9-15-2021 9:00 AM

Chronic Pain Following Musculoskeletal Injuries: Where Do Familial Factors, Depression, and Distress Fit in?

Shirin Modarresi, *The University of Western Ontario*

Supervisor: MacDermid, Joy C., *The University of Western Ontario*
Joint Supervisor: Walton, David M., *The University of Western Ontario*
A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Health and Rehabilitation Sciences

Abstract

Currently, there is a paucity of effective therapeutic options for chronic pain. A better understanding of the factors that can contribute to chronic pain development and maintenance can lead to more informed prevention and management strategies.

Purpose

The driving force for this thesis comes from the biopsychosocial model of pain. The main purpose was to investigate the contribution of various psychosocial factors to chronic pain with the following objectives: 1) to systematically review the literature on the existence of a familial sub-type of complex regional pain syndrome (fCRPS); 2) CRPS can follow injuries such as distal radius fractures (DRFs), therefore the second objective was to assess recovery trajectories of patients following DRFs and assess the contribution of various characteristics; 3) to examine the effect of post-trauma distress on pain one year following musculoskeletal injuries.

Results

There is a potential (<25%) for the existence of fCRPS. People with this sub-type may suffer from more severe symptoms and earlier age at onset. Following DRFs, a significantly higher proportion of people with depression were found in the non-recovery group (24%) compared to the slow-recovery (16%, p=0.04) and the rapid-recovery group (8%, p=0.03). Following musculoskeletal injuries, a subset of people continue to have persisting pain. In this subset of people, higher levels of distress were associated with higher levels of pain 12 months later.

Conclusion

Familial factors, depression, and post-trauma distress all have the potential to contribute to chronic pain development and maintenance. The results of this thesis provide further evidence for the biopsychosocial model of chronic pain.

Keywords

Chronic pain; musculoskeletal injuries; biopsychosocial; familial; depression; distress

Summary for Lay Audience

Pain that persists for a long time after an injury is a common problem. Currently, we do not have effective treatment options. To discover better treatment options, it is important to understand what contributes to the persistence of pain. This thesis includes three papers. In the first paper, we reviewed published papers to examine whether complex regional pain syndrome (CRPS) can run in families. We concluded that it is possible for CRPS to run in families (a familial sub-type). Those that reported this sub-type also reported more severe presentation and got the disease at a younger age. However, we do not know if this is because of genetics or shared environments between family members. As CRPS can happen following common injuries such as wrist fractures, in the second study we examined recovery patterns in people with wrist fractures. We found that there are three recovery patterns: 1) people that recover quickly, 2) people that take a little bit longer to recover, and 3) people that continue to have pain for a long time. We found that a larger number of people in the third group had depression compared to the other two groups. In the third study, we examined the relationship between distress right after any type of injury and the amount of pain one year later. We found that most people do not have pain one year later regardless of how much distress they had after the injury. However, some people continued to have pain. In this group of people, higher levels of distress were associated with higher levels of pain one year later. Overall, the results of these three papers tell us that long-lasting pain is more than just the injury to our body parts, but familial factors, depression, and distress can contribute as well.

Co-Authorship Statement

Chapter one: literature review and purpose

- Shirin Modarresi: conceptualization, research, and writing
- Joy C. MacDermid: supervision and editing
- David M. Walton: supervision and editing

Chapter two: Does a familial sub-type of familial complex regional pain syndrome exist? Results of a systematic review

- Shirin Modarresi: conceptualization, data collection, data analysis, critical appraisal, data interpretation, and writing
- Erfan Aref-Eshghi: data collection, critical appraisal, and editing
- Joy C. MacDermid: supervision, data interpretation, and editing
- David M. Walton: supervision, data interpretation, and editing

Chapter three: Depression affects the recovery trajectory of patients with distal radius fracture: A latent growth curve analysis

- Shirin Modarresi: conceptualization, data analysis, data interpretation, and writing
- Nina Suh: supervision
- Joy C. MacDermid: supervision, data collection, data interpretation, and editing
- David M. Walton: supervision, data interpretation, and editing

Chapter four: Quantile regression analysis of the association between peritraumatic distress and pain 12 months following non-catastrophic musculoskeletal injuries

- Shirin Modarresi: conceptualization, data analysis, data interpretation, and writing

- Joy C. MacDermid: supervision, data interpretation, and editing
- Nina Suh: supervision
- James M. Elliott: data collection and editing
- David M. Walton: supervision, data collection, and editing

Chapter 5: Discussion

- Shirin Modarresi: conceptualization, research, and writing
- Joy C. MacDermid: supervision and editing
- David M. Walton: supervision and editing

Acknowledgments

I would like to acknowledge everyone who has played a role in providing help and guidance through these years in order to make this achievement possible.

First and foremost, I would like to express my most sincere gratitude to my supervisors Drs. Joy C. MacDermid, and David M. Walton. Dr. MacDermid provided an immense amount of support and encouragement and gave me all the independence that I needed in order to bring my ideas to fruition. Dr. Walton's door was always open to answer my questions or have a discussion and always guided me towards the most optimal path. I deeply appreciate both Dr. MacDermid and Dr. Walton's help for expertly helping me become the best researcher that I can be.

I would like to thank Dr. Ruth Martin for kindly helping me get through some of the toughest times that a graduate student might go through. I am forever grateful for her understanding and support.

I would like to thank Dr. Erfan Aref-Eshghi for his unwavering support and always being available to answer my questions on statistics and data analysis. I emailed, called, and dropped by many times, and Dr. Aref-Eshghi was always willing to help.

I would like to thank all of my lab-mates from both labs. Special thanks goes to Dorota Maria Klubowicz who selflessly spent many hours with me in the anatomy lab and made sure I understand the science of anatomy fundamentally. I would also like to thank Hoda Seens for her friendship and making these years more fun and memorable for me.

I would like to thank my loving family: My beloved father, Dr. Gholam Hossein Modarresi, who taught me the value of knowledge and science and I am sure he would have been happy and proud of me if he was with me today; my loving mother, Mehri Penjvini, who is the source of all my courage and abilities, thank you for always believing in me and praying for me, I would not have been able to reach this stage without you; my beloved brother, Arash Modarresi, who was the most loving person that I will ever know and he would have been very happy to see me succeed; my loving sister, Dr. Golale Modarresi, who always supports

me and never hesitates to help in any way possible; and my loving brother Danesh Modarresi, who has always been a source of love in my life.

Last, but definitely not least, I would like to thank the love of my life, Dr. Uzair Hussain. Thank you for supporting me every single step of the way, for being a guiding light on how to get to this stage, and for teaching me what it takes to get a doctorate degree.

I dedicate this dissertation to my parents, my beloved father Dr. Gholam Hossein Modarresi and loving mother Mehri Penjvini.

Table of Contents

List of Tables

Chapter 2:

Chapter 3:

Chapter 4

List of Figures

Chapter 2

Chapter 3

Chapter 4

Chapter 1

1 Introduction: Pain and recovery following musculoskeletal injuries

This chapter is a literature review and covers concepts of pain definition, the mechanism of pain sensation, differentiating nociceptive and neuropathic pain, pain measurement, functional impairment as an important pain-related construct, measurement of function, the transition from acute to chronic pain, epidemiology of chronic pain, the biopsychosocial model of pain and detailed description of each component of this model, and methodological shortcomings in systematic reviews and statistical modeling of pain outcomes including recovery trajectories and skewed data.

1.1 Defining and measuring pain and pain-related constructs

1.1.1 Defining pain

The word "pain" is derived from the Latin word "Poena", which means "suffering inflicted as punishment". This word originates from a story that "the Greek goddess of revenge "Poine", was sent to punish mortal men who had dared to anger the gods" (Khan et al., 2015). Today, according to the International Association for the Study of Pain (IASP), the medical definition of pain is "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"(*IASP Announces Revised Definition of Pain*, 2020). Universally, pain is understood to be a pointer of disease or a warning system against noxious stimuli (Elavarasi & Hanoch Kumar, 2016), and it is the most common reason that people seek medical attention (McCarberg et al., 2008). This point is perfectly illustrated by a condition called congenital insensitivity to pain (CIP) in which a person cannot feel pain and, as a result, the person does not seek medical attention for illnesses or injuries and even engages in life-threatening behaviors. Therefore, people with CIP often have a shorter life expectancy (Daneshjou et al., 2012). Even though it is required for proper functioning and survival, pain can become a problem, when it has already served the

function of signaling disease, or when it is in excess or for a prolonged period of time. Pain is a great global issue that can have a negative impact on the quality of life of individuals (McCarberg et al., 2008). Moreover, pain not only affects the individual, but it also often has an impact on the family's well-being and social circle (Ojeda et al., 2014). Pain places a heavy economic burden on the individual and the society as a whole due to associated medical expenses, decreased efficiency, and loss of income (Stewart et al., 2003). Understanding and management of pain are therefore at the core of health care.

1.1.2 The mechanism of pain sensation

Early theories of the concept of pain date back to distant times: Aristotle in 384-322 BC argued pain to be an emotion, Galen in 130-201 AD recognized the brain to be the organ that produces the sensation of pain, and Avicenna in 980-1037 AD proposed that pain can be an independent sensation from touch or temperature (Perl, 2007). It wasn't until the 18th century that the importance of the nervous system was recognized and a leap of progress was taken with proposals by Newton and Hartley that "neural messages were vibrations of substance in nerves" (Perl, 2007). Today, our understanding of the mechanism of pain has greatly advanced. Described below is a brief overview of the complex array of machinery that allows the experience of pain.

Nociceptors are the population of nerve fibers that detect a noxious stimulus from the internal (i.e., within the body) or external environment (Basbaum & Jessell, 2000). Depending on the conduction velocity of their axons, nociceptors can be classified into two main types: type Aδ and type C. Type Aδ nociceptors are surrounded by the protective sheath of myelin which allows the message of noxious stimuli or pain to travel very fast (Ringkamp et al., 2013). The Aδ nociceptors are further subdivided into two categories of type I and type II (Treede et al., 1998). Type I Aδ nociceptors are sensitive to mechanical and chemical stimuli but have high heat thresholds. These fibers are responsible for the first and fast pain we perceive when stepping on a nail. Type II Aδ nociceptors have a lower heat threshold and high mechanical threshold. The type C nociceptors are unmyelinated and therefore convey signals slower, producing a poorly localized dull pain (Bell, 2018). This type of nociceptor is broadly distributed (i.e., larger receptive fields) which leads to the poor localization aspect (Mense, 2008).

Following musculoskeletal (MSK) injuries, nociceptors detect a noxious stimulus from the external environment (Basbaum & Jessell, 2000). Nociceptors have a peripheral branch that innervates target organs and receives the signal of a noxious stimulus. Harm information travels from the peripheral branch to the dorsal horn of the spinal cord. From the spinal cord, the signal continues through the spinothalamic tract to the brain stem and the thalamus. Finally, from there, signals travel to several subcortical and cortical regions including the amygdala, hypothalamus, periaqueductal grey, basal ganglia, insula, and anterior cingulate cortex. The cerebral cortex is where the information is processed, and the experience of pain is produced. This process is called nociception (Sneddon, 2018).

1.1.3 Nociceptive versus neuropathic pain

Examples of nociceptive pain include pain after surgery or injury, mechanical pain, or arthritis pain (Goucke, 2003). In contrast, pain that is initiated by dysfunction of or injury to peripheral nerves is termed neuropathic pain (Nicholson, 2006). Although the initiation process is different from nociceptive pain, the nerve lesions in neuropathic pain involve the nociceptive pathways (Boivie et al., 1989).

Neuropathic pain can be caused by a variety of injuries and conditions such as damage to the peripheral nerves as a result of amputation and fractures or conditions such as radiculopathy and diabetes, or it can be caused by infectious diseases (Nicholson, 2006). Neuropathic pain is common in cancer patients due to the compression of nerves by tumors or radiation and chemotherapy (Nicholson, 2006). The underlying pathophysiology of neuropathic pain is complex and can be multimodal. These include ion channel insertion onto nerve membranes which can cause abnormal levels of sodium, higher levels of inflammatory cytokines which can lead to structural changes of receptors, development of additional afferent terminals at the dorsal horn of the spine, and increased levels of glutamatergic neurotransmission, which causes increased excitability, and decreased number of gamma-aminobutyric acid (GABA)-containing neurons (i.e., inhibitory neurons) in the spinal cord (Nicholson, 2006).

Neuropathic pain can include sharp, jabbing, throbbing, burning or freezing pain, electrical sensations, numbness, prickling, tingling, and sensation of pain even when the

stimulus is not noxious (Colloca et al., 2017). The symptoms can persist for a long time (potentially many years) and resistance to pain medications may be developed (Colloca et al., 2017).

In order to diagnose neuropathic pain, clinicians need to achieve a certain level of confidence, for which a recent grading system has been proposed to assess whether the pain in question is neuropathic (Finnerup et al., 2016). According to this grading system, the term ‘possible neuropathic pain’ can be used when the patient has a history of a nerve lesion or disease, is experiencing related pain, and accordingly, the neuroanatomical distribution makes logical sense. On the other hand, the term ‘probable neuropathic pain’ is used when the evidence is obtained by examination of sensory symptoms through methods such as quantitative sensory testing. Lastly, the term ‘definite neuropathic pain’ should be used only when an objective diagnostic test confirms the presence of a lesion or disease of the nervous system (Finnerup et al., 2016). Since treating an injured or lesioned nervous system is often not possible, treatment of neuropathic pain is done by the management of the etiological condition (if known) or only through alleviation of pain symptoms (Colloca et al., 2017).

1.2 The transition from acute to chronic pain

One way to categorize pain is to describe it in terms of the length of time it lasts. Acute pain refers to pain that is short-lasting (i.e., less than three months) or confined to a given time and conversely, chronic pain refers to pain that persists for a long time (i.e., longer than three months) or in other words, past healing time (Treede et al., 2015). Many chronic pain conditions last for an unspecified amount of time (Chapman & Vierck, 2017). If acute pain is not treated properly, it can lead to chronic pain even when the causal factor is removed or the disease is healed (Treede et al., 2015). This transition is partially explained through a phenomenon called neuroplasticity (or neural plasticity), which is the process of reorganization and remodeling of neurons leading to structural and functional changes in the nervous system (Modarresi et al., 2016; Voscopoulos & Lema, 2010). Although it occurs continuously throughout life, heightened neuroplasticity happens in the early stages of development, which are often referred to as the critical or sensitive periods (Hensch & Bilimoria, 2012). Essentially, neuroplasticity is an adaptive

response of the nervous system to environmental inputs and experiences in order to learn, memorize, and become accustomed to life. However, in the case of transition from acute to chronic pain, this process can become maladaptive. These newly built-in changes are associated with the duration and intensity of the pain (Apkarian et al., 2011). A seminal study by Flor and colleagues demonstrated that increasing chronicity of pain is positively correlated with an expansion of the corresponding representation zone in the primary somatosensory cortex (Flor et al., 1997). The structural changes in the brains of patients with chronic pain have been studied at both macroscopic levels (i.e., quantifying cortical thickness) using Magnetic Resonance Imaging (Valet et al., 2009) and microscopic level using Diffusion Tensor Imaging (Ellingson et al., 2013).

As the pathophysiology of acute and chronic pain differ, the management of these two types of pain can differ as well. Depending on the condition, management of acute pain typically consists of treating the underlying cause and using medications to treat the pain symptoms such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAID). If not effective, a combination of acetaminophen and opioids, and in severe cases potent opioids, are used (Blondell et al., 2013). In treating chronic pain, the situation can become complicated due to several factors such as unclear causal mechanisms, detrimental neuroplasticity, and the risk of developing drug tolerance and/or addiction. Due to these factors, contemporary chronic pain management is more focused on rehabilitation and maximizing quality of life rather than treating the causes (Mills et al., 2016). Chronic pain is complex and multimodal (Gatchel, 2005). Therefore, the management of chronic pain is also complex and usually involves a combination of strategies entailing both pharmacological and non-pharmacological approaches including physical and psychological therapy (Mills et al., 2016).

1.2.1 Measuring pain

Given the importance of pain at the individual and system level, measuring pain is also important for the purposes of keeping track of treatment efficacy or to understand the effect of time on the course of a disease. One of the most widely used methods to assess the amount of pain a patient (or a participant in a research study) is experiencing is the Numeric Pain Rating Scale (NPRS) (Hjermstad et al., 2011; Kremer et al., 1981). To

complete the NPRS, the person is asked to rate the severity of their pain on a scale of zero to 10, with zero being no pain, and 10 being the worst pain imaginable (Jensen & McFarland, 1993). The NPRS is easy to use and interpret. The main advantage of using the NPRS is that it is quick; it often takes less than one minute to complete (Hawker et al., 2011). Patients often prefer this tool because it is comprehensible and easy (de Williams et al., 2000). The psychometric adequacy of the NPRS has been reported in many patient populations including illiterate and literate people (Ferraz et al., 1990). The minimal clinically important difference (MCID) has been reported to be one to two points for various MSK pain populations (Bijur et al., 2003; Salaffi et al., 2004). The inter- and intra-rater reliability, as well as test-retest reliability of the NPRS have also been reported to be adequate in various chronic pain conditions (Jensen & McFarland, 1993). The NPRS also has adequate criterion, construct, and face validity (Bijur et al., 2003; Herr et al., 2004). The main disadvantage of the NPRS is that it is unidimensional (Williamson A & Hoggart B, 2005).

There are variations of the NPRS as well, such as the Visual Analog Scale (VAS) and the Verbal Rating Scale (VRS) (Frank et al., 1982; Hawker et al., 2011). The VAS consists of a horizontal line (usually 10 cm) which shows the continuum of pain intensity. The patient is asked to mark the spot that represents their pain intensity on the line. The exact score is determined by measuring the distance of the marked point to the left extreme. Similar to the NPRS, the higher the score, the more intense the pain (Hawker et al., 2011). The VAS has moderate to good psychometric properties in MSK pain populations (Boonstra et al., 2008). The main limitation of the VAS is that it cannot be used over the phone as it requires a pen and paper, and it is more difficult to comprehend for people with lower levels of education (Joos et al., 1991). In VRS, the patient is asked to describe their level of pain intensity using a list of adjectives with zero corresponding to no pain, one to mild pain, two to moderate pain, three to severe pain, and four to very severe pain. The VRS is also simple and easy to understand and administer (“Handbook of Pain Assessment,” 2001). The VRS has been reported to have adequate psychometric properties in MSK pain populations (Hjermstad et al., 2011). The main disadvantage of using the VRS is that it assumes equal intervals between each adjective (Ohnhaus & Adler, 1975).

Pain severity is one of the most important dimensions of pain. However, pain is complex and multifaceted, and therefore a one-dimensional tool is sometimes not sufficient (Younger et al., 2009). There are many multidimensional outcome measures for this purpose. For instance, the Brief Pain Inventory (BPI) is one such tool (Cleeland & Ryan, 1994). The BPI has two subsections of pain severity and pain interference (Stanhope, 2016). The severity subsection is on a numeric rating scale between zero and 10 (Cleeland & Ryan, 1994). The pain interference subsection asks the patient to rate how much their pain in the past 24 hours has interfered with their daily functions (Cleeland & Ryan, 1994). The BPI also asks the patient to shade the location of their pain on a diagram, asks about their treatments or medications, as well as the amount of relief the treatments provided in the last 24 hours (Cleeland & Ryan, 1994). Although the BPI was originally developed to measure pain in cancer populations, its utility and adequate psychometric properties have been illustrated in other populations as well, including acute and chronic MSK pain (Celik et al., 2017; Song et al., 2016). Compared to the unidimensional pain measures such as the NPRS, the disadvantage of the BPI is that it is more time-consuming (Khanna et al., 2015).

1.2.2 Functional impairment as a pain-related construct

Pain is not only a noxious feeling, but it can also significantly impact a person's ability to carry out everyday life activities (Jones et al., 2008). Functional impairment is an important pain-related construct in both acute and chronic conditions (Horgas et al., 2008). A large study (n=46,394) that surveyed people with various types of pain across Europe reported that many people were not able to take part in various daily activities such as walking, household chores, driving, and participate in social activities due to their pain (Breivik et al., 2006). Functional limitations become more severe in people with more severe and widespread pain (McBeth et al., 2010). In many MSK conditions, pain and functional impairment are closely linked (Harris et al., 2014). The link between pain and function becomes further evident when treatments targeting pain lead to improvements in function as well (Wells et al., 2008). In addition, given the high interference of function by pain, the primary goal of many pain management programs is to reduce the adverse effects of pain on function (Wells et al., 2008). Some authors argue

that treatment outcomes are only successful if other aspects related to pain, such as function, are also managed (Schofferman, 2006).

Broadly speaking, pain-related functional impairment is related to psychological consequences and physical deconditioning (Schofferman, 2006), although there can be social/environmental reasons as well. Psychological factors that can lead to functional impairment due to pain are related to the fear of invoking or aggravating the pain so the patient avoids doing activities due to fear of pain (Müller, 1970). This concept is referred to as the fear-avoidance model of pain (Vlaeyen & Linton, 2000). Physical deconditioning in patients with pain results from muscle weakness and atrophy due to disuse (Hasenbring et al., 1994). If there is inactivity for about two weeks, muscle deconditioning can occur at a rate of 1% per day (Müller, 1970). Therefore, treatment targeting only the noxious feeling of pain may not always lead to functional restoration due to physical deconditioning and muscular weakness (Schofferman, 2006).

1.2.3 Measuring function

As an important pain-related consequence, but a separate construct, inclusion of functional evaluation should be a part of a comprehensive pain assessment protocol (Dansie & Turk, 2013). The evaluation of function can be done separately using specific tools that assess the overall functional ability of the patient in everyday activities such as the Patient-Specific Functional Scale (PSFS) (Stratford et al., 1995). The PSFS is widely used in MSK conditions with varying levels of dependence (Horn et al., 2012). The PSFS is a distinct tool for assessing function in that the patient is asked to identify five tasks that are difficult for them and rate the level of difficulty they are experiencing due to their health condition on a numeric rating scale (Stratford et al., 1995). Therefore, each patient's response in terms of the specific tasks that are difficult for them may be different. This feature of the PSFS makes it an individualized outcome measure that centers on the patient's goals (Horn et al., 2012).

Another type of outcome measure is one that encompasses both the assessment of subjective pain levels and evaluation of function specific to a body region. The patient-rated elbow evaluation (PREE) is one such tool (MacDermid, 2001). The pain section of

the PREE has five items and asks the patient to rate their pain on a numeric rating scale over a spectrum of provocations (i.e., rest to activity). In addition, the patient is asked to report how often they have pain. The function section of the PREE has two subsections of specific activities and usual activities and in both the patient is asked to rate their level of difficulty performing each item on a numeric rating scale. The specific activities subsection has 11 items related to the use of elbows for performing tasks. The usual activities subsection has four items that are more general and relate to the activities of daily living such as household work or recreational activities. The total score is obtained by adding both the pain scores and the function scores and the higher the score, the higher the level of pain and disability related to the elbow joint (MacDermid, 2001). The psychometric properties of the PREE have been established in people with elbow pathologies (Vincent & MacDermid, 2012).

1.3 The epidemiology of chronic pain

Epidemiology is "the study of the distribution and determinants of health-related states and events in specified populations which can be used to control health problems" (Dicker et al., 2011). Through epidemiological studies, important information regarding the prevalence of a specific disease and factors associated with its onset and persistence can be gained (O van Hecke et al., 2013). Thus, epidemiological knowledge can guide efforts for the prevention and management of a disease.

Chronic pain is one of the most common health problems worldwide with estimated prevalence rates of approximately 20% (Breivik et al., 2006; Dahlhamer et al., 2018). The prevalence rate of chronic pain increases with age (Wilson et al., 2015). As the world's population is aging, the global prevalence rate of chronic pain is expected to increase further (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Chronic pain poses a significant financial burden to the society due to direct (i.e., healthcare) and indirect reasons (i.e., loss of income), estimating annual costs to be more than $60 billion in Canada (O van Hecke et al., 2013; Wilson et al., 2015). Chronic pain can also lead to fatigue and lack of concentration, poor sleep, dependence on opioids, loss of employment and income, and reduced quality of life (Breivik et al., 2006; Gureje et al.,

1998). Despite the high prevalence and the recognition of its negative impact in various levels, we lack effective therapeutic methods and skills for the management of chronic pain (Campbell et al., 2019). Therefore, understanding factors that contribute to the development and maintenance of chronic pain is of high research priority.

The contributing factors to chronic pain can be broadly categorized as modifiable and non-modifiable. Modifiable factors are those that can be changed such as health-related behaviors. The majority of non-modifiable factors relate to demographic characteristics of patients such as sex-at-birth; factors that cannot be changed. For instance, compared to females, males report lower rates of chronic pain and fewer sites (Gobina et al., 2019). Older age is another non-modifiable risk for chronic pain (Schopflocher et al., 2011). Recent studies suggest that with increasing age the disability associated with chronic pain as well as the number of comorbidities increase and these can make the problem more complex (Mills et al., 2019; O van Hecke et al., 2013).

1.4 The biopsychosocial model of chronic pain

A more comprehensive perspective towards understanding the factors associated with chronic pain development and maintenance is described via the biopsychosocial model of chronic pain (Gatchel et al., 2007). This model was first described in a seminal paper published in 1977 (Engel, 1977). The biopsychosocial model of pain has been researched and studied extensively and its popularity has increased exponentially over the past four decades (Wade & Halligan, 2017). The International Classification of Functioning, Disability, and Health (ICF) developed by WHO is closely linked to the biopsychosocial model (Towards a Common Language for Functioning, Disability and Health ICF, 2002). The biopsychosocial model has been used to structure many clinical practice guidelines and research studies (Wade & Halligan, 2017). Since its original development, the biopsychosocial model of chronic pain has evolved and expanded to include more dimensions such as time in the pediatric analysis of illness (Hymovich & Hagopian, 1992). According to this model, not only the biomedical factors play a role, but psychological and social aspects are also important contributors to chronic pain. The bio part of the model is the more traditional view towards pain and refers to the factors

responsible for nociception which involves information about actual or potential tissue damage. However, the biological approach cannot fully explain all aspects of pain such as the various pain responses to the same injury. Additionally, in some people, pain continues to persist when the noxious stimuli have been removed or when the tissue has healed (Gatchel et al., 2007). This happens partly due to a process called central sensitization, which is an amplification of neural activation within the central nervous system leading to hyperexcitability, pain hypersensitivity, and neural excitability even in the absence of nociceptive input (Latremoliere & Woolf, 2009). This central sensitization has been shown in many chronic pain populations such as tennis elbow and subacromial impingement syndrome (Coombes et al., 2012; Paul et al., 2012). Research in the last few decades has provided evidence that the variable responses to pain occur due to various psychological and social inputs that people experience during their lifetime (Turk & Okifuji, 2002). In addition, psychological and social factors can lead to variable behaviors that can modulate pain differently (Wijma et al., 2016). Therefore, an understanding of various biomedical, psychological, and social factors are needed to fully grasp the contributors of chronic pain. This will allow for a more individualized, patient-centered interpretation of a patient's experience of pain and recovery, which can lead to more effective management strategies. In the following sections, each of the components of the biopsychosocial model of chronic pain is described in more detail.

1.4.1 The biological contributors to chronic pain

The 'bio' part of the biopsychosocial model of pain refers to biological factors that can contribute to the experience of pain. This part has been the predominant view towards chronic pain and other diseases which relates to biological changes that can lead to nociception (Gatchel et al., 2007). When trauma or injury occurs to the body or in the presence of infection, pain pathways get activated through stimulation of nociceptive transduction (Basbaum & Jessell, 2000). In neuropathic pain, damage has been done to a section of the nervous system such as peripheral nerves. Certain factors can modulate the intensity and duration of pain from this physical perspective. For instance, a study of 385 people with distal radius fractures (DRFs) reported that higher levels of baseline pain intensity are a strong predictor of developing chronic pain (Mehta et al., 2015). Some

authors argue that this is an important modifiable risk factor and highlights the importance of acute pain management not just in terms of short-lasting relief from the unpleasant feeling of pain, but also to provide protection against the transition from acute to chronic stages (Oliver van Hecke et al., 2013). The protective effects of this management method stem from studies that report neuroplastic changes associated with chronic pain can be reversible if treatment is provided in the acute stages (Rodriguez-Raecke et al., 2009). For instance, anatomical neuroplastic changes in pain transmitting areas, including mid-cingulate and somatosensory cortex, can be induced in healthy human brain by providing repetitive noxious stimuli and they can be reversed by stopping the nociceptive input (Teutsch et al., 2008). Another factor associated with chronic pain is the number of painful sites so the greater the number of painful sites, the higher the probability of developing and the higher the intensity of the pain (Bergman et al., 2002; Elliott et al., 2002). Another physical contributor to the development and maintenance of chronic pain is multi-morbidity (Barnett et al., 2012). Having other health conditions can greatly increase the overall burden and may lead to more challenges in treatment and lower quality of life (Oliver van Hecke et al., 2013). High Body Mass Index (BMI) has also been shown to be associated with chronic pain partly due to increased load on joints (Hitt et al., 2007), and increased inflammatory load (Ellulu et al., 2017). The association may also be due to other factors such as lower levels of physical activity (Cassidy et al., 2017). Previous research suggests that there is a correlation between weight loss and pain improvement (Schrepf et al., 2017).

1.4.2 The psychological contributors to chronic pain

The second component of the biopsychosocial model of chronic pain is the psychological aspect. Depression, anxiety, and catastrophizing pain beliefs are amongst the most commonly reported psychological factors associated with chronic pain development (Boersma & Linton, 2006; van der Windt et al., 2007). In a prospective cohort study of 607 participants with a 10-year follow-up period, depressive and distress symptoms were reported to be predicting factors for the development of chronic MSK pain in various regions such as the low back, neck, and shoulder pain (Leino & Magni, 1993). A study that controlled for various other risk factors such as depression, comorbidities,

socioeconomic status, education, age, and sex in a population of MSK pain with mixed etiology reported that high levels of baseline anxiety can lead to unfavorable treatment outcomes and chronic pain (Bair et al., 2013). Anxiety may lead to maladaptive beliefs such as fear of movement. A study of 559 participants with low back pain reported that fear-avoidance beliefs lead to maintenance of chronic pain and disability (Trinderup et al., 2018). Pain catastrophizing beliefs can include characterizations of pain as awful, horrible, and unbearable, and these beliefs are increasingly being recognized as psychological contributors to chronic pain. A study by Gracely and colleagues examined the association between catastrophizing pain beliefs and brain structures involved in pain processing while controlling for the influence of depressive symptoms (Gracely et al., 2004). The results indicated that catastrophizing beliefs were significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal anterior cingulate gyrus, dorsolateral prefrontal cortex), and emotional aspects of pain (claustrum, closely connected to the amygdala) (Gracely et al., 2004). Another psychological factor that has been shown to be associated with chronic pain is post-traumatic stress disorder (PTSD) (Kind & Otis, 2019). Previous research shows that even if a person does not meet all of the diagnostic criteria for PTSD, the symptoms can still be disabling (Kind & Otis, 2019). Studies that have investigated the association between PTSD symptoms and chronic pain have focused on certain specific populations such as those involved in combat or an automobile accident (Kind & Otis, 2019). The presence of both chronic pain and psychological problems can augment the negative consequences of each such as higher pain intensity, more functional impairment, additive impairment in social functioning, lower quality of life, and increased healthcare costs (Bair et al., 2003). This is an alarming consequence as the prevalence of the comorbid condition is higher than the prevalence rates of each condition alone (Bair et al., 2003).

