain (71.7%) compared to controls (72.6%), McNemar test $X^2 = 7.73$, $p = .005$. Residents with hypertension were significantly less likely to report all levels of pain on the PI-4: mild (*OR* = 0.88; 95% CI 0.83 – 0.94), moderate (*OR* = 0.86; 95% CI 0.81 – 0.91), and severe *(OR* = 0.69; 95% CI 0.63 – 0.76), all $p < .001$. The interaction between hypertension and sex showed that females with hypertension were at a 17% greater risk of reporting severe pain (PI-4) *OR* = 1.17 (95% CI 1.03 – 1.32), $p = .014$ than males with hypertension.

Discussion/Conclusions: The results confirm the relationship between hypertension and reduced pain sensitivity on a population level. More studies are needed to understand the causes of this relationship and potential consequences of hypertension-related hypoalgesia.

Introduction

Hypertension is a highly prevalent chronic condition among adults in Canada and is associated with a high rate of multimorbidity (Sarkar, Dodhia, Crompton, Schofield, White, Millett et al., 2015). Elevated blood pressure (BP) affects 40% of the global adult population

aged ≥ 25 years, which corresponds to more than 1 billion individuals worldwide (World Health Organization, 2013). In a population of individuals with complex chronic diseases, hypertension is often comorbid with a number of other diseases, including other cardiovascular diseases (CVD; e.g. coronary heart disease, stroke, congestive heart failure, peripheral vascular disease, and end-stage renal disease), diabetes, depression, anxiety, and acute and chronic pain (Carroll, Phillips, Gale & Batty, 2010; Hodgson & Cai, 2011).

In conjunction with hypertension, acute and chronic pain are also highly prevalent conditions that affect wellbeing and quality of life (Voscopoulos & Lema, 2010). There is interesting evolving research investigating the relationship between hypertension and pain, suggesting that hypertension is associated with reduced pain sensitivity (hypoalgesia), also referred to as hypertensive hypoalgesia (France, 1999; Olsen et al., 2014; Saccò et al., 2013). Hypertension-associated hypoalgesia, defined as lower pain sensitivity in people with high blood pressure, is an expanding area of research (France, 1999; Olsen et al., 2014; Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Ghione et al., 1985; Guasti et al., 1995a, 1995b, 1996; Rosa & Ghione, 1990; Rosa, Ghione, Panattoni, & Mezzasalma, 1986; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994; Sheps et al., 1992; Zamir & Shuber, 1980).

France (1999) conducted one of the first meta-analyses, reviewing the association between pain sensitivity and hypertension in animals and humans. In analyzing the existing research, France (1999) presented evidence that hypertension and decreased pain perception may result from a common physiological dysfunction, suggesting that decreased pain perception might serve as a behavioural marker for the risk of hypertension even prior to the onset of high blood pressure. A large portion of the early research in this area has been conducted with animal

models of hypertension, finding correlations between lower pain sensitivity and elevated blood pressure in rats (Ghione, 1996; Randich & Maixner, 1984; Zamir & Maixner, 1986). Collectively, these studies examined rats with a genetic predisposition for elevated resting blood pressure. On average, rats that were four-weeks-old had a systolic blood pressure of 120 mmHg, which increased to at least 200 mmHg or more at 12-weeks-old. Hypertensive rats demonstrated lower pain sensitivity compared to controls (normotensive rats), as evidenced by reduced reactions during experiments involving exposure to noxious stimuli including the tail flick and hot plate tests (Ghione, 1996; Randich & Maixner, 1984; Zamir & Maixner, 1986).

In addition to animal findings, France (1999) also reviewed literature examining the relationship between hypoalgesia and hypertension in humans, finding that hypertensive individuals had reduced pain sensitivity compared to those without hypertension (Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Ghione et al., 1985; Guasti et al., 1995a, 1995b, 1996; Rosa & Ghione, 1990; Rosa, Ghione, Panattoni, & Mezzasalma, 1986; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994; Sheps et al., 1992; Zamir & Shuber, 1980). Zamir and Shuber (1980) examined the differences in pain threshold between hypertensive and normotensive individuals with use of tooth pulp stimulation. Individuals with hypertension had significantly higher pain thresholds compared to controls (Zamir & Shuber, 1980), suggesting a relationship between hypertension and reduced pain sensitivity (Zamir & Shuber, 1980).

Results of more recent epidemiological studies also support the relationship between pain and hypertension (Bruehl et al., 2008; Gureje, Akinpelu, Uwakwe, Udofia & Wakil, 2007; Stang, Brandenberg, Lane, Merikangas, Von Koff & Kessler, 2006; Von Koff, Crane, Lane, Miglioretti, Simon, Saunders, Stang et al., 2005). In a prospective study by Chaing et al. (2019), 200

participants from a single-centered facility were categorized into three groups of normotensive, hypertensive without treatment, and hypertensive with treatment. Participant's pain levels were measured using a visual analysis scale (VAS) score and postoperative patient-controlled analgesia (PCA) dose. Findings were varied, with female participants in the normotensive group and both hypertensive groups showing a significant difference in analgesic dosage on postoperative days. There were no significant differences found between groups among male participants (Chaing, Huang, Lin, Chan & Chia, 2019). These results based on acute pain studies are interesting; however, there remain differences in the research regarding chronic and acute pain associations.

Pain and Hypertension

Additional research has supported the relationship between high blood pressure and higher pain thresholds or lower pain sensitivity in acute and chronic pain residents (Olsen et al., 2013), suggesting homeostatic interactions between pain and cardiovascular modulatory systems. Olsen and colleagues (2013) were the first to examine both hypertension prevalence and BP-related hypoalgesia as they relate to chronic pain. Olsen et al. built upon an existing epidemiological and prospective study of health problems, symptoms and chronic diseases, known as The Tromsø Study, which was performed in 2007-2008. The authors explored the association between resting blood pressure (BP) and acute and chronic pain, as well as the prevalence of hypertension, among chronic pain residents compared to residents without pain. The 10,135 chronic pain residents included in the study were between the ages of 30 and 87 years, and were exposed to a variety of pain-inducing tests. Hypertension was defined as having a diagnosis of HT with or without the use of HT medication to treat high blood pressure.

Questionnaires were administered to assess chronic pain, hypertension diagnoses, and medication utilization, as well as demographic variables of body mass index (BMI), height, weight, and resting blood pressure. Pain tolerance was evaluated by a standardized 106 second cold pressor test. Pain threshold was measured subjectively on a Likert scale from 0 to 10 (no pain to worst pain ever). Blood pressure was measured thirty minutes after the procedure (Olsen et al., 2013). Chronic pain was found to be associated with significantly increased likelihood of comorbid hypertension ($p < .001$). Overall, researchers proposed that mediators of pain and blood pressure are correlated, suggesting there are functional interactions between chronic pain and elevated blood pressure (Olsen et al., 2013).

Interestingly, other studies suggest an inverse relationship between chronic pain and hypertension (Maixner, Fillingim, Kincaid, Sigurdsson, & Harris, 1997). Maixner, Fillingim, Kincaid, Sigurdsson and Harris (1997) examined the relationship between pain sensitivity and hypertension for 64 females with chronic temporomandibular joint (TMJ) illnesses, compared to 23 age-matched controls with no pain. Thermal stimuli were administered to both experimental and control groups. Researchers found that participants with TMJ disorders had increased pain sensitivity compared to control conditions. Those in the control group had lower blood pressure and higher pain tolerances compared to TMJ participants (Maixner et al., 1997). Notably, the association between reduced pain sensitivity and acute pain appears to be more promising.

Acute pain serves an adaptive purpose for humans (Sacco et al., 2013), largely by assisting with survival by alerting the body about potential danger (Sacco et al., 2013). There are many changes that occur as a result of acute pain, including immune, cardiovascular, and endocrine adaptations (France, Froese, & Stewart, 2002). Although this is a typical response to

acute pain, individuals with hypertension typically report a higher pain threshold, or reduced pain sensitivity (France et al., 2002). France and Katz (1999) examined the relationship between post-surgical pain and hypertension for 159 males who underwent a radial-prostatectomy. Participants were from Toronto General Hospital in Toronto, Canada, ranging from 47 to 75 years of age, with an average blood pressure of 134/79. A previous diagnosis of hypertension was reported by 38% of participants (France & Katz, 1999). Participants were required to operate their PCA pumps, which delivered doses of morphine, with a maximum dose of 30 mg in a four-hour time frame. Pain was measured with a visual analog scale (VAS), requiring participants to rate their pain on a scale from 0 (no pain) to 10 (worst pain ever). The McGill Pain Questionnaire (MPQ) was also administered to assess pain levels. Researchers found that post-surgical pain was significantly associated with resting systolic blood pressure. Particularly, lower pain ratings on the MPQ and VAS were associated with higher systolic blood pressure 48 hours post-surgery. However, PCA and blood pressure did not show statistically significant results, suggesting that pain and blood pressure are not mediated by opiate medication (France & Katz, 1999).

Biological and Heritability Factors

Research over the past two decades has demonstrated that hypertension is reliably associated with reduced levels of perceived pain. Expanding on this research, there is an indication that hypoalgesia is a phenomenon that may actually precede the onset of hypertension (France, 1999). In examining parental and biological factors (e.g., resting blood pressure), studies have provided support for the notion that hypoalgesia precedes the development of high blood pressure (France, 1999; Jamerson & Julius, 1991; Julius & Schork, 1978; Yong, Kuller,

Rutan, & Bunker, 1993). When investigating parental history, children of parents with hypertension are two to four times more likely to develop high blood pressure compared to those without any parental history (Hunt, Williams & Barlow, 1986). France and colleagues (1991) were the first to explore the concept of pain sensitivity in individuals at genetic risk for hypertension by examining tolerance to a constrictive thigh cuff among young normotensive men with and without a parental history of hypertension (France, Ditto & Adler, 1991). Results highlighted that offspring of the hypertensive parents tolerated a higher inflation of the cuff before reporting pain when compared to controls. Beyond this, offspring of hypertensive individuals also rated the maximum cuff pressure to be significantly less painful than the offspring of normotensive individuals. Similar results were found in subsequent research using a variety of pain assessment strategies including cold pressor to the hand (D'Antono, Ditto, Rios & Moskowitz, 1999), venipuncture for blood donation (France, Adler, France & Ditto, 1994), forearm ischemia (Stewart & France, 1996), heat applied to the forearm (Bragdon, Light, Girdler & Maxiner, 1997), and electrocutaneous stimulation to the forearm (Ditto, France & France, 1997) and leg (Pagé & France, 1997). Normotensive offspring of hypertensive parents (i.e, offspring at genetic risk of developing hypertension) show hypoalgesia relative to controls in response to various pain stimuli suggesting that it is not hypertension per se that is related to the lower pain sensitivity.

Similarly, France, Ditto, and Adler (1991) examined the likelihood of pain sensitivity due to a family history of hypertension among 45 male participants. Of the participants, 21 had a family history of hypertension (M = 23 years, SD = 4.5 years) and 24 did not have a history of hypertension (M = 21 years, SD = 2.4 years). History of hypertension was confirmed by parental

report. Participants were paid $15 USD for participation in the study. Heart rate and blood pressure were measured pre- and post-intervention. The intervention involved a thigh cuff that inflated to the point of "pain". Participants were asked to report their pain as the cuff inflated, noting the most painful time (France, Ditto and Adler, 1991). Researchers indicated that subjective measures of pain may be related to a parental hypertension diagnosis. Those with the parental hypertension diagnosis reported reduced pain sensitivity compared to those without a paternal or maternal hypertension diagnosis. Notably, current hypertensive status may not indicate reduced pain sensitivity in this study, suggesting the genetic component may be valuable in identifying those with a higher pain tolerance (France et al., 1991).

As highlighted, those with a biological parental history of hypertension are more likely to develop the illness compared to those without hypertensive parents (France, 1999; Hunt, Williams, & Barlow, 1986). Although hypertension tends to develop later in life, researchers suggest offspring of hypertensives are likely to display reduced pain sensitivity, even in earlier years of life (Hunt et al., 1986). To evaluate this possibility, France, Taddio, Shah, Pagé, & Katz (2009) examined family history and pain sensitivity among 80 couples who were expecting children. Researchers conducted a double-blind, randomized controlled trial (RCT) at Mount Sinai Hospital in Toronto, Canada. Both fathers and mothers completed questionnaires prior to the birth, which included questions about typical blood pressure, individual or familial diagnoses of hypertension, and age. As part of routine medical practice, within 24 hours of birth, infants were administered 0.5ml Vitamin K injection and researchers assessed pain responses to the injection. Pain reactions included infant grimacing and crying. Facial reactions included assessment of eyebrows and eyes (e.g., eyebrow bulge, eye squeezing), a valid and reliable

system for evaluating pain in newborns (Grunau & Craig, 1987). Researchers found a significant correlation between maternal family history of hypertension, as evidenced by shorter duration of crying among infants, as well as reduced grimacing (France et al., 2009). These findings further suggest that biological history of hypertension is related to decreased pain sensitivity even before HT has manifested.

Hypertension, Pain and Complex Chronic Disease

Elevated blood pressure is the leading cause of disability and death worldwide, accounting for 7% of disability-adjusted life-years lost and 9.4 million deaths annually (Lim, Vos, Flaxman et al., 2012; World Health Organization, 2015). Hypertension is typically associated with various other diseases, including diabetes, renal failure, dementia, depression and anxiety, pain and a number of cardiovascular diseases (CVD). Death associated with hypertension stems primarily from cardiovascular disease, including myocardial infarction, stroke, peripheral vascular disease and heart failure (Haroun, Jaar, Hoffman et al., 2003; Nagai, Hoshide & Kario, 2009; Rapsomaniki, Timmis, George et al., 2014). Similar to other comorbid diseases, there are substantial costs associated to health care systems. In Canada and the United States, CVD accounts for almost half of all direct health care spending. In 2010, estimated health care costs to the Canadian healthcare system were estimated to be $13.9 billion, equaling 10.2% of total Canadian health care spending (Weaver, Clement, Campbell et al., 2015). As with other complex diseases, the additional costs of disability, work absenteeism, premature death, and secondary healthcare resources, costs are estimated to be 20 times higher (Gaziano, Bitton, Anand & Weinstein, 2009).