The specific underlying mechanism for how psychological pathologies can affect pain (and vice versa) or are associated with pain is still unclear. Shared neural mechanisms and neurotransmitters, and genetic components can partially explain this mechanism (Bair et al., 2003). However, certain behaviors may be part of the explanation as well. For instance, mental health issues can affect sleep and nutrition behaviors, which can impact

pain outcomes (Briguglio et al., 2020). In addition, mental health can can influence patients' adherence to exercise and rehabilitation programs (Lenze et al., 2004), which could be associated with reluctance and psychomotor retardation (Atay et al., 2016) or decreasing self-care abilities (Lieberman et al., 1999). Another factor that can potentially play a role in how psychological pathologies impact pain and recovery is that mental health issues can weaken the immune system (Phillips et al., 2013).

It should be noted that many studies have also reported chronic pain being a risk factor for developing psychological problems (Elbinoune et al., 2016). The temporal relationship between the presence of psychological factors and chronic pain development is still one of the topics in the present scientific literature that remains unclear. The relationship is currently known to be a bidirectional one with each of the factors having the potential to be the causal element for the other (Von Korff et al., 1993). Evidence for the bidirectionality of psychological problems and chronic pain comes from the shared neural mechanisms and their high co-occurrence prevalence with each factor reinforcing the other and then becoming part of the overall condition (Oliver van Hecke et al., 2013). Some authors refer to the interaction between the two conditions as depression-pain syndrome or depression-pain dyad (Bair et al., 2003). Therefore, researchers suggest that treatment of each component in isolation may lead to less favorable outcomes compared to a bimodal treatment strategy that addresses both (Kroenke et al., 2009).

1.4.3 The social contributors to chronic pain

The last component of the biopsychosocial model of chronic pain refers to the social aspects of a person's life. A large scale prospective cohort study (n=2425) that followed participants for three years, reported that a family history of chronic pain, a habit of drinking alcohol weekly, not having personal social support, and being an immigrant were significantly associated with developing chronic pain (Bergman et al., 2002). Employment and socioeconomic factors are also noteworthy social aspects in chronic pain (Oliver van Hecke et al., 2013). For instance, not being able to work, poor job control, and fear of re-injury at work have all been shown to be important in chronic pain development and maintenance (Shaw et al., 2006). Studies have also shown that lower

socioeconomic status and lower levels of education are associated with higher chronic pain prevalence (Jordan et al., 2008; Poleshuck & Green, 2008).

Another aspect associated with chronic pain is largely classed as familial factors which comprise both genetic and environmental influences. Some studies report that chronic pain conditions can run in families and suggest that children of parents with chronic pain have a higher probability to develop chronic pain as well (Grøholt et al., 2003). It might be more difficult to categorize this larger factor into biological or social as it has both components (Wright et al., 2010). The environmental influences in the familial context may relate to the ethnocultural background of the family. For example, certain ethnocultural groups report greater pain sensitivity and less favorable outcomes following receiving pain treatment (Oliver van Hecke et al., 2013). Pain beliefs and behaviors are influenced by ethnicity, culture, and race (Orhan et al., 2018). In addition, people in the same household may experience similar events such as abuse or domestic violence, which are associated with chronic pain development (Sachs-Ericsson et al., 2007). On the other hand, genetics can also play a role as many genes have been identified to be associated with pain pathways and behaviors such as sensitivity to painful stimuli and pain tolerability (Norbury et al., 2007). The behavior of ‘pain reporting’ has been identified to have a heritable phenotype (MacGregor et al., 2009). However, we need to be cognizant of the concept of familial aggregation in that genes may only play a role in it and they are not necessarily the causal factors. Therefore, the familial factor associated with chronic pain is potentially an interaction of two factors of genetics and shared environment.

As can be noted in the above sections on the biopsychosocial model, the experience of chronic pain is not caused by a single factor, it is rather the result of a dynamic and reciprocal relationship between biological, psychological, and social factors that interact with each other, leading to a complex and multidimensional problem. A thorough understanding of all the contributing factors relating to chronic pain can possibly lead to more effective management and preventative strategies.

1.5 Methodological shortcomings

1.5.1 Systematic reviews

Study designs form a hierarchy of evidence and quality, creating a pyramid of evidence. At the bottom of the pyramid are case reports and case series, followed by case-control studies, cohort studies, randomized control trials, and at the very top are systematic reviews and meta-analyses (Paul & Leibovici, 2014). Systematic reviews attempt to synthesize the available evidence regarding a specific question. Systematic reviews differ from the more traditional narrative reviews in that they follow a detailed search strategy that has been developed a priori and are not biased towards studies based on author selection (Uman, 2011). Therefore, the risk of bias is considered lower in systematic reviews (Uman, 2011). In addition, the question under investigation needs to be specific with detailed inclusion and exclusion criteria regarding population and other factors such as disease type and interventions. It is also common to synthesize and report the results of particular study designs such as randomized control trials or prospective cohort studies (Paul & Leibovici, 2014). When there is heterogeneity in the identified studies in terms of specific details in samples or analysis, researchers may opt for sub-group analysis and reporting. It is less common for systematic reviews to report the results of studies with various designs. However, when the information is scarce, then the evidence would need to be synthesized through investigating the best available data. If not, important information may not get the necessary attention and its usefulness may get diminished. The synthesized information from various study designs can provide valuable answers to the research question. Nonetheless, certain factors need to be taken into consideration to be able to appropriately synthesize the information in this way. For instance, the risk of bias and quality assessment of each study would potentially need to be according to the specific study design. In addition, meta-analysis or statistical pooling of these results is not appropriate as the heterogeneity of the designs would preclude the researcher from deriving meaningful estimations of the overall effect (Ioannidis et al., 2008). Therefore, a descriptive synthesis is an ideal approach to summarize the results of systematic reviews with various study designs.

1.5.2 Statistical issues in modeling pain outcomes – recovery trajectories

In longitudinal chronic pain research, outcome measures of interest are often administered repeatedly at many time points (days, months, or years). This type of data is used to address research questions that are about change over time such as assessing the magnitude of recovery. This methodology is relatively advantageous to cross-sectional data analysis where differences are investigated only at a single time point (Liu et al., 2010). The reason behind this advantage can be illustrated using an example: suppose a researcher is interested in assessing pain and treatment outcomes six months following an MSK injury using the NPRS. The mean score of the sample at six months is 6/10. This information shows that the participants are still suffering from a moderate amount of pain which can by itself be interpreted as a negative finding. However, if the researcher had more data at various timepoints such as baseline, three months, and six months, the mean scores could be compared across time and a trend may be observed. This later knowledge about the amount of change can be more informative regarding the recovery pattern, predictive factors, or treatment outcomes. However, one important statistical limitation concerning conventional modeling methods in longitudinal studies is regarding the assumption that all participants experience a similar pattern of recovery over time and can be combined into one group (Jung & Wickrama, 2008). This assumption can be problematic as there is heterogeneity in recovery patterns in almost all patient populations (Panken et al., 2016; Sterling et al., 2011). Using a single estimate of recovery to represent an entire population would be an oversimplification of potentially various complex recovery patterns (Jung & Wickrama, 2008). One way to mitigate this problem in assessing longitudinal outcomes and avoiding the issue of a ‘single pattern model’ is using the growth mixture modeling (GMM) and latent growth curve analysis approach. This approach can fully capture all the information about intraindividual changes taking into account that there can be different trajectories of recovery (Jung & Wickrama, 2008). The goal of this modeling approach is to group individuals into separate classes based on response patterns. This classification of patterns ensures that individuals within a class have a more similar trajectory than individuals between classes (Jung & Wickrama, 2008). Using GMM for modeling pain outcomes allows for the identification of distinct

recovery trajectories for various patient populations. Once the recovery trajectories are identified, the characteristics of each class can be compared for further analyses. This technique has been gaining more popularity in recent years. For instance, one study reported that there are three distinct classes of pain trajectory in people with low back pain and identified variables such as kinesiophobia as predictors for class membership (Panken et al., 2016).

1.5.3 Statistical issues in modeling pain outcomes – skewed data

Statistical regression methods are widely used to assess the association between a dependent variable and one or more independent variables (Gonzalez-Blanks et al., 2020). However, in order to use these common methods such as the ordinary least square (OLS), certain assumptions need to be met including normality of the dependent variables or their residuals (Osborne & Waters, 2002). One of the major issues in statistical modeling of outcomes in chronic pain research is the presence of highly skewed data. The skewed data may be obtained because the majority of people report no or minimal pain one year after an MSK injury (MacDermid et al., 2003; Thompson et al., 2017). When the majority of people report a certain score, the resulting dataset would contain many similar points, leading to the generation of skewed or non-normally distributed data. The reason skewed data cannot be used is that it would bias the estimation of parameters in regression models as the mean score is highly sensitive to extreme outliers (Gonzalez-Blanks et al., 2020). Using the mean to describe the association when the data is non-normal would lead to inaccurate parameter estimates and confidence intervals (Gonzalez-Blanks et al., 2020). In 1996, Curran and colleagues suggested that a skewness level of more than two would lead to unreliable results (Curran et al., 1996). More recent studies suggest that even more conservative levels are not reliable (Gonzalez-Blanks et al., 2020). Therefore, skewed data in chronic pain research poses a challenge concerning the type of analysis that can appropriately be used to describe patterns and associations.

Several transformation techniques have been proposed to circumvent the issue of skewness including log transformations, using square-root, and inverse transformations. However, these approaches have the limitation of not being able to correct for the over-

abundance of zeros in the dataset (Gonzalez-Blanks et al., 2020). Another technique that has been used to avoid the non-normality distribution is using logistic regression. However, using logistic regression requires setting an a priori cut-off value and dichotomizing the data. This technique is an appropriate one for truly binary outcome variables, but for one that is considered continuous, and no cut-off points have been set, it can lead to the loss of substantially important information (Fosdal, 2017).

Quantile regression can be considered an ideal approach for analyzing continuous non-normal data (Konstantopoulos et al., 2019). The quantile regression modeling technique was first introduced by econometricians Roger Koenker and Gilbert Bassett in 1978 (Koenker & Bassett, 1978). This technique does not rely on the mean of the variables, thus the skewness of the data will not have an effect on the results. Instead, quantile regression describes the association between the dependent and the explanatory variables in various points of the distribution. In this technique, the association can be explored in several quantiles such as the 10^{th}, 25^{th}, 50^{th} (median), 75^{th} , and 90^{th} (or any other intervals depending on the research question). By investigating the association at various quantiles of the entire distribution, quantile regression provides a more complete picture of the effects (Staffa et al., 2019). Quantile regression offers greater flexibility and opportunity to identify potentially distinct relationships at different points of the distribution (Lê Cook & Manning, 2013).

1.6 References

Apkarian, A. V., Hashmi, J. A., & Baliki, M. N. (2011). Pain and the brain: specificity and plasticity of the brain in clinical chronic pain. *Pain*, *152*(3 Suppl), S49-64. https://doi.org/10.1016/j.pain.2010.11.010

Atay, I. M., Aslan, A., Burc, H., Demirci, D., & Atay, T. (2016). Is depression associated with functional recovery after hip fracture in the elderly? *Journal of Orthopaedics*, *13*(2), 115–118. https://doi.org/10.1016/j.jor.2015.02.001

Bair, M. J., Poleshuck, E. L., Wu, J., Krebs, E. K., Damush, T. M., Tu, W., & Kroenke, K. (2013). Anxiety but not social stressors predict 12-month depression and pain

severity. *The Clinical Journal of Pain*, *29*(2), 95–101. https://doi.org/10.1097/AJP.0b013e3182652ee9

Bair, M. J., Robinson, R. L., Katon, W., & Kroenke, K. (2003). Depression and pain comorbidity: a literature review. *Archives of Internal Medicine*, *163*(20), 2433–2445. https://doi.org/10.1001/archinte.163.20.2433

Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S., & Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet (London, England)*, *380*(9836), 37–43. https://doi.org/10.1016/S0140-6736(12)60240-2

Basbaum, A., & Jessell, T. (2000). The Perception of Pain. In E. Kandel, J. Schwartz, & T. Jessell (Eds.), *Principles of Neuroscience* (pp. 472–491). Appleton and Lange.

Bell, A. (2018). The neurobiology of acute pain. *Veterinary Journal (London, England : 1997)*, *237*, 55–62. https://doi.org/10.1016/j.tvjl.2018.05.004

Bergman, S., Herrström, P., Jacobsson, L. T., & Petersson, I. F. (2002). Chronic widespread pain: a three year followup of pain distribution and risk factors. *The Journal of Rheumatology*, *29*(4), 818–825.

Bijur, P. E., Latimer, C. T., & Gallagher, E. J. (2003). Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine*, *10*(4), 390–392. https://doi.org/10.1111/j.1553-2712.2003.tb01355.x

Blondell, R. D., Azadfard, M., & Wisniewski, A. M. (2013). Pharmacologic therapy for acute pain. *American Family Physician*, *87*(11), 766–772.

Boersma, K., & Linton, S. J. (2006). Expectancy, fear and pain in the prediction of chronic pain and disability: a prospective analysis. *European Journal of Pain (London, England)*, *10*(6), 551–557. https://doi.org/10.1016/j.ejpain.2005.08.004

Boivie, J., Leijon, G., & Johansson, I. (1989). Central post-stroke pain--a study of the mechanisms through analyses of the sensory abnormalities. *Pain*, *37*(2), 173–185.

Boonstra, A. M., Schiphorst Preuper, H. R., Reneman, M. F., Posthumus, J. B., & Stewart, R. E. (2008). Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. *International Journal of Rehabilitation Research. Internationale Zeitschrift Fur Rehabilitationsforschung. Revue Internationale de Recherches de Readaptation*, *31*(2), 165–169. https://doi.org/10.1097/MRR.0b013e3282fc0f93

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *European Journal of Pain (London, England)*, *10*(4), 287–333. https://doi.org/10.1016/j.ejpain.2005.06.009

Briguglio, M., Vitale, J. A., Galentino, R., Banfi, G., Zanaboni Dina, C., Bona, A., Panzica, G., Porta, M., Dell'Osso, B., & Glick, I. D. (2020). Healthy Eating, Physical Activity, and Sleep Hygiene (HEPAS) as the Winning Triad for Sustaining Physical and Mental Health in Patients at Risk for or with Neuropsychiatric Disorders: Considerations for Clinical Practice. *Neuropsychiatric Disease and Treatment*, *16*, 55–70. https://doi.org/10.2147/NDT.S229206

Campbell, F., Hudspith, M., Anderson, M., Choiniere, M., El-Gabalwy, H., Laliberte, J., Swidrovich, J., & Wilhelm, L. (2019). *Chronic Pain in Canada: Laying a Foundation for Action*.

Cassidy, S., Chau, J. Y., Catt, M., Bauman, A., & Trenell, M. I. (2017). Low physical activity, high television viewing and poor sleep duration cluster in overweight and obese adults; a cross-sectional study of 398,984 participants from the UK Biobank. *International Journal of Behavioral Nutrition and Physical Activity*, *14*(1), 57. https://doi.org/10.1186/s12966-017-0514-y

Celik, E. C., Yalcinkaya, E. Y., Atamaz, F., Karatas, M., Ones, K., Sezer, T., Eren, I., Paker, N., Gning, I., Mendoza, T., & Cleeland, C. S. (2017). Validity and reliability

of a Turkish Brief Pain Inventory Short Form when used to evaluate musculoskeletal pain. *Journal of Back and Musculoskeletal Rehabilitation*, *30*(2), 229–233. https://doi.org/10.3233/BMR-160738

Chapman, C. R., & Vierck, C. J. (2017). The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *The Journal of Pain : Official Journal of the American Pain Society*, *18*(4), 359.e1-359.e38. https://doi.org/10.1016/j.jpain.2016.11.004

Cleeland, C. S., & Ryan, K. M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Annals of the Academy of Medicine, Singapore*, *23*(2), 129–138.

Collaborators, G. 2016 D. and I. I. and P. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet (London, England)*, *390*(10100), 1211–1259. https://doi.org/10.1016/S0140-6736(17)32154-2

Colloca, L., Ludman, T., Bouhassira, D., Baron, R., Dickenson, A. H., Yarnitsky, D., Freeman, R., Truini, A., Attal, N., Finnerup, N. B., Eccleston, C., Kalso, E., Bennett, D. L., Dworkin, R. H., & Raja, S. N. (2017). Neuropathic pain. *Nature Reviews. Disease Primers*, *3*, 17002. https://doi.org/10.1038/nrdp.2017.2

Coombes, B. K., Bisset, L., & Vicenzino, B. (2012). Thermal hyperalgesia distinguishes those with severe pain and disability in unilateral lateral epicondylalgia. *The Clinical Journal of Pain*, *28*(7), 595–601. https://doi.org/10.1097/AJP.0b013e31823dd333

Curran, P. J., West, S. G., & Finch, J. F. (1996). The robustness of test statistics to nonnormality and specification error in confirmatory factor analysis. *Psychological Methods*, *1*(1), 16–29.

Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., DeBar, L., Kerns, R., Von Korff, M., Porter, L., & Helmick, C. (2018). Prevalence of Chronic Pain and High-

Impact Chronic Pain Among Adults - United States, 2016. *MMWR. Morbidity and Mortality Weekly Report*, *67*(36), 1001–1006. https://doi.org/10.15585/mmwr.mm6736a2

Daneshjou, K., Jafarieh, H., & Raaeskarami, S.-R. (2012). Congenital Insensitivity to Pain and Anhydrosis (CIPA) Syndrome; A Report of 4 Cases. In *Iranian journal of pediatrics* (Vol. 22, Issue 3, pp. 412–416).

Dansie, E. J., & Turk, D. C. (2013). Assessment of patients with chronic pain. *British Journal of Anaesthesia*, *111*(1), 19–25. https://doi.org/10.1093/bja/aet124

de Williams, A. C., Davies, H. T. O., & Chadury, Y. (2000). Simple pain rating scales hide complex idiosyncratic meanings. *Pain*, *85*(3), 457–463. https://doi.org/10.1016/S0304-3959(99)00299-7

Dicker, R. C., Coronado, F., Koo, D., & Parrish, R. G. (2011). *Principles of epidemiology in public health practice* (3rd ed.). Centers for Disease Control & Prevention (CDC).

Elavarasi, P., & Hanoch Kumar, K. (2016). Definition of pain and classification of pain disorders. *Journal of Advanced Clinical & Research Insights*, *3*(3), 87–90.

Elbinoune, I., Amine, B., Shyen, S., Gueddari, S., Abouqal, R., & Hajjaj-Hassouni, N. (2016). Chronic neck pain and anxiety-depression: prevalence and associated risk factors. *The Pan African Medical Journal*, *24*, 89. https://doi.org/10.11604/pamj.2016.24.89.8831

Ellingson, B. M., Mayer, E., Harris, R. J., Ashe-McNally, C., Naliboff, B. D., Labus, J. S., & Tillisch, K. (2013). Diffusion tensor imaging detects microstructural reorganization in the brain associated with chronic irritable bowel syndrome. *Pain*, *154*(9), 1528–1541. https://doi.org/10.1016/j.pain.2013.04.010

Elliott, A. M., Smith, B. H., Hannaford, P. C., Smith, W. C., & Chambers, W. A. (2002). The course of chronic pain in the community: results of a 4-year follow-up study. *Pain*, *99*(1–2), 299–307. https://doi.org/10.1016/s0304-3959(02)00138-0

Ellulu, M. S., Patimah, I., Khaza'ai, H., Rahmat, A., & Abed, Y. (2017). Obesity and inflammation: the linking mechanism and the complications. *Archives of Medical Science : AMS*, *13*(4), 851–863. https://doi.org/10.5114/aoms.2016.58928

Engel, G. L. (1977). The need for a new medical model: a challenge for biomedicine. *Science (New York, N.Y.)*, *196*(4286), 129–136. https://doi.org/10.1126/science.847460

Ferraz, M. B., Quaresma, M. R., Aquino, L. R., Atra, E., Tugwell, P., & Goldsmith, C. H. (1990). Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. *The Journal of Rheumatology*, *17*(8), 1022–1024.

Finnerup, N. B., Haroutounian, S., Kamerman, P., Baron, R., Bennett, D. L. H., Bouhassira, D., Cruccu, G., Freeman, R., Hansson, P., Nurmikko, T., Raja, S. N., Rice, A. S. C., Serra, J., Smith, B. H., Treede, R.-D., & Jensen, T. S. (2016). Neuropathic pain: an updated grading system for research and clinical practice. *Pain*, *157*(8), 1599–1606. https://doi.org/10.1097/j.pain.0000000000000492

Flor, H., Braun, C., Elbert, T., & Birbaumer, N. (1997). Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neuroscience Letters*, *224*(1), 5–8. https://doi.org/10.1016/s0304-3940(97)13441-3

Fosdal, S. (2017). *The use of logistic regression and quantile regression in medical statistics*. Norwegian University of Science and Technology.

Frank, A. J., Moll, J. M., & Hort, J. F. (1982). A comparison of three ways of measuring pain. *Rheumatology and Rehabilitation*, *21*(4), 211–217. https://doi.org/10.1093/rheumatology/21.4.211

Gatchel, R. J. (2005). Clinical essentials of pain management. In *Clinical essentials of pain management.* American Psychological Association. https://doi.org/10.1037/10856-000

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions.

Psychological Bulletin, *133*(4), 581–624. https://doi.org/10.1037/0033-2909.133.4.581

Gobina, I., Villberg, J., Välimaa, R., Tynjälä, J., Whitehead, R., Cosma, A., Brooks, F., Cavallo, F., Ng, K., de Matos, M. G., & Villerusa, A. (2019). Prevalence of self-reported chronic pain among adolescents: Evidence from 42 countries and regions. *European Journal of Pain (London, England)*, *23*(2), 316–326. https://doi.org/10.1002/ejp.1306

Gonzalez-Blanks, A., Bridgewater, J. M., & Yates, T. M. (2020). Statistical Approaches for Highly Skewed Data: Evaluating Relations between Maltreatment and Young Adults' Non-Suicidal Self-injury. *Journal of Clinical Child and Adolescent Psychology : The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53*, *49*(2), 147–161. https://doi.org/10.1080/15374416.2020.1724543

Goucke, C. R. (2003). The management of persistent pain. *The Medical Journal of Australia*, *178*(9), 444–447.

Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A. B., Petzke, F., Williams, D. A., & Clauw, D. J. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain : A Journal of Neurology*, *127*(Pt 4), 835–843. https://doi.org/10.1093/brain/awh098

Grøholt, E.-K., Stigum, H., Nordhagen, R., & Köhler, L. (2003). Recurrent pain in children, socio-economic factors and accumulation in families. *European Journal of Epidemiology*, *18*(10), 965–975. https://doi.org/10.1023/a:1025889912964

Gureje, O., Von Korff, M., Simon, G. E., & Gater, R. (1998). Persistent pain and well-being: a World Health Organization Study in Primary Care. *JAMA*, *280*(2), 147–151. https://doi.org/10.1001/jama.280.2.147

Handbook of pain assessment. (2001). In *Handbook of pain assessment (2nd ed.)* (2nd ed.). Guilford Press, New York, NY. https://www.lib.uwo.ca/cgi-

bin/ezpauthn.cgi?url=http://search.proquest.com/docview/619590910?accountid=15115

Harris, K. K., Price, A. J., Beard, D. J., Fitzpatrick, R., Jenkinson, C., & Dawson, J. (2014). Can pain and function be distinguished in the Oxford Hip Score in a meaningful way? : an exploratory and confirmatory factor analysis. *Bone & Joint Research*, *3*(11), 305–309. https://doi.org/10.1302/2046-3758.311.2000313

Hasenbring, M., Marienfeld, G., Kuhlendahl, D., & Soyka, D. (1994). Risk factors of chronicity in lumbar disc patients. A prospective investigation of biologic, psychologic, and social predictors of therapy outcome. *Spine*, *19*(24), 2759–2765. https://doi.org/10.1097/00007632-199412150-00004

Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (S. *Arthritis Care & Research*, *63 Suppl 1*, S240-52. https://doi.org/10.1002/acr.20543

Hensch, T. K., & Bilimoria, P. M. (2012). Re-opening Windows: Manipulating Critical Periods for Brain Development. *Cerebrum : The Dana Forum on Brain Science*, *2012*, 11.

Herr, K. A., Spratt, K., Mobily, P. R., & Richardson, G. (2004). Pain intensity assessment in older adults: use of experimental pain to compare psychometric properties and usability of selected pain scales with younger adults. *The Clinical Journal of Pain*, *20*(4), 207–219. https://doi.org/10.1097/00002508-200407000-00002

Hitt, H. C., McMillen, R. C., Thornton-Neaves, T., Koch, K., & Cosby, A. G. (2007). Comorbidity of obesity and pain in a general population: results from the Southern Pain Prevalence Study. *The Journal of Pain*, *8*(5), 430–436. https://doi.org/10.1016/j.jpain.2006.12.003

Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H.,

Fainsinger, R., Aass, N., & Kaasa, S. (2011). Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. In *Journal of Pain and Symptom Management* (Vol. 41, Issue 6, pp. 1073–1093). https://doi.org/10.1016/j.jpainsymman.2010.08.016

Horgas, A. L., Yoon, S. L., Nichols, A. L., & Marsiske, M. (2008). The relationship between pain and functional disability in Black and White older adults. *Research in Nursing & Health*, *31*(4), 341–354. https://doi.org/10.1002/nur.20270

Horn, K. K., Jennings, S., Richardson, G., Vliet, D. Van, Hefford, C., & Abbott, J. H. (2012). The patient-specific functional scale: psychometrics, clinimetrics, and application as a clinical outcome measure. *The Journal of Orthopaedic and Sports Physical Therapy*, *42*(1), 30–42. https://doi.org/10.2519/jospt.2012.3727

Hymovich, D. P., & Hagopian, G. A. (1992). *Chronic illness in children and adults: A psychosocial approach*. WB Saunders Company.

IASP Announces Revised Definition of Pain. (2020). International Association for the Study of Pain. https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=10475

Ioannidis, J. P. A., Patsopoulos, N. A., & Rothstein, H. R. (2008). Reasons or excuses for avoiding meta-analysis in forest plots. *BMJ (Clinical Research Ed.)*, *336*(7658), 1413–1415. https://doi.org/10.1136/bmj.a117

Jensen, M. P., & McFarland, C. A. (1993). Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain*, *55*(2), 195–203. https://doi.org/10.1016/0304-3959(93)90148-I

Jones, J., Rutledge, D. N., Jones, K. D., Matallana, L., & Rooks, D. S. (2008). Self-assessed physical function levels of women with fibromyalgia: a national survey. *Women's Health Issues : Official Publication of the Jacobs Institute of Women's Health*, *18*(5), 406–412. https://doi.org/10.1016/j.whi.2008.04.005

Joos, E., Peretz, A., Beguin, S., & Famaey, J. P. (1991). Reliability and reproducibility of visual analogue scale and numeric rating scale for therapeutic evaluation of pain in rheumatic patients. In *The Journal of rheumatology* (Vol. 18, Issue 8, pp. 1269–1270).

Jordan, K. P., Thomas, E., Peat, G., Wilkie, R., & Croft, P. (2008). Social risks for disabling pain in older people: a prospective study of individual and area characteristics. *Pain*, *137*(3), 652–661. https://doi.org/10.1016/j.pain.2008.02.030

Jung, T., & Wickrama, K. (2008). An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. *Social and Personality Psychology Compass*, *2*, 302–317. https://doi.org/10.1111/j.1751-9004.2007.00054.x

Khan, M. A., Raza, F., & Khan, I. A. (2015). Pain: history, culture and philosophy. *Acta Medico-Historica Adriatica : AMHA*, *13*(1), 113–130.

Khanna, R., Kumar, A., & Khanna, R. (2015). Brief pain inventory scale: An emerging assessment modality for orofacial pain. *Indian Journal of Pain*, *29*(2), 61–63.

Kind, S., & Otis, J. D. (2019). The interaction between chronic pain and PTSD. *Current Pain and Headache Reports*, *23*(12), 91. https://doi.org/10.1007/s11916-019-0828-3

Koenker, R., & Bassett, G. (1978). Regression Quantiles. *Econometrica*, *46*(1), 33–50. https://doi.org/10.2307/1913643

Konstantopoulos, S., Li, W., Miller, S., & van der Ploeg, A. (2019). Using Quantile Regression to Estimate Intervention Effects Beyond the Mean. *Educational and Psychological Measurement*, *79*(5), 883–910. https://doi.org/10.1177/0013164419837321

Kremer, E., Atkinson, H. J., & Ignelzi, R. J. (1981). Measurement of pain: patient preference does not confound pain measurement. *Pain*, *10*(2), 241–248. https://doi.org/10.1016/0304-3959(81)90199-8

Kroenke, K., Bair, M. J., Damush, T. M., Wu, J., Hoke, S., Sutherland, J., & Tu, W.

(2009). Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. *JAMA*, *301*(20), 2099–2110. https://doi.org/10.1001/jama.2009.723

Latremoliere, A., & Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *The Journal of Pain*, *10*(9), 895–926. https://doi.org/10.1016/j.jpain.2009.06.012

Lê Cook, B., & Manning, W. G. (2013). Thinking beyond the mean: a practical guide for using quantile regression methods for health services research. *Shanghai Archives of Psychiatry*, *25*(1), 55–59. https://doi.org/10.3969/j.issn.1002-0829.2013.01.011

Leino, P., & Magni, G. (1993). Depressive and distress symptoms as predictors of low back pain, neck-shoulder pain, and other musculoskeletal morbidity: a 10-year follow-up of metal industry employees. *Pain*, *53*(1), 89–94. https://doi.org/10.1016/0304-3959(93)90060-3

Lenze, E. J., Munin, M. C., Dew, M. A., Rogers, J. C., Seligman, K., Mulsant, B. H., & Reynolds, C. F. 3rd. (2004). Adverse effects of depression and cognitive impairment on rehabilitation participation and recovery from hip fracture. *International Journal of Geriatric Psychiatry*, *19*(5), 472–478. https://doi.org/10.1002/gps.1116

Lieberman, D., Galinsky, D., Fried, V., Grinshpun, Y., Mytlis, N., & Tylis, R. (1999). Geriatric Depression Screening Scale (GDS) in patients hospitalized for physical rehabilitation. *International Journal of Geriatric Psychiatry*, *14*(7), 549–555. https://doi.org/10.1002/(sici)1099-1166(199907)14:7<549::aid-gps960>3.0.co;2-4

Liu, C., Cripe, T. P., & Kim, M.-O. (2010). Statistical issues in longitudinal data analysis for treatment efficacy studies in the biomedical sciences. *Molecular Therapy : The Journal of the American Society of Gene Therapy*, *18*(9), 1724–1730. https://doi.org/10.1038/mt.2010.127

MacDermid, J C. (2001). Outcome evaluation in patients with elbow pathology: issues in instrument development and evaluation. *Journal of Hand Therapy : Official Journal*

of the American Society of Hand Therapists, *14*(2), 105–114. https://doi.org/10.1016/s0894-1130(01)80040-5

MacDermid, Joy C, Roth, J. H., & Richards, R. S. (2003). Pain and disability reported in the year following a distal radius fracture: A cohort study. *BMC Musculoskeletal Disorders*, *4*(1), 24. https://doi.org/10.1186/1471-2474-4-24

MacGregor, A. J., Li, Q., Spector, T. D., & Williams, F. M. K. (2009). The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee. *Rheumatology (Oxford, England)*, *48*(3), 277–280. https://doi.org/10.1093/rheumatology/ken475

McBeth, J., Nicholl, B. I., Cordingley, L., Davies, K. A., & Macfarlane, G. J. (2010). Chronic widespread pain predicts physical inactivity: results from the prospective EPIFUND study. *European Journal of Pain (London, England)*, *14*(9), 972–979. https://doi.org/10.1016/j.ejpain.2010.03.005

McCarberg, B. H., Nicholson, B. D., Todd, K. H., Palmer, T., & Penles, L. (2008). The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an Internet survey. *American Journal of Therapeutics*, *15*(4), 312–320. https://doi.org/10.1097/MJT.0b013e31818164f2

Mehta, S. P., MacDermid, J. C., Richardson, J., MacIntyre, N. J., & Grewal, R. (2015). Baseline pain intensity is a predictor of chronic pain in individuals with distal radius fracture. *The Journal of Orthopaedic and Sports Physical Therapy*, *45*(2), 119–127. https://doi.org/10.2519/jospt.2015.5129

Mense, S. (2008). Anatomy of nociceptors. In M. Bushnell, D. Smith, G. Beauchamp, & S. Firestei (Eds.), *The Senses: A comprehensive Reference* (pp. 11–41). Academic Press Inc.

Mills, S. E. E., Nicolson, K. P., & Smith, B. H. (2019). Chronic pain: a review of its epidemiology and associated factors in population-based studies. *British Journal of*

Anaesthesia, *123*(2), e273–e283. https://doi.org/10.1016/j.bja.2019.03.023

Mills, S., Torrance, N., & Smith, B. H. (2016). Identification and Management of Chronic Pain in Primary Care: a Review. *Current Psychiatry Reports*, *18*(2), 22. https://doi.org/10.1007/s11920-015-0659-9

Modarresi, S., Mukherjee, B., McLean, J. H., Harley, C. W., & Yuan, Q. (2016). CaMKII mediates stimulus specificity in early odor preference learning in rats. *Journal of Neurophysiology*, *116*(2), 404–410. https://doi.org/10.1152/jn.00176.2016

Müller, E. A. (1970). Influence of training and of inactivity on muscle strength. *Archives of Physical Medicine and Rehabilitation*, *51*(8), 449–462.

Nicholson, B. (2006). Differential diagnosis: nociceptive and neuropathic pain. *The American Journal of Managed Care*, *12*(9 Suppl), S256-62.

Norbury, T. A., MacGregor, A. J., Urwin, J., Spector, T. D., & McMahon, S. B. (2007). Heritability of responses to painful stimuli in women: a classical twin study. *Brain : A Journal of Neurology*, *130*(Pt 11), 3041–3049. https://doi.org/10.1093/brain/awm233

Ohnhaus, E. E., & Adler, R. (1975). Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain*, *1*(4), 379–384. https://doi.org/10.1016/0304-3959(75)90075-5

Ojeda, B., Salazar, A., Duenas, M., Torres, L. M., Mico, J. A., & Failde, I. (2014). The impact of chronic pain: the perspective of patients, relatives, and caregivers. *Families, Systems & Health : The Journal of Collaborative Family Healthcare*, *32*(4), 399–407. https://doi.org/10.1037/fsh0000069

Orhan, C., Van Looveren, E., Cagnie, B., Mukhtar, N. B., Lenoir, D., & Meeus, M. (2018). Are Pain Beliefs, Cognitions, and Behaviors Influenced by Race, Ethnicity, and Culture in Patients with Chronic Musculoskeletal Pain: A Systematic Review. *Pain Physician*, *21*(6), 541–558.

Osborne, J., & Waters, E. (2002). Four Assumptions of Multiple Regression That Researchers Should Always Test. *Practical Assessment, Research & Evaluation*, *8*.

Panken, G., Hoekstra, T., Verhagen, A., van Tulder, M., Twisk, J., & Heymans, M. W. (2016). Predicting chronic low-back pain based on pain trajectories in patients in an occupational setting: an exploratory analysis. *Scandinavian Journal of Work, Environment & Health*, *42*(6), 520–527. https://doi.org/10.5271/sjweh.3584

Paul, M., & Leibovici, L. (2014). Systematic review or meta-analysis? Their place in the evidence hierarchy. In *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* (Vol. 20, Issue 2, pp. 97–100). https://doi.org/10.1111/1469-0691.12489

Paul, T. M., Soo Hoo, J., Chae, J., & Wilson, R. D. (2012). Central hypersensitivity in patients with subacromial impingement syndrome. *Archives of Physical Medicine and Rehabilitation*, *93*(12), 2206–2209. https://doi.org/10.1016/j.apmr.2012.06.026

Perl, E. R. (2007). Ideas about pain, a historical view. *Nature Reviews. Neuroscience*, *8*(1), 71–80. https://doi.org/10.1038/nrn2042

Phillips, A. C., Upton, J., Duggal, N. A., Carroll, D., & Lord, J. M. (2013). Depression following hip fracture is associated with increased physical frailty in older adults: the role of the cortisol: dehydroepiandrosterone sulphate ratio. *BMC Geriatrics*, *13*, 60. https://doi.org/10.1186/1471-2318-13-60

Poleshuck, E. L., & Green, C. R. (2008). Socioeconomic disadvantage and pain. *Pain*, *136*(3), 235–238. https://doi.org/10.1016/j.pain.2008.04.003

Ringkamp, M., Srinivasa, R., Campbell, J., & Meyer, R. (2013). Peripheral mechanisms of cutaneous nociception. In McMahon, Koltzenburg, Tracey, & Turk (Eds.), *Wall and Melzack's Textbook of Pain* (pp. 1–30). Elsevier.

Rodriguez-Raecke, R., Niemeier, A., Ihle, K., Ruether, W., & May, A. (2009). Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*,

29(44), 13746–13750. https://doi.org/10.1523/JNEUROSCI.3687-09.2009

Sachs-Ericsson, N., Kendall-Tackett, K., & Hernandez, A. (2007). Childhood abuse, chronic pain, and depression in the National Comorbidity Survey. *Child Abuse & Neglect*, *31*(5), 531–547. https://doi.org/10.1016/j.chiabu.2006.12.007

Salaffi, F., Stancati, A., Silvestri, C. A., Ciapetti, A., & Grassi, W. (2004). Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *European Journal of Pain (London, England)*, *8*(4), 283–291. https://doi.org/10.1016/j.ejpain.2003.09.004

Schofferman, J. (2006). Restoration of Function: The Missing Link in Pain Medicine? *Pain Medicine*, *7*(suppl_1), S159–S165. https://doi.org/10.1111/j.1526-4637.2006.00131.x

Schopflocher, D., Taenzer, P., & Jovey, R. (2011). The prevalence of chronic pain in Canada. *Pain Research & Management*, *16*(6), 445–450. https://doi.org/10.1155/2011/876306

Schrepf, A., Harte, S. E., Miller, N., Fowler, C., Nay, C., Williams, D. A., Clauw, D. J., & Rothberg, A. (2017). Improvement in the Spatial Distribution of Pain, Somatic Symptoms, and Depression After a Weight Loss Intervention. *The Journal of Pain*, *18*(12), 1542–1550. https://doi.org/10.1016/j.jpain.2017.08.004

Shaw, W. S., Linton, S. J., & Pransky, G. (2006). Reducing sickness absence from work due to low back pain: how well do intervention strategies match modifiable risk factors? *Journal of Occupational Rehabilitation*, *16*(4), 591–605. https://doi.org/10.1007/s10926-006-9061-0

Sneddon, L. U. (2018). Comparative Physiology of Nociception and Pain. *Physiology (Bethesda, Md.)*, *33*(1), 63–73. https://doi.org/10.1152/physiol.00022.2017

Song, C.-Y., Lin, S.-F., Huang, C.-Y., Wu, H.-C., Chen, C.-H., & Hsieh, C.-L. (2016). Validation of the Brief Pain Inventory in Patients With Low Back Pain. *Spine*, *41*(15), E937–E942. https://doi.org/10.1097/BRS.0000000000001478

Staffa, S. J., Kohane, D. S., & Zurakowski, D. (2019). Quantile Regression and Its Applications: A Primer for Anesthesiologists. *Anesthesia & Analgesia*, *128*(4). https://journals.lww.com/anesthesia-analgesia/Fulltext/2019/04000/Quantile_Regression_and_Its_Applications__A_Primer.28.aspx

Stanhope, J. (2016). Brief Pain Inventory review. *Occupational Medicine (Oxford, England)*, *66*(6), 496–497. https://doi.org/10.1093/occmed/kqw041

Sterling, M., Hendrikz, J., & Kenardy, J. (2011). Similar factors predict disability and posttraumatic stress disorder trajectories after whiplash injury. *Pain*, *152*(6), 1272–1278. https://doi.org/10.1016/j.pain.2011.01.056

Stewart, W. F., Ricci, J. A., Chee, E., Morganstein, D., & Lipton, R. (2003). Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*, *290*(18), 2443–2454. https://doi.org/10.1001/jama.290.18.2443

Stratford, P., Gill, C., Westaway, M., & Binkley, J. (1995). Assessing Disability and Change on Individual Patients: A Report of a Patient Specific Measure. *Physiotherapy Canada*, *47*(4), 258–263. https://doi.org/10.3138/ptc.47.4.258

Teutsch, S., Herken, W., Bingel, U., Schoell, E., & May, A. (2008). Changes in brain gray matter due to repetitive painful stimulation. *NeuroImage*, *42*(2), 845–849. https://doi.org/10.1016/j.neuroimage.2008.05.044

Thompson, J. Y., Byrne, C., Williams, M. A., Keene, D. J., Schlussel, M. M., & Lamb, S. E. (2017). Prognostic factors for recovery following acute lateral ankle ligament sprain: a systematic review. *BMC Musculoskeletal Disorders*, *18*(1), 421. https://doi.org/10.1186/s12891-017-1777-9

Towards a Common Language for Functioning, Disability and Health ICF. (2002). World Health Organization.

Treede, R. D., Meyer, R. A., & Campbell, J. N. (1998). Myelinated mechanically insensitive afferents from monkey hairy skin: heat-response properties. *Journal of*

Neurophysiology, *80*(3), 1082–1093. https://doi.org/10.1152/jn.1998.80.3.1082

Treede, R., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B., First, M. B., Giamberardino, M. A., Kaasa, S., Kosek, E., Lavand'homme, P., Nicholas, M., Perrot, S., Scholz, J., Schug, S., Smith, B. H., … Wang, S.-J. (2015). A classification of chronic pain for ICD-11. *Pain*, *156*(6), 1003–1007. https://doi.org/10.1097/j.pain.0000000000000160

Trinderup, J. S., Fisker, A., Juhl, C. B., & Petersen, T. (2018). Fear avoidance beliefs as a predictor for long-term sick leave, disability and pain in patients with chronic low back pain. *BMC Musculoskeletal Disorders*, *19*(1), 431. https://doi.org/10.1186/s12891-018-2351-9

Turk, D. C., & Okifuji, A. (2002). Psychological factors in chronic pain: evolution and revolution. *Journal of Consulting and Clinical Psychology*, *70*(3), 678–690. https://doi.org/10.1037//0022-006x.70.3.678

Uman, L. S. (2011). Systematic reviews and meta-analyses. *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie Canadienne de Psychiatrie de l'enfant et de l'adolescent*, *20*(1), 57–59. https://pubmed.ncbi.nlm.nih.gov/21286370

Valet, M., Gundel, H., Sprenger, T., Sorg, C., Muhlau, M., Zimmer, C., Henningsen, P., & Tolle, T. R. (2009). Patients with pain disorder show gray-matter loss in pain-processing structures: a voxel-based morphometric study. *Psychosomatic Medicine*, *71*(1), 49–56. https://doi.org/10.1097/PSY.0b013e31818d1e02

van der Windt, D. A. W. M., Kuijpers, T., Jellema, P., van der Heijden, G. J. M. G., & Bouter, L. M. (2007). Do psychological factors predict outcome in both low-back pain and shoulder pain? *Annals of the Rheumatic Diseases*, *66*(3), 313–319. https://doi.org/10.1136/ard.2006.053553

van Hecke, O, Torrance, N., & Smith, B. H. (2013). Chronic pain epidemiology and its clinical relevance. *British Journal of Anaesthesia*, *111*(1), 13–18.

https://doi.org/10.1093/bja/aet123

van Hecke, Oliver, Torrance, N., & Smith, B. H. (2013). Chronic pain epidemiology - where do lifestyle factors fit in? *British Journal of Pain*, *7*(4), 209–217. https://doi.org/10.1177/2049463713493264

Vincent, J., & MacDermid, J. C. (2012). The Patient-Rated Elbow Evaluation (PREE). *Journal of Physiotherapy*, *58*(4), 274. https://doi.org/10.1016/S1836-9553(12)70134-0

Vlaeyen, J. W., & Linton, S. J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*, *85*(3), 317–332. https://doi.org/10.1016/s0304-3959(99)00242-0

Von Korff, M., Resche, L. Le, & Dworkin, S. F. (1993). First onset of common pain symptoms: a prospective study of depression as a risk factor. *Pain*, *55*(2), 251–258. https://doi.org/10.1016/0304-3959(93)90154-H

Voscopoulos, C., & Lema, M. (2010). When does acute pain become chronic? *British Journal of Anaesthesia*, *105 Suppl*, i69-85. https://doi.org/10.1093/bja/aeq323

Wade, D. T., & Halligan, P. W. (2017). The biopsychosocial model of illness: a model whose time has come. *Clinical Rehabilitation*, *31*(8), 995–1004. https://doi.org/10.1177/0269215517709890

Wells, N., Pasero, C., & McCaffery, M. (2008). Improving the Quality of Care Through Pain Assessment and Management. In R. Hughes (Ed.), *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*. Agency for Healthcare Research and Quality.

Wijma, A. J., van Wilgen, C. P., Meeus, M., & Nijs, J. (2016). Clinical biopsychosocial physiotherapy assessment of patients with chronic pain: The first step in pain neuroscience education. *Physiotherapy Theory and Practice*, *32*(5), 368–384. https://doi.org/10.1080/09593985.2016.1194651

Williamson A, & Hoggart B. (2005). Pain:a review of three commonly used rating scales. *Journal of Clinical Nursing*, *14*(7), 798–804.

Wilson, M. G., Lavis, J. N., & Ellen, M. E. (2015). Supporting chronic pain management across provincial and territorial health systems in Canada: Findings from two stakeholder dialogues. *Pain Research & Management*, *20*(5), 269–279. https://doi.org/10.1155/2015/918976

Wright, L. J., Schur, E., Noonan, C., Ahumada, S., Buchwald, D., & Afari, N. (2010). Chronic pain, overweight, and obesity: findings from a community-based twin registry. *The Journal of Pain*, *11*(7), 628–635. https://doi.org/10.1016/j.jpain.2009.10.004

Younger, J., McCue, R., & Mackey, S. (2009). Pain outcomes: a brief review of instruments and techniques. *Current Pain and Headache Reports*, *13*(1), 39–43. https://doi.org/10.1007/s11916-009-0009-x

1.7 Thesis purpose and layout

The purpose of this thesis is to fill some of the current gaps of knowledge in the chronic pain literature within the context of the biopsychosocial model using novel methodological approaches. The aim of each of the following chapters is to gain a better understanding of the factors that are associated with chronic pain following MSK injuries. Having more information regarding these factors will help the fight against the increasing prevalence of chronic pain which will ultimately lead to improving the quality of life of people as well as decreasing the financial healthcare burden that accompanies chronic pain. The aforementioned methodological shortcomings will be addressed in the papers of this thesis. This thesis is completed in a manuscript style format in which following the current chapter (i.e., chapter one), which provides background information, each chapter is a separate manuscript that has been published/submitted to peer-reviewed journals.

Chapter two of this thesis is a systematic review of the literature on the existence of a familial sub-type of complex regional pain syndrome (CRPS). To the author's knowledge, this is the first systematic review on this topic. CRPS can be one of the consequences of MSK injuries. It is important to synthesize all the available evidence on familial cases to understand the role of genetics and family on its development. This systematic review required a novel approach to integrating unusual literature since the types of studies that look at familial cases are different from the studies usually synthesized in systematic reviews. This manuscript was published in the Canadian Journal of Pain.

Chapter three examines the recovery trajectories of patients with DRFs and how baseline characteristics can identify people belonging to each class of recovery trajectory. Various physical, psychological, and social factors were examined including baseline levels of pain intensity, depression, education level, smoking history, and work status. The evaluation of outcomes in this study was done using latent growth curve analysis and GMM. This manuscript was published in Musculoskeletal Science and Practice.

Chapter four investigates the association between peritraumatic distress and the development of chronic pain in people with MSK injuries of any etiology. The analysis of this study was done using quantile regression, which is a statistical technique that examines the associations in the entire distribution of the dependent variable (chronic pain in this study) without being influenced by skewed data. A version of this manuscript has been submitted to Clinical Orthopedics and Related Research.

Chapter five is the discussion section of this thesis, where a summary of all the manuscripts and their impact will be discussed. Limitations and future directions will be discussed. In addition, implications of this work in terms of professional training and practice as well as policy will be discussed. Furthermore, plans will be laid out regarding knowledge translation. Lastly, a lay summary of each of the manuscripts will be provided.

Chapter 2

2 Does a familial subtype of complex regional pain syndrome exist? Results of a systematic review

This manuscript is published in the Canadian Journal of Pain.

Citation: Modarresi, S., Aref-Eshghi, E., Walton, D. M., & MacDermid, J. C. (2019). Does a familial subtype of complex regional pain syndrome exist? Results of a systematic review. *Canadian Journal of Pain*, *3*(1), 157-166.

2.1 Abstract

Background and Objective: Complex regional pain syndrome (CRPS) is a chronic condition characterized by severe regional pain, allodynia, hyperalgesia, and functional impairment. The aim of this systematic review is to investigate whether a familial subtype of CRPS (fCRPS) exists and to determine whether people with fCRPS have specific characteristics.

Methods: Databases CINAHL, Medline, PsycINFO, and PubMed were searched with no date limitation. Quality of reporting was assessed using the Scottish Intercollegiate Guidelines Network scale and the Joanna Briggs Institute's checklists.

Results: Eight studies were included. Family relationships were defined as any immediate (i.e., parents or siblings) or blood relatives. A combination of participants with known or unknown causes for CRPS was recruited. The studies in this review support the potential for the existence of fCRPS, although this included less than 25% of those affected. People with potential fCRPS showed more severe symptoms, more sites involved, a higher percentage of spontaneous onset, and earlier age at onset. An elevated sibling recurrence risk ratio of 5.6 (95% confidence interval [CI], 3.0 to 9.8) was reported for people under 50. None of the studies established a pattern of heritability. Therefore, the most likely explanation for heritability would be a multifactorial model in which cumulative and interactive Gene × Environment effects may be involved.

Conclusions: This systematic review supports the potential for the existence of fCRPS; however, all identified studies used uncontrolled case reports, case series, and case–control designs that cannot provide evidence of causation. Further studies are required to reveal the heritability and genetic structure of fCRPS.

2.2 Introduction

Complex regional pain syndrome (CRPS) is a painful and disabling syndrome that can affect the upper and/or lower extremities (Goebel, 2011). CRPS can be categorized into two types: CRPS I occurs spontaneously in the absence of any confirmed injury to the nerves and CRPS II is a type in which there is a known nerve injury (Casale et al., 2015).

CRPS I or II occurs more often in women and can happen at any age, although most studies report an average age of onset of about 40 (Allen et al., 1999; Maleki et al., 2000; Sandroni et al., 2003) The clinical features of CRPS are diverse and can include severe regional but non-dermatomal pain; allodynia; hyperalgesia; changes in skin temperature, texture, or color; and sudomotor and vasomotor dysfunction (Albazaz et al., 2008). This multifactorial array of symptoms as well as several potential underlying pathophysiological mechanisms give rise to the term “complex” in CRPS. Due in part to this complexity, the incidence of CRPS, which varies by injury, is poorly understood. Two retrospective population-based studies reported an incidence of 5.46 and 26.2 per 100,000 person-years in 1999 (Sandroni et al., 2003) and 2007 (de Mos et al., 2007), respectively. The much higher incidence reported in 2007 could be because of differences in population characteristics such as ethnicity, socioeconomic aspects, or incidence of fractures but is more likely due to differences in case definitions and validation (de Mos et al., 2007).

One mechanism proposed to explain the genesis of CRPS is genetics, which, if accurate, can mean that a familial subtype of this syndrome exists. Human genetic studies have revealed associations between CRPS and several major histocompatibility complex alleles. These include human leukocyte antigen (HLA)-DR6, HLA-DR13, HLADR2, HLA-DQ1, HLA-B62, and HLA-DQ8 (Daliri et al., 2016; Mailis & Wade, 1994; van de Beek et al., 2000; van Hilten et al., 2000; van Rooijen et al., 2012) as well as a polymorphism in tumor necrosis factor alpha promotor gene (Vaneker et al., 2002). A report of the involvement of HLA-1 in the spontaneous development of CRPS provides evidence of an interaction between severity of nerve damage and genetic factors in CRPS susceptibility (van de Beek et al., 2003). Genome-wide expression profiling using the whole blood has shown that HLA-A29.1, matrix metallopeptidase 9, alanyl aminopeptidase, histidine decarboxylase, granulocyte colony-stimulating factor 3 receptor, and signal transducer and activator of transcription 3 genes were highly expressed in those with CRPS compared to healthy controls (Jin et al., 2013). These findings support a genetic component, indicating that hereditary factors might play a role in the susceptibility to CRPS.

A familial vulnerability to CRPS has been reported (Bruscas et al., 2004; Galer et al., 2000). However, in addition to the potential genetic susceptibility to CRPS, it is important to recognize the role of the shared family environment of people with CRPS in its development. A systematic review that investigated the influence of stressful life events on the development of CRPS in adults indicated that there is evidence to support that patients with more experienced stressful events have higher chances of developing CRPS (Beerthuizen et al., 2009). A more recent study by Wager and colleagues examined this association in children and their results indicated that children with CRPS experienced more stressful events (Wager et al., 2015). It is possible that siblings or relatives in shared familial environments develop CRPS due to experiencing similar stressful events. Therefore, both genetic and environmental factors associated with CRPS development can potentially contribute to a familial subtype of the disease. As preventive, personalized medicine efforts have become a priority in chronic pain research, understanding the inheritance pattern in addition to the family history of CRPS may offer valuable information regarding risk, prognosis, and treatment decisions.

Here, we systematically review the literature and synthesize studies that have reported on the familial occurrence of CRPS. We investigate whether the available data conclude the existence of a familial subtype of CRPS and, using a qualitative synthesis process, we examine whether the patients belonging to this category have specific characteristics distinguishing them from the nonfamilial cases.

2.3 Methods

Prior to commencing this systematic review, the detailed protocol was registered on PROSPERO, registration number CRD42018097359. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and checklist were used to plan and report the results of this study (Moher et al., 2009).

2.3.1 Data sources and search strategy

A detailed systematic search of the literature without date filter was conducted on January 7, 2019. Four major electronic databases were searched: CINAHL, MedLine, PsycINFO, and PubMed. The following keywords were used to search the databases:

“complex regional pain syndrome” OR “CRPS” OR “causalgia” OR “reflex sympathetic dystrophy” AND “familial” OR “family” OR “sibling” OR “relatives” OR “familial aggregation” OR “twin studies” OR “heredity” OR “hereditary” OR “heritability” OR “genetic” OR “genetics” OR “migration” OR “adoption.” In addition, the reference lists of extracted review articles and relevant articles with a focus on genetics and CRPS were manually searched.

2.3.2 Study selection

The following inclusion criteria were used to select the studies for this systematic review:

- Type of participants: At least one of the participant groups were people with CRPS.
- Type of investigation: Studies that fulfilled all or any of the following criteria:
    - compared the occurrence of CRPS between the relatives of the patients and the general population;
    - measured the concordance rate for the occurrence of CRPS among identical and fraternal twins;
    - described the occurrence of CRPS among related patients.

No restriction was set by age, sex, race, region of pain, duration of symptoms, or the type of study. The study selection process was performed in six stages by two independent reviewers (SM and EA): (1) databases were searched using the search strategy described above; (2) duplicate articles were removed, (3) the bibliography sections of relevant articles were manually searched; (4) titles were screened; (5) abstracts were screened; (6) and full text of articles was screened against the inclusion criteria. When there was uncertainty about the eligibility of an article, a discussion was held and agreement was achieved by consensus. We did not include conference proceedings, books, dissertations, or unpublished data in this systematic review.

2.3.3 Data extraction and synthesis

Using a pre-established data extraction table, the following information was extracted by SM and crosschecked by EA from each article that met the inclusion criteria: name of the first author, year of publication, country, sample size, mean age (in years) and its standard deviation, percentage of females in the sample, region of pain, whether there was a known cause, diagnostic criteria used to identify cases, proportion of participants having familial CRPS (fCRPS), study design, type of family relationship, and the specific CRPS characteristics. The studies included in this review have a variety of designs and methodologies, meaning that a meta-analysis of the results was not possible. Hence, the results are presented as a descriptive summary in accordance with the PRISMA guidelines (Moher et al., 2009).

2.3.4 Quality assessment of individual studies

The quality of the studies in this review was assessed independently by two reviewers (SM and EA). For case–control studies, the tool developed by the Scottish Intercollegiate Guidelines Network was used (Harbour & Miller, 2001). This checklist, which consists of two sections, is a simple tool to assess the risk of bias and quality of individual case–control studies, and it is one of the recommended tools by the Agency for Healthcare Research and Quality (West et al., 2002). Section 1 examines the internal validity of the study and consists of 11 questions about the selection of participants, assessment methods, confounders, and statistical analysis. Section 2 reviews the overall assessment of the study by rating the methodological quality of the study based on responses to section 1. For case reports and case series, the Joanna Briggs Institute's (JBI) checklists were used, which are specific tools designed explicitly for these types of studies (JBI Institute, 2014). These two JBI checklists are widely accepted tools that have been established by the JBI and collaborators and accepted by the JBI scientific committee following extensive peer review (JBI Institute, 2014). The JBI checklist for case reports contains eight questions covering areas such as patient's demographic characteristics, history and timeline, the current clinical condition of the patient, diagnostic tests or assessment methods, treatment procedure(s), postintervention clinical condition, adverse events, as well as takeaway lessons from the study. The JBI checklist for case series

contains ten areas including inclusion criteria, identification and measurement of the condition in a standard and reliable way, clear reporting of the clinical information of the participants, reporting of the outcomes or follow-up results of cases, clear reporting of the presenting site(s)/clinic(s), and appropriateness of the statistical analysis.

The interrater agreement of the quality appraisal evaluation was assessed with Cohen's kappa coefficient using the Statistical Package for the Social Sciences (version 24.0; SPSS, Inc, Chicago, IL), with a value of at least 0.70 considered acceptable (Landis & Koch, 1977).

In this systematic review, although the quality of evidence for each study is informed by the specific critical appraisal tool for that study design, given the differences in study designs and evaluation tools, the overall quality of evidence is based on the more traditional levels of evidence. According to the Oxford rating system, greater confidence is allocated to results drawn case–control studies, with confidence decreasing as study designs move through case series and case reports ("Oxford Centre for Evidence-based Medicine," 2009). Therefore, regardless of individual scores (based on their specific evaluation tool), case series and case reports are considered as having lower levels of evidence compared to case–control studies.

2.4 Results

In total, 1311 articles were retrieved from the electronic database search (CINAHL = 62, Medline = 358, PsychINFO = 495, PubMed = 396). After removing duplicates and adding articles from the manual search, 896 articles were title screened, of which 844 were excluded because they were clearly not related to the research question. The abstracts and full text of the remaining 52 articles were screened against the inclusion criteria and eight studies were chosen for inclusion. Figure 1 shows a flow diagram of the article selection process in accordance with the PRISMA guideline (Moher et al., 2009).