The cost of complex chronic disease (CCD) and pain are equally alarming. The CCD population, in particular, incurs a major financial burden to each province's health care budget, as well as the entire country's health care system, as a result of the specialized and often costly treatment required for these individuals (Fortin, Soubhi, Hudon, Bayliss & van den Akker, 2007; Hartmann et al., 2011; Willadsen et al., 2018). Of the total direct medical care expenses in Canada, 42% are allotted to the treatment of chronic disease (Mirolla, 2004), with up to $52,661, on average, per patient during the final year of life (Tanuseputro, Wodchis, Fowler et al., 2015). Managing the demands of the CCD population and the multiple associated needs can be difficult and problematic for primary health care providers and the residents themselves (Piette & Kerr, 2006). With respect to pain, some researchers suggest that chronic pain affects 15-29% of the Canadian population (Boulanger et al., 2007; Hogan, Taddio, Katz, Shah & Krahn, 2016; Schopflocher et al., 2011). Worldwide, chronic pain is estimated to affect 20% of people (Breivik, Collett, Ventafridda, Cohen & Gallacher, 2006; Goldberg & Summer, 2011), accounting for 15% to 20% of physician visits (Koleva, 2005). Chronic pain is associated with significant costs to both society and the individual (Meana et al., 2004). There is an abundance of literature suggesting the Canadian healthcare system is burdened by the increasing number of chronic pain cases (Hogan et al., 2016; Lim, Jacobs, & Klarenbach, 2006; Rayner, Hotopf, Petkova, Matcham, Simpson & McCracken, 2016; Sessle, 2011).

The predominance of cardiovascular disease, pain and complex chronic disease is alarming and yet, remains an important area to be evaluated more closely. With an increasing elderly population, the comorbidity of significant diseases is also rising (Meana et al., 2004). Developing a better understanding of the ways in which comorbid diseases interact with one

another is critical to developing strategies for better managing the increasing demands of the residents and the healthcare system. Examining the impact of hypertension on pain levels among a CCD population has yet to be studied, despite the prevalence of these common, often comorbid health issues. In light of this, the current study seeks to examine the association of hypertension and pain within a CCD population. Specifically, given the existing research suggesting hypertensive individuals may have a propensity to increased pain tolerance, the study seeks to further examine the phenomenon of hypertensive hypoalgesia among individuals with multiple comorbid diseases.

Methodology

Data source

This study used data from the Canadian Institute for Health Information (CIHI) Facility-Based Continuing Care Reporting System (CCRS), which captures information on individuals admitted to publicly-funded hospital facilities for complex chronic care in Canada (Continuing Care Reporting System, 2013-2014) between the years 2006-2016. Upon entry to a complex chronic care (CCC) facility, residents are administered a standardized assessment protocol, the Resident Assessment Instrument - Minimum Data Set/Full Assessment (RAI/MDS/FA 2.0 Canadian Version), within 14 days of admission. If the resident remains in the facility for longer than 92 days, quarterly assessments are conducted. These assessments are typically completed by the treating nurse or physician and include resident self-reports and information from medical files.

The RAI/MDS/FA 2.0 is an internationally validated clinical assessment instrument (Fries et al., 2001; Hartmaier et al., 1995; Hawes et al., 1995; Lawton et al., 1998; Mor, 1995;

Snowden et al., 1999). This standard tool collects a wide array of information, including basic demographic characteristics, diagnostic profiles, medication usage and treatment participation, and outcomes, as well as categorizes diseases.

Hypertension Diagnosis and Propensity Score Matching (PSM)

The original full CCRS dataset consisted of 139,920 residents, of whom 77,323 had a diagnosis of hypertension. The diagnosis of hypertension was taken directly from the CCRS RAI/MDS/FA 2.0. Propensity score matching was used to create two groups of residents: cases (with hypertension) and controls (no hypertension), using a 1:1 ratio ensuring the case and control residents had the exact same value for age, sex, marital status, assessment year and total disease count.

Pain measures

The CCRS RAI/MDS/FA 2.0 measures pain using two descriptive scales:

3) Frequency: no pain (0), pain less than daily (1), pain daily (2); and,
4) Intensity: mild pain (1), moderate pain (2), times when pain is horrible or excruciating (3).

For the present study, we created, three measures of pain by combining various items from the above two existing CCRS RAI/MDS/FA 2.0 scales:

1) Pain-Yes/No (P-Y/N): Pain prevalence dichotomous measure: no pain (0); pain (1) (mild, moderate, severe);
2) 4-point pain intensity scale (PI-4): no pain (0), mild pain (1), moderate pain (2), severe pain (3);

3) 7-point combined pain intensity and pain frequency scale (PIPF-7): no pain (0); mild pain less than daily (1); mild pain daily (2); moderate pain less than daily (3); moderate pain daily (4); severe pain less than daily (5); severe pain daily (6).

Research Objective and Data Analysis

All data used in this study is derived from the initial assessment of all residents, aged 18–101 years, from Ontario's CCC facilities between the years 2006 – 2016, reported in the CIHI CCRS dataset. Non-parametric statistical tests, specifically McNemar for dichotomous pain and Wilcoxon Signed Ranks test for ordinal pain, will be used.

To evaluate the secondary research objective of exploring the effect of hypertension, sex and hypertension by sex interaction, binary and multinomial logistic regression analysis were used for Pain-Y/N, and for PI-4 and PI-7 variables, respectively. All regression models were conducted controlling for the following potential confounders: Activities of Daily Living (ADL) scores, Depression Rating Scale (DRS) scores, Index of Social Engagement (ISE) Scores, number of medications taken, days taking analgesics, number of emergency room visits and physician visits).

All descriptive and inferential statistical analysis were performed in software package SPSS (version 25). Level of statistical significance was used for inferential tests, with $p < 0.05$ indicating statistically significant findings.

Results

The original dataset contained 139,920 residents, with 77,323 residents (55.3%) having hypertension. Propensity matching with a 1:1 ratio was applied to the sample, resulting in 40,799 non-hypertension residents matched with 40,799 hypertension residents. The matched dataset

includes 81,598 records, 40,799 residents with and 40,799 without hypertension. Table 6.1 provides descriptive information about matching criteria and controlled variables.

Table 6.1. Descriptive characteristics of matched samples, n= 40,799, Ontario CCC residents, 2006-2016

Characteristics	Matched hypertensive patients (n = 40799)	Control group patients (n = 40799)	Comparison between two groups
	N (%) or Mean ± SD Median (IQR)	N (%) or Mean ± SD Median (IQR)	
Sex			$\chi^2(1)=0.00$, $p = 1.00$
Males	17592 (43%)	17592 (43%)	
Females	23207 (57%)	23207 (57%)	
Age	78.66 ± 10.54	78.66 ± 10.54	$t(81596) = 0.00$, $p = 1.00$
Year of assessment			$\chi^2(1)=0.00$, $p = 1.00$
2006	4045 (10%)	4045 (10%)	
2007	3889 (10%)	3889 (10%)	
2008	3696 (9%)	3696 (9%)	
2009	3810 (9%)	3810 (9%)	
2010	3998 (10%)	3998 (10%)	
2011	4399 (11%)	4399 (11%)	
2012	4170 (10%)	4170 (10%)	
2013	4069 (10%)	4069 (10%)	
2014	3861 (9%)	3861 (9%)	
2015	4028 (10%)	4028 (10%)	
2016	834 (2%)	834 (2%)	
Number of diseases (excluding hypertension)	1.65 ± 1.07	1.65 ± 1.07	$\chi^2(6)=0.00$, $p = 1.00$
0	5675 (14%)	5675 (14%)	
1	13674 (33%)	13674 (33%)	
2	12929 (32%)	12929 (32%)	
3	6578 (16%)	6578 (16%)	
4	1747 (4%)	1747 (4%)	
5	192 (1%)	192 (1%)	
6	4 (0.01%)	4 (0.01%)	
Marital status			$\chi^2(5)=0.00$, $p = 1.00$
Never married	2860 (7%)	2860 (7%)	

Married	18483 (45%)	18483 (45%)	
Widowed	15491 (38%)	15491 (38%)	
Separated	340 (1%)	340 (1%)	
Divorced	1505 (4%)	1505 (4%)	
Unknown	2120 (5%)	2120 (5%)	
Activities of Daily Living (ADL) score [long form]	16.36 ± 7.88	16.82 ± 8.30	t(81596) = 8.08, $p < 0.001$
Depression Rating Scale (DRS) score	1.41 ± 2.11	1.42 ± 2.09	t(81013) = 0.41, $p = 0.68$
Index of Social Engagement (ISE)	2.97 ± 2.04	2.72 ± 2.04	t(81596) = 17.69, $p < 0.001$
Number of medications taken	12.73 ± 5.38 Median (IQR): 12 (7)	10.91 ± 5.18 Median (IQR): 10 (7)	t(81596) = 49.04, $p < 0.001$ M-W $p < 0.001$
Days taking analgesics	4.59 ± 3.04 Median (IQR): 7 (6)	3.56 ± 3.06 Median (IQR): 7 (6)	t(81596) = 1.33, $p = 0.19$ M-W $p = 0.29$
Number of emergency room visits	0.59 ± 0.90 Median (IQR): 0 (1)	0.59 ± 0.99 Median (IQR): 0 (1)	t(81437) = 0.79, $p = 0.43$ M-W $p = 0.57$
0	21944 (54%)	22111 (54%)	
1	15607 (38%)	15341 (38%)	
2	2165 (5%)	2226 (5%)	
4	584 (2%)	616 (2%)	
5 or more	407 (1%)	438 (1%)	
Number of physician visits	5.02 ± 3.30 Median (IQR): 4 (5)	5.15 ± 3.48 Median (IQR): 4 (5)	t(81596) = 5.36, $p < 0.001$ M-W $p = 0.002$
Hospital stays	1.14 ± 1.71 Median (IQR): 1 (0)	1.07 ± 1.27	t(81437) = 6.86, $p < 0.001$ M-W $p < 0.001$

0	8555 (21%)	Median
1	22926 (56%)	(IQR):
2	6792 (17%)	1 (0)
3	1722 (4%)	9263 (23%)
4 or more	712 (2%)	23214 (57%)
		6060 (15%)
		1598 (4%)
		597 (1%)

Note: M-W is Mann-Whitney non-parametric test

A comparison of pain between residents with and without hypertension was conducted using McNemar and Wilcoxon Signed Ranks tests (Table 6.2). We observed a significantly lower proportion of hypertension residents with pain (71.7%) compared to controls (72.6%), McNemar test $X^2 = 7.73$, $p = .005$. Wilcoxon Signed Ranks tests also showed significantly lower pain levels among cases compared to controls ($z = 3.46$, $p = .001$ for 4-level pain; $z = 3.55$, $p < .001$ for 7-level pain).

Table 6.2. Comparison of dichotomous pain (P-Y/N), 4-point pain scale (PI-4), and 7-point pain scale (PIFF-7) between cases (hypertension) and controls (no hypertension), n = 40,799 in each group, Ontario CCC residents, 2006-2016

Pain variable	Cases N (%)	Controls N (%)	Statistical test
P-Y/N			
No	11522 (28.3%)	11198 (27.4%)	McNemar test
Yes	29247 (71.7%)	29601 (72.6%)	$X^2 = 7.73$, $p = .005$
PI-4			
Mean ± SD*	1.28 ± 0.96	1.31 ± 0.97	
No pain (0)	11522 (28.3%)	11198 (27.4%)	Wilcoxon Signed
Mild pain (1)	9252 (22.7%)	9321 (22.8%)	Ranks test $z = 3.46$, p
Moderate pain (2)	16963 (41.6%)	16801 (41.2%)	$= .001$
Severe pain (3)	3032 (7.4%)	3479 (8.5%)	
PIPF-7			
Mean ± SD*	2.26 ± 1.90	2.31 ± 1.93	
No pain (0)	11552 (28.3%)	11198 (27.4%)	Wilcoxon Signed
Mild pain < daily (1)	6514 (16.0%)	6794 (16.7%)	Ranks test $z = 3.55$, p
Mild pain daily (2)	2738 (6.7%)	2527 (6.2%)	$< .001$
Moderate pain < daily (3)	5578 (13.7%)	5382 (13.2%)	

Moderate pain daily (4)	11385 (27.9%)	11419 (28.0%)
Severe pain < daily (5)	258 (0.6%)	270 (0.7%)
Severe pain daily (6)	2774 (6.8%)	3209 (7.9%)

* Mean and SD represent the mean and standard deviation of the rank ordered pain scores

Chi-Square and Mann Whitney tests were used to assess the proportion and severity of pain among females compared to males for both hypertension and control samples, respectively (Tables 6.3 and 6.4).

Table 6.3. Comparison of dichotomous pain (P-Y/N), 4-point pain scale (PI-4), and 7-point pain scale (PIPF-7) between males and females with hypertension (cases, n = 40,799), Ontario CCC residents, 2006-2016

Pain variable	Females n = 23207 (57%)	Males n = 17592 (43%)	Statistical comparison test
P-Y/N			
No	5653 (24%)	5899 (34%)	Chi-square test
Yes	17554 (76%)	11693 (66%)	$X^2 = 415$, $p < .001$
PI-4			
Mean ± SD	1.36 ± 0.94	1.18 ± 0.97	Mann-Whitney U test
No pain (0)	5653 (24%)	5899 (34%)	$z = 19.12$, $p < .001$
Mild pain (1)	5390 (23%)	3862 (22%)	
Moderate pain (2)	10301 (43%)	6662 (38%)	
Severe pain (3)	1863 (8%)	1169 (6%)	
PIPF-7			
Mean ± SD	2.42 ± 1.89	2.05 ± 1.90	Mann-Whitney U test
No pain (0)	5653 (24%)	5899 (34%)	$z = 21.00$, $p < .001$
Mild pain < daily (1)	3654 (16%)	2860 (16%)	
Mild pain daily (2)	1736 (7%)	1002 (5%)	
Moderate pain < daily (3)	3135 (14%)	2443 (14%)	
Moderate pain daily (4)	7166 (31%)	4219 (24%)	
Severe pain < daily (5)	154 (1%)	104 (1%)	
Severe pain daily (6)	1709 (7%)	1065 (6%)	

Table 6.4. Comparison of dichotomous pain (P-Y/N), 4-point pain scale (PI-4), and 7-point pain scale (PIPF-7) between males and females without hypertension (controls, n = 40,799), Ontario residents, 2006-2016

Pain variable	Females n = 23207 (57%)	Males n = 17592 (43%)	Statistical comparison test
P-Y/N			Chi-square test
No	5559 (24%)	5639 (32%)	$X^2 = 330$, $p < .001$
Yes	17648 (76%)	11953 (68%)	
PI-4			
Mean ± SD	1.37 ± 0.94	1.22 ± 0.99	Mann-Whitney U test
No pain (0)	5559 (24%)	5639 (32%)	$z = 15.33$, $p < .001$
Mild pain (1)	5473 (24%)	3848 (22%)	
Moderate pain (2)	10153 (44%)	6648 (38%)	
Severe pain (3)	2022 (8%)	1457 (8%)	
PIPF-7			
Mean ± SD	2.44 ± 1.91	2.14 ± 1.96	Mann-Whitney U test
No pain (0)	5559 (24%)	5639 (32%)	$z = 16.81$, $p < .001$
Mild pain < daily (1)	3869 (17%)	2925 (17%)	
Mild pain daily (2)	1604 (7%)	923 (5%)	
Moderate pain < daily (3)	3060 (13%)	2322 (13%)	
Moderate pain daily (4)	7093 (30%)	4326 (25%)	
Severe pain < daily (5)	146 (1%)	124 (1%)	
Severe pain daily (6)	1876 (8%)	1333 (8%)	

There were 23,207 female (57%) and 17,592 male (43%) residents in each of the two groups. Tables 3 and 4 show significantly higher pain (both proportion and severity) among females compared to males for both hypertension and control samples, respectively. Among both groups of residents, females were significantly more likely to report pain, on all pain measures (P2, PI-4, PIPF-7).

Binary and multinomial logistic regressions were conducted to evaluate the association of pain (P-Y/N, PI-4, PIPF-7) with hypertension, sex, and the interaction of hypertension and sex. For all models, the dependent variable was pain (with no pain being reference category) and the independent variables were hypertension (coding: 0 for cases; 1 for controls), sex (coding: 0 for males; 1 for females), and the sex by hypertension interaction.

Table 6.5. Binary and multinomial logistic regression models for dichotomous (P-Y/N), 4-level (PI-4) and 7-level pain (PIPF-7) variables, n = 40,799; reference categories 'no hypertension' and 'males'. Ontario CCC residents, 2006-2016.

Independent variable	Dependent variable	*p*-value	*Odds Ratio* (95% CI)
Model 1: P-Y/N			
Hypertension	Pain (Yes/No)	< .001	0.85 (0.81 – 0.90)
Female	Pain (Yes/No)	< .001	1.33 (1.26 – 1.40)
Hypertension × Female	Pain (Yes/No)	.315	1.04 (0.97 – 1.11)
Model 2: PI-4			
Hypertension	Mild pain (1)	< .001	0.88 (0.83 – 0.94)
	Moderate pain (2)	< .001	0.86 (0.81 – 0.91)
	Severe pain (3)	< .001	0.69 (0.63 – 0.76)
Female	Mild pain (1)	< .001	1.31 (1.24 – 1.39)
	Moderate pain (2)	< .001	1.36 (1.29 – 1.44)
	Severe pain (3)	< .001	1.22 (1.12 – 1.33)
Hypertension × Sex	Mild pain (1)	.786	1.01 (0.93 – 1.10)
	Moderate pain (2)	.350	1.04 (0.96 – 1.12)
	Severe pain (3)	.014	1.17 (1.03 – 1.32)
Model 3: PIPF-7			
Hypertension	Mild pain < daily (1)	< .001	0.86 (0.81 – 0.92)
	Mild pain daily (2)	.187	0.93 (0.84 – 1.03)
	Moderate pain < daily (3)	.023	0.92 (0.86 – 0.99)
	Moderate pain daily (4)	< .001	0.83 (0.77 – 0.88)
	Severe pain < daily (5)	.012	0.71 (0.54 – 0.93)
	Severe pain daily (6)	< .001	0.68 (0.62 – 0.75)
Female	Mild pain < daily (1)	< .001	1.27 (1.19 – 1.35)
	Mild pain daily (2)	< .001	1.54 (1.40 – 1.69)

	Moderate pain < daily (3)	< .001	1.25 (1.16 – 1.34)
	Moderate pain daily (4)	< .001	1.46 (1.37 – 1.56)
	Severe pain < daily (5)	.560	1.08 (0.84 – 1.37)
	Severe pain daily (6)	< .001	1.27 (1.16 – 1.39)
Hypertension × Female	Mild pain < daily (1)	.998	1.00 (0.91 – 1.09)
	Mild pain daily (2)	.690	1.03 (0.90 – 1.17)
	Moderate pain < daily (3)	.920	1.00 (0.91 – 1.11)
	Moderate pain daily (4)	.158	1.07 (0.98 – 1.16)
	Severe pain < daily (5)	.112	1.33 (0.94 – 1.90)
	Severe pain daily (6)	.022	1.16 (1.02 – 1.32)

As shown in Table 6.5, examining the dichotomous pain variable, significantly fewer residents with hypertension had pain than residents without hypertension, *OR* = 0.85 (95% CI 0.81 – 0.90), $p < .001$. Females were 33% more likely than males to report pain, *OR* = 1.33 (95% CI 1.26 – 1.40), $p < .001$. The hypertension by sex interaction effect was not significant.

Residents with hypertension were significantly less likely to report all levels of pain on the PI-4: mild (*OR* = 0.88; 95% CI 0.83 – 0.94), moderate (*OR* = 0.86; 95% CI 0.81 – 0.91), and severe *(OR* = 0.69; 95% CI 0.63 – 0.76), all $p < .001$. Similar results were found using the PIPF-7 scale, with hypertensive residents reporting significantly less pain for mild, moderate and severe pain less than daily. ORs were similar to the PI-4 scale, with a range from 0.86 for mild pain less than daily to 0.68 for severe pain less than daily, all $p < .001$.

Females reported higher pain (PI-4; mild, moderate and severe) than males, with ORs ranging between 1.22 and 1.36, all $p < .001$. Results for the PIPF-7 were similar in that females typically reported significantly more pain than males. The interaction between hypertension and sex showed that females with hypertension were at a 17% greater risk of reporting severe pain (PI-4) than males with hypertension, *OR* = 1.17 (95% CI 1.03 – 1.32), $p = .014$. Similarly, on the

PIPF-7, hypertensive females were significantly more likely to report severe pain that occurs on a daily basis (*OR* = 1.16; 95% CI 1.02 – 1.31, *p* = 0.022). Overall, on both 4-level and 7-level pain variables, results similarly highlighted less pain among hypertensive residents, higher pain among female residents, and higher severe pain (daily for the PIPF-7) among females than males with hypertension.

Table 6.6. Percentage of male and female residents with and without hypertension reporting severe pain on the 4-level pain scale (PI-4) and severe pain daily on the 7-level pain scale (PIPF-7). N = 40,799, Ontario CCC residents, 2006-2016

Pain level	Male	Female
PI-4: Severe pain		
No hypertension	8.28%	8.71%
Hypertension	6.65%	8.03%
PIPF-7: Severe pain daily		
No hypertension	7.58%	8.08%
Hypertension	6.05%	7.36%

Discussion

The results of the present large-scale study indicate that the presence and severity of pain was significantly lower in CCC residents with a history of hypertension compared to a propensity matched cohort without hypertension, even after adjusting for potential confounding variables including psychological factors such as depression, activities of daily living and social engagement, and medical factors, including physician visits, emergency room visits and medication and analgesic usage, which all may influence both hypertension and pain risks. Further analysis showed that residents with hypertension were 15% less likely to report pain than those without hypertension (Table 6.5). Until now, despite the significant health care concerns, the CCD population has remained unexplored in relation to hypertensive hypoalgesia. Among a population of CCD residents, the current study utilized a case-control design using propensity

matching, which allowed for the comparison of two demographically similar groups of residents with and without hypertension. Groups were matched with a 1:1 ratio on important demographic variables, including sex, age, marital status, assessment date and comorbid disease count. The present results support the emerging evidence of a relationship between hypertension and reduced pain sensitivity (France, 1999; Olsen et al., 2014; Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Ghione et al., 1985; Guasti et al., 1995a, 1995b, 1996; Rosa & Ghione, 1990; Rosa, Ghione, Panattoni, & Mezzasalma, 1986; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994; Sheps et al., 1992; Zamir & Shuber, 1980). Hypertension-associated hypoalgesia has been observed in rat (Ghione, 1996; Randich & Maixner, 1984; Zamir & Maixner, 1986) and human subjects (Ghione et al., 1988; Ghione et al., 1985; Guasti et al., 1995a, 1995b, 1996; Rosa & Ghione, 1990; Rosa et al., 1986; Rosa et al., 1994; Sheps et al., 1992; Zamir & Shuber, 1980). Consistent with the existing pain literature (e.g. Fillingim, 2017; Kleiman, Clarke & Katz, 2011; Rogers, Gallaghan, Garey, Ditre, Williams & Zvolensky, 2020; Sorge & Totsch, 2017), we found that females residents were 33% more likely to report pain compared to males (*OR* = 1.33, 95% CI 1.26 – 1.40, $p < .001$). In the context of BP-related hypoalgesia research, results from this study supported previous findings suggesting hypertensive hypoalgesia differs by sex; such that, females exhibit greater hypoalgesia (al'Absi, Buchanan, Marrero, & Lovallo, 1999; France, Taddio, Shah, Page, & Katz, 2009; Olsen et al., 2013; Sheffield, Biles, Orom, Maixner, & Sheps, 2000). Specifically, we also observed a significant interaction between hypertension and sex such that hypertensive females were between 16% and 17% more likely than hypertensive males to report severe pain (Tables 6.4 and 6.5) (PI-4, 8.03% versus 6.65%, for females and males respectively; PIPF-7, 7.36% versus 6.05%, for females and males respectively).

Strengths and Limitations

The results of the present study support emerging evidence for the concept of hypertensive hypoalgesia among a large sample of complex chronic disease residents. Although many factors contribute to pain intensity and frequency, the use of propensity matching to create demographically similar groups while also controlling for important psychological and medical variables allowed for a conservative comparison of pain variables among residents with and without hypertension. Propensity matching statistics allow for a stringent comparison between groups, similar to a randomized controlled design (Hill, 2008).

Further, the benefits of examining secondary, standardized, electronic sources of longitudinal data arguably outweigh the limitations, particularly in epidemiological research. For instance, many of the challenges associated with primary data collection are avoided, including time and resources that are required to hire research personnel and recruit participants (Belletti, Zacker & Mullins, 2010). A further strength of our study is the large, province-wide sample of CCD residents with and without hypertension in Ontario, between the ages of 18 and 101 years, further contributing to the generalizability of the study. The large sample size of more than 40,000 residents per group, also allows for greater power in the analysis. The data utilized is of high quality, given the use of standardized electronic records through the CIHI Facility-Based Continuing Care Reporting System, which captures information on residents admitted to publicly funded hospital facilities for complex chronic care in Canada. The RAI/MDS/FA 2.0 utilized in this validated tool, further contributing to the quality of the data (Fries et al., 2001).

Nonetheless, there are limitations to the present study that should be addressed. Notably, the dataset used in this study did not include accessibility to more detailed resident histories,

including body mass index (BMI), pain location and duration, and systolic, diastolic and resting blood pressure readings. The consideration of these health, medication and demographic factors may provide additional information about the hypertension and pain relationship. Finally, the information on pain status is based on self-report; however, this is a common limitation among pain research and relevant studies suggest that there is a moderate to strong agreement between self-reported disease status and medical records (National Center for Health Statistics, 1994).

Implications

This is the first study, to our knowledge, to explore the relation of hypertension and pain among a large population of CCD residents. The results are consistent with previous research that supports the hypertensive hypoalgesia phenomenon, even after controlling for potential confounders. Given the complexity of the CCD population, information that may better inform the understanding of disease combinations and subsequent treatment care of this specific population is invaluable in an aging society.

Chapter 7: Study 3 - Missing Limb Pain among a Complex Chronic Care Population

Disclosure Notes

The current study has been submitted for publication and is currently under review for the Journal of Pain Research, as of May 2021. An abstract of this study was accepted for poster presentation at the April 2021 Annual Meeting of the Canadian Pain Society and published in the Canadian Journal of Pain (Ferguson, Svendrovski, & Katz, 2021) (in press).

Abstract

Introduction: Limb loss occurs for various reasons (trauma, infection, vascular diseases, tumors, congenital absence). Limb loss is known to result in several types of pain. Little is known about pain in residents with missing limbs admitted to complex chronic care (CCC) facilities. This study examined the presence of pain and its intensity in CCC residents with and without missing limbs.