2.4.1 Study characteristics

The included studies featured two case reports (Albert & Ott, 1983; Erdmann & Wynn-Jones, 1992), three case series (Higashimoto et al., 2008; Shirani et al., 2010; Veldman et

al., 1993), and three case–control studies (de Rooij et al., 2009; de Rooij et al., 2009; Hühne et al., 2004). The studies in this review represent 1460 people with CRPS, among whom 153 were deemed to be familial cases. Sample sizes ranged from two (Erdmann & Wynn-Jones, 1992) to 829 (Veldman et al., 1993), and the age range of participants was from infancy to 85 (Veldman et al., 1993). Five of the eight studies included more females than males (de Rooij et al., 2009; de Rooij et al., 2009; Hühne et al., 2004; Shirani et al., 2010; Veldman et al., 1993). The types of family relationship were any immediate family member, including parents (Hühne et al., 2004; Shirani et al., 2010) and siblings (Albert & Ott, 1983; de Rooij et al., 2009; Erdmann & Wynn-Jones, 1992; Higashimoto et al., 2008) or any other blood relative (de Rooij et al., 2009; Veldman et al., 1993). In the clinical samples, various regions of pain were reported, including hips (Albert & Ott, 1983), arms (de Rooij et al., 2009; de Rooij et al., 2009; Erdmann & Wynn-Jones, 1992; Shirani et al., 2010; Veldman et al., 1993), legs (de Rooij et al., 2009; de Rooij et al., 2009; Shirani et al., 2010; Veldman et al., 1993), or both extremities (de Rooij et al., 2009; de Rooij et al., 2009; Higashimoto et al., 2008). In one study the cause of CRPS for all patients was unknown (Albert & Ott, 1983), in two studies the cause was known for all participants (Erdmann & Wynn-Jones, 1992; Hühne et al., 2004), and in the rest a mixture of participants with known or unknown causes for CRPS were recruited; however, it was noted that in these studies the percentage of participants with no cause was less than 25% (de Rooij et al., 2009; de Rooij et al., 2009; Higashimoto et al., 2008; Shirani et al., 2010; Veldman et al., 1993). All five studies that were published after 1994 stated that their method of CRPS diagnosis was based on the criteria endorsed by the International Association for the Study of Pain (IASP) in 1994 (de Rooij et al., 2009; de Rooij et al., 2009; Higashimoto et al., 2008; Hühne et al., 2004; Shirani et al., 2010). One study explicitly stated that a medical doctor used these criteria for diagnosis (de Rooij et al., 2009). One study used the following criteria for CRPS diagnosis:

● Criterion 1: Four out of 5 positive tests from

- unexplained diffuse pain,
- difference in skin color relative to the other limb,

- diffuse oedema,
- difference in skin temperature relative to the other limb,
- limited active range of motion.

● Criterion 2: Occurrence or increase of above signs and symptoms after use

● Criterion 3: Above signs and symptoms present in an area larger than the area of primary injury or operation and including the area distal to the primary injury (Veldman et al., 1993).

The method for CRPS diagnosis was not reported in two studies (Albert & Ott, 1983; Erdmann & Wynn-Jones, 1992). It should be noted that these three studies were published before the official diagnostic criteria for CRPS became available in 1994. Ethics statement was not reported in four studies (Albert & Ott, 1983; Erdmann & Wynn-Jones, 1992; Shirani et al., 2010; Veldman et al., 1993). A summary of study characteristics is presented in Table 1.

2.4.2 Quality assessment results

The quality assessment showed that all of our studies had an adequately acceptable quality with a mean score of 64% for case–control studies (de Rooij et al., 2009; de Rooij et al., 2009; Hühne et al., 2004), 87% for case reports (Albert & Ott, 1983; Erdmann & Wynn-Jones, 1992), and 90% for all of the case series (Higashimoto et al., 2008; Shirani et al., 2010; Veldman et al., 1993). When interpreting these scores, it is important to note that they are measured on independent tools specific to the type of study, and these scores cannot be compared with each other across the studies with different designs. Common deficits in reporting among the studies included not using specific criteria for CRPS diagnosis (Albert & Ott, 1983; Erdmann & Wynn-Jones, 1992; Shirani et al., 2010), not comparing participants and nonparticipants (de Rooij et al., 2009; de Rooij et al., 2009; Hühne et al., 2004), and not taking confounding factors into account (de Rooij et al., 2009; de Rooij et al., 2009; Hühne et al., 2004). In this systematic review, it is paramount to recognize that the evidence comes from observational studies, the majority of which

are case reports (Albert & Ott, 1983; Erdmann & Wynn-Jones, 1992) and case series (Higashimoto et al., 2008; Shirani et al., 2010; Veldman et al., 1993). Thus, even though the quality of individual studies is acceptable, our confidence in the results is not high because of the design of these studies. The interrater agreement between the raters was assessed using the Cohen's kappa, which showed a value of 0.82 (95% confidence interval [CI], 0.68 to 0.96, $P < 0.001$), corresponding to a substantial level of agreement (Landis & Koch, 1977).

2.4.3 Incidence of familial occurrence of CRPS

A search among studies to identify the rate of fCRPS reveals that indicators of familial aggregation are defined variably and confined to a small portion of the participants. This extent of familial aggregation across studies has been reported to range from negligible (Veldman et al., 1993) to 25% (Higashimoto et al., 2008) of the CRPS population. It should be noted that in the study with negligible reporting of fCRPS (0.6%), the question regarding fCRPS was not consistently asked from all participants (Veldman et al., 1993), and we consider this a major methodological limitation. Due to this shortcoming, the incidence of fCRPS in this study may have been underestimated and not reflect the true rate of occurrence. In a study by de Rooij and colleagues, which examined the risk of CRPS in 405 cases, the rate of fCRPS was reported to be 4% in "confirmed" cases (de Rooij et al., 2009). When including "possibly affected" cases in that same study, the incidence of fCRPS occurrence increased to 6% (de Rooij et al., 2009). In this study, confirmed cases were those for which a clinician had made a formal diagnosis, but information regarding the possibly affected cases was obtained through self-report by the siblings. In another study of 60 people with CRPS with a history of injury prior to the disease onset, 12 cases (20%) were found to also have affected family members (Hühne et al., 2004). A clinical review of an additional 69 cases of CRPS identified a total of four families with more than two members (13%) affected by the condition (Shirani et al., 2010). This rate increased to 15% when both confirmed and unconfirmed cases were considered. In this study, the "unconfirmed" cases were not formally examined but the family history was only reported by the patients (Shirani et al., 2010). The authors of this study failed to confidently assign a Mendelian pattern of inheritance to the pedigrees and

proposed that the fCRPS occurrence might be modified by genetic heterogeneity, variable penetrance, epigenetic regulations, or environmental factors (Shirani et al., 2010).

2.4.4 Characteristics of familial CRPS

The earliest study in this systematic review was published in 1983, reporting the first evidence for a familial form of CRPS (Albert & Ott, 1983). This case report presented three brothers with sudden occurrences of pain in the hip without any previous injury or trauma. The occurrence of CRPS in hips is rare; however, the authors argue that there was no evidence of other diseases, including cardiac, endocrine, pulmonary, or neurological. The clinical presentations, radiological findings, or course of progression and improvement of the disease was reported to follow the common patterns seen in patients with CRPS; however, the occurrence in a familial form led the authors to propose that a genetic predisposition could be involved (Albert & Ott, 1983). Of interest, all three brothers had an identical HLA formula (A 1–30 or 31; B 8–37;BW4–6; DR 7-x;MT3–1, 2), which is also a rare coincidence (Albert & Ott, 1983). No article on the familial incidence of CRPS is found again until 1993 when Erdmann and Wynn-Jones described the cases of two siblings presenting with CRPS four years apart (Erdmann & Wynn-Jones, 1992). Both events happened within six weeks following mild injuries to the upper extremities and progressed to vascular pathology, osteoporosis, and eventually distal gangrene. The two cases shared striking similarities in the initiation, progression, and outcome of the disease; both had an initial encouraging response to treatment with the later deterioration of the symptoms leading to distal limb amputations but, interestingly, neither of the siblings suffered from phantom limb pain. In addition, they shared some common psychological factors that are known to be associated with poor prognosis, including lack of motivation and suspected self-interference, ranging from the tight squeezing of the arm through to ligature bruising (Erdmann & Wynn-Jones, 1992). These features indicated that a shared family history might be involved in both the incidence and prognosis of CRPS, but whether the common psychological factor was causal or consequential was not addressed (Erdmann & Wynn-Jones, 1992). Two other studies reported psychological disturbances but only in two of their participants with fCRPS, and they were less severe, including stress (Higashimoto et al., 2008), emotional

irritability, and anxiety (Shirani et al., 2010). Similarly, it is not clear from these studies whether the psychological disturbances are symptoms of CRPS or they are shared consequences of the severe symptoms. de Rooij and colleagues reported on 31 families with two to five affected family members (84 people with fCRPS), comparing those against cases with no obvious familial connection (de Rooij, de Mos, Sturkenboom, et al., 2009). Those with familial links had a younger age at onset, a higher percentage of spontaneous onset, more temperature and color asymmetry, more sweating and trophic disturbances, and more often had multiple affected extremities and dystonia (de Rooij et al., 2009). A study by Shirani and colleagues also reported that those with a familial connection qualitatively developed the disease at an earlier age and had more migraine headaches and more bilateral involvement compared to the nonfamilial cases (Shirani et al., 2010). Another study hypothesized that a subset of pediatric cases of CRPS that also presented with additional neuromuscular conditions might be caused by mitochondrial DNA defects (Higashimoto et al., 2008). Their investigation of 500 patients with CRPS identified seven families with such functional features, mostly gastrointestinal dysmotility, migraine, cyclic vomiting, and chronic fatigue. All of these families met the criteria for a maternal mitochondrial inheritance (Higashimoto et al., 2008). This finding suggested that mitochondrial inheritance might explain some familial cases of CRPS that also present with additional functional symptoms (Higashimoto et al., 2008).

2.4.5 The magnitude of familial involvement in CRPS

The study by de Rooij et al. is the only one to date to have reported on familial aggregation of CRPS (de Rooij et al., 2009). The analysis of 405 patients with CRPS using sibling recurrence risk ratio in all “possibly affected” siblings was estimated to be 1.8 (95% CI, 1.1 to 2.7), meaning that there is a 1.8-fold increased risk of CRPS occurrence among siblings of affected persons as compared to the general population. When all possibly affected siblings were stratified into age groups, the risk ratio for people under the age of 50 was estimated at 5.6 (95% CI, 3.0 to 9.8), indicating that the risk is much higher in younger persons. The analysis of this cohort for people older than 50 revealed that the risk was not significantly different from the general population (0.6; 95% CI, 0.3 to 1.0). Further detailed evaluation identified 16 confirmed cases in their

siblings, which did not indicate a significant aggregation when compared with the incidence of the disease in the general population. Similarly, again restricting the analysis to cases younger than 50 years old, a recurrence risk ratio of 3.4 (95% CI, 1.5 to 6.8) was found, indicating a more pronounced role for hereditary factors in the cases with a younger age of onset (de Rooij et al., 2009).

2.5 Discussion

This systematic review examined the limited pool of evidence on familial occurrences of CRPS to elucidate the extent of risk given family history and whether differences in phenotypes might characterize a familial subtype of CRPS. Given the dearth of evidence, we did not exclude by study design because the available literature is mainly composed of individual case reports, case series, and identification of familial cases among populations affected by CRPS. Only one article specifically studied the familial aggregation in CRPS (de Rooij et al., 2009). Though the evidence is limited, it does point to the potential for a familial form of CRPS, which accounts for a minority of those affected (i.e., <25%). Less frequent history of trauma and more associated symptoms, diffuse symptoms, and a larger component of central and systemic symptoms may characterize this phenotype. These include more migraine headaches (Higashimoto et al., 2008; Shirani et al., 2010), more temperature and color asymmetry (de Rooij et al., 2009), more sweating and trophic disturbances (de Rooij et al., 2009), vascular pathology (Erdmann & Wynn-Jones, 1992), osteoporosis (Erdmann & Wynn-Jones, 1992), distal gangrene (Erdmann & Wynn-Jones, 1992), gastrointestinal motility (Higashimoto et al., 2008), cyclic vomiting (Higashimoto et al., 2008), chronic fatigue (Higashimoto et al., 2008), dystonia (de Rooij et al., 2009), more sites involved (de Rooij et al., 2009), bilateral involvement, (Shirani et al., 2010) a higher percentage of spontaneous onset (de Rooij et al., 2009), and earlier age at onset (de Rooij et al., 2009; de Rooij et al., 2009; Shirani et al., 2010), though in every case these have been qualitatively explored without inferential analyses. Despite some consistency, the study designs preclude inference and offer little evidence of causation. As such, the current state of evidence can best be summarized as presenting potentially testable hypotheses in more rigorous designs.

One criterion for causation is biologic plausibility (Hill, 1965), which the current evidence has started to provide, but the mechanisms underlying familial aggregation are still far from clear. Mitochondrial involvement has been observed in a subset of cases presenting with neuromuscular symptoms in addition to the typical CRPS features (Higashimoto et al., 2008), which may represent an understudied mechanism of this condition. No study was able to establish a pattern of inheritance for the familial group according to Mendel's laws; thus, the most likely explanation for heritability would be a polygenic or multifactorial model, although other forms of non-Mendelian genetic involvement, such as Gene × Environment and gene–gene interactions, and epigenetics cannot be ruled out. For instance, it has been found that people living in disadvantaged neighborhoods have a higher chance of developing chronic pain after motor vehicle collisions; of interest, this effect is modifiable by a single nucleotide polymorphism in the promoter of FKBP5, a functional regulator of glucocorticoid receptor sensitivity (Ulirsch et al., 2014). In addition, epigenetic modifications including DNA methylation and histone modifications are proposed to be involved in the establishment of gene regulatory status in primary sensory neurons of dorsal root ganglion associated with pain hypersensitivity in chronic pain conditions (Liang et al., 2015). Epigenetic markers are modifiable, and at least one study has shown that downregulating phosphorylation of serine 10 (S10) in histone 3 in superficial spinal dorsal horn neurons reduces hyperalgesia and provides a promising new direction for chronic pain therapy (Torres-Perez et al., 2017). Shared environments by siblings and relatives should also be accounted for as a plausible mechanism for the occurrence of fCRPS. Previous research has shown that adverse life events are associated with the development of CRPS (Beerthuizen et al., 2009; Wager et al., 2015), and there is a high chance for the possibility of family members to share adverse life events. In fact, the most significant stressful life events that have been shown to be associated with the development of CRPS are family related (Wager et al., 2015). Sherry and Weisman examined the social environment of children with CRPS and indicated that CRPS can be a stress-related disease because their participants experienced stressful events such as marital discord between parents and sexual abuse (Sherry & Weisman, 1988). These results were further confirmed in a study by Kachko and colleagues that reported that migration history, low socioeconomic status,

divorced parents, chronic disorders of other family members, and controlling behavior of parents were seen in patients with CRPS (Kachko et al., 2008).

Due to the clinical heterogeneity of CRPS and its rarity, genome-wide association studies have been difficult to design, and the only genome-wide association study performed to date has failed to identify a common single nucleotide polymorphism to be associated with the disease (Janicki et al., 2016). The only genetic associations reported for CRPS are with HLA genotypes (de Rooij et al., 2009; van de Beek et al., 2003; van Rooijen et al., 2012), which were not reproduced in a subsequent study (Janicki et al., 2016), possibly due to phenotype heterogeneity, which may have weakened the association signals. All of these studies have been conducted on small sample sizes. Therefore, large-scale genetic association studies aimed at detecting slight genetic variations associated with CRPS are still needed to identify genetic variants contributing to the heritability of CRPS. Given that our systematic review indicates that hereditary factors may have a more prominent role in a subset of patients, performing such studies on familial cases has the potential to improve power in detecting such small genetic variant associations.

The major limitation of this systematic review rests on the limitation of the existing literature in that there are no publications attempting to answer the question regarding the involvement of genetics versus the environment in fCRPS. A lack of consistent case definitions, inconsistent collection of family history, retrospective data (subject to recall bias), poor integration of clinical and genetic phenotype test protocols, and the lack of large cohorts needed to estimate rare events with precision have all undermined the confidence in the findings to date. Familial aggregation measures should not be confused with evidence for causation by genetics. At best, they may reveal a potential role for shared characteristics between family members, composed of both genetics and environment. To distinguish between the involvement of genetics versus environment, the heritability of CRPS should be estimated using indices most commonly measured using twin studies. According to our search, no such twin studies have been conducted, and doing so would be challenging if not impossible in humans, in that both twins would also need to have been exposed to the same or similar inciting event (e.g., trauma). This may be more readily conducted using animal models. A second limitation is that the

current literature is lacking in data from participants stratified by phenotype. Phenotypic heterogeneity in CRPS is an important indicator that is not accounted for in estimating the familial recurrence risk ratio of CRPS. In addition, the only aggregation study performed to date on CRPS will need to be replicated in a different cohort. This is of particular importance given that both familial aggregation and heritability can be population specific (Aref-Eshghi et al., 2014). Another limitation is that all of the studies used uncontrolled case reports, case series, and case–control designs that cannot provide evidence of causation. However, they provide evidence of association, which can construct a basis for investigation of the causative factors. Finally, three of our included studies were published before the IASP diagnostic criteria for CRPS became available in 1994; therefore, the diagnostic accuracy of these studies may be lower. It is essential to state that the diagnosis (and treatment) of CRPS has been a challenge to clinicians for a long time, often leading to false diagnoses even following the 1994 release of IASP official diagnostic criteria (Chang et al., 2019). Our inclusion of results from papers published prior to these criteria may add heterogeneity to the results, but we felt that it is important, given the dearth of literature, to conduct a comprehensive review that highlights the gaps in current knowledge. Despite the limitations in the pool of evidence, prior authors have identified the potential for a familial subtype of CRPS and, given that the presentation and prognosis for this familial type seems to be particularly negative, this systematic review does have the potential to impact clinical decisions. In our opinion, awareness of this potential is a valuable contribution of this article. We have provided potential mechanistic explanations that appear to be promising directions for further exploration in this relatively understudied clinical condition.

In summary, the findings of this review indicate the potential for a familial risk for CRPS to exist, particularly in those with an earlier age at onset and more severe presentation. Establishment of a familial subtype of CRPS justifies estimating the role of environment versus genetics in the disease and conducting molecular studies and searching for predisposing genes. This will require substantial improvements in standardized data collection and the use of other study designs, such as twin and genetic association studies. Such studies might provide a clearer understanding of the pathophysiology of the disease and help targeted screening and therapy for patients at risk.

2.6 References

Albazaz, R., Wong, Y. T., & Homer-Vanniasinkam, S. (2008). Complex regional pain syndrome: a review. Annals of Vascular Surgery, 22(2), 297–306. https://doi.org/10.1016/j.avsg.2007.10.006

Albert, J., & Ott, H. (1983). Three brothers with algodystrophy of the hip. Annals of the Rheumatic Diseases, 42(4), 421–424.

Allen, G., Galer, B. S., & Schwartz, L. (1999). Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients. Pain, 80(3), 539–544.

Aref-Eshghi, E., Rahman, P., Hongwei, Z., Martin, G., Furey, A., Roger, G., … Zhai, G. (2014). Attempt to replicate the published osteoarthritis-associated genetic variants in the Newfoundland & Labrador Population. Journal of Orthopedics and Rheumatology, 1(3), 5.

Beerthuizen, A., van 't Spijker, A., Huygen, F. J. P. M., Klein, J., & de Wit, R. (2009). Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1) in adults? A systematic review. Pain, 145(1–2), 52–59. https://doi.org/10.1016/j.pain.2009.05.003

Bruscas Izu, C., Beltran Audera, C. H., & Jimenez Zorzo, F. (2004). [Polytopic and recurrent reflex sympathetic dystrophy in lower limbs in two siblings]. Anales de medicina interna (Madrid, Spain : 1984), 21(4), 183–184.

Casale, R., Atzeni, F., & Sarzi-Puttini, P. (2015). From Mitchell's causalgia to complex regional pain syndromes: 150 years of definitions and theories. Clinical and Experimental Rheumatology. Italy.

Chang, C., McDonnell, P., & Gershwin, M. E. (2019). Complex regional pain syndrome - False hopes and miscommunications. Autoimmunity Reviews, 18(3), 270–278. https://doi.org/10.1016/j.autrev.2018.10.003

Daliri, K., Aref-Eshghi, E., Taranejoo, S., Modarresi, S., Ghorbani, A., Nariman, A., … Askari, H. (2016). Emerging Cytokines in Allergic Airway Inflammation: A Genetic Update. Current Immunology Reviews (Vol. 12). https://doi.org/10.2174/1573395511666150615230640

de Mos, M., de Bruijn, A. G. J., Huygen, F. J. P. M., Dieleman, J. P., Stricker, B. H. C., & Sturkenboom, M. C. J. M. (2007). The incidence of complex regional pain syndrome: a population-based study. Pain, 129(1–2), 12–20. https://doi.org/10.1016/j.pain.2006.09.008

de Rooij, A. M., de Mos, M., Sturkenboom, M. C. J. M., Marinus, J., van den Maagdenberg, A. M. J. M., van Hilten, J. J., … JJ, van H. (2009). Familial occurrence of complex regional pain syndrome. European Journal of Pain, 13(2), 171–177. https://doi.org/10.1016/j.ejpain.2008.04.004

de Rooij, A. M., de Mos, M., van Hilten, J. J., Sturkenboom, M. C. J. M., Gosso, M. F., van den Maagdenberg, A. M. J. M., … Marinus, J. (2009). Increased risk of complex regional pain syndrome in siblings of patients? Journal of Pain, 10(12), 1250–1255. https://doi.org/10.1016/j.jpain.2009.05.006

de Rooij, A. M., Florencia Gosso, M., Haasnoot, G. W., Marinus, J., Verduijn, W., Claas, F. H. J., … van Hilten, J. J. (2009). HLA-B62 and HLA-DQ8 are associated with Complex Regional Pain Syndrome with fixed dystonia. Pain, 145(1–2), 82–85. https://doi.org/10.1016/j.pain.2009.05.015

Erdmann, M. W., & Wynn-Jones, C. H. (1992). “Familial” reflex sympathetic dystrophy syndrome and amputation. Injury, 23(2), 136–138.

Galer, B. S., Henderson, J., Perander, J., & Jensen, M. P. (2000). Course of symptoms and quality of life measurement in Complex Regional Pain Syndrome: a pilot survey. Journal of Pain and Symptom Management, 20(4), 286–292.

Goebel, A. (2011). Complex regional pain syndrome in adults. Rheumatology, 50(10), 1739–1750. Retrieved from http://dx.doi.org/10.1093/rheumatology/ker202

Harbour, R., & Miller, J. (2001). A new system for grading recommendations in evidence based guidelines. BMJ (Clinical Research Ed.), 323(7308), 334–336.

Higashimoto, T., Baldwin, E. E., Gold, J. I., & Boles, R. G. (2008). Reflex sympathetic dystrophy: complex regional pain syndrome type I in children with mitochondrial disease and maternal inheritance. Archives of Disease in Childhood, 93(5), 390–397. https://doi.org/10.1136/adc.2007.123661

Hill, A. B. (1965). The environment and disease: Association or causation? Proceedings of the Royal Society of Medicine, 58, 295–300.

Hühne, K., Leis, S., Schmelz, M., Rautenstrauss, B., Birklein, F., Huhne, K., … Birklein, F. (2004). A polymorphic locus in the intron 16 of the human angiotensin-converting enzyme (ACE) gene is not correlated with complex regional pain syndrome I (CRPS I). European Journal of Pain, 8(3), 221–225. https://doi.org/http://dx.doi.org/10.1016/j.ejpain.2003.08.004

Institute, T. J. B. (2014). Joanna Briggs Institute Reviewers' Manual: 2014 edition. (E. Aromataris, Ed.) (2014th ed.). The Joanna Briggs Institute.

Janicki, P. K., Alexander, G. M., Eckert, J., Postula, M., & Schwartzman, R. J. (2016). Analysis of Common Single Nucleotide Polymorphisms in Complex Regional Pain Syndrome: Genome Wide Association Study Approach and Pooled DNA Strategy. Pain Medicine (Malden, Mass.), 17(12), 2344–2352. https://doi.org/10.1093/pm/pnw133

Jin, E.-H., Zhang, E., Ko, Y., Sim, W. S., Moon, D. E., Yoon, K. J., … Lee, W. H. (2013). Genome-wide expression profiling of complex regional pain syndrome. PloS One, 8(11), e79435. https://doi.org/10.1371/journal.pone.0079435

Kachko, L., Efrat, R., Ben Ami, S., Mukamel, M., & Katz, J. (2008). Complex regional pain syndromes in children and adolescents. Pediatrics International : Official Journal of the Japan Pediatric Society, 50(4), 523–527. https://doi.org/10.1111/j.1442-200X.2008.02625.x

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. Biometrics, 33(1), 159–174.

Liang, L., Lutz, B. M., Bekker, A., & Tao, Y.-X. (2015). Epigenetic regulation of chronic pain. Epigenomics, 7(2), 235–245. https://doi.org/10.2217/epi.14.75

Mailis, A., & Wade, J. (1994). Profile of Caucasian women with possible genetic predisposition to reflex sympathetic dystrophy: a pilot study. The Clinical Journal of Pain, 10(3), 210–217.

Maleki, J., LeBel, A. A., Bennett, G. J., & Schwartzman, R. J. (2000). Patterns of spread in complex regional pain syndrome, type I (reflex sympathetic dystrophy). Pain, 88(3), 259–266.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of Clinical Epidemiology, 62(10), 1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005

Oxford Centre for Evidence-based Medicine. (2009). Oxford Centre for Evidence-Based Medicine - Level of Evidence. Retrieved from https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

Sandroni, P., Benrud-Larson, L. M., McClelland, R. L., & Low, P. A. (2003). Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain, 103(1–2), 199–207.

Sherry, D. D., & Weisman, R. (1988). Psychologic aspects of childhood reflex neurovascular dystrophy. Pediatrics, 81(4), 572–578.

Shirani, P., Jawaid, A., Moretti, P., Lahijani, E., Salamone, A. R., Schulz, P. E., & Edmondson, E. A. (2010). Familial occurrence of complex regional pain syndrome. The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques, 37(3), 389–394.

Torres-Perez, J. V., Santha, P., Varga, A., Szucs, P., Sousa-Valente, J., Gaal, B., … Nagy, I. (2017). Phosphorylated Histone 3 at Serine 10 Identifies Activated Spinal Neurons and Contributes to the Development of Tissue Injury-Associated Pain. Scientific Reports, 7, 41221. https://doi.org/10.1038/srep41221

Ulirsch, J. C., Weaver, M. A., Bortsov, A. V, Soward, A. C., Swor, R. A., Peak, D. A., … McLean, S. A. (2014). No man is an island: living in a disadvantaged neighborhood influences chronic pain development after motor vehicle collision. Pain, 155(10), 2116–2123. https://doi.org/10.1016/j.pain.2014.07.025

van de Beek, W.-J. T., Roep, B. O., van der Slik, A. R., Giphart, M. J., & van Hilten, B. J. (2003). Susceptibility loci for complex regional pain syndrome. Pain, 103(1–2), 93–97.

van de Beek, W. J., van Hilten, J. J., & Roep, B. O. (2000, August). HLA-DQ1 associated with reflex sympathetic dystrophy. Neurology. United States.

van Hilten, J. J., van de Beek, W. J., & Roep, B. O. (2000). Multifocal or generalized tonic dystonia of complex regional pain syndrome: a distinct clinical entity associated with HLA-DR13. Annals of Neurology, 48(1), 113–116.

van Rooijen, D. E., Roelen, D. L., Verduijn, W., Haasnoot, G. W., Huygen, F. J. P. M., Perez, R. S. G. M., … AM, van den M. (2012). Genetic HLA Associations in Complex Regional Pain Syndrome With and Without Dystonia. Journal of Pain, 13(8), 784–789. https://doi.org/10.1016/j.jpain.2012.05.003

Vaneker, M., Laan, L., Allebes, W., & Goris, R. J. (2002). Genetic factors associated with complex regional pain syndrome 1: HLA DRB and TNF alpha promotor gene polymorphism. Disabil Med (Vol. 2).

Veldman, P. H., Reynen, H. M., Arntz, I. E., & Goris, R. J. (1993). Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet (London, England), 342(8878), 1012–1016.

Wager, J., Brehmer, H., Hirschfeld, G., & Zernikow, B. (2015). Psychological distress and stressful life events in pediatric complex regional pain syndrome. Pain Research &

Management, 20(4), 189–194. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26035287

West, S., King, V., Carey, T. S., Lohr, K. N., McKoy, N., Sutton, S. F., & Lux, L. (2002). Systems to rate the strength of scientific evidence. Evidence Report/Technology Assessment (Summary), (47), 1–11.

2.7 Figures

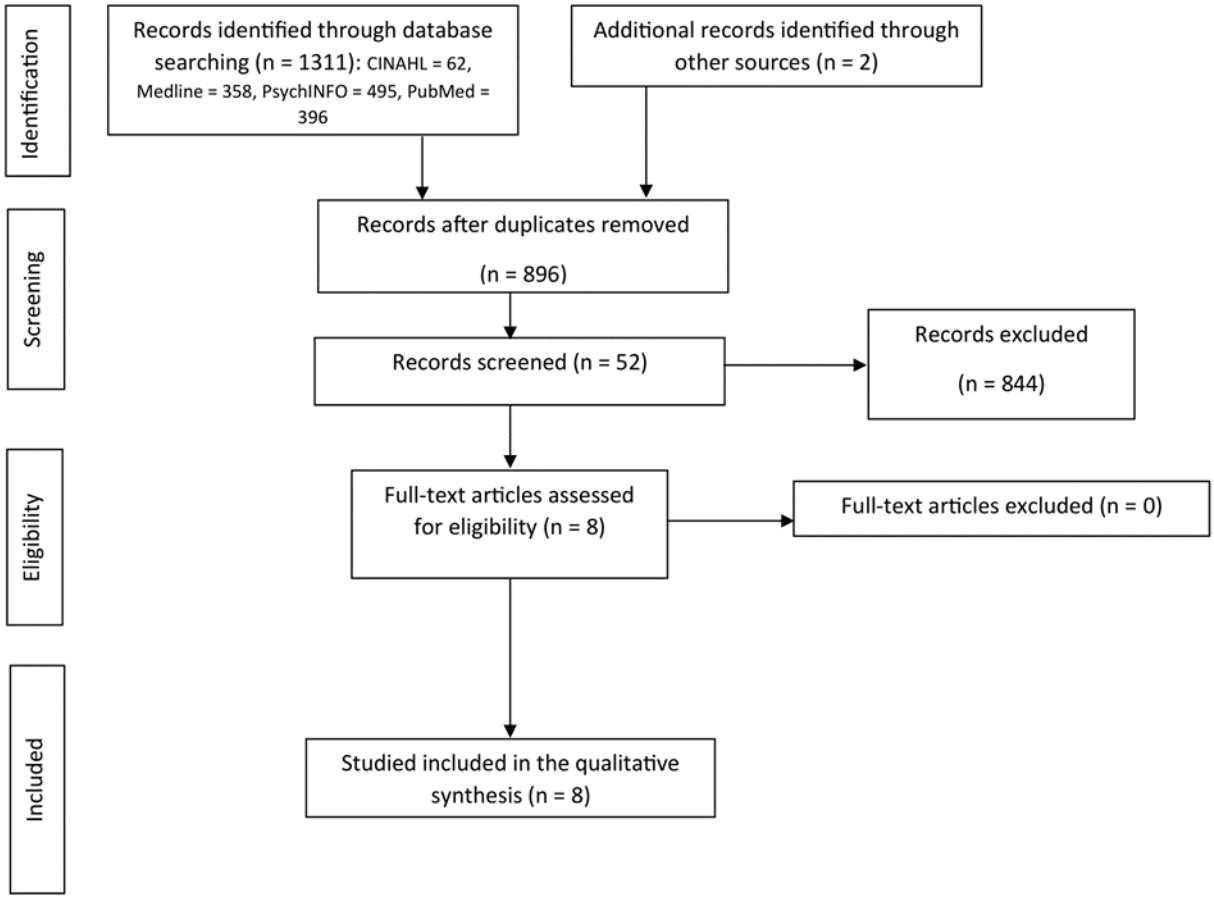


Figure 1. Flow diagram of the study selection process.