Methods: The Continuing Care Reporting System was accessed for data from residents admitted to Ontario complex chronic care facilities assessed with the Resident Assessment Instrument Minimum Data Set, V2.0. Propensity score matching (1:1 ratio) was used to identify a control resident without missing limbs for each case. McNemar's test was used for dichotomous pain (Y/N) and Wilcoxon Signed Ranks test for ordinal pain (4-level and 7-level pain variables). Binary and multinomial logistic regression were used to quantify the relationship between missing limbs and reports of pain.

Results: Missing limbs were reported by 2,961 residents (2.1%, original n=139,920) resulting in 2,212 propensity matched pairs. A significantly higher proportion of missing limb cases had pain (80%) versus controls (70%), X^2=64.43, p<.001. Significantly higher pain levels were found in cases versus controls (z=8.47, p<.001 for 4-level pain; z=8.57, p<.001 for 7-level pain). Residents with missing limbs were 1.86 (95% CI:1.64–2.12) times more likely to report pain than controls, p<.001, even after adjusting for confounders (OR:1.46;95% CI:1.26–1.70).

Discussion/Conclusions: The results point to the need to better manage pain in CCC residents with missing limbs.

Introduction

Limb amputation can occur for various reasons including trauma, infection, vascular diseases, and tumors. Following limb amputation, it is alarmingly common for patients to continue to experience painful sensations referred to the phantom limb. Phantom limb sensations (PLS) are often present following amputation and described as if the limb was still present (Lundeberg, Bondesson, & Lundströom, 1985). These sensations can manifest as itching, tingling, and feelings of warmth or coldness (Flor, 2002; Kooijman, Dijkstra, Geertzen, Elzinga, & van der Schans, 2000). Others report the phantom limb sensations to be the same as those experienced before the amputation (Katz & Melzack, 1990). Many patients, unfortunately, report these experiences to be extremely painful. Post-amputation pain is commonly separated into two categories: residual limb pain (RLP), formally known as "stump pain" and defined as pain that originates from the actual site of the amputation; and, phantom limb pain (PLP), clinically defined as pain that is experienced as arising from the missing limb (Ehde et al., 2000; Le Feuvre & Aldington, 2014; Lundeberg et al., 1985; Sherman, Sherman, & Bruno, 1987). PLP is characterized by intense episodes of pain, described by patients as throbbing, "electric shock", cramped, and stabbing sensations, and can be a debilitating condition that can significantly reduce mobility, quality of life, and psychological wellbeing (Rothgangel, Braun, Smeets, & Beurskens, 2019). Epidemiological studies indicate that up to 95% of patients report post-amputation pain (Hanyu-Deutmeyer, Cascella, & Varacallo, 2020) and 85% reported significant pain even decades after amputation (Sherman, 1996).

Although PLP and RLP are most commonly reported in the literature, with noted incidence rates of 50%-80% (Caddick et al., 2019; Ebrahimzadeh & Hariri, 2009; Robbins, Vreeman, Sothmann, Wilson, & Oldridge, 2009), there is significant supporting research

suggesting that pain in other bodily sites is a prominent problem for amputees. Mazzone et al. (2020) recently found that 49% of amputees experience recurrent back pain, while Esfandiari et al. (2011) reported a staggering 69% of patients reported chronic back pain. Back pain is most commonly reported (Caddick et al., 2019; Ebrahimzadeh & Hariri, 2009; Ebrahimzadeh et al., 2013; Hoaglund, Jergesen, Wilson, Lamoreux, & Roberts, 1983; Taghipour et al., 2009), as is neck and shoulder pain (Davidson, 2004; Durance & O'Shea, 1988; D. M. Ehde et al., 2000; Jones & Davidson, 1995; Morgan, Friedly, Amtmann, Salem, & Hafner, 2017), contra-lateral and ipsilateral knee pain, and ipsilateral hip pain (Caddick et al., 2019; Ebrahimzadeh & Hariri, 2009).

Complicating this profile further, there is a high prevalence of comorbidities and pain identified across studies with amputees (Caddick et al., 2019). In a systematic review, Caddick (2019) identified three studies that reported a high incidence of ‘cumulative trauma disorder’ (CTD; injuries related to overuse of the intact limb), as well as studies highlighting comorbid arthritis (Dougherty et al., 2010; McFarland, Hubbard Winkler, Heinemann, Jones, & Esquenazi, 2010), knee and hip osteoarthritis (Jai Kulkarni, Adams, Thomas, & Silman, 1998; Norvell et al., 2005), aging related difficulties (Foote, Mac Kinnon, Robbins, Pessagno, & Portner, 2015), mental health problems (Caddick et al., 2019; Ebrahimzadeh & Hariri, 2009; Foote et al., 2015; Taghipour et al., 2009), and poorer quality of life (Dougherty, 2003; Ebrahimzadeh et al., 2013; Epstein, Heinemann, & McFarland, 2010; Gailey et al., 2010), further underscoring the importance of identifying pain difficulties within this population.

Similar to many other clinical conditions, the presence of PLP, RLP and general pain among amputees can be exacerbated by the presence of additional disease morbidity, and

subsequently increase the demand for medications and treatments, and contribute to poorer prognoses (Sherman et al., 1987; Weeks, Anderson-Barnes, & Tsao, 2010). The complex chronic disease (CCD) population may be especially vulnerable (Lee, Wong, & Sabanayagam, 2015). A CCD is a condition involving multiple morbidities (MM) and a combination of functional (Bayliss et al., 2004; Rijiken et al., 2005), social (Noël et al., 2005), vocational (Kuluski et al., 2014) and/or mental health challenges (Fortin et al., 2006). Although the disease combinations that comprise multimorbidity are diverse, the five most common diagnoses are: cancer, neurological, heart/circulation, musculoskeletal, and endocrine/metabolic/nutritional (Ferguson, Svendrovski, et al., 2020; Kuluski et al., 2013; Pefoyo et al., 2015). Complicating this complex health profile further, many individuals experience chronic pain in association with multiple other medical and health problems (Scherer et al., 2016; Wolff et al., 2002).

Despite the complexities associated with pain among amputees, as well as the challenges of MM among a CCD population, very little is known about the comorbidity and interaction of these clinical presentations, particularly as they relate to pain. In light of this lack of understanding of amputee-related pain and disease complexity within an elderly, health complicated population, the current study seeks to investigate pain variables among a CCD population with limb amputations.

Methodology

Data source.

This study used data from the Canadian Institute for Health Information (CIHI) Facility-Based Continuing Care Reporting System (CCRS), which captures information on individuals admitted to publicly-funded hospital facilities for complex chronic care in Canada (Continuing

Care Reporting System, 2013-2014) between the years 2006-2016. Upon entry to a complex chronic care (CCC) facility, residents are administered a standardized assessment protocol, the Resident Assessment Instrument - Minimum Data Set/Full Assessment (RAI-MDS/FA 2.0 Canadian Version), within 14 days of admission. If the resident remains in the facility for longer than 92 days, quarterly assessments are conducted. These assessments are typically completed by the treating nurse or physician and include resident self-reports and information from medical files.

The RAI-MDS/FA 2.0 is an internationally validated clinical assessment instrument (Fries et al., 2001; Hartmaier et al., 1995; Hawes et al., 1995; Lawton et al., 1998; Mor, 1995; Snowden et al., 1999). This standard tool collects a wide array of information, including basic demographic characteristics, diagnostic profiles, medication usage and treatment participation, and outcomes, as well as categorizes diseases.

Missing limb diagnosis and Propensity Score Matching (PSM)

The original full CCRS dataset consisted of 139,920 residents, of whom 2,961 reportedly have a missing limb. The diagnosis of missing limb was taken directly from the CCRS RAI-MDS/FA 2.0. Propensity score matching was used to create two groups of residents: cases (with missing limb) and controls (no missing limb), using a 1:1 ratio ensuring the case and control residents had the exact same value for age, sex, marital status, assessment year and total disease count.

Pain measures

The CCRS RAI-MDS/FA 2.0 measures pain using two descriptive scales:

5) Frequency: no pain (0), pain less than daily (1), pain daily (2); and,

6) Intensity: mild pain (1), moderate pain (2), times when pain is horrible or excruciating (3).

For the present study, we created three measures of pain by combining various items from the above two existing CCRS RAI/MDS/FA 2.0 scales:

1) Pain-Yes/No (P-Y/N): Pain prevalence dichotomous measure: no pain (0); pain (1) (mild, moderate, severe);
2) 4-point pain intensity scale (PI-4): no pain (0), mild pain (1), moderate pain (2), severe pain (3);
3) 7-point combined pain intensity and pain frequency scale (PIPF-7): no pain (0); mild pain less than daily (1); mild pain daily (2); moderate pain less than daily (3); moderate pain daily (4); severe pain less than daily (5); severe pain daily (6).

Research Objective and Data Analysis

The primary research objective was to examine the difference in pain between residents with and without missing limbs. All data used in this study is derived from the initial assessment of all residents, aged 18–101 years, from Ontario's CCC facilities between the years 2006 – 2016, reported in the CIHI CCRS dataset. For non-parametric data, we used Mann-Whitney test, McNemar test for dichotomous pain and Wilcoxon Signed Ranks test for ordinal pain (PI-4; PIPF-7).

Multinomial binary logistic regression analysis was conducted to evaluate the secondary research objective of exploring the relationship between missing limb, sex and the missing limb by sex interaction and pain (Pain-Y/N, PI-4 and PI-7). All regression models were conducted controlling for the following potential confounders: Activities of Daily Living (ADL) scores,

Depression Rating Scale (DRS) scores, Index of Social Engagement (ISE) Scores, number of medications taken, and days taking analgesics. All descriptive and inferential statistical analyses were performed using SPSS (version 25), $p < 0.05$ was considered statistically significant.

Results

The original dataset contained 139,920 resident records of whom 2,961 were coded as missing limb. The propensity score matching algorithm found exact matches for 2,212 cases. Each of the 2,212 missing limb cases was matched with a similar resident in the control subgroup without a missing limb, this representing a final dataset of 2,212 paired samples for analysis.

Table 7.1. Descriptive characteristics of matched samples, n = 2,212, Ontario CCC residents, 2006-2016

Characteristics	Cases (n = 2212)	Controls (n = 2212)	Comparison between two groups
	N (%) or Mean ± SD Median (IQR)	N (%) or Mean ± SD Median (IQR)	
Sex			$\chi^2(1)=0.00$, $p = 1.00$
Females	826 (37%)	826 (37%)	
Males	1386 (63%)	1386 (63%)	
Age	73.58 ± 11.11	73.58 ± 11.11	t(4422) = 0.00, $p = 1.00$
Year of assessment			$\chi^2(10)=0.00$, $p = 1.00$
2006	202 (9%)	202 (9%)	
2007	194 (9%)	194 (9%)	
2008	186 (8%)	186 (8%)	
2009	221 (10%)	221 (10%)	
2010	211 (10%)	211 (10%)	
2011	226 (10%)	226 (10%)	
2012	228 (10%)	228 (10%)	
2013	242 (11%)	242 (11%)	
2014	232 (11%)	232 (11%)	
2015	227 (10%)	227 (10%)	
2016	43 (2%)	43 (2%)	

Number of comorbidities (excluding missing limb)	5.89 ± 2.52	5.89 ± 2.52	$\chi^2(9)=0.00$, $p = 1.00$
0-1	47 (2%)	47 (2%)	
2	119 (6%)	119 (6%)	
3	228 (10%)	228 (10%)	
4	304 (14%)	304 (14%)	
5	336 (15%)	336 (15%)	
6	347 (16%)	347 (16%)	
7	267 (12%)	267 (12%)	
8	215 (10%)	215 (10%)	
9	163 (7%)	163 (7%)	
10+	186 (8%)	186 (8%)	
Marital status			$\chi^2(5)=0.00$, $p = 1.00$
Never married	266 (12%)	266 (12%)	
Married	1135 (51%)	1135 (51%)	
Widowed	560 (25%)	560 (25%)	
Separated	26 (1%)	26 (1%)	
Divorced	123 (6%)	123 (6%)	
Unknown	102 (5%)	102 (5%)	
Activities of Daily Living (ADL) score [long form]	15.20 ± 7.75	16.46 ± 8.07	t(4422) = 5.30, $p < 0.001$
Depression Rating Scale (DRS) score	1.31 ± 2.02	1.57 ± 2.27	t(4407) = 3.94, $p < 0.001$
Index of Social Engagement (ISE)	3.40 ± 1.99	2.92 ± 2.03	t(4422) = 8.04, $p < 0.001$
Number of medications taken	14.20 ± 5.73 Median (IQR): 14 (6)	12.43 ± 5.16 Median (IQR): 12 (6)	t(4422) = 10.82, $p < 0.001$ M-W $p < 0.001$
Days taking analgesics	5.17 ± 2.81 Median (IQR): 7 (4)	4.42 ± 3.12 Median (IQR): 7 (7)	t(4422) = 8.44, $p < 0.001$ M-W $p < 0.001$

Number of emergency room visits	0.57 ± 1.22	0.57 ± 0.89	t(4422) = 0.11,
	Median	Median	p = 0.91
	(IQR):	(IQR):	M-W p = 0.001
0	0 (1)	0 (1)	
1	1353 (61%)	1218 (55%)	
2	660 (30%)	825 (37%)	
3	123 (5%)	111 (5%)	
4	32 (2%)	28 (1%)	
5 or more	17 (1%)	14 (1%)	
	22 (1%)	11 (1%)	
Number of physician visits	4.78 ± 3.13	4.98 ± 3.29	t(4422) = 2.11,
	Median	Median	p = 0.035
	(IQR):	(IQR):	M-W p = 0.13
	4 (4)	4 (5)	
Hospital stays	1.17 ± 1.04	1.08 ± 1.29	t(4412) = 2.44,
	Median	Median	p = 0.015
	(IQR):	(IQR):	M-W p < 0.001
0	1 (1)	1 (0)	
1	510 (23%)	543 (25%)	
2	1108 (50%)	1204 (55%)	
3	401 (18%)	336 (15%)	
4 or more	126 (6%)	86 (4%)	
	62 (3%)	38 (1%)	

Note: M-W is Mann-Whitney non-parametric test

The comparison of pain between patients with and without missing limb was conducted using McNemar test and Wilcoxon Signed Ranks tests (Table 7.2). We observed a significantly higher proportion of missing limb cases with pain (80%) compared to controls (70%), McNemar test $X^2 = 64.43$, $p < .001$. Wilcoxon Signed Ranks tests also showed significantly higher pain levels among cases compared to controls ($z = 8.47$, $p < .001$ for 4-level pain; $z = 8.57$, $p < .001$ for 7-level pain). We observed a higher proportion of cases reporting moderate pain (48%) and severe pain (11%) compared to controls (39% and 9%, respectively).

Table 7.2. Comparison of dichotomous pain (P-Y/N), 4-point pain scale (PI-4), and 7-point pain scale (PIPF-7) between cases (missing limb) and controls (no missing limb), n = 2212 in each group. Ontario CCC residents, 2006-2016

Pain variable	Cases (missing limb) N (%)	Controls (no missing limb) N (%)	Statistical comparison test
P-Y/N			McNemar test
No pain	441 (20%)	672 (30%)	$X^2 = 64.43$, $p < .001$
Pain (mild, moderate or severe)	1771 (80%)	1540 (70%)	
PI-4			
Mean ± SD*	1.50 ± 0.94	1.26 ± 0.99	
No pain (0)	441 (20%)	672 (30%)	Wilcoxon Signed Ranks test $z = 8.47$, $p < .001$
Mild pain (1)	463 (21%)	484 (22%)	
Moderate pain (2)	1059 (48%)	863 (39%)	
Severe pain (3)	249 (11%)	193 (9%)	
PIPF-7			Wilcoxon Signed Ranks test $z = 8.57$, $p < .001$
Mean ± SD*	2.71 ± 1.91	2.21 ± 1.96	
No pain (0)	441 (20%)	672 (30%)	
Mild pain < daily (1)	320 (15%)	358 (16%)	
Mild pain daily (2)	143 (7%)	126 (6%)	
Moderate pain < daily (3)	318 (14%)	315 (14%)	
Moderate pain daily (4)	741 (33%)	548 (25%)	
Severe pain < daily (5)	21 (1%)	10 (1%)	
Severe pain daily (6)	228 (10%)	183 (8%)	

* Mean and SD represent the mean and standard deviation of the rank ordered pain scores

Figure 7.1. Comparison of proportions of patients reporting 4-level pain between cases and controls, n = 2,212, Ontario CCC residents, 2006-2016

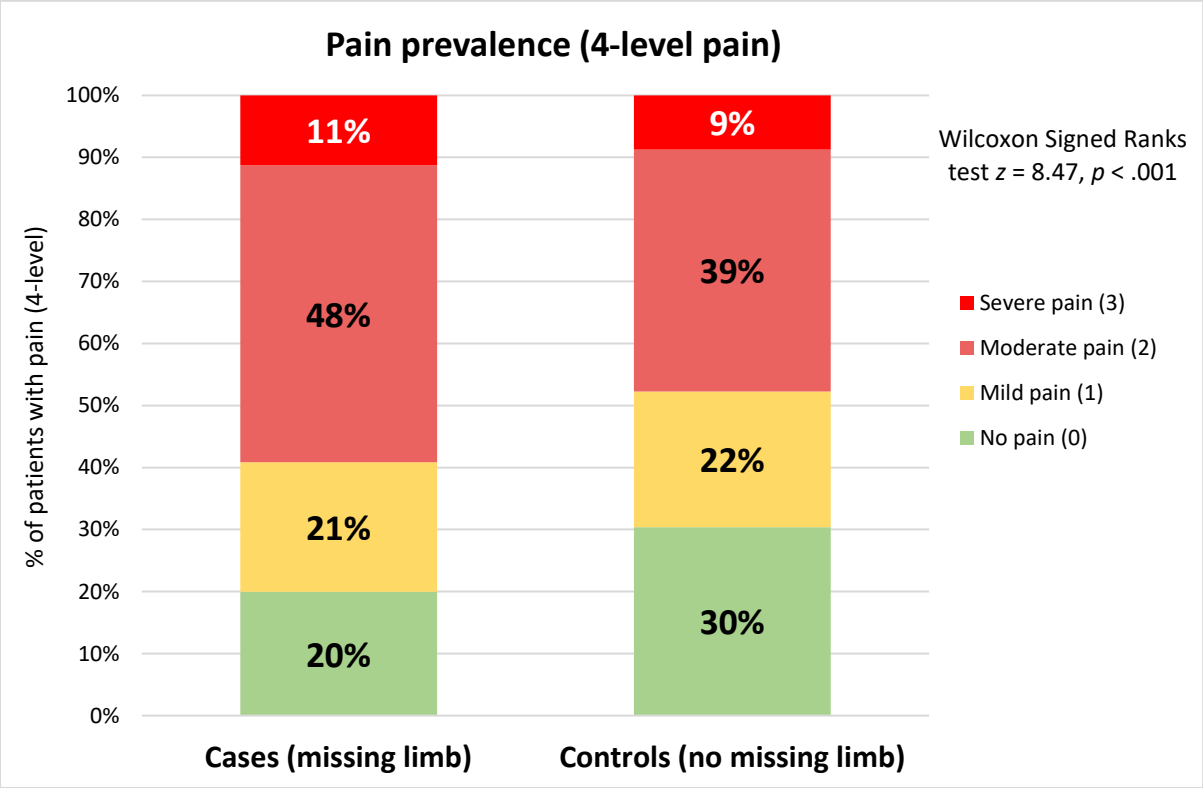


Figure 7.2. Comparison of proportions of patients reporting 7-level pain between cases and controls, n = 2,212, Ontario CCC residents, 2006-2016

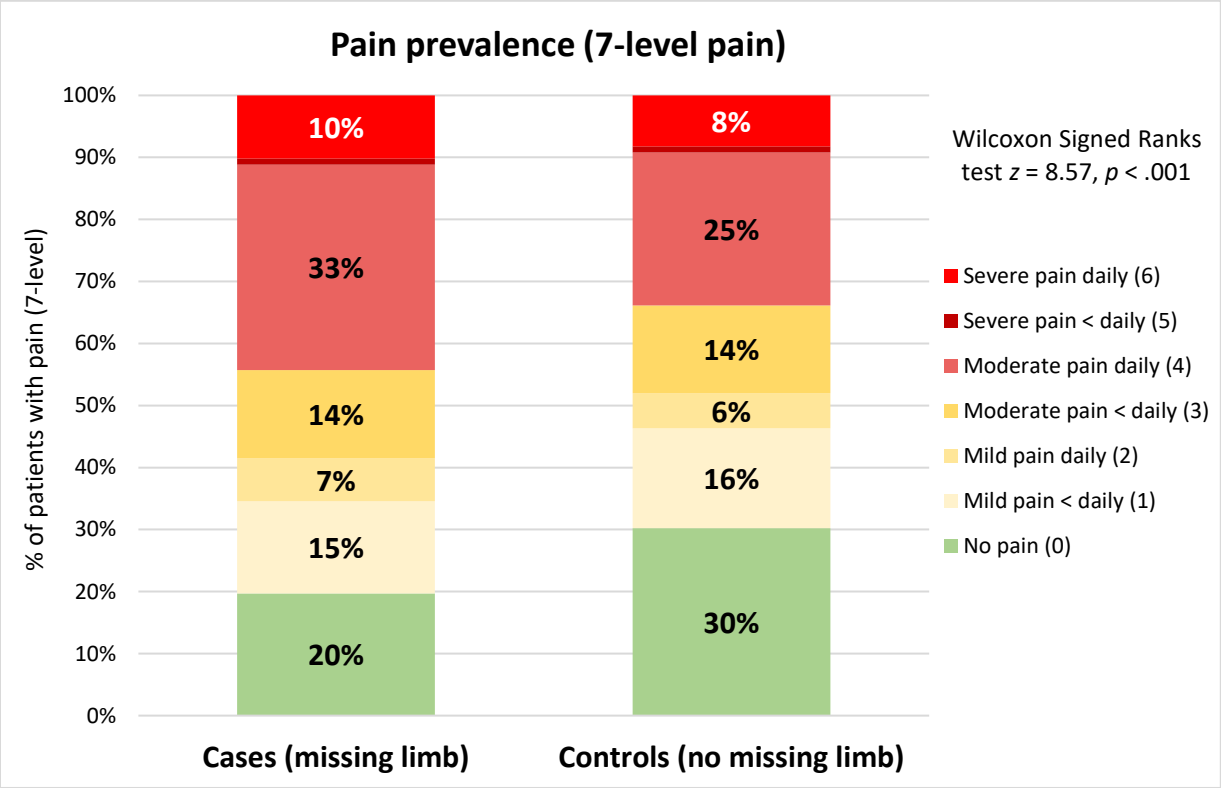


Table 7.3. Comparison of dichotomous pain (P-Y/N), 4-point pain scale (PI-4), and 7-point pain scale (PIPF-7) between males and females with missing limb (cases, n = 2,212). Ontario CCC residents, 2006-2016

Pain variable	Females n = 826 (37%)	Males n = 1386 (63%)	Statistical comparison test
P-Y/N			
No	142 (17%)	299 (22%)	Chi-square test
Yes	684 (83%)	1087 (78%)	$X^2 = 6.23$, $p = .013$
PI-4			
Mean ± SD*	1.58 ± 0.92	1.46 ± 0.94	Mann-Whitney U test
No pain (0)	142 (17%)	299 (22%)	$z = 2.90$, $p = .004$
Mild pain (1)	166 (20%)	297 (21%)	
Moderate pain (2)	415 (50%)	644 (47%)	
Severe pain (3)	103 (13%)	146 (10%)	
PIPF-7			
Mean ± SD*	2.87 ± 1.89	2.62 ± 1.92	Mann-Whitney U test
No pain (0)	142 (17%)	299 (22%)	$z = 2.90$, $p = .004$
Mild pain < daily (1)	112 (14%)	208 (15%)	
Mild pain daily (2)	54 (6%)	89 (6%)	
Moderate pain < daily (3)	123 (15%)	195 (14%)	
Moderate pain daily (4)	292 (35%)	449 (32%)	
Severe pain < daily (5)	7 (1%)	14 (1%)	
Severe pain daily (6)	96 (12%)	132 (10%)	

* Mean and SD represent the mean and standard deviation of the rank ordered pain scores

Among patients with missing limb, females reported significantly higher pain compared to males, $p = .013$ dichotomous pain, $p = .004$ 4-point pain scale, $p = .004$ 7-point pain scale. 83% of females and 78% of males reported pain (based on dichotomous measure).

Table 7.4. Comparison of dichotomous pain (P-Y/N), 4-point pain scale (PI-4), and 7-point pain scale (PIPF-7) between males and females without missing limb (controls, n = 2212), Ontario CCC residents, 2006-2016

Pain variable	Females n = 826 (37%)	Males n = 1386 (63%)	Statistical comparison test
P-Y/N			
No	197 (24%)	475 (34%)	Chi-square test
Yes	629 (76%)	911 (66%)	$X^2(1) = 26.58$, $p < .001$
PI-4			
Mean ± SD*	1.39 ± 0.95	1.18 ± 1.00	Mann-Whitney U test
No pain (0)	197 (24%)	475 (34%)	$z = 4.90$, $p < .001$
Mild pain (1)	186 (22%)	298 (22%)	
Moderate pain (2)	364 (44%)	499 (36%)	
Severe pain (3)	79 (10%)	114 (8%)	
PIPF-7			
Mean ± SD*	2.47 ± 1.93	2.06 ± 1.96	Mann-Whitney U test
No pain (0)	197 (24%)	475 (34%)	$z = 5.22$, $p < .001$
Mild pain < daily (1)	137 (16%)	221 (16%)	
Mild pain daily (2)	49 (6%)	77 (5%)	
Moderate pain < daily (3)	119 (14%)	196 (14%)	
Moderate pain daily (4)	245 (30%)	303 (22%)	
Severe pain < daily (5)	3 (1%)	7 (1%)	
Severe pain daily (6)	76 (9%)	107 (8%)	

* Mean and SD represent the mean and standard deviation of the rank ordered pain scores

Among control residents (without missing limb), females reported significantly higher pain compared to males, $p < .001$ dichotomous pain, $p < .001$ 4-point pain scale, $p < .001$ 7-point pain scale.

Binary logistic regression was used to further quantify the relationship between missing limb and pain reports. The dependent variable for this model was dichotomous pain. The independent variable was missing limb (with no missing limb as the reference category). Results are presented in Table 7.5. We observed that residents with missing limb were 1.86 (95% CI 1.64 – 2.12) times more likely to report pain compared to controls, $p < .001$. When controlling for ADL, number of medications taken, DRS, days taking analgesics, the effect of missing limb remained statistically significant ($p < .001$) and cases are 1.46 (95% CI 1.26 – 1.70) times more likely to report pain compared to the control group.