2.8 Tables

Authors, Year, Country	Sample size	Mean age (SD)	% female	Region of pain	Known cause?	CRPS diagnostic criteria	% fCRPS	Method of study	Type of family relationship	Quality
Albert and Ott, 1983, Switzerland	3 fCRPS	37 (5.9)	0%	hips	No	n/r	100%	Case report	Sibling	87%
M. de Rooji et al, 2009b, Netherland	405 CRPS (38 fCRPS)	40.6 (15.3)	85%	52% arm, 48% leg	13% no cause, 87% trauma, 22% fracture, 27% surgery, 13% soft tissue, 25% other	IASP	9.4%	Case control	Sibling	62%
M. de Rooji et al, 2009a, Netherland	84 fCRPS	36.7 (14.5)	83%	49% arm, 44% leg, 7% both	23% no cause, 77% trauma, 27% fracture, 20% surgery, 20% soft tissue, 9% other	IASP	100%	Case control	Any blood relative	54%
Veldman et al., 1993, Netherland	829 CRPS (5 fCRPS)	Varied between 9 and 85, median: 42	CRPS: 76%	CRPS: 59% arm, 41% leg	10% no cause, 65% trauma (mostly fracture), 19% surgery 15% inflammatory process, 4% other (injection, intravenous infusion, cerebrovascular accident)	Specific diagnostic criteria (similar to IASP)	0.6%	Case series	Any blood relative	90%
Erdmann and Wynn-Jones, 1992, England	2 fCRPS	35.5	50%	Both cases: hands	1: injury – slipped 1: injury – vehicle accident	n/r	100%	case report	Sibling	87%
Shirani et al., 2010, USA	69 CRPS (9 fCRPS)	fCRPS: 33.8 (12)	fCRPS : 70%	77.8% arm, 22.2% leg	22% no cause, 78% trauma or surgery	IASP	13%	Case series	Immediate family (parents/siblings)	90%
Higashimoto et al., 2008, USA	8 CRPS	1 at birth. The rest: 6.3 (4.8)	n/r	37.5% leg, 12.5% arm, 37.5% both, 12.5% n/r	28% no cause 2: surgery 1: traumatic fracture 1: a fall	IASP	25%, the rest unclear.	Case series	2 siblings	90%
Huhne et al., 2004, Germany	60 (12 fCRPS) 21 unaffected relatives	n/r	fCRPS : 92%, sCRPS : 71%	n/r	100% known cause – traumatic fracture or surgery	IASP	20%	Case control	Immediate family	76%

Table 1. Summary of study details for papers included in this systematic review (n=8).

SD, standard deviation; CRPS, complex regional pain syndrome; fCRPS, familial complex regional pain syndrome; n/r, not reported; IASP, International Association for the Study of Pain; sCRPS, sporadic complex regional pain syndrome

Chapter 3

3 Depression affects the recovery trajectories of patients with distal radius fractures: A latent growth curve analysis

This manuscript is published in Musculoskeletal Science and Practice.

Citation: Modarresi, S., Suh, N., Walton, D. M., & MacDermid, J. C. (2019). Depression affects the recovery trajectories of patients with distal radius fractures: A latent growth curve analysis. *Musculoskeletal Science and Practice*, *43*, 96-102.

3.1 Abstract

Background: Distal radius fractures (DRFs) are common and can lead to substantial pain and disability. Most people recover in six months, but some experience persistent pain and disability for one year or longer after injury. Therefore, it is important to understand the factors that can help predict poor recovery.

Objective: To identify recovery trajectories in DRF patients and to determine the factors that can help predict poor recovery.

Methods: Recovery was assessed in 318 patients using the Patient-Rated Wrist Evaluation scale at baseline, three, six, and 12 months. Demographic information was collected in addition to the Self-Administered Comorbidity Questionnaire, from which data regarding depression were extracted. Latent growth curve analysis (LGCA) was used to identify the recovery trajectories. Comparisons of proportion between the emergent classes were then conducted using chi-square and Kruskal-Wallis tests.

Results: The LGCA revealed three distinct trajectories (rapid-recovery: (69%), slow-recovery: (23%), and nonrecovery: (8%) as the best fit to the data. The proportion of people with depression was significantly greater in the non-recovery class (24%) compared to the slow (16%, p=0.04) and rapid-recovery (8%, p=0.03) classes. Additionally, the proportion of females was significantly lower in the non-recovery (64%, p=0.03) compared to the slow (85%, p=0.03) and the rapid-recovery classes (81%, p=0.048).

Conclusion: Recovery from DRF was best described using three different trajectories. Greater self-reported depression and a lower proportion of females in the non-recovery class were distinguishing factors between the classes. Patients who appear to be in slow-recovery or non-recovery classes may be followed more closely.

3.2 Introduction

Distal radius fractures (DRFs) are common injuries among all age groups, can lead to severe pain and disability (MacDermid et al., 2003; Porrino et al., 2014), and impose a

considerable economic burden on society (Shauver et al., 2011). MacDermid and colleagues describe recovery following DRFs as occurring in two phases; reparative, which is the soft tissue and bone healing phase, and rehabilitative, during which the slower, more sustained improvements occur (MacDermid et al., 2003). Most recovery happens in the first six months following the injury, however, a subset develop chronic pain and disability when measured at least one year later (Dewan et al., 2017; Lalone et al., 2014; MacDermid et al., 2001; MacDermid et al., 2003).

Previous studies that have used the Patient Rated Wrist Evaluation (PRWE) scale as an outcome measure to address predictors of functional outcomes following DRFs have evaluated the role of anatomic indicators (e.g., dorsal angulation and <15o radial inclination) (Cibulka et al., 2009; Grewal & MacDermid, 2007; Lalone et al., 2016; Lalone et al., 2014), patient characteristics (e.g., age and gender) (Bobos et al., 2017), bone health (Dewan et al., 2018), associated soft-tissue injury, (Kasapinova & Kamiloski, 2015, 2017), injury compensation (MacDermid et al., 2002), patient-centered care (Constand et al., 2014), occupation (MacDermid et al., 2007), and social support (Symonette et al., 2013). All of these factors have been shown to have some influence on PRWE outcomes after DRF, but they have provided limited information on mechanisms to explain the variance in functional recovery among people. A common characteristic of these prior studies is the modeling of outcomes at a single time point (e.g., six or 12 months) rather than exploring longitudinal trajectories.

Psychological factors have also been considered as predictors of recovery following DRF. In a cross-sectional study of people with various wrist conditions including DRF, kinesiophobia and catastrophic thinking were found to be significant predictors of outcome [measured with Disabilities of the Arm, Shoulder, and Hand (DASH)] (Das De et al., 2013). Depression is known to affect outcomes of many health conditions (Atay et al., 2016; Lichtman et al., 2008; Morris et al., 1992), and has been investigated as a predictor in DRF (Das De et al., 2013; Ring et al., 2006; Yeoh et al., 2016). In two cross-sectional studies the associations were shown using Pearson's correlation, where higher depression scores were associated with greater levels of disability (Das De et al., 2013; Ring et al., 2006). Yeoh and colleagues used multivariate regression to examine the effect

of depression [measured with Centre of Epidemiologic Studies Depression (CES-D)] on one-year post-DRF outcomes (using DASH scores) in a sample of older (>55 years) adults (Yeoh et al., 2016). After removing the effects of age, gender, treatment, comorbidities, and the occurrence of complications, they found that depression was the strongest predictor of DASH scores, where for every one point change in CES-D score, a proportional 2.9 point difference was observed in DASH scores (Yeoh et al., 2016). Still needed, are studies that define and predict the recovery trajectories rather than just predicting functional scores at a single time point.

There has yet to be a rigorous exploration of recovery trajectories in this population, and how baseline characteristics may predict those trajectories. This type of exploration has been conducted in other musculoskeletal trauma populations including traumatic neck (Sterling et al., 2010) and low back pain (Downie et al., 2016) and has led to the creation of clinical prognosis tools (Ritchie et al., 2013).

The first objective of this study was to identify the recovery trajectories in a large existing database of people following DRF using latent growth curve analysis (LGCA). The second objective was to compare proportions of potential predictor variables, including the presence of depression, age, sex, education level, smoking history, and work status across the emergent trajectories. The results may help clinicians identify those patients who are less likely to recover quickly.

3.3 Methods

3.3.1 Study design and participants

This was an exploratory study conducted using an existing database previously collected from consecutive patients of the Roth McFarlane Hand and Upper Limb Center in London, Ontario, Canada. The results of this study were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Elm et al., 2007). All participants in the database were diagnosed with DRF by a specialized hand surgeon. Other inclusion criteria were: the ability to speak and understand English, 18 years of age or older, and no other chronic or systemic disorders that would affect the participants' level of pain and disability. We only included

participants that had baseline data and were followed for six to 12 months post-injury. All data in the database were collected after obtaining informed consent from the participants. As a secondary analysis, the primary researcher received only de-identified data. The process for data collection and storage was approved by the Western University Research Ethics Board.

3.3.2 Primary outcome measure

The level of pain and disability experienced by patients at four time points (baseline, three, six, and 12 months) post-injury were measured using the PRWE. The PRWE is a 15-item region-specific patient-reported outcome measure that provides two subscales: pain and disability about the wrist and forearm (MacDermid, 1996). The maximum possible score on this scale is 100, with a higher number indicating higher pain or functional limitation. A recent systematic review of measurement properties of PRWE supported this tool's reliability and validity in this patient population (Mehta et al., 2015a).

3.3.3 Participants' demographics and characteristics

Participants' baseline characteristics and demographic information such as age, sex, education level, smoking status, and work status were collected through a standardized form during the initial visit that occurred within two to seven days from injury (baseline). Participants also completed a Self-Administered Comorbidity Questionnaire (SCQ) upon entry into the study. In this questionnaire, participants were asked to indicate whether they have any number of health conditions by answering yes or no. For the purposes of this study, the single item pertaining to depression was extracted and used as a binary potential predictor variable in our models.

3.3.4 Analytical approach

Participants' demographic data were calculated as means and standard deviations (SDs) or frequencies and percentages as appropriate. To compare the proportion of females and males, and to compare the age of females and males in the entire sample we used the t-test and chi-square test, respectively. A preliminary analysis was conducted using

Repeated measures one-way Analysis of Variance (RM ANOVA) to assess whether participants' PRWE scores differed significantly from one time point to the next. Time was the repeated variable and the PRWE scores were the dependent variables. Significant main effects were explored using Bonferroni's post-hoc test. LGCA was conducted in Mplus (version 6.12) (Muthén & Muthén, 2012) using Maximum likelihood-based Growth Mixture Modeling (GMM) with the quadratic term variance constrained at zero, to identify the classes of recovery trajectories based on PRWE scores at the four time points. This is a data-driven technique that is robust to missing values and for which hypotheses are emergent rather than set a priori. To determine the best number of classes that adequately described the data with the smallest number of distinct trajectories, we used the Bayesian Information Criterion (BIC)(Schwarz, 1978) and Akaike Information Criterion (AIC) (Akaike, 1998), entropy values (Celeux & Soromenho, 1996), and the Vuong Lo-Mendell-Rubin (VLMR) likelihood ratio test (Aitkin & Rubin, 1985). While there are no set thresholds for what is considered acceptable, smaller BIC and AIC levels and higher entropy indicate a better fit of the data to the model. The VLMR likelihood ratio test offers a statistical comparison of the fit of the data (residuals) of the k number of latent classes to a model with k-1 latent classes. An inferential statistic associated with the p-value is calculated and, if significant, the model with the k-1 number of latent classes is rejected (Geiser, 2012). This continues until the fit no longer improves in a meaningful way, at which point the last model to offer significant improvement that also made theoretical sense and had no class with less than 5% of the sample was accepted (Patrick, 2009). All participants were then coded according to their most likely class for comparison of baseline characteristics across groups. Proportions of those endorsing depression (yes/no), sex (male/female), education level (no post-secondary education/completed post-secondary education), smoking status (non-smoker/smoker), and work status (unable to work due to other reasons/unable to work due to injury/working part- or full-time), we used the chi-square test. To determine class differences with respect to age, we used the Kruskal-Wallis test, since the assumptions of Analysis of Variance were not met.

In this study, we employed the complete case approach in dealing with missing data for depression, PRWE (at baseline and three months), age, and sex variables. The complete

case approach is the simplest, most expedient way of handling missing data in which data from participants that have missing values for variables of interest are excluded from the statistical analysis (Mukaka et al., 2016). To handle the missing data for PRWE scores at six and 12 months we used the full maximum-likelihood estimation, which is a method of directly fitting the model to raw data without imputation. This is an accepted technique given that previous research has shown minimal change occurs between six and 12 months (MacDermid et al., 2001). All between-class comparisons were conducted using the Statistical Package for the Social Sciences (version 25.0) program (SPSS, Inc, Chicago, Illinois) accepting an alpha error rate (p-value) of 0.05 to indicate statistical significance.

3.4 Results

In total 318 participants with complete PRWE data for at least six months post-injury, depression, age, and sex were included in this study. Baseline characteristics and demographic information, as well as the PRWE scores (at all time points) of all participants without data imputation, are summarized in Table 1. The age range of participants was 20 to 87, a significant majority of participants were females (81%), and females were significantly older than males (mean age of 60.6 versus 55.4, $p < 0.01$). The mean PRWE score was 66.5/100 (SD = 21.2) at baseline and overall mean scores improved significantly at each follow-up time point ($F = 859.7$, $p < 0.001$, Figure 1). The majority of participants were non-smokers (88%), did not have post-secondary education (80%), and were not working due to various other reasons (e.g., other medical reasons, retired, student) (54%). Figure 1 is a plot of PRWE scores of all participants at all time points (i.e., baseline, 3-month, 6-month, and 1-year). Visual inspection indicated that recovery was not linear and so LGCA was conducted including a quadratic term to conform to the nature of the data. Table 2 presents the fit indicators for one, two, three, and four-class solutions. The three-class solution was accepted as the optimal model for describing the data based on BIC, AIC, entropy, and VLMR likelihood ratio test. Classification accuracy of the three-class model was high (all >85%) with no class having fewer than 5% of the overall sample. A sensitivity analysis (not shown) compared fit indicators of the quadratic model against a similar three-class linear model that further

supported better fit when the quadratic term was included. Figure 2 shows the recovery trajectories of the three classes. Class one (69% of the sample) started with a relatively lower score but recovered rapidly to report mild to no pain and disability at three months and was labeled a ‘rapid recovery’ class. Class two (23% of the sample) started with higher levels of pain and disability and a moderate and steady level of recovery with a mild residual disability at six months, labeled a ‘slow recovery’ class. Class three (8% of the sample) started with the highest level of pain and disability scores at baseline, showed little recovery, and continued to report high pain and disability at six months and one year, and was labeled a ‘non-recovery’ class.

Table 3 presents the characteristics of the independent patient variables across the three classes. When compared with the non-recovery class (64%), both the slow-recovery (85%, $x2 = 5.02$, $p = 0.03$) and the rapid-recovery class (81%, $x2 = 3.89$, $p < 0.05$) had a significantly higher percentage of females. Proportions of people with likely depression were higher in the non-recovery class (24%) compared to both the rapid-recovery (8%, $x2 = 6.36$, $p = 0.01$) and slow-recovery (16%, $x2 = 4.07$, $p = 0.04$) classes. None of the other patient characteristics were present in significantly greater proportion between classes.

Table 3 also shows other potential differences in participant variables between classes that did not reach statistical significance but may be worthy of further exploration. These include: the rapid-recovery class had the lowest baseline PRWE score and proportion of smokers, and the highest proportion of people that had finished post-secondary education and were working at baseline. The non-recovery class had the highest proportion of smokers, people that were unable to work due to the injury, and people with no post-secondary education, in addition to the highest baseline PRWE scores.

3.5 Discussion

In this study, we took a unique approach to answer the question of how patient factors affect health outcomes by categorizing patients with DRFs based on their recovery trajectories over a course of one year post-injury using LGCA. Patients who appear to be

in slow-recovery or non-recovery classes may require additional assessments, closer monitoring, supervised therapy, or other interventions to improve outcomes.

The majority of people in this study belonged to the rapid-recover class which is consistent with previous research showing that following DRF most people recover within six months (MacDermid et al., 2003). Additionally, earlier studies have shown that patients that take no or minimal time off work after DRFs have lower baseline PRWE scores and improve at each re-evaluation point (MacDermid et al., 2007), which is also in line with the trajectory of the rapid recovery class in our sample. While low rates of depression and a high proportion of females were the only significant predictors of rapid recovery, this class may be further described by a cluster of factors including lower baseline PRWE scores, early return to work, highest rates of non-smokers and people with post-secondary education. This is consistent with a previous study that found people with the highest level of education and lowest rates of smoking had the best outcome one year following DRFs (Grewal et al., 2007). An outcome model proposed for DRF suggests that when minimal physical and psychological impairments are present, minimal supervision (e.g., home exercise programs) might suffice for rehabilitation (Mehta et al., 2010).

A small number of people experience chronic pain and disability post-DRF(MacDermid et al., 2003; Swart et al., 2012), which can negatively affect daily activities and cause increased dependence (Vergara et al., 2016). In this study, the non-recovery class was described by the lowest proportion of females, the highest proportion of people endorsing co-morbid depression, and other trends towards having the highest baseline PRWE scores, being current smokers, not working due to this injury, and having no post-secondary education. A prior study that did not control for depression showed that when the PRWE pain subscale was greater than 35/50 at baseline, the risk of chronic pain at one year was 8.4 times higher (Mehta et al., 2015b). Golkari and colleagues also found that depression was associated with higher baseline pain or being off work longer following DRF (Golkari et al., 2015). In addition, Yeoh and colleagues found that people with baseline depression had significantly poorer one-year recovery than nondepressed patients (Yeoh et al., 2016). This association was also reported in a previous study that

used the PRWE to assess pain and compared patient characteristics and comorbidities of people with DRFs and found that certain disorders including depression were significantly higher in people that got worse one year post fracture (Lalone et al., 2017). Another study reported that depression was strongly associated with pain intensity and disability in patients recovering from one or more fractures (Vranceanu et al., 2014). Collectively, these and the current study suggest that there is a negative link between depression and recovery from DRF.

Pain is measured routinely, making it a convenient predictor for clinicians. However, it is arguably a coarse measure that provides little guidance for clinical decisions, in that it is hard to know how a clinician should modify their intervention in patients with a pain score of 40/50 rather than 30/50. As we used the consolidated PRWE score that included both pain and functional interference in a single number, we had the opportunity to explore other potential mechanisms for predicting recovery. In this study the single depression item from the SCQ was used, being a similarly low burden but a coarse measure that offered different insights into the potential mechanisms for predicting recovery. There are several such other tools that exist, such as the single 'downhearted and blue' question on the 36-item Short Form Health Survey (question #9) that is nearly identical to the question from SCQ, and has shown to be a powerful detector for depression (Berwick et al., 1991). While screening for depressive symptoms may not be part of a routine clinical evaluation, the results of the current and prior studies indicate that it may be of value and can be done with relatively low burden. The underlying mechanism of how depression can affect recovery following DRF is potentially complex. Depression could affect recovery directly or affect the way that it is self-assessed. Depression might affect recovery through health behaviors such as sleep, exercise, and nutrition. Other potential contributing factors are patients' adherence to rehabilitation programs during the recovery process (Lenze et al., 2004), which could be associated with reluctance and psychomotor retardation (Atay et al., 2016). It has also been suggested that depression can weaken the immune system which might contribute to an extended recovery period (Phillips et al., 2013). Furthermore, according to the cognitive-bias model of depression, people with depressive symptoms have a negative perspective about themselves (Beck, 1967), therefore, it is also possible that our participants with

depression had a negative outlook about their recovery and their self-reports were negatively biased despite no actual difference in outcomes to nondepressed counterparts.

Another finding of this study is that the proportion of females was the lowest in the non-recovery class. Studies that have compared DRF outcomes with respect to sex, report conflicting results (Amorosa et al., 2011; Cowie et al., 2015; Dewan et al., 2017; Grewal et al., 2007; Kurimoto et al., 2012; Lalone et al., 2017; MacDermid et al., 2002; Mehta et al., 2015b; Moore & Leonardi-Bee, 2008). Some studies that also used PRWE as the outcome measure six months (MacDermid et al., 2002), one year (Grewal et al., 2007; Lalone et al., 2017; Mehta et al., 2015b), and four years (Dewan et al., 2017) post-DRF concluded that sex has no influence on recovery (Grewal et al., 2007; Lalone et al., 2017; Mehta et al., 2015b). Similarly, using the DASH, sex was reported as a non-significant predictor of outcome one year post-DRF (Moore & Leonardi-Bee, 2008). Still, other studies have reported that women experience worse outcomes when examined at 18 months using the Hand20 (Kurimoto et al., 2012), 30 months using the DASH (Amorosa et al., 2011), and one year post-DRF using manual examinations (Cowie et al., 2015). It is important to note that these studies assessed outcome at one point in time, but here, we compared people based on their recovery trajectories. However, our finding that more men experienced a non-recovery trajectory was unexpected, and the potential reasons are merely hypotheses. First, it is possible that since DRF occurs more commonly in women and most studies have a majority of female volunteers, treatment algorithms may be more optimized for women. Second, due to the high prevalence of osteoporosis (which is a risk factor for poor prognosis) in women in the age group where DRF is most common, osteoporosis in men may have been under-recognized. Previous research has also shown that men are more likely not to receive treatment for osteoporosis (Jennings et al., 2010), possibly because of insufficient osteoporosis awareness (Cawthon, 2011). Third, poorer nutritional status and a larger number of comorbidities are known to contribute to poorer recovery amongst men with hip fractures (Carpintero et al., 2005). Additionally, male gender has been shown to be a risk factor for the development of postoperative medical complications in patients with hip fractures (Endo et al., 2005). Thus, the greater predominance of poor outcome trajectories in men could have a number of underlying reasons.

3.5.1 Strengths and limitations

The study undertook a unique approach using LGCA to categorize recovery trajectories post-DRF using the valid and reliable outcome measure of PRWE, in a relatively large cohort of patients. Depression was measured prior to knowledge of the outcome trajectory, which mitigates any potential for response bias. The principal limitation of this study is that depression data was acquired through self-report using the SCQ and not a depression screen test, therefore accuracy of the depression diagnosis is unknown. However, self-reported depressive symptoms are easily collected in clinical practice and may represent a more practical predictor. In addition, our depression data was only collected at baseline and changes in depressive status could have occurred over time. Thus, we were unable to control for people's recovery from depression or circumstances that cause depression affecting outcomes over time. Nevertheless, we were able to discover that baseline self-reported depression acquired through a single question from the SCQ is a distinguishing factor between people in the non-recovery and rapid-recovery classes.

In summary, using LGCA we identified three classes of recovery post-DRF: rapid-recovery, slow-recovery, and non-recovery. The distinguishing factors between the classes were greater self-reported depression and a higher proportion of males in the non-recovery class. Although not significant, the rapid-recovery class had the lowest baseline PRWE score and proportion of smokers and the highest proportion of people that had finished post-secondary education and were working. The non-recovery class had the highest proportion of smokers, people not working due to the injury, people with no post-secondary education, and the highest baseline PRWE scores. The results may help clinicians identify patients who would benefit from closer monitoring early to facilitate optimal recovery after DRF.

3.6 References

Aitkin, M., & Rubin, D. B. (1985). Estimation and Hypothesis Testing in Finite Mixture Models. Journal of the Royal Statistical Society. Series B (Methodological), 47(1), 67–75. Retrieved from http://www.jstor.org/stable/2345545

Amorosa, L. F., Vitale, M. A., Brown, S., & Kaufmann, R. A. (2011). A functional outcomes survey of elderly patients who sustained distal radius fractures. Hand (New York, N.Y.), 6(3), 260–267. https://doi.org/10.1007/s11552-011-9327-7

Atay, I. M., Aslan, A., Burc, H., Demirci, D., & Atay, T. (2016). Is depression associated with functional recovery after hip fracture in the elderly? Journal of Orthopaedics, 13(2), 115–118. https://doi.org/10.1016/j.jor.2015.02.001

Beck, A. T. (1967). Depression: Clinical, Experimental, and Theoretical Aspects. New York, NY: Hoeber Medical Division.

Berwick, D. M., Murphy, J. M., Goldman, P. A., Ware, J. E. J., Barsky, A. J., & Weinstein, M. C. (1991). Performance of a five-item mental health screening test. Medical Care, 29(2), 169–176.

Bobos, P., Lalone, E. A., Grewal, R., & MacDermid, J. C. (2017). Recovery, age, and gender effects on hand dexterity after a distal radius fracture. A 1-year prospective cohort study. Journal of Hand Therapy : Official Journal of the American Society of Hand Therapists. https://doi.org/10.1016/j.jht.2017.08.002

Carpintero, P., Lopez, P., Leon, F., Lluch, M., Montero, M., & Aguilera, C. (2005). Men with hip fractures have poorer nutritional status and survival than women: a prospective study of 165 patients. Acta Orthopaedica, 76(3), 331–335.

Cawthon, P. M. (2011). Gender differences in osteoporosis and fractures. Clinical Orthopaedics and Related Research, 469(7), 1900–1905. https://doi.org/10.1007/s11999-011-1780-7

Celeux, G., & Soromenho, G. (1996). An Entropy criterion for assessing the number of clusters in a mixture model. Journal of Classification (Vol. 13). https://doi.org/10.1007/BF01246098

Cibulka, M. T., White, D. M., Woehrle, J., Harris-Hayes, M., Enseki, K., Fagerson, T. L., … Godges, J. J. (2009). Hip pain and mobility deficits--hip osteoarthritis: clinical practice guidelines linked to the international classification of functioning, disability, and health

from the orthopaedic section of the American Physical Therapy Association. The Journal of Orthopaedic and Sports Physical Therapy, 39(4), A1-25. https://doi.org/10.2519/jospt.2009.0301

Constand, M. K., MacDermid, J. C., Law, M., & Dal Bello-Haas, V. (2014). Patient-centered care and distal radius fracture outcomes: a prospective cohort study analysis. Journal of Hand Therapy : Official Journal of the American Society of Hand Therapists, 27(3), 177–183; quiz 184. https://doi.org/10.1016/j.jht.2014.04.001

Cowie, J., Anakwe, R., & McQueen, M. (2015). Factors associated with one-year outcome after distal radial fracture treatment. Journal of Orthopaedic Surgery (Hong Kong), 23(1), 24–28. https://doi.org/10.1177/230949901502300106

Das De, S., Vranceanu, A.-M., & Ring, D. C. (2013). Contribution of kinesophobia and catastrophic thinking to upper-extremity-specific disability. The Journal of Bone and Joint Surgery. American Volume, 95(1), 76–81. https://doi.org/10.2106/JBJS.L.00064

Dewan, N., MacDermid, J. C., Grewal, R., & Beattie, K. (2017). Recovery patterns over 4 years after distal radius fracture: Descriptive changes in fracture-specific pain/disability, fall risk factors, bone mineral density, and general health status. Journal of Hand Therapy : Official Journal of the American Society of Hand Therapists. https://doi.org/10.1016/j.jht.2017.06.009

Dewan, N., MacDermid, J. C., Grewal, R., & Beattie, K. (2018). Risk factors predicting subsequent falls and osteoporotic fractures at 4 years after distal radius fracture-a prospective cohort study. Archives of Osteoporosis, 13(1), 32. https://doi.org/10.1007/s11657-018-0445-5

Downie, A. S., Hancock, M. J., Rzewuska, M., Williams, C. M., Lin, C.-W. C., & Maher, C. G. (2016). Trajectories of acute low back pain: a latent class growth analysis. Pain, 157(1), 225–234. https://doi.org/10.1097/j.pain.0000000000000351

Elm, E. von, Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2007). Strengthening the reporting of observational studies in epidemiology (STROBE)

statement: guidelines for reporting observational studies. BMJ, 335(7624), 806 LP – 808. Retrieved from http://www.bmj.com/content/335/7624/806.abstract

Endo, Y., Aharonoff, G. B., Zuckerman, J. D., Egol, K. A., & Koval, K. J. (2005). Gender differences in patients with hip fracture: a greater risk of morbidity and mortality in men. Journal of Orthopaedic Trauma, 19(1), 29–35.

Geiser, C. (2012). Data analysis with Mplus. New York, NY: Guilford Press.

Golkari, S., Teunis, T., Ring, D., & Vranceanu, A.-M. (2015). Changes in Depression, Health Anxiety, and Pain Catastrophizing Between Enrollment and 1 Month After a Radius Fracture. Psychosomatics, 56(6), 652–657. https://doi.org/10.1016/j.psym.2015.03.008

Grewal, R., & MacDermid, J. C. (2007). The risk of adverse outcomes in extra-articular distal radius fractures is increased with malalignment in patients of all ages but mitigated in older patients. The Journal of Hand Surgery, 32(7), 962–970. https://doi.org/10.1016/j.jhsa.2007.05.009

Grewal, R., MacDermid, J. C., Pope, J., & Chesworth, B. M. (2007). Baseline predictors of pain and disability one year following extra-articular distal radius fractures. Hand (New York, N.Y.), 2(3), 104–111. https://doi.org/10.1007/s11552-007-9030-x

Akaike, H. (1998). Information Theory and an Extension of the Maximum Likelihood Principle. In Selected Papers of Hirotugu Akaike. Springer Series in Statistics (Perspectives in Statistics). New York, NY: Springer. https://doi.org/https://doi.org/10.1007/978-1-4612-1694-0_15

Jennings, L. A., Auerbach, A. D., Maselli, J., Pekow, P. S., Lindenauer, P. K., & Lee, S. J. (2010). Missed opportunities for osteoporosis treatment in patients hospitalized for hip fracture. Journal of the American Geriatrics Society, 58(4), 650–657. https://doi.org/10.1111/j.1532-5415.2010.02769.x

Kasapinova, K., & Kamiloski, V. (2015). Influence of associated lesions of the intrinsic ligaments on distal radius fractures outcome. Archives of Orthopaedic and Trauma Surgery, 135(6), 831–838. https://doi.org/10.1007/s00402-015-2203-0

Kasapinova, K., & Kamiloski, V. (2017). Outcomes of surgically treated distal radial fractures with associated triangular fibrocartilage complex injury. Journal of Hand Therapy : Official Journal of the American Society of Hand Therapists. https://doi.org/10.1016/j.jht.2017.09.002

Kurimoto, S., Tatebe, M., Shinohara, T., Arai, T., & Hirata, H. (2012). Residual wrist pain after volar locking plate fixation of distal radius fractures. Acta Orthopaedica Belgica, 78(5), 603–610.