Table 7.5. Binary logistic regression models dichotomous pain (P-Y/N), n = 2,212, Ontario CCC residents, 2006-2016

Independent variable	Dependent variable	*p*-value	*OR* (95% CI)
Missing limb	P-Y/N		
	Yes	< .001	1.86 (1.64 – 2.12)
		< .001	1.37 (1.16 – 1.61)[1]

Note: OR = odds ratio

[1]effect of missing limb controlling for ADL, number of medications taken, DRS, ISE, days taking analgesics, number of emergency room visits and days of physician visits

Multinomial logistic regression model was used to further quantify the relationship between missing limb status and ordinal level of pain (PI-4). The dependent variable for this model was 4-level pain. The independent variable was missing limb (no missing limb was the reference category). Results are presented in Table 6. We observed that residents with missing limb were 1.45 (95% CI 1.23 – 1.71) times more likely to report mild pain compared to controls, $p < .001$. They were also 1.99 (95% CI 1.73 – 2.29) times more likely to report moderate pain ($p < .001$) and 2.32 (1.88 – 2.85) times more likely to report severe pain ($p < .001$). All findings are

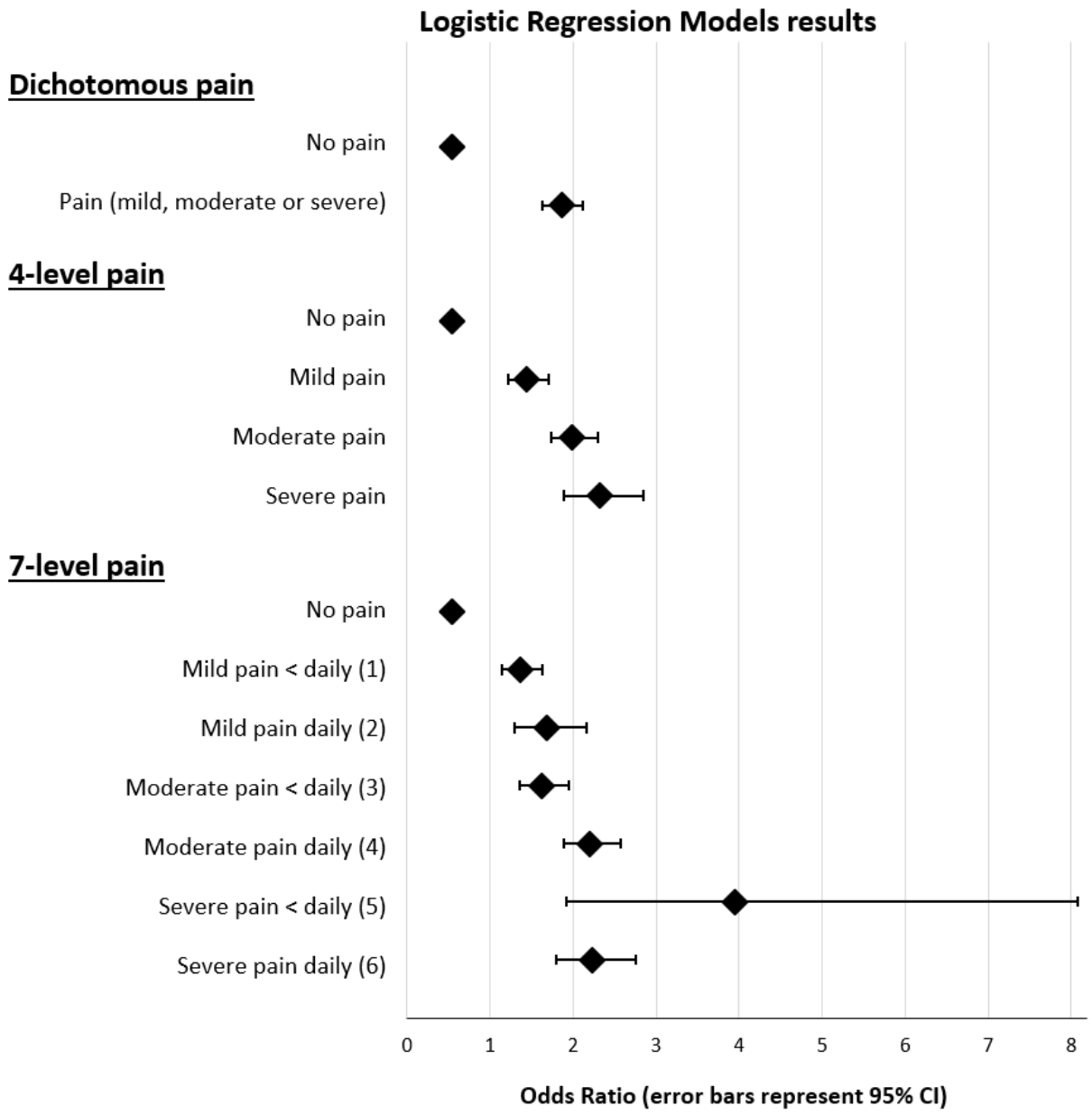
statistically significant and remain significant when controlling for the effects of ADL, number of medications taken, DRS, days taking analgesics (as shown in Table 7.6).

Table 7.6. Multinomial logistic regression models for 4-point pain scale (PI-4), and 7-point pain scale (PIPF-7). Reference category 'no missing limb', n = 2,212, Ontario CCC residents, 2006-2016

Independent variable	Dependent variable	*p*-value	*OR* (95% CI)
Missing limb	PI-4		
	No pain	< .001	0.54 (0.47 – 0.61)
		< .001	0.73 (0.62 – 0.86)[1]
	Mild pain	< .001	1.45 (1.23 – 1.71)
		.043	1.22 (1.01 – 1.47)[1]
	Moderate pain	< .001	1.99 (1.73 – 2.29)
		< .001	1.47 (1.23 – 1.75)[1]
	Severe pain	< .001	2.32 (1.88 – 2.85)
		< .001	1.57 (1.22 – 2.03)[1]
Missing limb	PIPF-7		
	No pain	< .001	0.54 (0.47 – 0.61)
		< .001	0.73 (0.62 – 0.86)[1]
	Mild pain < daily (1)	.001	1.37 (1.14 – 1.64)
		.111	1.18 (0.96 – 1.45)[1]
	Mild pain daily (2)	< .001	1.68 (1.30 – 2.17)
		.023	1.40 (1.05 – 1.88)[1]
	Moderate pain < daily	< .001	1.63 (1.35 – 1.95)
	(3)	.022	1.28 (1.04 – 1.58)[1]
	Moderate pain daily (4)	< .001	2.21 (1.89 – 2.57)
		< .001	1.63 (1.34 – 1.98)[1]
	Severe pain < daily (5)	< .001	3.95 (1.93 – 8.08)
		.015	2.65 (1.21 – 5.82)[1]
	Severe pain daily (6)	< .001	2.23 (1.80 – 2.75)
		.001	1.57 (1.21 – 2.04)[1]

Note: OR = odds ratio, no missing limb (control) is the reference category
[1]effect of missing limb controlling for ADL, number of medications taken, DRS, ISE, days taking analgesics, number of emergency room visits and days of physician visits

Figure 7.4. Results of logistic regression models. n = 2,212, Ontario CCC residents, 2006-2016



Multinomial logistic regression models were used to test the relationship between pain (dichotomous, 4-level, 7-level) and missing limb, sex and their interaction term. The dependent variable for this model was pain. Independent variables were missing limb, sex, and the missing limb by sex interaction. Models also include the following covariates: ADL, number of medications taken, DRS, ISE, days taking analgesics, number of emergency room visits and days of physician visits. Results are presented in Table 7.7.

Table 7.7. Binary and multinomial logistic regression models for dichotomous pain (P-Y/N), 4-point pain scale (PI-4) and 7-point pain scale (PIPF-7). Reference category 'no missing limb' and 'males'. N = 2,212, Ontario CCC residents, 2006-2016

Independent variable	Dependent variable	*p*-value	*Odds Ratio* (95% CI)
Model 1: P-Y/N			
Missing limb	No pain	< .001	0.67 (0.55 – 0.82)
	Pain	< .001	1.50 (1.23 – 1.83)
Female	No pain	.001	0.69 (0.55 – 0.87)
	Pain	.001	1.45 (1.15 – 1.82)
Missing limb ×	No pain	.137	1.29 (0.92 – 1.82)
Female	Pain	.137	0.77 (0.55 – 1.09)
Model 2: PI-4			
Missing limb	No pain	< .001	0.67 (0.55 – 0.82)
	Mild pain (1)	.017	1.33 (1.05 – 1.68)
	Moderate pain (2)	< .001	1.62 (1.30 – 2.01)
	Severe pain (3)	.003	1.63 (1.18 – 2.25)
Female	No pain	.001	0.69 (0.55 – 0.87)
	Mild pain (1)	.020	1.37 (1.05 – 1.78)
	Moderate pain (2)	.001	1.52 (1.18 – 1.95)
	Severe pain (3)	.072	1.40 (0.97 – 2.04)
Missing limb ×	No pain	.137	1.29 (0.92 – 1.82)
Female	Mild pain (1)	.194	0.77 (0.52 – 1.14)
	Moderate pain (2)	.138	0.76 (0.52 – 1.09)
	Severe pain (3)	.620	0.88 (0.52 – 1.47)
Model 3: PIPF-7			
Missing limb	No pain	< .001	0.67 (0.55 – 0.82)
	Mild pain < daily (1)	.036	1.31 (1.02 – 1.68)
	Mild pain daily (2)	.032	1.49 (1.04 – 2.15)
	Moderate pain < daily (3)	.029	1.34 (1.03 – 1.74)
	Moderate pain daily (4)	< .001	1.87 (1.46 – 2.39)

	Severe pain < daily (5)	.033	2.78 (1.09 – 7.13)
	Severe pain daily (6)	.004	1.63 (1.17 – 2.27)
Female	No pain	.001	0.69 (0.55 – 0.87)
	Mild pain < daily (1)	.019	1.40 (1.06 – 1.86)
	Mild pain daily (2)	.147	1.37 (0.90 – 2.08)
	Moderate pain < daily (3)	.063	1.33 (0.98 – 1.79)
	Moderate pain daily (4)	< .001	1.70 (1.28 – 2.25)
	Severe pain < daily (5)	.944	0.95 (0.24 – 3.74)
	Severe pain daily (6)	.045	1.47 (1.01 – 2.16)
Missing limb × Female	No pain	.137	1.29 (0.92 – 1.82)
	Mild pain < daily (1)	.161	0.74 (0.48 – 1.13)
	Mild pain daily (2)	.522	0.82 (0.45 – 1.49)
	Moderate pain < daily (3)	.508	0.86 (0.56 – 1.34)
	Moderate pain daily (4)	.075	0.69 (0.46 – 1.04)
	Severe pain < daily (5)	.853	0.85 (0.16 – 4.62)
	Severe pain daily (6)	.635	0.88 (0.52 – 1.50)

Note: all analyses (reported odds ratios) are controlled for ADL, number of medications taken, DRS, ISE, days taking analgesics, number of emergency room visits and days of physician visits

Missing limb was statistically significantly related to all levels of pain in all models. With the exception of severe pain, mild pain daily, moderate pain < daily, and severe pain < daily, females had statistically significantly higher odds of reporting pain than males. The sex by missing limb interaction term was not significant for any of the three pain variables.

Discussion

The results of the present large-scale study indicate that the presence and severity of pain was significantly higher in CCC residents with a missing limb, compared to a propensity matched cohort not missing a limb, even after adjusting for potential confounding variables including psychological factors such as depression, activities of daily living and social engagement, and medical factors, including physician visits, emergency room visits and medication and analgesic usage, which all may influence pain risks. In fact, residents with missing limbs were 1.45 (95% CI 1.23 – 1.71) times more likely to report mild, moderate and

severe pain compared to controls, $p < .001$ (Table 7.6). Additional analysis showed that residents with a missing limb were more likely to report moderate pain (48%) and severe pain (11%), compared to controls (39% and 9%, respectively) (Table 7.2 and Figure 7.2).

Despite the significant health care concerns and pain problems among this population, the CCD population with missing limbs has remained unexplored in relation to pain. Among a population of CCD residents, the current study utilized a case-control design using propensity matching, which allowed for the comparison of two demographically similar groups of residents with and without missing limbs. Groups were matched with a 1:1 ratio on important demographic variables, including sex, age, marital status, assessment date and comorbid disease count. The present results provide evidence of a relationship between pain and CCD residents with missing limbs. However, it is important to note that the CCRS coding system used to denote whether or not a resident received a code of "missing limb" is crude and the database did not contain important information typically provided in studies of people who have undergone amputation (e.g., time since amputation; reason for amputation; limb, level, and side of amputation; number of limbs amputated; whether the pain recorded was residual limb pain, phantom limb pain or pain unrelated to amputation). Nevertheless, the results clearly show that CCC residents who received a code of 'missing limb' reported greater pain severity and were significantly more likely to report moderate and severe pain than the matched sample not coded as 'missing limb' even after controlling for important confounders including psychosocial factors and medication use.

Although PLP and RLP are the most commonly reported types of pain among amputees, there is evidence to suggest that pain not directly related to the surgical amputation, but possibly

associated with the limb loss due to biomechanical sequelae, is also problematic among amputee patients. Musculoskeletal pain (Østlie et al., 2012; Postema et al., 2016), particularly upper and lower back pain (Caddick et al., 2019; Ebrahimzadeh et al., 2013; D. M. Ehde et al., 2000; Ephraim, Wegener, MacKenzie, Dillingham, & Pezzin, 2005; Esfandiari, Sanjari, Jamshidi, Kamyab, & Yazdi, 2018; Hammarlund, Carlström, Melchior, & Persson, 2011; J. Kulkarni, Gaine, Buckley, Rankine, & Adams, 2005; Mazzone et al., 2020; Morgenroth et al., 2010; Robbins et al., 2009), neck and shoulder pain (Davidson, 2004; Durance & O'Shea, 1988; D. M. Ehde et al., 2000; Jones & Davidson, 1995; Morgan et al., 2017), contra-lateral knee pain (Ebrahimzadeh & Hariri, 2009; Morgan et al., 2017), ipsilateral hip pain (Ebrahimzadeh & Hariri, 2009; D. M. Ehde et al., 2000), as well as other regional sites including knees (Morgan et al., 2017), leg and foot, buttocks and hips, arms and hands, abdomen, and head (D. M. Ehde et al., 2000), are also commonly reported, even on non-amputated sides (Morgan et al., 2017).