Lalone, E. A., Grewal, R., & MacDermid, J. C. (2016). Impact of Radius Malunion on Wrist Contact Mechanics. The Journal of Orthopaedic and Sports Physical Therapy, 46(5), 399. https://doi.org/10.2519/jospt.2016.0406

Lalone, E. A., Rajgopal, V., Roth, J., Grewal, R., & MacDermid, J. C. (2014). A cohort study of one-year functional and radiographic outcomes following intra-articular distal radius fractures. Hand (New York, N.Y.), 9(2), 237–243. https://doi.org/10.1007/s11552-013-9586-6

Lalone, E., MacDermid, J., Grewal, R., & King, G. (2017). Patient Reported Pain and Disability Following a Distal Radius Fracture: A Prospective Study. The Open Orthopaedics Journal, 11, 589–599. https://doi.org/10.2174/1874325001711010589

Lenze, E. J., Munin, M. C., Dew, M. A., Rogers, J. C., Seligman, K., Mulsant, B. H., & Reynolds, C. F. 3rd. (2004). Adverse effects of depression and cognitive impairment on rehabilitation participation and recovery from hip fracture. International Journal of Geriatric Psychiatry, 19(5), 472–478. https://doi.org/10.1002/gps.1116

Lichtman, J. H., Bigger, J. T. J., Blumenthal, J. A., Frasure-Smith, N., Kaufmann, P. G., Lesperance, F., … Froelicher, E. S. (2008). Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on. Circulation, 118(17), 1768–1775. https://doi.org/10.1161/CIRCULATIONAHA.108.190769

MacDermid, J C. (1996). Development of a scale for patient rating of wrist pain and disability. Journal of Hand Therapy : Official Journal of the American Society of Hand Therapists, 9(2), 178–183.

MacDermid, J C, Richards, R. S., & Roth, J. H. (2001). Distal radius fracture: a prospective outcome study of 275 patients. Journal of Hand Therapy : Official Journal of the American Society of Hand Therapists, 14(2), 154–169.

MacDermid, Joy C, Donner, A., Richards, R. S., & Roth, J. H. (2002). Patient versus injury factors as predictors of pain and disability six months after a distal radius fracture. Journal of Clinical Epidemiology, 55(9), 849–854.

MacDermid, Joy C, Roth, J. H., & McMurtry, R. (2007). Predictors of time lost from work following a distal radius fracture. Journal of Occupational Rehabilitation, 17(1), 47–62. https://doi.org/10.1007/s10926-007-9069-0

MacDermid, Joy C, Roth, J. H., & Richards, R. S. (2003). Pain and disability reported in the year following a distal radius fracture: A cohort study. BMC Musculoskeletal Disorders, 4(1), 24. https://doi.org/10.1186/1471-2474-4-24

Mehta, S., MacDermid, J., & Tremblay, M. (2010). The implications of chronic pain models for rehabilitation of distal radius fracture. Hand Therapy, 16(1), 2–11. https://doi.org/10.1258/ht.2010.010022

Mehta, S. P., MacDermid, J. C., Richardson, J., MacIntyre, N. J., & Grewal, R. (2015a). A systematic review of the measurement properties of the patient-rated wrist evaluation. The Journal of Orthopaedic and Sports Physical Therapy, 45(4), 289–298. https://doi.org/10.2519/jospt.2015.5236

Mehta, S. P., MacDermid, J. C., Richardson, J., MacIntyre, N. J., & Grewal, R. (2015b). Baseline pain intensity is a predictor of chronic pain in individuals with distal radius fracture. The Journal of Orthopaedic and Sports Physical Therapy, 45(2), 119–127. https://doi.org/10.2519/jospt.2015.5129

Moore, C. M., & Leonardi-Bee, J. (2008). The prevalence of pain and disability one year post fracture of the distal radius in a UK population: a cross sectional survey. BMC Musculoskeletal Disorders, 9, 129. https://doi.org/10.1186/1471-2474-9-129

Morris, P. L., Raphael, B., & Robinson, R. G. (1992). Clinical depression is associated with impaired recovery from stroke. The Medical Journal of Australia, 157(4), 239–242.

Mukaka, M., White, S. A., Terlouw, D. J., Mwapasa, V., Kalilani-Phiri, L., & Faragher, E. B. (2016). Is using multiple imputation better than complete case analysis for estimating a prevalence (risk) difference in randomized controlled trials when binary outcome observations are missing? Trials, 17, 341. https://doi.org/10.1186/s13063-016-1473-3

Muthén, L. K., & Muthén, B. O. (2012). Mplus User's Guide (Seventh). Los Angeles, CA.

Patrick, H. A. and N. C. and A. D. R. T. and. (2009). Latent Class Growth Modelling: A Tutorial. Tutorials in Quantitative Methods for Psychology, 5(1), 11-24.

Phillips, A. C., Upton, J., Duggal, N. A., Carroll, D., & Lord, J. M. (2013). Depression following hip fracture is associated with increased physical frailty in older adults: the role of the cortisol: dehydroepiandrosterone sulphate ratio. BMC Geriatrics, 13, 60. https://doi.org/10.1186/1471-2318-13-60

Porrino, J. A. J., Maloney, E., Scherer, K., Mulcahy, H., Ha, A. S., & Allan, C. (2014). Fracture of the distal radius: epidemiology and premanagement radiographic characterization. AJR. American Journal of Roentgenology, 203(3), 551–559. https://doi.org/10.2214/AJR.13.12140

Ring, D., Kadzielski, J., Fabian, L., Zurakowski, D., Malhotra, L. R., & Jupiter, J. B. (2006). Self-reported upper extremity health status correlates with depression. The Journal of Bone and Joint Surgery. American Volume, 88(9), 1983–1988. https://doi.org/10.2106/JBJS.E.00932

Ritchie, C., Hendrikz, J., Kenardy, J., & Sterling, M. (2013). Derivation of a clinical prediction rule to identify both chronic moderate/severe disability and full recovery

following whiplash injury. Pain, 154(10), 2198–2206. https://doi.org/10.1016/j.pain.2013.07.001

Schwarz, G. (1978). Estimating the dimension of a model. Annals of Statistics, 6(2), 461–464. https://doi.org/10.1214/aos/1176344136

Shauver, M. J., Clapham, P. J., & Chung, K. C. (2011). An Economic Analysis of Outcomes and Complications of Treating Distal Radius Fractures in the Elderly. Journal of Hand Surgery, 36(12), 1912-1918.e3. https://doi.org/10.1016/j.jhsa.2011.09.039

Sterling, M., Hendrikz, J., & Kenardy, J. (2010). Compensation claim lodgement and health outcome developmental trajectories following whiplash injury: A prospective study. Pain, 150(1), 22–28. https://doi.org/10.1016/j.pain.2010.02.013

Swart, E., Nellans, K., & Rosenwasser, M. (2012). The effects of pain, supination, and grip strength on patient-rated disability after operatively treated distal radius fractures. The Journal of Hand Surgery, 37(5), 957–962. https://doi.org/10.1016/j.jhsa.2012.01.028

Symonette, C. J., Macdermid, J., & Grewal, R. (2013). Social Support Contributes to Outcomes following Distal Radius Fractures. Rehabilitation Research and Practice, 2013, 867250. https://doi.org/10.1155/2013/867250

Vergara, I., Vrotsou, K., Orive, M., Garcia-Gutierrez, S., Gonzalez, N., Las Hayas, C., & Quintana, J. M. (2016). Wrist fractures and their impact in daily living functionality on elderly people: a prospective cohort study. BMC Geriatrics, 16, 11. https://doi.org/10.1186/s12877-015-0176-z

Vranceanu, A.-M., Bachoura, A., Weening, A., Vrahas, M., Smith, R. M., & Ring, D. (2014). Psychological factors predict disability and pain intensity after skeletal trauma. The Journal of Bone and Joint Surgery. American Volume, 96(3), e20. https://doi.org/10.2106/JBJS.L.00479

Yeoh, J. C., Pike, J. M., Slobogean, G. P., O'Brien, P. J., Broekhuyse, H. M., & Lefaivre, K. A. (2016). Role of Depression in Outcomes of Low-Energy Distal Radius Fractures in

Patients Older Than 55 Years. Journal of Orthopaedic Trauma, 30(5), 228–233. https://doi.org/10.1097/BOT.0000000000000514

3.7 Tables

	Mean (SD)	Valid Percent
Age	59.6 (11.9)	-
Sex (% female)	-	80.5%
Smoking	-	
Non-smoker		88%
Smoker		12%
Education	-	
Didn't complete post-secondary education		80%
Completed post-secondary education		20%
Work status	-	
Unable to work (due to various reasons)		54%
Unable to work (due to this injury)		19%
Part-time or full-time work		27%
Depression (% yes)	-	11.3%
Baseline Patient-Rated Wrist Evaluation	66.5 (21.2)	-
Month 3 Patient-Rated Wrist Evaluation	31.8 (21.6)	-
Month 6 Patient-Rated Wrist Evaluation	19.8 (18.2)	-
Year 1 Patient-Rated Wrist Evaluation	13.5 (17.1)	-

Table 1. Baseline characteristics and demographic information as well as Patient-Rated Wrist Evaluation scores of all time points of all participants.

Classes	AIC	BIC	Entropy	VLMR Log (p)
1	10044.36	10081.98	-	-
2	9899.03	9951.7	0.94	-5012.18 (0.004)
3	9846.06	9913.78	0.86	-4935.52 (0.03)
4	9825.40	9908.17	0.87	-4905.03 (0.86)

Table 2. Latent growth curve analysis model fit statistics for classification of recovery rates following distal radius fracture.

AIC, akaike information criterion; BIC, Bayesian information criterion; VLMR, Vuong Lo-Mendell-Rubin; p, probability value

	Class one (rapid-recovery, 69%)	**Class two (slow-recovery, 23%)**	**Class three (non-recovery, 8%)**
Mean age (SD)	60 (12.2)	60 (10.6)	55 (12.8)
Sex (% female)	**81%**	**84%**	**65%***
Smoking			
Non-smoker	89%	84%	80%
Current smoker	11%	16%	20%
Education (%)			
Didn't complete post-secondary education	80%	77%	84%
Completed post-secondary education	20%	23%	16%
Work status			
Unable to work (due to various reasons)	54%	55%	52%
Unable to work (due to this injury)	18%	20%	28%
Part-time or full-time work	28%	25%	20%
Depression (% yes)	**8%**	**16%**	**24%***
Baseline_PRWE (SD)	63.2 (21.2)	72.6 (19.4)	77.3 (19)
Month 3 PRWE (SD)	22.5 (16.4)	47.8 (14.5)	66.6 (16.7)
Month 6_PRWE (SD)	9.5 (7.0)	35.0 (9.8)	60.0 (12.0)
Year 1_PRWE (SD)	6.1 (6.6)	22.0 (12.1)	63.4 (13.3)

Table 3. Baseline characteristics and Patient Rated Wrist Evaluation (PRWE) scores of all timepoints of participants based on class membership.

*: Proportions are significantly different between the non-recovery class compared to the other two classes. Proportions between the rapid and slow-recovery classes were not significantly different.

3.8 Figures

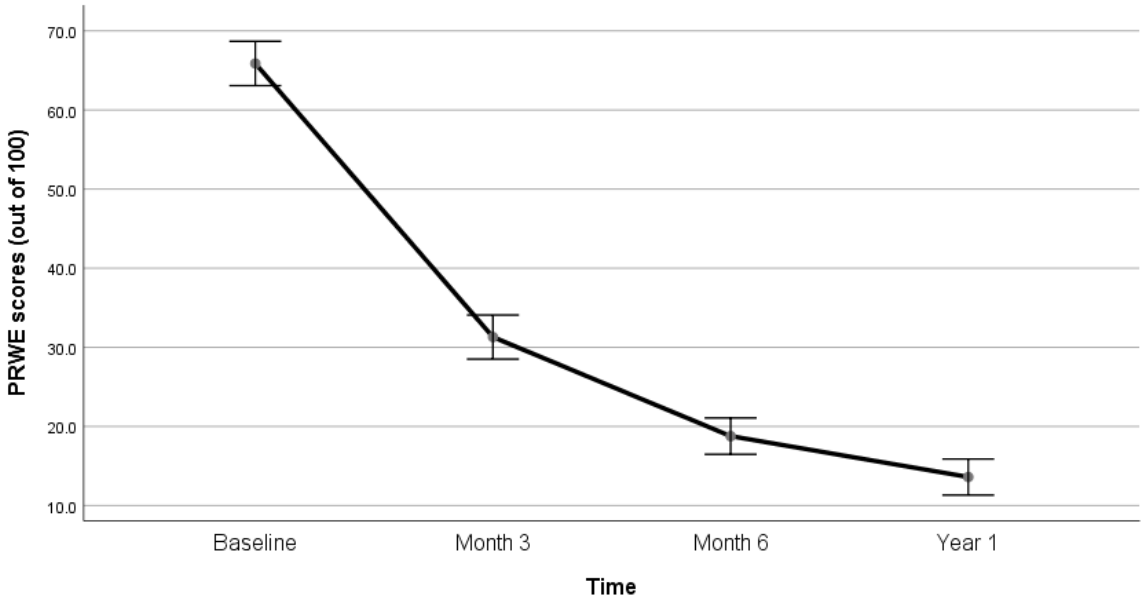


Figure 1. Patient Rated Wrist Evaluation (PRWE) scores at four time points of baseline, month three, month six, and year 1.

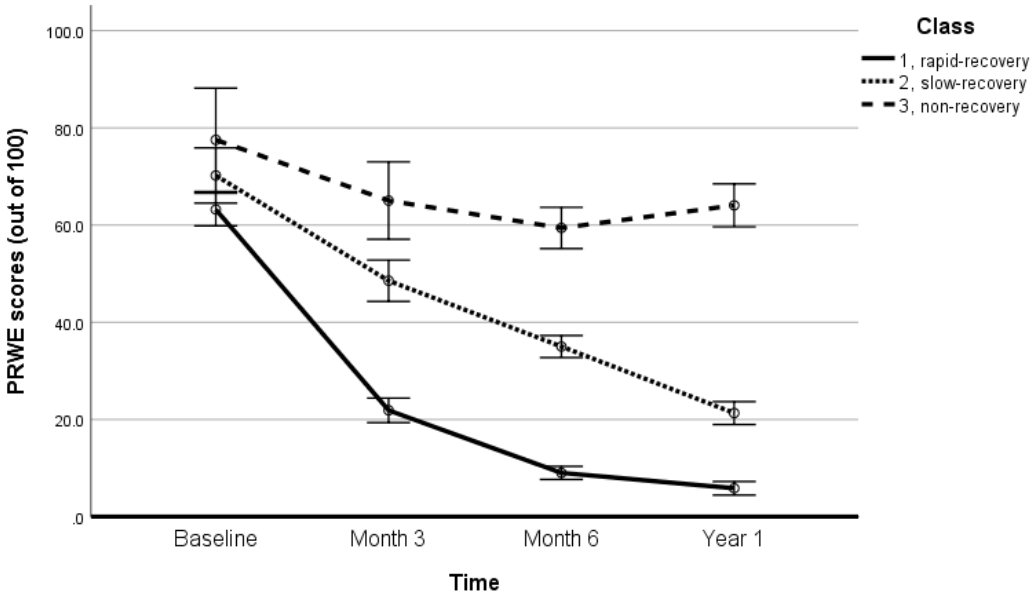


Figure 2. The three classes of recovery trajectory following a distal radius fracture. Class one is defined as rapid-recovery, class two is slow-recovery, and class three is non-recovery. Error bars are 95% confidence intervals.

Chapter 4

4 Quantile regression analysis of the association between peritraumatic distress and pain 12 months following non-catastrophic musculoskeletal injuries

A version of this manuscript is submitted to *Clinical Orthopedics and Related Research*.

4.1 Abstract

Background and purpose: Psychological factors have been shown to be consistent predictors of chronic pain in people with musculoskeletal injuries. The purpose of this study is to describe the effect of peritraumatic distress on the development of chronic pain using quantile regression, which allows us to examine how factors might act differently across the spectrum of outcomes.

Methods: Participants were adults with acute non-catastrophic (i.e., not requiring surgery or hospitalization) musculoskeletal injuries of any etiology with various locations of injury. The Traumatic Injuries Distress Scale (TIDS) was used to evaluate distress at baseline; defined as the timepoint of entry to the study (<4 weeks post-injury). The Numeric Pain Rating Scale (NPRS) was used to assess the level of pain at baseline and again 12 months post-injury. Paired samples t-test was used to assess recovery by comparing NPRS scores at baseline and 12 months. Quantile regression was used to describe the effect of baseline distress on pain levels one year later.

Results: 116 participants (age range=18-66, 69% female) were included. 52% of participants reported no pain (NPRS=0) and 15% reported minimal pain (NPRS=1) 12 months post-injury. Mean pain intensity scores improved from 4.8 at baseline to 1.6 at 12-month follow-up ($p<0.001$). The results of the quantile regression indicated that for the 30^{th} quantile of the NPRS at 12 months, acute distress is not associated with having pain at 12 months. From the 50^{th} quantile onwards, a significant effect is observed: 50^{th} quantile ($\beta=0.11$, $p=0.01$), 70^{th} quantile ($\beta=0.27$, $p<0.001$), 90^{th} quantile ($\beta=0.31$, $p=0.01$). The changing slopes illustrate the value of describing the effect in different quantiles of the distribution because as we move up in quantiles, the higher the baseline distress, the higher pain levels at 12 months post-injury.

Conclusion: Most (~2/3) of patients with non-catastrophic musculoskeletal injuries report no or minimal pain within 12 months regardless of their distress level at baseline. However, ~1/3 will experience higher levels of pain at 12 months and in this group of people, peritraumatic distress was a significant contributing factor. Targeting higher

levels of distress in the aftermath of trauma may help to reduce, if not prevent, the transition to chronicity.

4.2 Introduction

Chronic pain is referred to as I) pain persisting beyond the expected time for physiological healing, or II) pain lasting longer than three months post-injury (Treede et al., 2015). The economic impact of chronic pain imposes a significant burden on the patient, the family, and society, taxing healthcare resources, increasing rates of absenteeism with corresponding reductions in work productivity (Phillips, 2009). As the overall burden is expected to increase as the world's population ages (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017), many have endorsed a focus on prevention through more informed acute pain management, rather than attempting to remediate a chronic problem where there is a paucity of effective therapeutic options (Campbell et al., 2019). In addition, according to the perspective of people with chronic pain and their families, the most prioritized research topic should be strategies that effectively prevent acute pain from becoming chronic (Birnie et al., 2019). As a result, a growing body of research has emerged aimed at understanding those variables associated with the development of chronic pain after MSK injuries. A mechanistic understanding of risk factors could potentially reveal new pathways for informed assessments and effective treatments.

Many factors have been identified to be associated with chronic pain following MSK injuries, such as high levels of baseline pain intensity (Mehta et al., 2015), having more pre-injury comorbidities (Barnett et al., 2012; Beneciuk et al., 2018), lower education levels (Larsson et al., 2019; Sharma et al., 2018), lower annual income (Mills et al., 2019; Sharma et al., 2018), smoking (Ekholm et al., 2009; Mills et al., 2019), and low levels of physical activity (Geneen et al., 2017; Marley et al., 2017). Other consistent predictors of chronic pain have been classed largely as psychological factors (Mills et al., 2019). Several prior studies have found prognostic associations between long-term pain outcomes in various MSK conditions and psychological factors such as depression, anxiety, catastrophic beliefs about pain, and low expectations of recovery (Jonsdottir et al., 2019; Modarresi et al., 2019; Richter et al., 2004; Sieberg et al., 2017). Although the

association between chronic pain and post-traumatic stress disorder (PTSD) has been consistently reported (Kind & Otis, 2019), it is also important to note that acute distress and chronic pain not only can occur following more severe injuries resulting from motor vehicle collisions (Pozzato et al., 2020), but they can also occur after seemingly benign injuries such as an ankle inversion injury (van Rijn et al., 2008; Walton et al., 2016). Research on the experience of peri- or post-traumatic distress has been increasing for its potential role in the persistence of pain from MSK injury. For example, Ross and colleagues found that symptoms of psychological distress are strong predictors of pain and disability following wrist and hand fractures (Ross et al., 2015). Recently, members of our research team found that a new scale, the Traumatic Injuries Distress Scale (TIDS), was able to predict pain-related outcomes following acute MSK injuries (Walton et al., 2021). However, we recognize that those analyses, conducted using what are largely considered accepted methods in the field, may have provided an incomplete estimate of the true effect owing to the skewed distribution of the primary outcomes.

One methodological limitation of the studies investigating the relationship between psychological pathologies and chronic pain is that they rely and report on the mean of the variables to describe the association. Using the average leads one to assume no transition points or variability in the outcome variable. This assumption is consequently reflected in the research designs and statistical methods used to study the associations, for example opting for the use of methods such as the Ordinary Least Square (OLS). Although a common and effective method if used appropriately, OLS is limited to the average effect of the predictor variables on the outcome, and this can potentially mask the variations in the distribution of the outcome variable. This is especially true if the data are non-homogenous as the mean score is sensitive to extreme outliers or skewed data (as happens in populations such as MSK injuries where the majority of people experience good outcomes), tending to over- or under-inflate prognostic associations and as such OLS regression is vulnerable to being biased (Konstantopoulos et al., 2019). While such data could be dichotomized and explored through logistic regression, that approach leads to substantial loss of potentially important information. Another method of analyzing the data is through quantile regression which offers flexibility to identify associations at different quantiles of the distribution of the dependent variable (Lê Cook & Manning,

2013). In this method, the average score is not assumed to be a true representation of the entire sample, rather the association is investigated with more detail at various points (quantiles) of the distribution.

The purpose of this study is to investigate the association between peritraumatic distress and reports of persistent post-trauma pain using quantile regression. The findings of this study may help clinicians gain better insight into how peritraumatic distress contributes to the persistence of pain, in particular, with quantile regression we are able to see the effect of distress not just on an average or typical patient but rather on the whole distribution of patients.

4.3 Methods

4.3.1 Study design and participants

The data in this study are from two cohorts: cohort 1. the Systematic Merging of Biology, Mental Health, and Environment (SYMBIOME, clinicaltrials.gov ID NCT02711085) longitudinal cohort study collected in London, Ontario, Canada, and cohort 2. the Neuromuscular Mechanisms Underlying Poor Recovery from Whiplash Injuries (clinical trials.gov ID no. NCT02157038) collected in Chicago, Illinois, United States. In both studies, participants were recruited from local urgent or emergency care centers if they were presenting with a recent (less than four weeks) non-catastrophic MSK injury such as falls, motor vehicle collisions, or sports injuries. Non-catastrophic was defined as injuries that did not require inpatient hospital admission or surgery. After getting medical clearance, a research assistant provided all the information to potential participants, answered any questions, screened potential participants against the inclusion/exclusion criteria, and recruited participants after obtaining informed written consent. Consistent inclusion criteria in both studies were recent MSK trauma, the ability to understand and speak conversational English or French, and being of working age (i.e., 18 to 70 years old). The exclusion criteria were any cognitive, systemic, or neuromuscular disease that would interfere with recovery, following instructions, or participating in the study. The primary differences between the two cohorts were that the Chicago cohort recruited exclusively those with whiplash-associated disorder (WAD) after motor vehicle

collisions, while the London cohort recruited all-cause MSK injuries (including both axial and extremity injuries), in addition to the medicolegal contextual differences between American and Canadian healthcare systems. Participants were given a package of questionnaires and were asked to complete them within 24 hours. Data were collected at baseline, and again at regular intervals up to 12 months post-injury. For the purposes of the current analysis, only the baseline and the 12 months data are used. The study protocols were approved by the respective Research and hospital ethics board prior to participant recruitment.

4.3.2 Outcome measures

Demographic information such as self-reported sex and year of birth were collected using study-specific forms at baseline (defined as the point of entry to the study). The level of pain experienced by participants was captured using a numeric pain rating scale (NPRS) with zero indicating no pain and 10 indicating extreme pain. Distress was captured in both cohorts using the TIDS, a screening tool specifically designed to capture distress experienced following acute MSK injuries (Walton et al., 2016). The TIDS has 12 items and three subscales: uncontrolled pain, negative affect, and intrusion/hyperarousal (Walton et al., 2016). Each item is scored on a scale of zero (i.e., never or not at all) to two (i.e., often or all of the time) and the maximum possible score is 24. The TIDS is a freely accessible tool and it has been translated to French, Spanish, and Persian (Modarresi et al., 2021). Other tools were captured as part of the data collection for the respective studies, but only those variables listed were extracted and used for the current analyses.

4.3.3 Analytical approach

4.3.3.1 Descriptive and preliminary analysis

Participants' characteristics and baseline patient-reported scores were explored descriptively (frequencies or means and standard deviations). The data normality was assessed using the Shapiro-Wilk test. Mean NPRS scores at baseline and 12 months were compared using the paired samples t-test as an omnibus first-pass evaluation of the sample recovery status.

4.3.3.2 Evaluation of variables to inform subsequent regression analysis

If the variables met the assumptions of constant variance (using Leven's test) and linearity (using the F statistic), Pearson's *r* and if not, Spearman's *rho* was used to evaluate the correlation between age and NPRS at baseline and between age and NPRS scores at 12 months. Paired samples t-test was used to compare mean NPRS scores at 12 months between males and females.

4.3.3.3 Quantile regression

Next, we employed the quantile regression approach to evaluate the influence of peritraumatic emotional distress (using TIDS scores) on developing chronic pain 12 months later, using the 12-month NPRS score as the primary outcome. Since quantile regression is a relatively new technique in this field, we provide a few key points that may aid the reader. The marrow of quantile regression lies in modeling an entire conditional distribution and not just the mean, as is the goal of OLS regression (Das et al., 2019).

The way the conditional distribution is modeled is through its quantiles; given a conditional distribution P(Y|X), a quantile, q, is the probability P(Y < Yq (X)|X) where Yq (X) is such that the proportion of the population with a response less than Yq (X) is q. For example, if q=0.5, Yq (X) is the median value. The median is familiar, it splits the data into two equal proportions, it (and the other quantiles) are robust since they are immune to outliers and very extreme values, unlike the mean (Mayr, 2021). The regression procedure for finding quantiles bears some similarity to OLS with the noted difference of weighting distances based on the quantile level, for example when q=0.9, negative distances would be weighted less than positive ones. It should be noted that for each quantile the entire dataset is used and there is no subsampling as the name may suggest (Lê Cook & Manning, 2013).

Variables (age, sex, baseline NPRS scores) that were significant (P < 0.05) in the previous step were entered in the quantile regression. The coefficients for the predictor variable (TIDS score at baseline) were estimated from the 10th to 90th quantile of the 12-

month NPRS scores, with an increment of 20 percentile points per step. The regression (prediction) lines resulting from these coefficients were then plotted for each quantile to visualize the slopes. A second plot is also constructed to visualize the slope coefficients and confidence intervals (CIs) with respect to the quantiles.

4.3.3.4 Missing data

Rather than attempting to impute missing data, we elected to include those who provided complete data sets for NPRS and TIDS scores (i.e., complete case approach) for this novel analysis. When only participants with complete data for NPRS and TIDS scores were included in the dataset, there were no missing values for sex. The List-wise deletion method was used to handle the missing data for age, which was less than 10% of the total dataset.

All analyses were conducted using the Statistical Package for the Social Sciences (version 26.0) program (SPSS, Inc, Chicago, Illinois) accepting a p-value of 0.05 or less to indicate statistical significance.

4.4 Results

4.4.1 Sample description

Across both cohorts, 222 participants consented to participate and provided baseline data. Of those, 116 (52%) provided complete data through 12 months. Age, sex, NPRS scores at baseline and 12 months, and TIDS scores of the study sample are summarized in Table 1. The age range of participants was 18 to 66 and the majority were females (69%). Mean NPRS score improved significantly from 4.8 (SD 2.1) at baseline to 1.6 (SD 1.6) at 12 months ($t=12.8$, $p<0.001$) with a modal score of zero at 12 months (52% of the sample). The results of the Shapiro-Wilk test indicated that NPRS scores at 12 months ($p<0.001$) were not normally distributed.

4.4.2 Results of the preliminary analysis to inform the regression

Since the data did not meet the assumptions of Pearson's *r*, we used Spearman's *rho* to assess the correlation between the variables. There was no correlation between age and

NPRS at 12 months (*rho*=-0.10, p=0.30). The correlation between baseline NPRS scores and NPRS at 12 months was small but significant (*rho*=0.18, p=0.05). In addition, there were no significant differences between males and females in NPRS scores at 12 months (t=1.80, p=0.07). Based on these results, sex and age were not, but baseline NPRS scores were initially included in the subsequent quantile regression analysis.

4.4.3 Quantile regression

As the dependent variable (NPRS at 12 months) was not normally distributed, quantile regression was chosen as the ideal approach to explore the association. Based on the results of the analysis in the previous step, baseline NPRS and TIDS scores were entered in the quantile regression at the same time. The coefficient values for baseline NPRS scores as predictors of 12-month NPRS in all of its quantiles were not significant (30^{th} quantile: β=0, no p-value, 50^{th} quantile: β=-0.67, p=0.61, 70^{th} quantile: β=0, p=1.00, 90^{th} quantile: β=0.41, p=0.11). Therefore, this variable was subsequently removed from the quantile regression. The results of the quantile regression for baseline TIDS scores as the only independent variable indicated that for the lower 30^{th} quantile of the NPRS scores at 12 months, there was no association between pain at 12 months and peritraumatic distress at baseline (β=0, no p-value). Starting from the 50^{th} quantile, increasing and significant effects are detected (β=0.11, p=0.01), 70^{th} quantile (β=0.27, p<0.001), 90^{th} quantile (β=0.31, p=0.01). Since the quantiles below the 50^{th} (the median) have β=0, we can deduce that approximately half of the participants in the dataset fully recovered (i.e., reported no pain) regardless of their level of baseline peritraumatic distress. This is in line with the descriptive statistics that show 52% reported NPRS value of zero at 12 months. But for the other half (i.e., quantiles greater than the median), there was a positive and significant association between NPRS scores at 12 months and baseline distress. We observe that higher quantiles are more severely affected by distress as indicated by the increasing slope, i.e., the β values increase with subsequent quantiles (Figure 1).