Consistent with the general pain literature (Fillingim, 2017a, 2017b; Kleiman et al., 2011; Rogers et al., 2020; Sorge & Totsch, 2017), we found that female residents had statistically significantly higher odds of reporting pain than males. However, within the phantom limb pain research, there is no clear difference in the incidence of pain between sexes (Neil, 2016). In line with these previous findings, the sex by missing limb interaction term was not significant for any of the three pain variables (Table 7.7), indicating pain that females and males with missing limbs experience? did not differ from their counterparts without a missing limb. Overall, the results from this study point to the need to better manage pain in CCC residents with missing limbs.

Strengths and Limitations

The results of the present study show that among a complex chronic disease population, residents with missing limbs have more pain than those not missing limbs. Although many factors contribute to pain intensity and frequency, the use of propensity matching to create demographically similar groups while also controlling for important psychological and medical variables allowed for a conservative comparison of pain among residents with and without missing limbs. Propensity matching statistics allow for a stringent comparison between groups, similar to a randomized controlled design (Hill, 2008).

Further, the benefits of examining secondary, standardized, electronic sources of longitudinal data arguably outweigh the limitations, particularly in epidemiological research. For instance, many of the challenges associated with primary data collection are avoided, including time and resources that are required to hire research personnel and recruit participants (Belletti et al., 2010). A further strength of our study is the large, province-wide sample of CCD residents with and without missing limbs in Ontario, between the ages of 18 and 101 years, further contributing to the generalizability of the study. The large sample size of more than 2,000 residents per group, also allows for greater power in the analysis. The data utilized is of high quality, given the use of standardized electronic records through the CIHI Facility-Based Continuing Care Reporting System, which captures information on residents admitted to publicly funded hospital facilities for complex chronic care in Canada. The RAI/MDS/FA 2.0 utilized in this validated tool, further contributing to the quality of the data (Fries et al., 2001).

Nonetheless, there are limitations to the present study that should be addressed. Notably, the dataset used in this study did not include accessibility to more detailed resident histories, including the reason for amputation, the year of injury or surgery, the level, extremity, or site of the missing limb, number of missing limbs, and whether the pain recorded was residual limb pain, phantom limb pain, and/or some other source of pain. Consideration of these health and demographic factors may provide additional information about the missing limb and pain relationship. Finally, the information on pain status is based on self-report; however, this is a common limitation among pain research and relevant studies suggest that there is a moderate to strong agreement between self-reported disease status and medical records (National Center for Health, 1994).

Implications

This is the first study, to our knowledge, to explore the relationship of having a missing limb and experiencing pain among a large population of CCD residents. The results are consistent with previous research that supports the phenomenon associated with amputations/missing limbs and pain. Given the complexity of the CCD population, information that may better inform the understanding of pain and multimorbid diseases, and the subsequent treatment care of this specific population is invaluable in an aging society.

Chapter 8: General Discussion

CCD and Pain Review

As life expectancy increases with every passing decade, more and more individuals are developing multiple chronic health problems (Oeppen & Vaupel, 2002). A growing number of Canadians live with chronic health conditions that can be classified as complex chronic disease

(CCD). Although the disease combinations that comprise multimorbidity are diverse, the results of Study 1 show that among the institutionalized population of Ontario residents with CCD, the top five most prevalent combinations of MM disease patterns are endocrine/metabolic/nutrition, heart/circulation, musculoskeletal, neurological and psychiatric/mood (Ferguson, Svendrovski, et al., 2020).

Managing the demands of the CCD population and their multiple health needs can be difficult and problematic for primary health care providers and the patients themselves (Piette & Kerr, 2006). People with CCD represent one of the heaviest users of the Canadian health care system as a whole (Hartmann et al., 2011; Maaten et al., 2008; C. Salisbury et al., 2011; Vogeli et al., 2007). Complicating the CCD health profile further, many individuals experience chronic pain in association with multiple other medical and health problems (Scherer et al., 2016; Wolff et al., 2002). Unfortunately, there are very few studies that closely examine the experience of patients with complex chronic diseases and their relationship to pain. Moreover, this specific population tends to be excluded from research, including clinical trials, due to the presence of multimorbidity (Kuluski et al., 2013). In light of this information and the lack of understanding of pain and disease complexity within an elderly, health complicated population, the current dissertation sought to examine pain among specific populations of CCD residents in CCC facilities in Ontario.

Summary of Findings

The aim of the present dissertation was to examine the relationship between pain and several other variables among a CCD population from Ontario CCC facilities between the years of 2006-2016. Chapters 1 and 2 provided an introduction and literature review including an

overview of complex chronic disease, multimorbidity and pain. A CCD was defined as a condition involving multiple morbidities (MM) and a combination of functional (Bayliss et al., 2004; Rijken et al., 2005), social (Noël et al., 2005), vocational (Kuluski et al., 2014) and/or mental health challenges (Fortin et al., 2006). A description of pain measures was also provided. Pain was assessed using 3 pain variables: dichotomous pain (P-Y/N); pain intensity (PI-4); and, pain intensity and frequency (PIPF-7). A description of the sample was provided, including information on demographics, disease profiles, and reported pain.

Chapters 3 and 4 outlined the research objectives of the dissertation and the overall methodology, including a description of the CCRS dataset, Resident Assessment Instrument – Minimum Data Set/Full Assessment (RAI-MDS/FA 2.0 Canadian Version), and statistical analysis plans. As described in these sections, each individual study included in this dissertation used data from this dataset. The strengths and limitations of this dataset and assessment tool, as well as future recommendations, will be addressed in subsequent sections.

Chapter 5 (Study 1) explored the complex problem of disease multimorbidity and pain among the CCD population in Ontario. Disease multimorbidity and pain is a challenging, yet common, problem for the aging population, and a significant burden on health care systems around the world. Despite this, disease comorbidity and the association with pain in a complex chronic care population is not well understood. In light of this, Study 1 examined and compared demographic, medication usage and their relationships to pain variables among the CCD population (n = 139,573; 57% female; mean age = 77.3 years; 40% married; 36% widowed) and identified the top five most frequent single disease category and most frequent multimorbid two, three, four and five disease categories. The association of pain with specific disease categories,

as well as number of disease categories was also explored. And finally, the study identified and compared the prevalent disease categories and the most prevalent multimorbid combinations of two, three, four and five disease categories.

Descriptive and chi square statistics were used to summarize and compare the sample characteristics. Binary logistic regression analyses were used to examine the association between multimorbid disease categories and pain. Residents took an average of 11.9 medications, with 77% using analgesic medications. On average, residents had diagnoses from 3.06 disease categories (*SD* = 1.43). Heart/circulation diseases were the most prevalent among the sample (73%), with neurological second (46%) and musculoskeletal third (44%). Overall, 73% of residents reported pain, with 43% reporting moderate pain severity. Residents with multiple disease categories were more likely to report the presence of pain (OR = 1.08, 95% CI: 1.07 – 1.08, $p < .001$), with each additional disease category associated with an 8% increase in the odds of reporting pain.

Multimorbidity patterns have been examined by other researchers. Similar to Study 1 in the present dissertation, a retrospective study using exploratory factor analysis and electronic medical record data from 275,682 adult patients in Spain, reported five commonly detected patterns of multimorbidity: cardio-metabolic (e.g., diabetes), psychiatric (e.g., psychosis), mechanical-obesity-thyroidal (e.g., musculoskeletal pain), psychogeriatric (e.g., dementia), and depressive (e.g. depression, insomnia) (Alexandra Prados-Torres et al., 2012). In a later systematic review, Prados-Torres et al (2014) concluded the three most prevalent combinations of chronic diseases were classified as: cardiovascular and metabolic diseases; musculoskeletal

disorders, and mental health (A. Prados-Torres, Calderon-Larranaga, Hancco-Saavedra, Poblador-Plou, & van den Akker, 2014).

Similar results were found by Willadsen et al. (2018), who reported that the most prevalent combination of comorbidities included musculoskeletal-cardiovascular diseases. This group was also shown to have double the mortality rate (OR, 2.03; 95% Confidence Intervals were not reported) compared to patients not belonging to any of the diagnosis groups (Willadsen et al., 2018). Furthermore, diagnostic groupings including diagnoses from neurological, cancer, lung, cardiovascular, and mental diagnosis, had the highest mortality, with the neurological-cancer combination having the highest OR (6.35; 95% confidence interval (CI): 5.71-7.06), followed by neurological-endocrine (5.94; 95% CI: 5.42-6.50) and cardiovascular-lung (5.75; 95% CI: 5.42-6.10). The combination of five groups including musculoskeletal, endocrine, mental, neurological and cardiovascular had by far the highest mortality (Willadsen et al., 2018).

The findings from Study 1 the present dissertation further support previous findings about multimorbidity among a CCD population; however, Study 1 is the first to examine pain in relation to the pattern of multimorbidity in a CCD population and sheds light on the prevalence of pain among this population and the potential influence of various disease combinations. The findings from this study help identify common comorbid disease patterns related to pain in an institutionalized, complex chronic care population. This information contributes to both the pain and multimorbidity literature, and is invaluable for creating care plans to meet the demands of a challenging population.

Chapter 6 (Study 2) investigated the phenomenon of hypertension-related hypoalgesia among a CCD population. Hypertension is a highly prevalent chronic condition among adults in

Canada, affecting 40% of the global adult population aged ≥25 years, and is associated with a high rate of multimorbidity. In a population of individuals with complex chronic diseases (CDD), hypertension is often comorbid with a number of other conditions, including other cardiovascular diseases (e.g. coronary heart disease, stroke, congestive heart failure, peripheral vascular disease, and end-stage renal disease), diabetes, depression, anxiety, and acute and chronic pain. In conjunction with hypertension, acute and chronic pain are also highly prevalent conditions that affect wellbeing and quality of life. There is evolving research investigating the relationship between hypertension and pain, suggesting that hypertension may be associated with reduced pain sensitivity (hypoalgesia), referred to as hypertensive hypoalgesia. With a few exceptions, hypertension-related hypoalgesia has been studied in small samples, and to date no study has examined this relationship using a large Canadian database of complex care residents.

Again, the Continuing Care Reporting System database was used, and hypertension was reported among 77,323 (55.3%) of the total number of residents (n=139,573). Propensity score matching, with a 1:1 ratio, was used to identify a control case without hypertension for each case with hypertension (matched on age, sex, assessment date, number of medications and marital status). McNemar's test was used to evaluate the dichotomous pain variable and Wilcoxon Signed Ranks test for ordinal pain levels (PI-4; PIPF-7). Multinomial logistic regression was used to quantify the effect of hypertension on dichotomous and 4-level and 7-level pain intensity variables, controlling for potential confounders. Binary and multinomial logistic regression models were also used to test hypertension, sex and the interaction effect on pain (P-Y/N; PI-4; PIPF-7).

The matched dataset included n=40,799 cases with and n=40,799 without hypertension, with 57% female and 43% male. Results showed a significantly lower proportion of hypertension residents with pain (71.7%) compared to controls (72.6%), McNemar test $X^2 = 7.73$, $p = .005$. Wilcoxon Signed Ranks tests also showed significantly lower pain levels among cases compared to controls ($z = 3.46$, $p = .001$ for 4-level pain). On all measures of pain, significantly higher pain was reported among females compared to males for both hypertension and control samples, respectively. Dichotomous pain variables indicated that significantly fewer residents with hypertension had pain than residents without hypertension, $OR = 0.85$ (95% CI 0.81 – 0.90), $p < .001$. Females were 33% more likely than males to report pain, $OR = 1.33$ (95% CI 1.26 – 1.40), $p < .001$. The hypertension by sex interaction effect was not significant. Examining pain intensity, residents with hypertension were significantly less likely to report all levels of pain on the PI-4: mild ($OR = 0.88$; 95% CI 0.83 – 0.94), moderate ($OR = 0.86$; 95% CI 0.81 – 0.91), and severe *(*$OR = 0.69$; 95% CI 0.63 – 0.76), all $p < .001$. Again, females reported higher pain (mild, moderate and severe) than males, with ORs ranging between 1.22 and 1.36, all $p < .001$. Almost identical results were found for all analyses with PIPF-7 variable.

The results support the emerging evidence of a relationship between hypertension and reduced pain sensitivity (France & Katz, 1999; Ghione, 1996; Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Ghione et al., 1985; Luigina Guasti et al., 1996; L. Guasti et al., 1997; Luigina Guasti, Cattaneo, et al., 1995; Luigina Guasti, Merlo, et al., 1995; Olsen et al., 2013; Rosa & Ghione, 1990; Rosa, Ghione, Panattoni, Mezzasalma, & Giuliano, 1986; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994). Hypertension-associated hypoalgesia has been observed in rat (Ghione, 1996; Randich & Maixner, 1984) and human subjects (Ghione, 1996; Ghione et al.,

1988; Ghione et al., 1985; Rosa & Ghione, 1990; Rosa et al., 1986; Zamir & Shuber, 1980). Also, consistent with the existing pain literature (e.g. Fillingim, 2017; Kleiman, Clarke & Katz, 2011; Rogers, Gallaghan, Garey, Ditre, Williams & Zvolensky, 2020; Sorge & Totsch, 2017), we found that female residents were 33% more likely to report pain compared to males (*OR* = 1.33, 95% CI 1.26 – 1.40, $p < .001$). We also observed a significant interaction between hypertension and sex such that hypertensive females were between 16% and 17% more likely than hypertensive males to report severe pain.