According to this model, at a baseline TIDS value of 21 (which was the highest reported value), the NPRS score at 12 months is predicted to be zero at the 30^{th} quantile, 2.20 at the 50^{th} quantile, 5.67 at the 70^{th} quantile, and 8.59 at the 90^{th} quantile of the distribution. At a lower baseline TIDS value of 12, the NPRS score at 12 months is predicted to be

zero at the 30th quantile, 1.21 at the 50th quantile, 3.24 at the 70th quantile, and 5.8 at the 90th quantile of the distribution. This means for those that continue to report pain, the higher the peritraumatic distress, the higher the pain at 12 months. Figure 1 shows the prediction lines for all the estimated quantiles. The regression line for the 30th quantile overlap with the x-axis line as there was no association. Figure 2 shows the parameter estimates along with 95% CIs as a function of the quantile level. This plot illustrates that the slope increases with increasing quantiles, indicating a dose-response relationship for those that continue to report pain at 12 months post-injury. Parameter estimates of the quantiles are summarized in Table 2.

4.5 Discussion

In this study, we report that 52% of the participants did not experience any injury-related pain one year later. This is in line with previous studies which show that only a subset of patients develop chronic pain following an MSK injury (MacDermid et al., 2001; Pierik et al., 2016). This study adds to a prior analysis of the prognostic value of the TIDS that relied on linear associations and OLS regression to identify potential predictors (Walton et al., 2021), by showing that peritraumatic distress post-MSK injuries is a significant contributor to the development of chronic pain in those that have higher pain scores at 12 months, but not in those with low pain scores.

In this study, we used quantile regression to assess the association between peritraumatic distress and pain levels at 12 months. This technique allowed us to have a better understanding of the association in a way that the OLS technique would not have due to the data being highly skewed. In the current study, we observed that there was no association between peritraumatic distress and pain for participants below the median of the NPRS distribution. In other words, some people recovered from their injury regardless of their level of distress at baseline. However, as we moved up in the quantiles, the effect of distress became more pronounced which is indicative of a dose-response relationship. Quantile regression detected a significant effect at the 50th quantile and the slope of the coefficients became consistently steeper at the 70th and 90th quantiles, meaning higher distress levels were associated with higher amounts of pain 12 months post-injury. The clinical significance of this result is that now we have the understanding

that not everyone will be equally negatively impacted by peritraumatic distress. However, we need to be cognizant of the people that develop chronic pain and the significant role that peritraumatic emotional distress plays in this effect. Lê Cook and Manning argue that using the mean in other regression methods in health research is useful when one is interested in the average patient, but not every patient falls into the 'average' category, rather the clinical course for some can be complex, accounting for larger personal and societal burden (Lê Cook & Manning, 2013). In this study, in people that developed chronic pain, the higher the baseline peritraumatic distress, the higher was their pain 12 months later. Therefore, targeting higher levels of peritraumatic distress could potentially benefit the clinical course in the long term. Clinicians should carefully monitor and screen for distress following acute MSK injuries with an aim to intervene accordingly.

Although the use of quantile regression in medical research has gained more popularity over the past few years, many researchers are still unaware of its use and applicability (Fosdal, 2017). As computing powers have increased substantially over the past few years, quantile regression functions are now available in many statistical packages (introduced as a function in SPSS in the year 2019, version 26.0) and statisticians believe that the use of this method will be increasing in future studies (Lê Cook & Manning, 2013).

The importance of distress in developing chronic pain is in line with previous research (Gatchel et al., 2007). However, distress has been mostly shown to be a strong predictor of chronic pain following major injuries such as WAD as a result of road traffic accidents (Carroll et al., 2008), or following severe injuries. For example, Edgley and colleagues found that acute emotional distress is a significant predictor of chronic pain in a sample of 303 patients following severe orthopedic injuries that required surgical interventions (Edgley et al., 2019). Recently, Gopinath and colleagues reported that distress is a significant predictor of chronic pain in one year following non-catastrophic road traffic collisions (Gopinath et al., 2019). However, chronic pain can also follow seemingly innocuous injuries such as an ankle sprain (van Rijn et al., 2008), and distress can also be one of the outcomes of such injuries (Haahr & Andersen, 2003; Walton et al., 2016). For instance, Haahr and Anderson reported that the majority of their participants (83%) with

elbow pathologies improved after one year, but distress is a significant predictor of poor prognosis (Haahr & Andersen, 2003). Given that our sample consisted of people with injuries of mixed etiology, it is important to recognize that acute distress can potentially happen in any acute MSK injury and this can be a contributing factor in the persistence of pain. Identifying the contributing factors to the persistence of pain at any point in the recovery process can allow clinicians to better direct their clinical decisions and choose the most appropriate treatment strategy. Given that the TIDS is a short outcome measure that takes less than five minutes to complete, it can be a useful addition to the toolbox of clinicians to assess peritraumatic distress following MSK injuries.

Previous research has endorsed the use of techniques such as cognitive behavioral therapy in people with chronic pain to reduce catastrophic thinking, pain-related fear, and negative appraisals of pain and recovery in order to improve patients' health-related behavior and ultimately improve both psychological and physical symptoms (Knoerl et al., 2016). A recent randomized controlled trial of psychological intervention patients undergoing total knee arthroplasty reported that at six months and two years following surgery, those that received the psychological intervention had better outcomes in terms of psychological symptoms, function, and physical characteristics such as range of motion (Geng et al., 2021). In the acute MSK population, psychological interventions studied to date have mainly focused on people that have suffered severe or catastrophic injuries (De Silva et al., 2009). Future research is needed to discover specific biopsychosocial interventions that can be implemented for people following acute MSK injuries that may seem minor.

4.5.1 Strengths and limitations

One of the main strengths of this study is that we did not include only one type of injury, but rather the sample consisted of injuries of any etiology. The importance of this factor is that we can be more confident that the observed effects are not confined to a specific patient population but rather more generalizable. Another strength of this study is that we took a unique approach in analyzing the data using quantile regression, which is better suited to skewed data and allows us to examine the relationship across different quantiles of the distribution of the outcome variable (in this case amount of pain at 12 months). An

additional strength is that we evaluated distress with the TIDS which is a distress screening tool that has been specifically designed for people with an acute MSK injury. This tool evaluates distress from three perspectives of uncontrolled pain, negative affect, and intrusion/hyperarousal. The principal limitation is that we used two different cohorts of participants. Although this may have introduced some unaccounted for variations in samples and test procedures, this would only have undermined our ability to detect associations and so we are confident in the relationships that were significant. It is important to note that the inclusion/exclusion criteria were similar in the two cohorts and the same outcome measures were used. Another limitation is that we did not account for the severity and type of injury in our analyses. Although this could potentially affect the results, it was safe to assume that all injuries were similar in severity because one of the exclusion criteria was that the injury should not be catastrophic (i.e., did not require hospitalization or surgery).

4.6 Conclusion

In this study, we demonstrated that approximately two-thirds of our cohort report no pain one year after non-catastrophic MSK injuries regardless of their level of baseline distress. However, some people continue to have persisting pain, and in those people, peritraumatic distress is a significant contributing factor. Future studies are needed to understand the importance and efficacy of implementing additional interventions aimed to reduce baseline distress following acute MSK injuries.

4.7 References

Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S., & Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet (London, England), 380(9836), 37–43. https://doi.org/10.1016/S0140-6736(12)60240-2

Beneciuk, J. M., Lentz, T. A., He, Y., Wu, S. S., & George, S. Z. (2018). Prediction of Persistent Musculoskeletal Pain at 12 Months: A Secondary Analysis of the Optimal

Screening for Prediction of Referral and Outcome (OSPRO) Validation Cohort Study. Physical Therapy, 98(5), 290–301. https://doi.org/10.1093/ptj/pzy021

Birnie, K. A., Dib, K., Ouellette, C., Dib, M. A., Nelson, K., Pahtayken, D., … Stinson, J. (2019). Partnering For Pain: a Priority Setting Partnership to identify patient-oriented research priorities for pediatric chronic pain in Canada. CMAJ Open, 7(4), E654–E664. https://doi.org/10.9778/cmajo.20190060

Campbell, F., Hudspith, M., Anderson, M., Choiniere, M., El-Gabalwy, H., Laliberte, J., … Wilhelm, L. (2019). Chronic Pain in Canada: Laying a Foundation for Action.

Carroll, L. J., Holm, L. W., Hogg-Johnson, S., Côté, P., Cassidy, J. D., Haldeman, S., … Guzman, J. (2008). Course and prognostic factors for neck pain in whiplash-associated disorders (WAD): results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine, 33(4 Suppl), S83-92. https://doi.org/10.1097/BRS.0b013e3181643eb8

Das, K., Krzywinski, M., & Altman, N. (2019, June). Quantile regression. Nature Methods. United States. https://doi.org/10.1038/s41592-019-0406-y

De Silva, M., MacLachlan, M., Devane, D., Desmond, D., Gallagher, P., Schnyder, U., … Patel, V. (2009). Psychosocial interventions for the prevention of disability following traumatic physical injury. Cochrane Database of Systematic Reviews, (4). https://doi.org/10.1002/14651858.CD006422.pub3

Edgley, C., Hogg, M., De Silva, A., Braat, S., Bucknill, A., & Leslie, K. (2019). Severe acute pain and persistent post-surgical pain in orthopaedic trauma patients: a cohort study. British Journal of Anaesthesia, 123(3), 350–359. https://doi.org/10.1016/j.bja.2019.05.030

Ekholm, O., Grønbaek, M., Peuckmann, V., & Sjøgren, P. (2009). Alcohol and smoking behavior in chronic pain patients: the role of opioids. European Journal of Pain (London, England), 13(6), 606–612. https://doi.org/10.1016/j.ejpain.2008.07.006

Fosdal, S. (2017). The use of logistic regression and quantile regression in medical statistics. Norwegian University of Science and Technology.

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychological Bulletin, 133(4), 581–624. https://doi.org/10.1037/0033-2909.133.4.581

Geneen, L. J., Moore, R. A., Clarke, C., Martin, D., Colvin, L. A., & Smith, B. H. (2017). Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. The Cochrane Database of Systematic Reviews, 1(1), CD011279. https://doi.org/10.1002/14651858.CD011279.pub2

Geng, X., Wang, X., Zhou, G., Li, F., Li, Y., Zhao, M., … Tian, H. (2021). A Randomized Controlled Trial of Psychological Intervention to Improve Satisfaction for Patients with Depression Undergoing TKA: A 2-Year Follow-up. The Journal of Bone and Joint Surgery. American Volume, 103(7), 567–574. https://doi.org/10.2106/JBJS.20.00169

Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. (2017). Lancet (London, England), 390(10100), 1211–1259. https://doi.org/10.1016/S0140-6736(17)32154-2

Gopinath, B., Jagnoor, J., Kifley, A., Nicholas, M., Blyth, F., Kenardy, J., … Cameron, I. D. (2019). Differential Predictors of Pain Severity Over 12 Months Following Noncatastrophic Injury Sustained in a Road Traffic Crash. The Journal of Pain, 20(6), 676–684. https://doi.org/10.1016/j.jpain.2018.11.011

Haahr, J. P., & Andersen, J. H. (2003). Prognostic factors in lateral epicondylitis: a randomized trial with one-year follow-up in 266 new cases treated with minimal occupational intervention or the usual approach in general practice. Rheumatology (Oxford, England), 42(10), 1216–1225. https://doi.org/10.1093/rheumatology/keg360

Jonsdottir, S., Ahmed, H., Tómasson, K., & Carter, B. (2019). Factors associated with chronic and acute back pain in Wales, a cross-sectional study. BMC Musculoskeletal Disorders, 20(1), 215. https://doi.org/10.1186/s12891-019-2477-4

Kind, S., & Otis, J. D. (2019). The Interaction Between Chronic Pain and PTSD. Current Pain and Headache Reports, 23(12), 91. https://doi.org/10.1007/s11916-019-0828-3

Knoerl, R., Lavoie Smith, E. M., & Weisberg, J. (2016). Chronic Pain and Cognitive Behavioral Therapy: An Integrative Review. Western Journal of Nursing Research, 38(5), 596–628. https://doi.org/10.1177/0193945915615869

Konstantopoulos, S., Li, W., Miller, S., & van der Ploeg, A. (2019). Using Quantile Regression to Estimate Intervention Effects Beyond the Mean. Educational and Psychological Measurement, 79(5), 883–910. https://doi.org/10.1177/0013164419837321

Larsson, B., Dragioti, E., Grimby-Ekman, A., Gerdle, B., & Björk, J. (2019). Predictors of chronic pain intensity, spread, and sensitivity in the general population: A two-year follow-up study from the SWEPAIN cohort. Journal of Rehabilitation Medicine, 51(3), 183–192. https://doi.org/10.2340/16501977-2519

Lê Cook, B., & Manning, W. G. (2013). Thinking beyond the mean: a practical guide for using quantile regression methods for health services research. Shanghai Archives of Psychiatry, 25(1), 55–59. https://doi.org/10.3969/j.issn.1002-0829.2013.01.011

MacDermid, J. C., Richards, R. S., & Roth, J. H. (2001). Distal radius fracture: a prospective outcome study of 275 patients. Journal of Hand Therapy : Official Journal of the American Society of Hand Therapists, 14(2), 154–169.

Marley, J., Tully, M. A., Porter-Armstrong, A., Bunting, B., O'Hanlon, J., Atkins, L., … McDonough, S. M. (2017). The effectiveness of interventions aimed at increasing physical activity in adults with persistent musculoskeletal pain: a systematic review and meta-analysis. BMC Musculoskeletal Disorders, 18(1), 482. https://doi.org/10.1186/s12891-017-1836-2

Mayr, A. (2021). Prediction Inference with Ensemble Methods.

Mehta, S. P., MacDermid, J. C., Richardson, J., MacIntyre, N. J., & Grewal, R. (2015). Baseline pain intensity is a predictor of chronic pain in individuals with distal radius fracture. The Journal of Orthopaedic and Sports Physical Therapy, 45(2), 119–127. https://doi.org/10.2519/jospt.2015.5129

Mills, S. E. E., Nicolson, K. P., & Smith, B. H. (2019). Chronic pain: a review of its epidemiology and associated factors in population-based studies. British Journal of Anaesthesia, 123(2), e273–e283. https://doi.org/10.1016/j.bja.2019.03.023

Modarresi, S., Modarresi, G., Farzad, M., Shafiee, E., Maleki, M., MacDermid, J. C., & Walton, D. M. (2021). Translation and cross-cultural adaptation of the Traumatic Injuries Distress Scale to Persian. Journal of Advanced Medical Sciences and Applied Technologies. https://doi.org/10.30476/jamsat.2021.89502.1017

Modarresi, S., Suh, N., Walton, D. M., & MacDermid, J. C. (2019). Depression affects the recovery trajectories of patients with distal radius fractures: A latent growth curve analysis. Musculoskeletal Science & Practice, 43, 96–102. https://doi.org/10.1016/j.msksp.2019.07.012

Phillips, C. J. (2009). The Cost and Burden of Chronic Pain. Reviews in Pain, 3(1), 2–5. https://doi.org/10.1177/204946370900300102

Pierik, J. G. J., IJzerman, M. J., Gaakeer, M. I., Vollenbroek-Hutten, M. M. R., van Vugt, A. B., & Doggen, C. J. M. (2016). Incidence and prognostic factors of chronic pain after isolated musculoskeletal extremity injury. European Journal of Pain (London, England), 20(5), 711–722. https://doi.org/10.1002/ejp.796

Pozzato, I., Craig, A., Gopinath, B., Kifley, A., Tran, Y., Jagnoor, J., & Cameron, I. D. (2020). Outcomes after traffic injury: mental health comorbidity and relationship with pain interference. BMC Psychiatry, 20(1), 189. https://doi.org/10.1186/s12888-020-02601-4

Richter, M., Ferrari, R., Otte, D., Kuensebeck, H.-W., Blauth, M., & Krettek, C. (2004). Correlation of clinical findings, collision parameters, and psychological factors in the outcome of whiplash associated disorders. Journal of Neurology, Neurosurgery, and Psychiatry, 75(5), 758–764. https://doi.org/10.1136/jnnp.2003.026963

Ross, C., Juraskova, I., Lee, H., Parkitny, L., Stanton, T. R., Moseley, G. L., & McAuley, J. H. (2015). Psychological Distress Mediates the Relationship Between Pain and Disability in Hand or Wrist Fractures. The Journal of Pain, 16(9), 836–843. https://doi.org/10.1016/j.jpain.2015.05.007

Sharma, S., Pathak, A., Jha, J., & Jensen, M. P. (2018). Socioeconomic factors, psychological factors, and function in adults with chronic musculoskeletal pain from rural Nepal. Journal of Pain Research, 11, 2385–2396. https://doi.org/10.2147/JPR.S173851

Sieberg, C. B., Klajn, J., Wong, C., Bowen, G., Simons, L. E., & Millis, M. B. (2017). Predictors and trajectories of chronic postoperative pain following hip preservation surgery. Journal of Hip Preservation Surgery, 4(1), 45–53. https://doi.org/10.1093/jhps/hnx003

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., … Wang, S.-J. (2015). A classification of chronic pain for ICD-11. Pain, 156(6), 1003–1007. https://doi.org/10.1097/j.pain.0000000000000160

van Rijn, R. M., van Os, A. G., Bernsen, R. M. D., Luijsterburg, P. A., Koes, B. W., & Bierma-Zeinstra, S. M. A. (2008). What is the clinical course of acute ankle sprains? A systematic literature review. The American Journal of Medicine, 121(4), 324-331.e6. https://doi.org/10.1016/j.amjmed.2007.11.018

Walton, D. M., Elliott, J. M., Lee, J., Fakhereddin, M., & Seo, W. (2021). Identification of clinically-useful cut scores of the Traumatic Injuries Distress Scale (TIDS) for predicting rate of recovery following musculoskeletal trauma. PloS One, 16(3), e0248745. https://doi.org/10.1371/journal.pone.0248745

Walton, D. M., Krebs, D., Moulden, D., Wade, P., Levesque, L., Elliott, J., & MacDermid, J. C. (2016). The Traumatic Injuries Distress Scale: A New Tool That Quantifies Distress and Has Predictive Validity With Patient-Reported Outcomes. The Journal of Orthopaedic and Sports Physical Therapy, 46(10), 920–928. https://doi.org/10.2519/jospt.2016.6594

4.8 Tables

	Mean (standard deviation) and range or frequency
Age	39.3 (13.9) Range: 18 to 66
Sex (% female)	69%
Pain (measured using Numeric Pain Rating Scale) at baseline	4.8 (2.0) Range: 0 to 10
Pain (measured using Numeric Pain Rating Scale) at 12 months	1.6 (2.2) Range: 0 to 8
Scores on the Traumatic Injuries Distress Scale (TIDS) at baseline	8.3 (5.4) Range: 0 to 21

Table 1. Demographic information as well as descriptive statistics of NPRS and TIDS scores.

Quantile	**Intercept**	**Coefficient β**	**Standard error**	**t-value**	**p-value**	**95% confidence interval**
0.3	0	0	0	-	-	-
0.5	-0.11	0.22	0.04	2.53	0.01	0.02 to 0.20
0.7	0	0.27	0.06	4.15	<0.001	0.14 to 0.40
0.9	2.08	0.31	0.12	2.61	0.01	0.07 to 0.54

Table 2. Parameter estimates of all quantiles of the Numeric Pain Rating distribution with scores on the Traumatic Injuries Distress Scale as the independent variable.

4.9 Figures

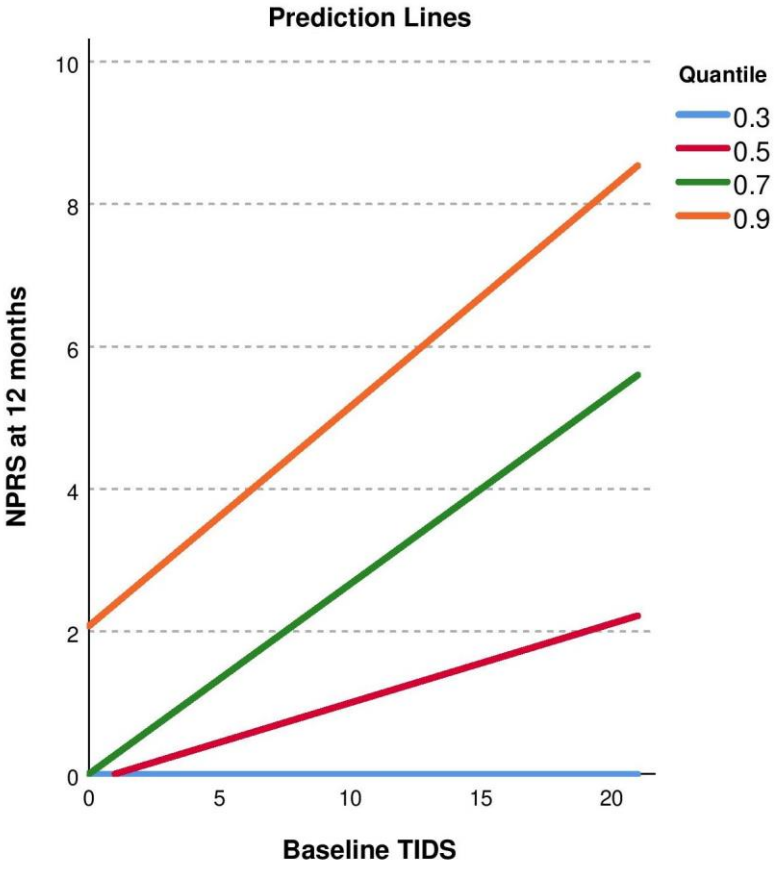


Figure 1. Regression lines for all the estimated quantiles.

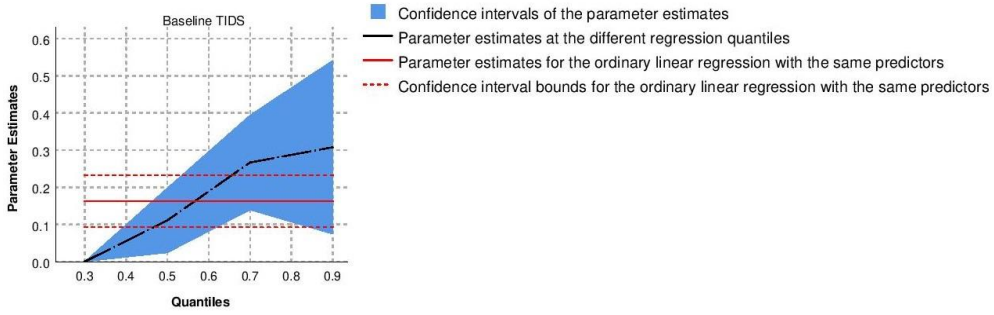


Figure 2. Parameter estimates along with 95% confidence intervals are shown as a function of the quantile level.

Chapter 5

5 Discussion

This chapter provides a summary of key findings of each manuscript, the overall thesis contributions to knowledge, limitations, directions for future research, and implications in terms of clinical practice, professional training, and policy. In addition, efforts made and plans for knowledge translation are outlined, and a lay summary of each manuscript is provided.

5.1 Summary of key findings

Given that chronic pain is a prevalent, disabling, and costly problem worldwide (Breivik et al., 2006), understanding the factors that can potentially contribute to its development and maintenance is of high research priority. This thesis focuses on understanding the psychosocial contributors of chronic pain following MSK injuries. All three manuscripts expand the knowledge basis and fill a gap in the current literature.

Chapter two is a systematic review of the literature on familial CRPS entitled: “Does a familial subtype of complex regional pain syndrome exist? Results of a systematic review”. Understanding CRPS and its management have been a challenge for clinicians for a long time (Shim et al., 2019). CRPS can develop with no apparent cause but more than 90% of cases happen following a traumatic injury such as a fracture (Bruehl, 2015). However, its precise pathophysiology is still unclear. Researchers believe that a single causal factor for CRPS development is unlikely and it is conceivably due to an elaborate combination of various factors (Shim et al., 2019). There are reports of genetic influences on CRPS development (de Rooij et al., 2009; Jin et al., 2013). In this systematic review, we investigated the literature to discover whether a familial subtype of CRPS (fCRPS) exists and if people with this subtype have any distinguishing features. The results of this study support the potential for the existence of fCRPS. In addition, we report that people with this subtype present with more severe symptoms, have more sites involved, a higher percentage of spontaneous onset, and earlier age at onset. However, it is important to note that there are still no studies that show a clear pattern of heritability. This means that the

familial presentation of CRPS may be due to a combination of genetic influences and shared environments. It is important to point out that all the studies included in this review were uncontrolled case reports, case series, and case-control designs which do not provide evidence of causation. This manuscript is published (Modarresi et al., 2019).

Chapter three is a prospective cohort data analysis of recovery following DRFs entitled: "Depression affects the recovery trajectories of patients with distal radius fractures: A latent growth curve analysis". DRFs are amongst the most common types of fractures of the upper extremity and can lead to chronic pain and disability (MacDermid et al., 2003). This study aimed to identify recovery trajectories of participants and to evaluate person characteristics that would predict recovery. According to data from 318 participants with DRF and using latent growth curve analysis, three distinct recovery trajectories were identified: (1) rapid-recovery which comprised of the majority (69%), (2) slow-recovery which comprised 23% of participants, and (3) non-recovery which comprised of a small subset of people (8%). It was determined that depression was the most distinguishing factor between the recovery trajectories in that a greater proportion of people with depression belonged to the non-recovery group. This manuscript is published (Modarresi et al., 2019).

Chapter four is a prospective cohort study entitled: "Quantile regression analysis of the association between peritraumatic distress and pain 12 months after non-catastrophic musculoskeletal injuries". In this study, the objective was to investigate the association between distress following acute MSK injuries of any etiology and pain levels one year later. Distress was assessed at baseline (within four weeks of the injury) using the Traumatic Injuries Distress Scale (TIDS) and pain levels were also assessed at baseline and again 12 months later using the Numeric Pain Rating Scale (NPRS). The association between baseline distress and pain at 12 months was assessed using quantile regression. The results of this analysis indicated that approximately 2/3 of participants reported no or minimal injury-related pain at 12 months regardless of their level of distress at baseline. However, for those that continued to have persisting pain, the higher the level of distress at baseline, the higher was their pain at 12 months. A version of this manuscript is submitted to the journal Clinical Orthopedics and Related Research.

5.2 Overall thesis contribution to knowledge

This thesis provides knowledge regarding the biopsychosocial contributors of persisting pain following MSK injuries. From the first study (chapter two), we learned that a potential combination of genetics and environmental factors can play a role in a familial presentation of CRPS, a chronic pain condition, which most often happens following a traumatic injury. From the second study (chapter three), we learned that depression can significantly affect the recovery trajectories of people following DRF, which is one of the most common injuries of the upper extremity. Then from the third study (chapter four), we learned that distress can not only happen following severe injuries such as motor vehicle collisions but also following injuries that may seem benign. However, not everyone will be equally negatively impacted as the majority of participants recovered by one year. In those people that continued to have persistent pain one year after the injury, higher levels of peritraumatic distress were significantly associated with higher levels of pain.

Overall, we learned the importance of familial factors (genetics plus shared environment), psychological factors such as depression, and distress in the persistence of pain following MSK injuries. The central conclusion of these three studies is that the experience of pain is not a stand-alone sensation caused by tissue injury, but rather it is a complex phenomenon with a plethora of biopsychosocial factors contributing to its development and maintenance.

5.3 Limitations

Each of the manuscripts in this thesis had certain limitations that are stated in previous chapters. In this section, other limitations that were not previously stated are discussed.

The main limitation in the first study (chapter two) that was not discussed in the manuscript is that some of the studies reported on familial cases of CRPS, but this was not the main objective of the study. As such, it is possible that some studies were missed if they reported on fCRPS as only a descriptive statistic of their paper without having any of the related keywords that were used in the search strategy.

The main limitation of the second and third studies (chapters three and four) that was not discussed in the manuscripts is that although in both studies several variables were considered, there always remain factors that could have potentially played a role in the results including (but not limited to): the amount and type of medications used by participants, use of conservative rehabilitation strategies, physical and psychological comorbidities, diet and nutrition, physical activity level, family environment, other social relationships and supports, and childhood or previous adverse events.

5.4 Future research

Each of the manuscripts in this thesis has provided detailed and specific directions for further research. Collectively, the studies in this thesis lay the groundwork for future research in the field of biopsychosocial exploration of chronic and complex pain syndromes following MSK injuries. With the understanding that potentially modifiable factors of shared environment, depression, and distress can play important roles in chronic pain development and maintenance, naturally, the next step would be to investigate specific management strategies that could mitigate the negative consequence of these factors. This type of study would involve a carefully planned longitudinal research design with appropriate control and intervention groups.

5.5 Implications

5.5.1 Practice

This thesis provides further evidence that chronic pain is more than nociception. It is a dynamic interaction between biological, psychological, and social factors that are unique to each person. With this knowledge of multifactorial contributors, chronic pain should be assessed and managed through a biopsychosocial lens taking into account all three components of biological, psychological, and social factors. Recent evidence supports this approach in assessment and treatment (van Erp et al., 2019). However, many recent publications still report that chronic pain management remains in the biomedical realm with a strong emphasis on nociception (Darnall et al., 2017). Many physical therapists have reported not integrating the biopsychosocial strategies into their clinical practice (Bishop & Foster, 2005). In many healthcare settings, psychosocial factors are often not

the first priority, and they are viewed mostly as reactions to pain (Edwards, Dworkin, Sullivan, Turk, & Wasan, 2016). Although the relationship between psychosocial factors and chronic pain can be a bidirectional one, the results of the studies in this thesis point us towards the psychosocial factors being important preceding factors to chronic pain. Therefore, based on the results of this thesis, we recommend clinicians to screen for familial presentations of CRPS, depression in fracture populations specifically DRF, and signs of distress following non-catastrophic MSK injuries of any etiology.