The results are consistent with the hypothesis that individuals with a diagnosis of hypertension experience less pain than those without hypertension, even when controlling for possible cofounders. To our knowledge, this is the first study to demonstrate that hypertension is associated with hypoalgesia in a complex chronic disease population. More studies are needed to understand the nature of this relationship and potential consequences of hypertension-related hypoalgesia.

Chapter 7 (Study 3) compared the presence and intensity/frequency of pain between Ontario CCC residents with and without missing limbs. The term “missing limb” is the descriptive label used in the RAI-MDS/FA 2.0 Canadian Version assessment tool from the CCRS dataset to describe residents who have undergone limb amputation. Post-amputation pain is a commonly reported phenomenon, commonly described as phantom limb pain (PLP) or residual limb pain (RLP). Epidemiological studies indicate that up to 95% of patients report post-amputation pain (Hanyu-Deutmeyer et al., 2020) and 85% report significant pain even decades after amputation (Sherman, 1996). This pain is often characterized by intense episodes of pain and can be a debilitating condition that can significantly reduce mobility, quality of life and

psychological wellbeing (Rothgangel et al., 2019). Despite the complexities associated with post-amputation pain, as well as the challenges of multimorbidity among a CCD population, very little is known about the comorbidity and interaction of these clinical presentations, particularly as they relate to pain.

The Continuing Care Reporting System database was used, and a diagnosis of missing limb was reported among 2,961 residents of the total number of residents (n=139,573). Propensity score matching, with a 1:1 ratio, was used to identify a control case without missing limb for each case with missing limb (matched on age, sex, assessment date, number of medications and marital status), resulting in the final matched sample of 2,212 residents (37% female; 51% married; mean age = 73.5 years). McNemar's test was used to evaluate dichotomous pain and Wilcoxon Signed Ranks test for ordinal pain levels (PI-4; PIPF-7). Multinomial logistic regression was used to quantify the effect of missing limb on dichotomous and 4-level and 7-level pain intensity variables, controlling for potential confounders. Binary and multinomial logistic regression models were also used to test missing limb, sex and the interaction effect on pain (P-Y/N; PI-4; PIPF-7).

Specifically, residents with missing limbs were 1.86 (95% CI 1.64-2.12) times more likely to report pain compared to controls. More specifically, findings on the PI-4 and PIPF-7 also indicated that residents with missing limbs were more likely to report mild, moderate and severe pain, even after controlling for various other factors (activities of daily living, number of medications taken, depression rating scale scores, social engagement scores, number of emergency room visits, days of physician visits and days taking analgesics). These results are consistent with the existing literature studying patients with limb loss/amputation, which

indicates that pain, whether RLP, PLP, or pain due to biomedical sequelae, is highly problematic among this population (Caddick et al., 2019; Davidson, 2004; Ebrahimzadeh & Hariri, 2009; D. M. Ehde et al., 2000; Ephraim et al., 2005; Katz & Melzack, 1990; J. Kulkarni et al., 2005). Also consistent with the general pain literature (Fillingim, 2017a, 2017b; Kleiman et al., 2011; Rogers et al., 2020; Sorge & Totsch, 2017), the study findings indicated that among all residents (with missing limbs and without), females reported significantly higher pain compared to males. However, within the phantom limb pain research, there is no clear difference in the incidence of pain between sexes (Neil, 2016). In line with these previous findings, the sex by missing limb interaction term was not significant for any of the three pain variables, indicating pain that females and males with missing limbs did not differ from their counterparts without a missing limb.

The results of Study 3 presented in Chapter 7 support evidence for the concept of pain associated with missing limbs. This is the first study to examine the relationship of having a missing limb and experiencing pain among a large population of CCD residents. Given the complexity of these populations, the results lend to the understanding of pain and multimorbid disease.

Strengths and Limitations

All three studies included as part of this dissertation use data from CIHI Facility-Based Continuing Care Reporting System (CCRS), which captures information on individuals admitted to publicly-funded hospital facilities for complex chronic care in Canada (Continuing Care Reporting System, 2013-2014). Upon entry to a complex chronic care (CCC) facility, residents are administered a standardized assessment protocol, the Resident Assessment Instrument -

Minimum Data Set/Full Assessment (RAI-MDS/FA 2.0 Canadian Version), within 14 days of admission. The assessment tool utilized upon admission is the Minimum Data Set (MDS 2.0), an internationally validated clinical assessment instrument (Fries et al., 2001; Hartmaier et al., 1995; Hawes et al., 1995; Lawton et al., 1998; Mor, 1995; Snowden et al., 1999). This RAI-MDS/FA 2.0 collects a wide array of information, including basic demographic characteristics, diagnostic profiles, medication usage and treatment participation, and outcomes.

The assessment results become part of the Continuing Care Reporting System (CCRS), created to be a resource for standardized clinical and administrative information on continuing care in Canada. The dataset includes information on the clinical and functional status of continuing care residents. Given the richness of the information collected as part of these intake assessments, the Facility-Based Continuing Care Reporting System provides valuable demographic, clinical and resource utilization data which is critical to providing a framework for better understanding the clinical needs of this highly specific population of chronically ill Canadians (Canadian Institute for Health Information, 2006).

The use of the CCRS dataset also allows for large-scale research, including large sample sizes and numerous variables to incorporate and examine. The sample used throughout this dissertation comprised 139,920 CCC residents from Ontario, with information gathered between 1996-07-01 until 2016-04-30. This large, province-wide sample of CCC residents in Ontario between the ages of 18 and 101 years, further contributes to the generalizability within the studies.

The data used in each study is of high quality, given the use of standardized electronic records. The use of structured electronic records can provide valuable, point-of-care data to

inform academic research and clinical practice (Manca, 2015). Within epidemiological research, the use of standardized, longitudinal data can be particularly advantageous to capture important health information among a sample of the target population of interest. Additionally, information captured at multiple points in health care service, as well as across various settings throughout the province, provides the opportunity for population-level analysis in clinical settings. The benefits of utilizing secondary, standardized, electronic sources of longitudinal data can be particularly useful in epidemiological research. This is because many of the challenges associated with primary data collection are avoided, including time and resources that are required to hire research personnel and recruit sufficient number of participants (Belletti et al., 2010).

Despite these benefits, it is necessary to also address the inherent limitations. Specifically, although standardization is the ultimate goal, there remains room for subjectivity among patient responses or clinician interpretation when completing surveys, either at one-time or during cyclic administration (Barber et al., 2010); however, this is also a limitation of self-report measures in general. Similarly, surveys may not truly capture the level of morbidity in a population, as many symptoms, conditions, or diseases a patient may have are not brought to the attention of the care provider or clinician completing the survey. This may be particularly true for the data captured in the RAI-MDS/FA 2.0, as specific questions pertaining to disease level (e.g., cancer stage and type) were also not included in the assessment tool. The vast majority of this assessment tool is scaled dichotomously (yes/no); thus, information about disease severity, type, location, onset, specific treatment and resident history is unavailable. This was particularly problematic for several reasons. First, for the hypertensive hypoalgesia study, it was not possible

to obtain information about specific variables that would have been valuable to consider; specifically, body mass index (BMI), diastolic and systolic blood pressure and specific medications used. Similarly, the study examining pain among residents with and without missing limbs, was also limited in that the extremity and level of missing limb, the cause for amputation and medication and treatment history were unavailable, and arguably important variables to have considered. Secondly, the lack of additional disease details limits the methodology options for defining multimorbidity. With more information, specific indices of multimorbidity such as the Charlson Comorbidity Index (Charlson et al., 1987) and the Index of Co-Existent Diseases (ICED) (Greenfield et al., 1993), could have provided more weighted information by incorporating aspects of severity, disease type, mortality outcomes, and possible resource utilization. This limitation was accommodated for by using a straightforward disease count method, which is arguably the most common approach in epidemiological research (Huntley et al., 2012).

A further limitation was the RAI-MDS/FA 2.0 assessment description of "pain". The pain variables used to collect information from residents were based on a 4-point pain intensity scale (no pain, mild pain, moderate pain, times when pain is horrible or excruciating) and a 3-point pain frequency scale (no pain, pain less than daily, pain daily). The description of pain levels used in this tool are inconsistent with pain scales typically used in the pain literature. Most commonly, pain intensity is measured with a scale that has been proven valid, reliable, and appropriate for clinical use, such as the Visual Analogue Scale (VAS), the Verbal Descripoe Scale, (VDS), Verbal Rating Scale (VRS) or the Numerical Rating Scale (NRS) (Karcioglu, Topacoglu, Dikme & Dikme, 2018). Given that a validated pain scale was not available, pain

variables in each study of this dissertation were based on the pain scales provided in the RAI-MDS/FA 2.0. Compiling the information available, pain variables were divided into dichotomous pain (P-Y/N) and 4- and 7-level pain scales (PI-4; PIPF-7) created by combining pain intensity and pain frequency.

Future versions of the RAI-MDS/FA 2.0 should strongly consider using a standardized, validated pain measure, which would be more consistent and generalizable to the existing literature. For example, the well-validated 4-point verbal rating scale (no pain, mild pain, moderate pain, severe pain) could replace the non-validated 4-point scale currently used by the RAI-MDS/FA 2.0 assessment tool (i.e., no pain, mild pain, moderate pain, times when pain is horrible or excruciating).

The large sample size used throughout this dissertation made it possible to not only explore the impact of specific diseases, but also combinations of disease categories. Given the sample size and numerous relevant variables included in the dataset, it was possible to employ propensity matching statistics in both the hypertensive hypoalgesia study and the missing limb and pain study, in order to provide a more stringent assessment. Propensity matched groups allows for the design and analysis of an observational study to mimic some of the particular characteristics of a randomized trial. It also provides a method to summarize covariate information into scaler value and reducing selection bias. Many factors contribute to pain, thus the use of propensity matching to create demographically similar groups, while also controlling for important psychological and medical variables allowed for a conservative comparison of pain among residents in both the studies. There are however, some limitations to propensity matching, including disagreements pertaining to the proper analysis of the data following matching.

Specifically, it has been argued that further analysis should take the matching into account (Hill, 2008); while others suggest this is over-restrictive (Austin et al., 2005). There are also arguments within the statistical literature suggesting that propensity score matching is not an equally comparable alternative to RCT designs (Dahabreh et al., 2012; Forbes & Dahabreh, 2020).

Clinical and Research Implications and Future Directions

The complexity of CCD and pain can be difficult to assess, treat and manage, as well as expensive on healthcare systems and burdensome to clinicians and patients alike. As such, it is critical that research continue to inform clinical care within this population. The contributions of each of the three studies presented in this dissertation allows for more information about the demographic, medical and pain experiences of this unique population, which in turn can be used in a clinical context to inform training for current and future health care providers, as well as in the policy context to guide intervention efforts. The first study presented, highlighting frequently common multimorbid disease patterns and particularly painful disease groupings, can be used to understand complex patient profiles and incorporated into educational curriculums and CCD treatment facilities. Future research could continue to build upon this foundation and contribute increased awareness about the severity and frequency of specific disease combinations and how some disease and pain profiles transition from acute to chronic. Similarly, it would be beneficial to further explore how certain combinations of diseases and pain may increase (or decrease) susceptibility to additional diseases. Taking this further, the additional inclusion of treatment and medication usage among CCD patients may provide better insight into how pain levels are impacted when treating multiple diseases at once. The inclusion of additional variables in each of the studies would also provide an excellent teaching and research opportunity to more closely

examine how CCD and pain are related, potentially toward late-stage disease progressions. To this point, future versions of the RAI-MDS/FA 2.0 assessment tool may consider including additional disease-related information, which would provide a more comprehensive overview of the complexities of the disease profiles. As well, the inclusion of a validated 10-point pain scale for residents (or healthcare workers) to complete would provide a better understanding of the pain experiences of this population. Given how prominent pain is among this population, and the association it has with multimorbidity, it may be useful for clinicians to evaluate resident's pain levels early on in the assessment process. This may provide an opportunity to intervene with treatments prior to the pain and disease complexity worsening.

From a research perspective, the completion of this work indicates three main areas in which future multimorbidity research may be particularly beneficial. Firstly, as discussed in the earlier in this dissertation, there are inconsistencies in the definitions and measures of multimorbidity, which could be improved upon by additional information about disease combinations. Systematic comparison among studies exploring a CCD population may provide a more robust understanding of patterns and the true burden of multimorbidity among clinical populations. Secondly, the inclusion of disease specifics, personal and family medical and treatment histories, socioeconomic factors, social support and pain management may help predict what factors make a patient more susceptible to developing multiple illnesses and/or chronic pain. Finally, understanding and addressing the impact of CCD and pain on the healthcare system in Canada and elsewhere, could be important for building and sustaining an efficient and effective system among a population where additional resources and supports are needed for patients, healthcare and support providers. Research that identifies the successful approaches to

managing CCD and pain would be invaluable to delivering individualized, adaptive and patient-centered care for this growing population. This research is necessary for ensuring that this significant patient population is receiving the highest quality of care from multidisciplinary health care teams.

Conclusions

The review of the literature and the findings from all three studies highlight the importance of assessing pain within a CCD population. There are a number of specific disease combination possibilities that may impact pain and it would be well served if future research examined these patterns more closely. The aging population presents an even more pressing need for such research, as demands for healthcare inevitably rise. The multidimensional impact that multimorbidity and pain has on a patient's life should be considered a central concern among this population. As such, the continuation of large scale quantitative, as well as smaller scale qualitative research, should be encouraged as we work toward better serving the needs of this population.

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