5.5.2 Professional training

The implementation of the biopsychosocial approach to chronic pain in clinical practice starts with its inclusion in professional training programs. Training future clinicians with the biopsychosocial model can potentially lead to better implementation of this model in clinical practice (Overmeer et al., 2009). Although the inclusion of a biopsychosocial approach in education curricula has steadily increased over the years, it remains one of the lower priorities in professional programs as evidenced by the low number of hours dedicated to this topic. This holds for programs that are “bio” focused such as physical therapy and medicine as well as programs that are “psych” focused such as clinical psychology. A systematic review of pain education internationally, reported that pain education in medical schools is primarily focused on neurophysiology and pharmacology worldwide (Shipton et al., 2018). Similarly, in physical therapy schools, a limited number of hours are dedicated to pain education from a psychosocial perspective (Wideman et al., 2018). A national study on pain psychology training in the United States reported that 72% of psychotherapists and psychologists reported having little or no formal training in pain, and 55% reported low comfort levels in treating pain (Darnall et al., 2016). However, there is potential for the inclusion of a more comprehensive model for effective pain management. For instance, one study suggested that physical therapists are capable of providing assessment and treatment strategies based on a biopsychosocial model, but appropriate training needs to be provided (Nicholas & George, 2011). Another study concluded that delivering both physical and psychological interventions are more effective than exercise alone in people with acute whiplash associated disorder (Sterling et al., 2019). The authors of this study also reported that with training, physiotherapists

are capable of providing effective and successful psychological interventions (Sterling et al., 2019). It is worth mentioning that the IASP has proposed a special pain education curriculum for various healthcare professionals including physiotherapists (Slater et al., 2018). The main objective of this curriculum is to provide a more comprehensive education and training for students enrolled in professional physiotherapy programs. This curriculum is intended for pre-licensure students, but the information can also be used by learners well beyond pre-licensure training (Slater et al., 2018). The curriculum contains four main competency domains. Competency domain one focuses on the multidimensional nature of pain and provides information on how various factors such as culture and family can affect the experience of pain. Competency domain two focuses on pain assessment and measurement and explains how pain can be quantified and communicated and how various factors such as the society can affect this activity with an emphasis on the integration of psychological measures and societal components. Competency domain three focuses on pain management and demonstrates the importance of risk management and flexibility in care with the integration of a biopsychosocial approach. Competency domain four focuses on pain conditions and how they can vary depending on populations and settings (Slater et al., 2018). The results of this thesis also encourage the integration of a biopsychosocial approach to care in professional training programs in order to prepare future healthcare providers with a more comprehensive toolbox.

5.5.3 Policy

The need for more effective treatment strategies for chronic pain through a biopsychosocial approach has steadily gained recognition over the years. However, there are certain barriers in primary care settings that make the transition from a purely biomedical perspective to a biopsychosocial model more difficult. These barriers include lack of or poor insurance coverage for psychological services and the limited resources and staff at hospitals and other primary care settings (Darnall et al., 2017). However, given that solely relying on biomedical treatment of chronic pain has not been greatly successful and has had certain adverse consequences such as an over-reliance on pain medications and opioid addiction (Hulla et al., 2019), one might wonder if a cost-benefit

analysis would address the financial concerns. A systematic review on this topic reported that implementing a multidisciplinary biopsychosocial approach to chronic low back pain would substantially reduce costs associated with its management (Salathé et al., 2018). Whether implementing these strategies in other MSK patient populations such as DRF would also lead to cost reductions is still unclear but given the importance of the psychosocial predictors of its outcome, the potential to reduce the negative impacts is high. Therefore, all stakeholders for chronic pain management are encouraged to revisit the concept of including a multi-dimensional approach to the assessment and management of chronic pain and revise the associated policies.

5.6 Thesis knowledge translation

Knowledge translation is the process of transferring the results of research studies into clinical practice (Graham et al., 2006). Often, this process is slow, which means that patients do not benefit from the most recent research findings because it takes a long time for the knowledge to be transferred and implemented into clinical practice (Graham et al., 2006). A clear and purposeful knowledge translation plan can lead to a better and more efficient implementation of the findings of this thesis to clinical practice.

5.6.1 Plan

In an effort to make the knowledge translation process of the results of this thesis more efficient many steps have been taken including:

The findings of all three studies in this thesis have been published/submitted in respected journals of Canadian Journal of Pain, Musculoskeletal Science and Practice, and Clinical Orthopedics and Related Research.

Each study has been presented in many conferences and seminars with a wide variety of audiences. Study number one (chapter two) has been presented at the International Congress on Neuropathic Pain in London United Kingdom, At the Chronic Pain Network in Toronto Canada, and at the London Health Research Day in London Canada. Study number two (chapter three) has been presented at the 40th Annual Scientific Meeting of Canadian Pain Society in Toronto Canada, at Western Research Forum in London

Canada and at the 12th Annual Health and Rehabilitation Sciences Graduate Research Conference in London Canada. Study number three (chapter four) has been presented at the International Consortium for Addressing Mental and Social Health in Musculoskeletal Care which was a virtual conference. Additionally, the findings of all three studies have been presented during clinical placements at The Arthritis Society of Canada, the Canadian Center for Activity and Aging, and the University Hospital in London Canada.

In addition to the above activities that have taken place, plans have been made to further improve the knowledge translation from this work to other settings such as clinical practice. The Canadian Institutes of Health Research recommends that knowledge translation focus on non-academic ways to communicate and use lay language and popular formats such as YouTube videos and art ("Guide to Knowledge Translation Planning at CIHR: Integrated and End-of-Grant Approaches," 2015). One approach to knowledge translation through art is using infographics (information graphics). An infographic is a tool to disseminate research findings and key messages through a quick visual representation and lay language. Research has shown that infographics meet knowledge needs, and people use them to build their knowledge and educate others (Provvidenza et al., 2019). An infographic will be made to summarize the key findings of the studies in this thesis. This infographic will be posted on various social media platforms.

5.6.2 Lay summary of thesis papers

Scientific papers, including the manuscripts in this thesis, are written using technical terminology and jargon, which can be difficult to understand for people outside of the field (Gudi, Tiwari, & Panjwani, 2021). Therefore, providing summaries of research studies in plain language is a knowledge translation tool that can help researchers disseminate their findings to a wider audience (Gudi et al., 2021). In this last section of this thesis, summaries of the thesis papers are provided in lay language. To accomplish this task, Microsoft Word's readability statistics were used to assess the readability of the passages. A Flesch-Kincaid grade level of nine was set as the threshold.

Thesis paper one: In this project, we wanted to find out whether complex regional pain syndrome runs in families. To do this, we searched the available papers that have been published on this topic online. We found eight papers. The results of these eight papers suggested that it is possible for this disease to run in families. Also, people that reported having this disease run in their families also reported more severe presentations and they got it at a younger age. What we do not know is the reason why it runs in families. The reason could be genetics or being in the same environment. Future projects need to examine two things. 1) Which factor (genetics or shared environment) is more important in this disease? And 2) if it is because of a shared environment, what can we do about it?

Thesis paper two: After a wrist fracture, most people recover in just a few months. But some people continue to have pain for a long time. In this project, we found that there are three groups of recovery patterns. One group of people recover quickly. One group takes a little bit longer. And one group continues to have pain for a long time. Then we found that the biggest difference between those people that recover quickly and those who do not is depression. People who continued to report pain for a long time reported being depressed. Future projects need to find out if treating depression can have a positive effect on recovery in people with wrist fractures.

Thesis paper three: After an injury, people may suffer from distress. This distress can affect recovery. In this project, we used a novel statistical method to understand the relationship between distress after an injury and pain levels 12 months later. We found that most people do not have any pain 12 months later. But some people continue to have pain. In those people, the higher their distress after their injury, the higher their pain was 12 months later. Future studies need to find out if monitoring distress and treating it can positively affect outcomes.

5.7 References

Bishop, A., & Foster, N. E. (2005). Do physical therapists in the United kingdom recognize psychosocial factors in patients with acute low back pain? Spine, 30(11), 1316–1322. https://doi.org/10.1097/01.brs.0000163883.65321.33

Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. European Journal of Pain (London, England), 10(4), 287–333. https://doi.org/10.1016/j.ejpain.2005.06.009

Bruehl, S. (2015). Complex regional pain syndrome. BMJ (Clinical Research Ed.), 351, h2730.

Darnall, B. D., Carr, D. B., & Schatman, M. E. (2017). Pain Psychology and the Biopsychosocial Model of Pain Treatment: Ethical Imperatives and Social Responsibility. Pain Medicine (Malden, Mass.), 18(8), 1413–1415. https://doi.org/10.1093/pm/pnw166

Darnall, B. D., Scheman, J., Davin, S., Burns, J. W., Murphy, J. L., Wilson, A. C., … Mackey, S. C. (2016). Pain Psychology: A Global Needs Assessment and National Call to Action. Pain Medicine (Malden, Mass.), 17(2), 250–263. https://doi.org/10.1093/pm/pnv095

de Rooij, A. M., Florencia Gosso, M., Haasnoot, G. W., Marinus, J., Verduijn, W., Claas, F. H. J., … van Hilten, J. J. (2009). HLA-B62 and HLA-DQ8 are associated with Complex Regional Pain Syndrome with fixed dystonia. Pain, 145(1–2), 82–85. https://doi.org/10.1016/j.pain.2009.05.015

Edwards, R. R., Dworkin, R. H., Sullivan, M. D., Turk, D. C., & Wasan, A. D. (2016). The Role of Psychosocial Processes in the Development and Maintenance of Chronic Pain. The Journal of Pain, 17(9 Suppl), T70–T92. https://doi.org/10.1016/j.jpain.2016.01.001

Graham, I. D., Logan, J., Harrison, M. B., Straus, S. E., Tetroe, J., Caswell, W., & Robinson, N. (2006). Lost in knowledge translation: time for a map? The Journal of Continuing Education in the Health Professions, 26(1), 13–24. https://doi.org/10.1002/chp.47

Gudi, S. K., Tiwari, K. K., & Panjwani, K. (2021). Plain-language summaries: An essential component to promote knowledge translation. International Journal of Clinical Practice, e14140. https://doi.org/10.1111/ijcp.14140

Guide to Knowledge Translation Planning at CIHR: Integrated and End-of-Grant Approaches. (2015).

Hulla, R., Brecht, D., Stephens, J., Salas, E., Jones, C., & Gatchel, R. (2019). The biopsychosocial approach and considerations involved in chronic pain. Healthy Aging Research, 8(1), 7–12.

Jin, E.-H., Zhang, E., Ko, Y., Sim, W. S., Moon, D. E., Yoon, K. J., … Lee, W. H. (2013). Genome-wide expression profiling of complex regional pain syndrome. PloS One, 8(11), e79435. https://doi.org/10.1371/journal.pone.0079435

MacDermid, J. C., Roth, J. H., & Richards, R. S. (2003). Pain and disability reported in the year following a distal radius fracture: A cohort study. BMC Musculoskeletal Disorders, 4(1), 24. https://doi.org/10.1186/1471-2474-4-24

Modarresi, S, Aref-Eshghi, E., Walton, D. M., & MacDermid, J. C. (2019). Does a familial subtype of complex regional pain syndrome exist? Results of a systematic review. Canadian Journal of Pain, 3(1), 157–166. https://doi.org/10.1080/24740527.2019.1637249

Modarresi, Shirin, Suh, N., Walton, D. M., & MacDermid, J. C. (2019). Depression affects the recovery trajectories of patients with distal radius fractures: A latent growth curve analysis. Musculoskeletal Science & Practice, 43, 96–102. https://doi.org/10.1016/j.msksp.2019.07.012

Nicholas, M. K., & George, S. Z. (2011). Psychologically informed interventions for low back pain: an update for physical therapists. Physical Therapy, 91(5), 765–776. https://doi.org/10.2522/ptj.20100278

Overmeer, T., Boersma, K., Main, C. J., & Linton, S. J. (2009). Do physical therapists change their beliefs, attitudes, knowledge, skills and behaviour after a biopsychosocially orientated university course? Journal of Evaluation in Clinical Practice, 15(4), 724–732. https://doi.org/10.1111/j.1365-2753.2008.01089.x

Provvidenza, C. F., Hartman, L. R., Carmichael, J., & Reed, N. (2019). Does a picture speak louder than words? The role of infographics as a concussion education strategy. Journal of Visual Communication in Medicine, 42(3), 102–113. https://doi.org/10.1080/17453054.2019.1599683

Salathé, C., Melloh, M., Crawford, R., Scherrer, S., Boos, N., & Elfering, A. (2018). Treatment Efficacy, Clinical Utility, and Cost-Effectiveness of Multidisciplinary Biopsychosocial Rehabilitation Treatments for Persistent Low Back Pain: A Systematic Review. Global Spine Journal, 8, 219256821876548. https://doi.org/10.1177/2192568218765483

Shim, H., Rose, J., Halle, S., & Shekane, P. (2019). Complex regional pain syndrome: a narrative review for the practising clinician. British Journal of Anaesthesia, 123(2), e424–e433. https://doi.org/10.1016/j.bja.2019.03.030

Shipton, E. E., Bate, F., Garrick, R., Steketee, C., Shipton, E. A., & Visser, E. J. (2018). Systematic Review of Pain Medicine Content, Teaching, and Assessment in Medical School Curricula Internationally. Pain and Therapy, 7(2), 139–161. https://doi.org/10.1007/s40122-018-0103-z

Slater, H., Sluka, K., Bement, M. H., & Soderlund, A. (2018). IASP Curriculum Outline on Pain for Physical Therapy.

Sterling, M., Smeets, R., Keijzers, G., Warren, J., & Kenardy, J. (2019). Physiotherapist-delivered stress inoculation training integrated with exercise versus physiotherapy

exercise alone for acute whiplash-associated disorder (StressModex): a randomised controlled trial of a combined psychological/physical intervention. British Journal of Sports Medicine, 53(19), 1240–1247. https://doi.org/10.1136/bjsports-2018-100139

van Erp, R. M. A., Huijnen, I. P. J., Jakobs, M. L. G., Kleijnen, J., & Smeets, R. J. E. M. (2019). Effectiveness of Primary Care Interventions Using a Biopsychosocial Approach in Chronic Low Back Pain: A Systematic Review. Pain Practice : The Official Journal of World Institute of Pain, 19(2), 224–241. https://doi.org/10.1111/papr.12735

Wideman, T. H., Miller, J., Bostick, G., Thomas, A., & Bussières, A. (2018). Advancing Pain Education in Canadian Physiotherapy Programmes: Results of a Consensus-Generating Workshop. Physiotherapy Canada. Physiotherapie Canada, 70(1), 24–33. https://doi.org/10.3138/ptc.2016-57

Appendices

Appendix A – Ethics approvals

Western Research

Date: 4 December 2020

To: Joy MacDermid

Project ID: 5697

Study Title: Wrist and Elbow Outcomes Measures Database -15602E

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

Date Approval Issued: 04/Dec/2020

REB Approval Expiry Date: 10/Dec/2021

Dear Joy MacDermid,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

The Office of Human Research Ethics

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Delegated Initial Approval Notice

Principal Investigator: Dr. Dave Walton
Department & Institution: Health Sciences\Physical Therapy,Western University

Review Type: Expedited
HSREB File Number: 106140
Study Title: Modeling post-traumatic pain and recovery: The SYMBIOME longitudinal cohort study
Sponsor: Canadian Institutes of Health Research

HSREB Initial Approval Date: November 17, 2015
HSREB Expiry Date: November 17, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Other	Instructional pamphlet for biomarker collection	2014/11/28
Instruments	Intake questionnaires package	2014/12/05
Instruments	Follow-up questionnaires package	2014/12/05
Instruments	Intake questionnaire package	2015/10/29
Instruments	Screening form	2015/10/29
Instruments	Follow-up forms	2015/10/06
Advertisement	flyer	2015/11/02
Other	Crisis management protocol (received for information only)	2015/10/29
Recruitment Items	consent to contact form	2015/05/29
Western University Protocol		2015/11/15
Letter of Information & Consent		2015/11/15

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer to Contact for Further Information: Erika Basile ___ Nicole Kaniki ___ Grace Kelly ___ Mina Mekhail ___ Vikki Tran ___

This is an official document. Please retain the original in your files

Institutional Review Board Office
Northwestern University

Biomedical IRB
750 North Lake Shore Drive
Rubloff Building, Suite 700
Chicago, Illinois 60611
312-503-9338

Social and Behavioral Sciences IRB
600 Foster Street
Chambers Hall, Second Floor
Evanston, Illinois 60208
847-467-1723

NORTHWESTERN
UNIVERSITY

APPROVAL OF MODIFICATION AND CONTINUING REVIEW

DATE: December 5, 2016

TO: Dr. James Elliott

FROM: Office of the IRB

DETERMINATION DATE: 12/1/2016

APPROVAL DATE: 12/1/2016

EFFECTIVE DATE: 12/1/2016

EXPIRATION DATE: 11/30/2017

The Northwestern University IRB has reviewed and approved the submission described below:

Type of Submission:	Modification and Continuing Review
Review Level:	Expedited
Expedited Category:	- (2)(a) Blood samples from healthy, non-pregnant adults - (4) Noninvasive procedures - (5) Data, documents, records, or specimens - (7) Behavioral research/social science methods
Title of Study:	Neuromuscular Mechanisms Underlying Poor Recovery from Whiplash Injuries
Principal Investigator:	James Elliott
IRB ID:	STU00090769-MODCR0002
Funding Source:	National Institutes of Health, Funding Source ID: R01HD079076
IND, IDE, or HDE:	None
Documents Reviewed:	• Pilot study-brain imaging, Category: Consent Form; • MRI & muscle info letter updated.docx, Category: Other; • MRI info letter_updated.docx, Category: Other; • email_script_brain pilot w STU.docx, Category: Recruitment Materials; • Protocol_6.30.16_TRACKED_CHANGES-2.pdf, Category: IRB Protocol; • 11.16.2016_consent_form_tracked_changes.docx, Category: Consent Form; • telephone script-brain pilot study, Category: Recruitment Materials;

	• Campus Map, Category: Other; • DHI_EAT, Category: Questionnaire/Survey; • CPT Questionnaire, Category: Questionnaire/Survey; • email script.docx, Category: Recruitment Materials; • flyer_clean_copy-revised_04-1.2014.docx, Category: Recruitment Materials; • FU_questionnaire, Category: Questionnaire/Survey; • Initial Assessment Screen Form.doc, Category: Interview; • initial_questionnaire, Category: Questionnaire/Survey; • NIH Grant Application, Category: Other; • Screening questionnaire, Category: Interview; • Social Media Recruitment language, Category: Recruitment Materials; • Telephone script, Category: Recruitment Materials; • TIDS, Category: Questionnaire/Survey; • Twitter language, Category: Recruitment Materials.

Description of the modification:

1. Change in study members.
2. Delete language from the consent form that does not apply to study.
3. Update contact information on consent form.

The IRB requires the following actions:

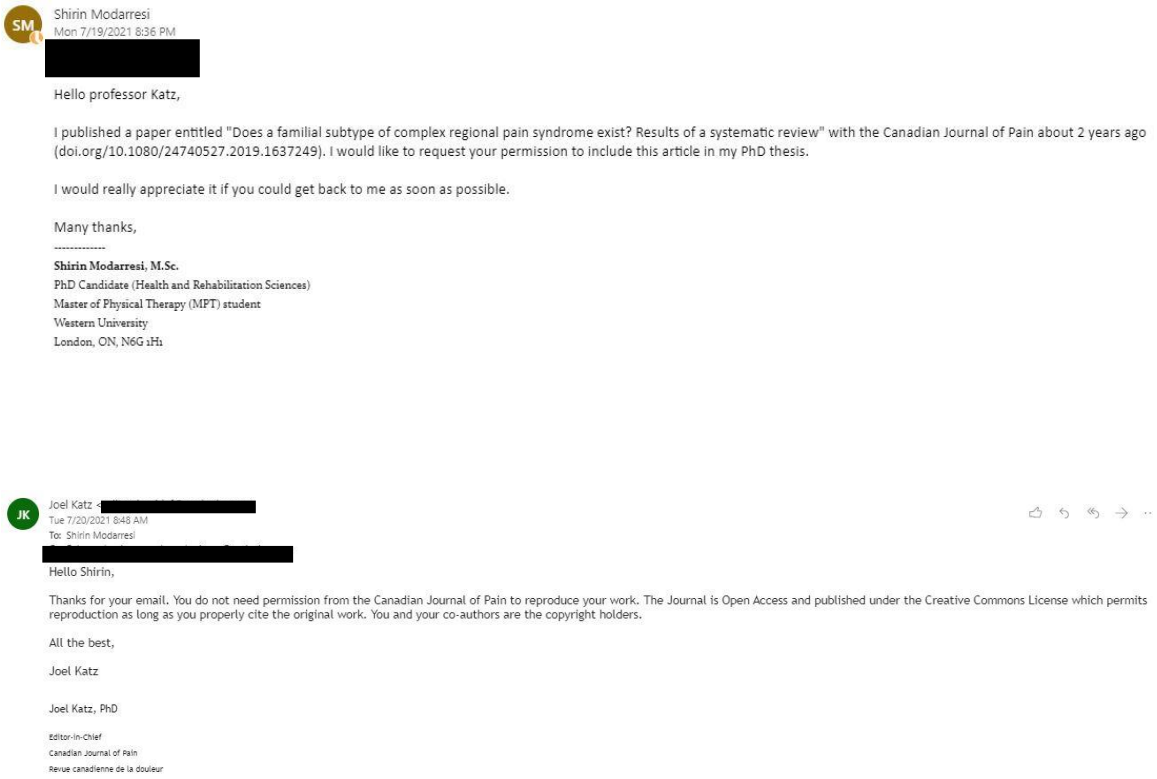
- Current subjects will be notified of these changes.

In conducting this study, you are required to follow the requirements listed in the Northwestern University (NU) Investigator Manual (HRP-103), which can be found by navigating to the IRB Library within the eIRB+ system.

NU IRB approval does not constitute or guarantee institutional approval and/or support. Investigators and study team members must comply with all applicable federal, state, and local laws, as well as NU Policies and Procedures, which may include obtaining approval for your research activities from other individuals or entities.

For IRB-related questions, please consult the NU IRB website at http://irb.northwestern.edu. For general research questions, please consult the NU Office for Research website at www.research.northwestern.edu.

Appendix B – Copyright permission



Shirin Modarresi
Mon 7/19/2021 8:36 PM
[redacted]

Hello professor Katz,

I published a paper entitled "Does a familial subtype of complex regional pain syndrome exist? Results of a systematic review" with the Canadian Journal of Pain about 2 years ago (doi.org/10.1080/24740527.2019.1637249). I would like to request your permission to include this article in my PhD thesis.

I would really appreciate it if you could get back to me as soon as possible.

Many thanks,

Shirin Modarresi, M.Sc.
PhD Candidate (Health and Rehabilitation Sciences)
Master of Physical Therapy (MPT) student
Western University
London, ON, N6G 1H1

Joel Katz [redacted]
Tue 7/20/2021 8:48 AM
To: Shirin Modarresi
[redacted]

Hello Shirin,

Thanks for your email. You do not need permission from the Canadian Journal of Pain to reproduce your work. The Journal is Open Access and published under the Creative Commons License which permits reproduction as long as you properly cite the original work. You and your co-authors are the copyright holders.

All the best,

Joel Katz

Joel Katz, PhD

Editor-in-Chief
Canadian Journal of Pain
Revue canadienne de la douleur

Shirin Modarresi
Tue 7/20/2021 7:06 PM
[redacted]

Hello Professors Jull and Moore,

I published a paper entitled "Depression affects the recovery trajectories of patients with distal radius fractures: A latent growth curve analysis." with Musculoskeletal Science and Practice about 2 years ago (doi.org/10.1016/j.msksp.2019.07.012). I would like to request your permission to include this article in my PhD thesis.

I would really appreciate it if you could get back to me as soon as possible.

Many thanks,

Shirin Modarresi, M.Sc.

PhD Candidate (Health and Rehabilitation Sciences)

Master of Physical Therapy (MPT) student

Western University

London, ON, N6G 1H1

Gwendolen Jull [redacted]
Tue 7/20/2021 7:12 PM
[redacted]

Dear Shirin
It is fine to include the publication in your thesis. It is necessary to state that it is published and the journal details provided, which I am sure you will do automatically
Regards
Gwen Jull
Co-Editor
Musculoskeletal Science and Practice

Gwendolen Jull AO MPhty, PhD, FACP
Emeritus Professor Physiotherapy
School of Health and Rehabilitation Sciences
The University of Queensland
Brisbane Qld 4072 Australia

SM Shirin Modarresi
Fri 9/24/2021 2:17 PM
To: CORR Email [redacted]

Hello professor Leopold,

Thank you for accepting our revised manuscript (CORR-D-21-00877R1) entitled: "How is the proportion of patients that report various levels of pain 12 months after non-catastrophic injuries associated with the level of peritraumatic distress?". I would like to request your permission to include a version of this manuscript (without the revisions, with the previous title) in my PhD dissertation. I would state in the dissertation that a version of this manuscript is submitted and accepted at CORR. I am delaying the publication of the dissertation until Jan 2022.

I would really appreciate it if you could get back to me as soon as possible.

Best regards,

From: [redacted]@wolterskluwer.com>
Sent: Monday, September 27, 2021 2:45 PM
To: [redacted]@clinorthop.org>
Subject: RE: Permission for Dissertation

We generally allow submitted articles to be posted one year after publication. For a dissertation, I would say we don't have to wait, and they can go ahead and use without charge.

[redacted]
Senior Publisher

Curriculum Vitae

Name:

Shirin Modarresi

Post-secondary Education and Degrees:

Ph.D. candidate in health and rehabilitation sciences (physical therapy stream), Western University (2021)

Master of physical therapy, Western University (2021)

Master of science in medicine (neuroscience stream), Memorial University of Newfoundland (2015)

Bachelor (honors) of science in psychology and biology, University of Toronto (2013)

Honours and Awards:

1. Ontario Graduate Scholarship (OGS) (2020)
2. Canadian Physiotherapy Association (CPA) travel award (2019)
3. Second prize for best manuscript from the University of Toronto Medical Journal (2019)
4. People's Choice Award for best poster presentation at the Western Research Forum (WRF), London, Ontario, Canada (2019)
5. Best Ph.D. poster presentation award at the 12th Health and Rehabilitation Sciences Graduate Student Conference (HRSGRC), London, Ontario, Canada (2019)
6. Western University, Faculty of Health Sciences travel award (2019)
7. Western University, Health and Rehabilitation Sciences travel award (2019)
8. Western University, Society of Graduate Students travel award (2019)
9. Western University, Health and Rehabilitation Sciences travel award (2018)

10. 9th Canadian Conference on Dementia (CCD) travel award (2017)
11. Fellow of The School of Graduate Studies, Memorial University of Newfoundland (2015)
12. Golden Synapse Art Award (Neuroscience Research Symposium at Memorial University of Newfoundland) (2014)
13. 3rd place at the 3-Minute Thesis Competition, Memorial University of Newfoundland (2014)

Related Work Experience

1. London Health Science Center – University Hospital, Motor Neuron Diseases Clinic

   Student physiotherapist – July to August 2021

1. London Health Science Center – University Hospital, Inpatient Clinical Neurosciences

   Student physiotherapist – July to August 2021

2. London Health Science Center – University Hospital, Outpatient Clinical Neurosciences

   Student physiotherapist – July to August 2021

3. London Health Science Center – University Hospital, Inpatient Orthopedic department

   Student physiotherapist – April 2021

4. London Health Science Center – University Hospital, Outpatient Orthopedic department

   Student physiotherapist – May 2021

5. Canadian Center for Activity and Aging

   Student physiotherapist – March to April 2021

6. The Arthritis Society of Canada

   Student physiotherapist – November to December 2020

Publications:

1. **Modarresi, S.**, Lucas, JM., Ghodrati, M., Salim, S., MacDermid., JC., Walton, DM. (2021) A systematic review and synthesis of psychometric properties of the Numeric Pain Rating Scale and the Visual Analog Scale for use in people with neck pain. Clinical Journal of Pain.
2. Modarresi G., **Modarresi S.** (2021) Depression and anxiety can be the main aggravating factors of pain in Morton's Neuroma: A Case Report. McGill Journal of Medicine.
3. Seens, H., **Modarresi, S.**, Grewal, R., Walton, DM., MacDermid., JC. (2021) Examining fracture prevalence in people with attention deficit hyperactivity disorder: a systematic review. BMC Pediatrics.
4. **Modarresi, S.**, Janssen, S., Seens, H., Modarresi, G. (2021) Building effective therapeutic relationships in pelvic floor rehab: a commentary. RehabINK. 11.
5. **Modarresi, S.**, Modarresi, G., Farzad, M., Shafiee, E., Maleki, M., MacDermid, JC., Walton, DM. (2021) Translation and cross-cultural adaptation of the Traumatic Injuries Distress Scale to Persian. Journal of Advanced Medical Sciences and Applied Technologies.
6. **Modarresi, S.**, Walton, DM. (2020) Reliability, discriminative accuracy, and an exploration of response shift as measured using the satisfaction and Recovery Index over 12 months from musculoskeletal trauma. Musculoskeletal Science and Practice. 51
7. Lu, Z., Nazari, G., **Modarresi, S.**, MacDermid, JC., Killip, S. (2020) Measurement properties of a two-dimensional movement analysis system: A Systematic Review & Meta-analysis. Archives of Physical Medicine and Rehabilitation.
8. **Modarresi, S.**, Suh, N., Walton, DM., MacDermid, JC. (2019). Depression affects the recovery trajectories of patients with distal radius fracture: a latent growth curve analysis. Musculoskeletal Science and Practice. 43
9. **Modarresi, S.,** Aref-Eshghi, E., MacDermid, JC., Walton, DM. (2019). Does a familial subtype of complex regional pain syndrome exist? Results of a systematic review. Canadian Journal of Pain. 157-166

10. **Modarresi, S.** (2019). Rurality in Canadian physiotherapy studies: a literature search and synthesis. University of Toronto Medical Journal, 96(2), 16-20.
11. **Modarresi, S.**, Divine, A., Grahn, J., Overend, T. J., & Hunter, S. W. (2018). Gait parameters and characteristics associated with increased risk of falls in people with dementia: a systematic review. International Psychogeriatrics. 1-17
12. **Modarresi, S.**, Ghodrati, M., Aref-Eshghi, E. (2018). Using precision medicine to reduce falls in individuals with Alzheimer's disease. Health Science Inquiry, 9(1), 33-35.
13. **Modarresi, S.**, Mukherjee, B., McLean, J. H., Harley, C. W., & Yuan, Q. (2016). CaMKII mediates stimulus specificity in early odor preference learning in rats. Journal of neurophysiology, 116(2), 404-410.
14. Daliri, K., Aref-Eshghi, E., Taranejoo, S., **Modarresi, S.**, Ghorbani, A., Nariman, A., ... & Askari, H. (2016). Emerging cytokines in allergic airway inflammation: a genetic update. Current Immunology Reviews, 12(1), 4-9.